ALCOHOL RESEARCH
Current Reviews

THE JOURNAL OF THE NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

WOMEN AND ALCOHOL

VOLUME 40, NUMBER 2, 2020

DEPARTMENT OF HEALTH AND HUMAN SERVICES • USA

NIH National Institute on Alcohol Abuse and Alcoholism

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ALCOHOL RESEARCH
Current Reviews

Alcohol Res. 2020;40(2):14 • https://doi.org/10.35946/arcr.v40.2.14

Published: 5 November 2020

From the Editors

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Recent epidemiological research has identified alarming trends in drinking patterns of girls and women in the United States. In recent years, the amount and frequency of alcohol use are increasing in White and Hispanic girls and young women in contrast to decreasing patterns of heavy alcohol use in boys and young men.[1,2] Similarly, current and binge alcohol use is rising among older women,[3,4] resulting in increased morbidity and mortality in this growing segment of the U.S. population. For example, emergency room visits associated with both acute and chronic drinking[5] and alcohol-related inpatient diagnoses in U.S. middle-aged adults[6] have accelerated more rapidly in women than men. Overall, these changes have narrowed the long-established gender gap in alcohol consumption and associated problems, with women's drinking patterns across the life cycle approaching those of men.

These epidemiological trends have increased the urgency of sex-specific, gender-focused research on alcohol.[7] Historically, because they were underrepresented among heavy/problem drinkers, women often were omitted from a wide range of alcohol studies, including basic science on alcohol effects in women, alcohol-related medical morbidities, social/behavioral consequences of drinking, and treatment intervention studies. With this topic series on women and alcohol, *Alcohol Research: Current Reviews (ARCR)* seeks to close these knowledge gaps and identify important areas for future research directions.

"Gender Differences in the Epidemiology of Alcohol Use and Related Harms in the United States" provides an update on the diminishing sex differences in alcohol consumption, related health problems, hospitalizations, emergency department visits, and death across the life span.[8] Of particular concern, White highlights the reversal in historical alcohol consumption patterns of underage drinkers, such that adolescent girls now report higher rates of monthly alcohol use and binge drinking compared with adolescent boys.[8] Findings have important implications for prevention of fetal alcohol spectrum disorders.

As illustrated in articles throughout this *ARCR* topic series, many alcohol-related sex differences—including development and maintenance of alcohol misuse, alcohol-driven cognitive and medical problems, and even psychiatric comorbidities—derive from key differences in the neurobiology of men and women. In "Sex Differences in the Neurobiology of Alcohol Use Disorder," Flores-Bonilla and Richardson explore preclinical and human research on neural differences using a three-stage framework of addiction.[9] Specifically, they examine how neurobiological differences contribute to initial development of binge/intoxicated drinking, the transition into withdrawal, negative affect and dysfunctional behaviors associated with continued heavy drinking, and finally development of preoccupation with or craving for alcohol and compulsive drinking, and relapse.[9]

In "The Endocrine System and Alcohol Drinking in Females," Finn extends this neurobiological review by examining the multidirectional interactions of alcohol, stress, and key gonadal sex steroid hormones and stress steroid hormones.[10] Findings suggest promising directions for development of novel pharmacological treatments for alcohol use disorder (AUD).

In "Alcohol's Unique Effects on Cognition in Women: A 2020 (Re)view to Envision Future Research and Treatment," Fama, Le Berre, and Sullivan provide a wide-ranging update on the interrelationships between alcohol and cognition, including effects of acute and chronic alcohol consumption across the drinking continuum.[11] Although current research indicates many overall similarities in structural and functional effects of alcohol in women and men, the authors bring focus to factors that may influence sex-specific differences, such as age, drinking patterns, abstinence duration, and medical history and psychiatric comorbidities.[11] One area of particular relevance for women is the effects of alcohol on social and emotional cognition; this relatively young area of cognitive research has important implications for both development and consequences of AUD. Overall, it is clear that women who are chronic heavy drinkers experience cognitive deficits relative to age-matched women who are social drinkers or do not drink. These findings should be used to inform development and adaptations of alcohol treatment interventions and recovery programs for women.

It is well established that women experience higher prevalence of mood and anxiety disorders[12] and more frequent interpersonal trauma associated with higher prevalence of post-traumatic stress disorder[13] compared with men, and that these negative factors have a role in the development and maintenance of heavy drinking and associated problems in women. In "The Role of Stress, Trauma, and Negative Affect in the Development of Alcohol Misuse and Alcohol Use Disorder in Women," Barros Guinle and Sinha examine the sex-specific neurobiological underpinnings of the biological, psychosocial, and psychiatric factors that may be contributing to the accelerating drinking patterns recently observed in girls and women.[14] Of particular concern is the growing evidence of a sex-related, chronic negative feedback cycle in which childhood maltreatment and trauma lead to the development of a maladaptive, blunted stress response in girls and women.[14] In turn, this blunted neurobiological response escalates alcohol consumption, further blunting neuroendocrine responses, and contributing to the progression from alcohol misuse to AUD.

Given differences between women and men in risk factors, developmental course, and health and psychosocial consequences of alcohol misuse and AUD, tailored approaches to alcohol identification, prevention, and intervention for girls and women may be necessary to maximize treatment outcomes. Indeed, specialized screening instruments that are more sensitive and specific to women are available to improve case identification.[15] Although evidence suggests that women and men have comparable outcomes in mixed-gender, nonspecialized alcohol treatments,[16] women cared for in specialized, women-specific programs may experience greater improvements in key areas such as pregnancy outcomes, psychiatric health, HIV risk reduction, and psychosocial well-being.[17] These areas are reviewed in several key articles in this topic series.

In "Maternal Substance Use: Consequences, Identification, and Interventions," Chang reviews prevalence and addresses the importance of early identification and intervention for substance use among pregnant women, with emphasis on alcohol, tobacco, cannabis, and opioid exposure.[18] She reviews strengths and shortcomings of available screening tools specific to pregnant women, legal and social barriers to implementation of universal screening, and available prevention intervention strategies, particularly for fetal alcohol spectrum disorders.[18]

In "Alcohol Screening, Brief Intervention, and Referral to Treatment (SBIRT) for Girls and Women," Hammock, Velasquez, Alwan, and von Sternberg provide a comprehensive review of

the effectiveness of this evidence-based, public health approach to identifying and intervening in heavy/harmful alcohol use across the life span, specifically examining SBIRT for girls, women of childbearing age, and older women.[19] This clinically relevant, evidence-based article offers information on age-appropriate screening tools and intervention approaches.[19] It also summarizes facilitators and barriers to SBIRT implementation in social service and health care settings,[19] including recently identified unanticipated consequences of state-level policies related to alcohol use during pregnancy.[20]

"Treatment Interventions for Women With Alcohol Use Disorder" examines women's barriers to treatment seeking and referral, program services to address these barriers, and efficacy of women-specific services relative to traditional mixed-gender care.[21] Importantly, McCrady, Epstein, and Fokas address mechanisms of change, which often are overlooked but highly relevant to successful development of strategies to tailor treatment to women more effectively.[21] Finally, the article considers the effects of women-specific substance abuse services on a breadth of outcomes, ranging from the primary targets of alcohol and drug use to secondary outcomes such as psychosocial well-being, psychiatric health, pregnancy outcomes, and HIV risk reduction.[21]

Although much of the research discussed in this topic series addresses sex-specific findings, it is critical to bear in mind that this literature often obscures important differences among women as a group. In "Alcohol-Related Disparities Among Women: Evidence and Potential Explanations," Mulia and Bensley address key foci of diversity research, including race, ethnicity, socioeconomic and social status, and sexual orientation.[22] Although the research to date is quite limited, these factors have been shown to influence not only effects of acute and chronic alcohol consumption, but also alcohol-related health disparities and access to care. The article highlights the "alcohol harm paradox"[23]—that certain racial/ethnic minority groups, particularly African Americans, and lower socioeconomic groups experience greater harm despite comparable or lower alcohol consumption. The authors consider possible explanations and interventions for these disparities.[22]

Finally, we have known for decades that women are more vulnerable to many of the negative health consequences of alcohol consumption, in part, due to their higher blood alcohol levels achieved at comparable alcohol doses compared with men. Now, research is providing system-specific findings of the interplay of alcohol and health in women. Indeed, this topic series addresses sex-specific health effects of alcohol in four key areas. In "Alcohol and Liver Function in Women," Maddur and Shah address the increasing rates of liver disease in women, the key role that estrogen plays in the greater vulnerability and more rapid progression to alcohol-related liver disease in women compared with men, and sex differences in liver transplant availability and outcomes.[24]

In "Alcohol's Effects on Breast Cancer in Women," Freudenheim highlights the compelling evidence that any alcohol use increases breast cancer risk and that risk increases as total consumption increases, emphasizing the importance of targeting this modifiable risk factor for public education and intervention.[25] Current findings suggest that these effects are independent of alcohol beverage type or age at alcohol exposure. The author reviews possible mechanisms for this increased risk including direct carcinogenic effects of alcohol and acetaldehyde, changes in hormones associated with drinking, and alterations in DNA methylation.[25]

Cardiovascular (CV) diseases (e.g., hypertension, coronary heart disease, stroke) are the leading cause of death in women.[26] In "Effects of Alcohol on the Cardiovascular System in Women," Piano, Thur, Hwang, and Phillips address the sex-specific findings about the contribution of alcohol consumption to CV morbidity and mortality.[27] Unlike the generally linear relationship between drinking and CV disease in men, there appears to be a J-shaped function for women, with no or lower CV risk at one or two drinks per day and increased risk at and above three or four drinks per day.[27] The

authors examine the contributions of estrogen to these relationships.[27]

Women are more likely to experience insomnia and other common forms of sleep dysregulation compared with men and, in turn, sleep disruption has more severe health consequences for women compared with men.[28] Despite the fact that sleep disturbance is one of the most frequent complaints among persons with AUD,[29] sex differences in sleep have been understudied and underreported in alcohol research. In "Sleep and Alcohol Use in Women," Inkelis, Hasler, and Baker consider important bidirectional effects of alcohol and sleep disruption, examining both how poor sleep quality may contribute to alcohol consumption and how acute and chronic alcohol consumption can lead to sleep dysregulation.[30] The authors review biological, psychological, and social factors that contribute to these bidirectional relationships as well as their treatment implications.[30]

All of the articles in this topic series highlight critical, ongoing, sex-specific knowledge gaps in our understanding of the epidemiology of alcohol use, the interplay of physiology and alcohol, and best approaches to prevention and treatment. This research supports the importance of the National Institutes of Health mandate not only to include female subjects in research, but also to include them in sufficient numbers to permit sex-specific analyses of findings. As evidenced by these articles, the National Institute on Alcohol Abuse and Alcoholism has successfully targeted many of these areas for support in recent years, yet much remains to be learned as we confront the rapidly changing characteristics of women's alcohol misuse and harms.

Acknowledgments

This article was supported by grants AA020801, AA027054, AA020890, AA023483, and DA042094.

Financial Disclosure

The authors have no competing financial interests to disclose.

References

1. Cheng HG, Cantave MD, Anthony JC. Taking the first full drink: Epidemiological evidence on male-female differences in the United States. *Alcohol Clin Exp Res.* 2016;40:816-825. https://doi.org/10.1111/acer.13028.
2. Williams E, Mulia N, Karriker-Jaffe KJ, et al. Changing racial/ethnic disparities in heavy drinking trajectories through young adulthood: A comparative cohort study. *Alcohol Clin Exp Res.* 2018;42:135-143. https://doi.org/10.1111/acer.13541.
3. Breslow RA, Castle IP, Chen CM, et al. Trends in alcohol consumption among older Americans: National Health Interview Surveys, 1997 to 2014. *Alcohol Clin Exp Res.* 2017;41(5):976-986. https://doi.org/10.1111/acer.13365.
4. Grucza RA, Sher KJ, Kerr WC, et al. Trends in adult alcohol use and binge drinking in the early 21st-century United States: A meta-analysis of 6 national survey series. *Alcohol Clin Exp Res.* 2018;42(10):1939-1950. https://doi.org/10.1111/acer.13859.
5. White AM, Slater ME, Ng G, et al. Trends in alcohol-related emergency department visits in the United States: Results from the Nationwide Emergency Department Sample, 2006 to 2014. *Alcohol Clin Exp Res.* 2018;42:352-359. https://doi.org/10.1111/acer.13559.
6. Sacco P, Unick GJ, Kuerbis A, et al. Alcohol-related diagnoses in hospital admissions for all causes among middle-aged and older adults: Trends and cohort differences from 1993 to 2010. *J Aging Health.* 2015;27:1358-1374. https://doi.org/10.1177/0898264315583052.
7. McCaul ME, Roach D, Hasin DS, et al. Alcohol and women: A brief overview. *Alcohol Clin Exp Res.* 2019;43(5):774-779. https://doi.org/10.1111/acer.13985.
8. White AM. Gender differences in the epidemiology of alcohol use in the United States. *Alcohol Res.* 2020;40(2):01. https://doi.org/10.35946/arcr.v40.2.01.
9. Flores-Bonilla A, Richardson HN. Sex differences in the neurobiology of alcohol use disorder. *Alcohol Res.* 2020;40(2):04. https://doi.org/10.35946/arcr.v40.2.04.
10. Finn DA. The endocrine system and alcohol drinking in females. *Alcohol Res.* 2020;40(2):02. https://www.arcr.niaaa.nih.gov/arcr402/article02.htm.
11. Fama R, Le Berre A-P, Sullivan EV. Alcohol's unique effects on cognition in women: A 2020 (re)view to envision future research and treatments. *Alcohol Res.* 2020;40(2):03. https://doi.org/10.35946/arcr.v40.2.03.
12. Steel Z, Marnane C, Iranpour C, et al. The global prevalence of common mental disorders: A systematic review and meta-analysis 1980-2013. *Int J Epidemiol.* 2014;43(2):476-493. https://doi.org/10.1093/ije/dyu038.

13. Breslau N, Chilcoat HD, Kessler RC, et al. Vulnerability to assaultive violence: Further specification of the sex difference in post-traumatic stress disorder. *Psychol Med.* 1999;29:813-821. https://doi.org/10.1017/S0033291799008612.
14. Barros Guinle MI, Sinha R. The development of alcohol misuse and AUD in women. *Alcohol Res.* 2020;40(2):05. https://doi.org/10.35946/arcr.v40.2.05.
15. Chang, G. Screening for alcohol and drug use during pregnancy. *Obstet Gynecol Clin North Am.* 2014;41(2):205-212. https://doi.org/10.1016/j.ogc.2014.02.002.
16. Greenfield SF, Trucco EM, McHugh RK, et al. Substance abuse treatment entry, retention, and outcome in women: A review of the literature. *Drug Alcohol Depend.* 2007;86(1):121. https://doi.org/10.1016/j.drugalcdep.2006.05.012.
17. Orwin RG, Francisco L, Bernichon T, for Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration. Effectiveness of women's substance abuse treatment programs: A meta-analysis. *National Evaluation Data Services. NEDS Analytic Summary #21.* 2001;21:18. https://pdfs.semanticscholar.org/046e/4530032b7491649b10599e3987ed600b5e15.pdf.
18. Chang G. Maternal substance use: Consequences, identification, and interventions. *Alcohol Res.* 2020;40(2):06. https://doi.org/10.35946/arcr.v40.2.06.
19. Hammock K, Velasquez MM, Alwan H, et al. Alcohol screening, brief intervention, and referral to treatment (SBIRT) for girls and women. *Alcohol Res.* 2020;40(2):07. https://doi.org/10.35946/arcr.v40.2.07.
20. Jarlenski M, Hogan C, Bogen DL, et al. Characterization of U.S. state laws requiring health care provider reporting of perinatal substance use. *Womens Health Issues.* 2017;27(3):264-270. https://doi.org/10.1016/j.whi.2016.12.008.
21. McCrady BS, Epstein EE, Fokas KF. Treatment interventions for women with alcohol use disorders. *Alcohol Res.* 2020;40(2):08. https://doi.org/10.35946/arcr.v40.2.08.
22. Mulia N, Bensley KM. Alcohol-related disparities among women: Evidence and potential explanations. *Alcohol Res.* 2020;40(2):09. https://doi.org/10.35946/arcr.v40.2.09.
23. Katikireddi SV, Whitley E, Lewsey J, et al. Socioeconomic status as an effect modifier of alcohol consumption and harm: Analysis of linked cohort data. *Lancet Public Health*. 2017;2(6);e267-e376. https://doi.org/10.1016/S2468-2667(17)30078-6.
24. Maddur H, Shah VH. Alcohol and liver function in women. *Alcohol Res.* 2020;40(2):10. https://doi.org/10.35946/arcr.v40.2.10.
25. Freudenheim JL. Alcohol's effects on breast cancer in women. *Alcohol Res.* 2020;40(2):11. https://doi.org/10.35946/arcr.v40.2.11.
26. Garcia M, Mulvagh SL, Merz CNB, et al. Cardiovascular disease in women: Clinical perspectives. *Circ Res.* 2016;118(8):1273-1293. https://doi.org/10.1161/CIRCRESAHA.116.307547.
27. Piano MR, Thur LA, Hwang C-L, et al. Effects of alcohol on the cardiovascular system in women. *Alcohol Res.* 2020;40(2):12. https://doi.org/10.35946/arcr.v40.2.12.
28. Mong JA, Cusmano DM. Sex differences in sleep: Impact of biological sex and sex steroids. *Philos Trans R Soc Lond B Biol Sci.* 2016;371(1688):20150110. https://doi.org/10.1098/rstb.2015.0110.
29. Chakravorty S, Chaudhary NS, Brower KJ. Alcohol dependence and its relationship with insomnia and other sleep disorders. *Alcohol Clin Exp Res.* 2016;40(11):2271-2282. https://doi.org/10.1111/acer.13217.
30. Inkelis SM, Hasler BP, Baker FC. Sleep and alcohol use in women. *Alcohol Res.* 2020;40(2):13. https://doi.org/10.35946/arcr.v40.2.13.

ALCOHOL RESEARCH
Current Reviews

Alcohol Res. 2020;40(2):01 • https://doi.org/10.35946/arcr.v40.2.01

Published: 29 October 2020

Gender Differences in the Epidemiology of Alcohol Use and Related Harms in the United States

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Over the past century, differences in alcohol use and related harms between males and females in the United States have diminished considerably. In general, males still consume more alcohol and experience and cause more alcohol-related injuries and deaths than females do, but the gaps are narrowing. Among adolescents and emerging adults, gaps in drinking have narrowed primarily because alcohol use among males has declined more than alcohol use among females. Among adults, alcohol use is increasing for women but not for men. Rates of alcohol-related emergency department visits, hospitalizations, and deaths all have increased among adults during the past two decades. Consistent with the changing patterns of alcohol use, increases in these outcomes have been larger for women. Recent studies also suggest that females are more susceptible than males to alcohol-induced liver inflammation, cardiovascular disease, memory blackouts, hangovers, and certain cancers. Prevention strategies that address the increases in alcohol consumption and unique health risks for women are needed.

KEY WORDS: alcohol use disorder, sex, brain, development, stress, mental health, alcohol

INTRODUCTION

Alcohol consumption has long been a male-dominated activity. Globally, men consume more alcohol and account for more alcohol-related harms to self and others than women do. In 2016, 54% of males (1.46 billion) and 32% of females (0.88 billion) age 15 and older worldwide consumed alcohol.[1] Alcohol caused roughly 3 million deaths (5% of all deaths) that year, including 2.3 million deaths for men (8% of deaths) and 0.7 million deaths for women (3% of deaths). Although gender gaps in alcohol use seemingly are universal, the size of the gaps varies between countries and their respective cultures, from a male to female ratio for

current drinking of 1:1 in New Zealand and Norway to 12.3:1 in India.[1-3] Large variations between countries suggest that culturally prescribed gender roles, above and beyond physiological sex differences, are central in shaping gender-specific drinking patterns.[4]

In the United States, more males than females drink each year (68% males, 64% females). Males drinkers tend to drink more often and more heavily than females do,[5] consuming nearly three times as much pure alcohol per year (19.0 liters for males, 6.7 liters for females).[1,6] Males also are more likely to be arrested for driving under the influence of alcohol (DUI),[7] treated in emergency departments and hospitals for alcohol-related harms,[8-10] and to die from alcohol-related causes.[11] In addition, more males (7%) than females (4%) are diagnosed with an alcohol use disorder (AUD) each year. Among those with AUD, roughly similar percentages of males (9%) and females (9%) receive treatment.[6] Research examining harms experienced due to another person's drinking suggests women are more likely than men to suffer consequences as a result of alcohol use by a spouse/partner/ex-partner (4.2% vs. 1.8%) or a family member (5.6% vs. 3.7%).[12,13]

NARROWING GENDER GAPS

Although males still outpace females for most alcohol-related measures, the gaps are narrowing[5,14] (see Figure 1). In the 85 years since the end of Prohibition, drinking habits of males and females have converged. For cohorts born near 1900, males outnumbered females roughly 3:1 for measures of alcohol consumption (e.g., prevalence, frequency) and problematic drinking (e.g., binge drinking, early-onset drinking). Many of these ratios are closer to 1:1 today, and the differences continue to become smaller (see the box **Summary Statistics on Female and Male Alcohol Use and Outcomes in the United States** and Figure 1).[14] An analysis of six different national surveys between 2000 and 2016 suggests that the number of women age 18 and older who drink each year increased by 6% but decreased by 0.2% for men, and the number of women who binge drink increased by 14% but by only 0.5% for men.[15] As this article explores, gender gaps are narrowing for different reasons among adolescents and emerging adults relative to adults. Specifically, alcohol use is declining faster for adolescent and emerging adult males than for females, whereas gaps are narrowing among adults because of increases in drinking by women but not by men.[15,16]

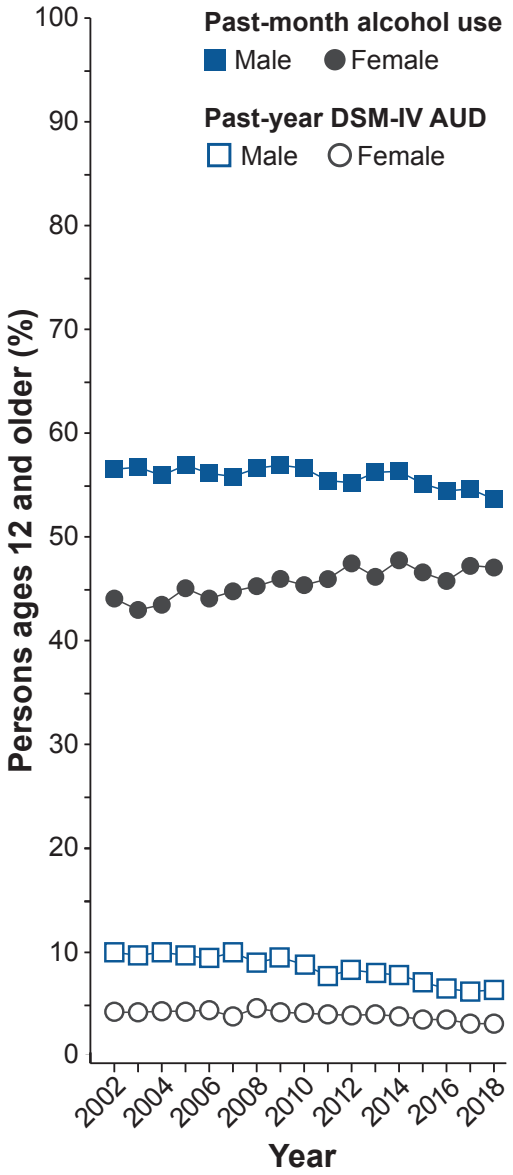

Figure 1 Narrowing gender gaps in the prevalence of past-month alcohol use and past-year DSM-IV AUD between females and males age 12 and older using data from NSDUH 2002–2012. Gender gaps narrowed for both measures, primarily due to increases in alcohol use among females and smaller declines in AUD among females than males. *Source:* White et al., 2015.[5]

Summary Statistics on Female and Male Alcohol Use and Outcomes in the United States

Drinking patterns

- Female drinkers consume about one-third as much total pure alcohol per year as male drinkers (6.7 liters for females, 19.0 liters for males).[1]
- Alcohol use among people age 12 and older: *Lifetime*—82% male, 78% female; *Past year*—68% male, 62% female; *Past month*—55% male, 46% female; *Binge* (4+/5+)* *past month*—29% male, 20% female[28]

DSM-IV AUD† (alcohol abuse or dependence) age 12 and older

- Past-year AUD—males, 9.2 million (7%); females, 5.3 million (4%)[28]
- Percentage who needed and received treatment for DSM-IV alcohol abuse or dependence—males, 9%; females, 9%[28]

Overall deaths

- In 2017, 72,558 death certificates listed alcohol as a factor (18,072 females and 54,486 males).[64]
- Using death certificates and estimates, the Centers for Disease Control and Prevention calculated that 93,296 people died from alcohol-related causes each year between 2011 and 2015 (26,778 females and 66,519 males).[11]
- The World Health Organization reported that excessive drinking accounted for roughly 3 million deaths (5% of all deaths) worldwide, including 2.3 million deaths for men (8% of deaths) and 0.7 million deaths for women (3% of deaths).[1]

Cirrhosis deaths

- In 2017 there were 44,478 deaths due to cirrhosis and 50% (22,246) were caused by alcohol (15,470 deaths among males; 6,776 deaths among females).[10]
- Overall, the rate of death from alcohol-related cirrhosis is more than twice as high for men (9.7 per 100,000) than for women (4.1 per 100,000).[10]

Driving under the influence

- More men (10%) than women (5%) reported driving under the influence of alcohol (DUI) in the past year in 2017.[19]

Gender gaps are narrowing

- Differences are shrinking in drinking patterns, AUD, hospitalizations, emergency department visits, DUI, liver disease, and deaths.[5,14-16,31]

***Binge drinking:** Defined as four or more drinks on an occasion for females and five or more drinks on an occasion for males (4+/5+).

†**AUD:** According to criteria for alcohol abuse and alcohol dependence in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).

ADOLESCENTS

Alcohol use, like other drug use, becomes more likely as young people enter and progress through adolescence, which encompasses the second decade of life or more.[17] Data from the 2018 National Survey on Drug Use and Health (NSDUH) suggest that, by age 12, approximately 1 in 100 (1%) adolescents report consuming alcohol in the previous month.[6] The prevalence increases to nearly 1 in 4 (23%) by age 17. Racial, ethnic, and gender differences in alcohol use also emerge during this period (see Table 1). Among students ages 12 to 17, past-month alcohol use is reported by 12% of White students, 9% of Hispanic or Latino students, 8% of American Indian or Alaska Native students, 6% of Black or African American students, 6% of Asian students, and 11% of students of two or more races.[6] Although more boys (19%) than girls (13%) start drinking before age 14, girls who begin drinking in early adolescence have a shorter time period between first drink and first episode of binge drinking.[6,18]

Table 1 Percentage of Past-Month Alcohol Consumption and Binge Drinking (4+/5+) and Past-Year DSM-IV AUD Among Female and Male Adolescents and Young Adults by Race/Ethnicity, NSDUH 2018

	Females						Males					
	Ages 12-17			Ages 18-25			Ages 12-17			Ages 18-25		
Race/ Ethnicity*	Drink	Binge†	AUD‡	Drink	Binge†	AUD‡	Drink	Binge†	AUD‡	Drink	Binge†	AUD‡
Overall	9.6	5.3	1.9	55.5	34.9	8.8	8.8	4.6	1.5	54.4	35.0	11.1
Hispanic	8.0	3.9	1.6	49.3	33.0	8.5	6.9	3.8	1.8	49.6	21.3	10.7
NH Asian	5.6	3.7	1.8	45.1	23.4	8.0	3.7	2.0	0.0	43.0	32.1	10.8
NH AI/AN	5.8	2.1	1.1	45.1	31.1	15.5	4.7	2.9	0.7	49.8	33.0	7.0
NH Black	6.3	2.9	0.5	43.7	23.0	4.4	3.6	1.7	0.9	41.2	23.6	5.8
NH Multiple	13.3	9.2	6.7	55.7	36.3	12.5	8.4	3.4	1.2	58.9	36.9	9.7
NH H/OPI	14.9	11.1	4.5	24.7	17.3	18.4	1.8	1.8	0.4	54.7	46.3	15.9
NH White	11.5	6.6	2.2	62.8	40.3	10.0	11.6	6.2	1.8	61.0	30.6	12.7

***Race/ethnicity:** Hispanic, non-Hispanic (NH) Asian, NH American Indian or Alaska Native (AI/AN), NH Black, NH more than one race (NH Multiple), NH Hawaiian or other Pacific Islander (H/OPI), NH White.
†Binge drinking: Defined as four or more drinks on an occasion for females and five or more drinks on an occasion for males (4+/5+).
‡AUD: Either DSM-IV alcohol abuse or alcohol dependence.
Source: SAMHSA, 2019.[19]

In contrast, when drinking starts at age 15 or later, males progress more quickly to binge drinking.

Data from the 2018 NSDUH (see Table 1) suggest that 5% of adolescents (5% of females and 5% of males) ages 12 to 17 engage in binge drinking each month, defined as having four or more drinks on an occasion for females or five or more on an occasion for males.[19] The National Institute on Alcohol Abuse and Alcoholism defines binge drinking as reaching a blood alcohol concentration (BAC) of 0.08%, the legal limit for operating a motor vehicle for adults age 21 and older, which takes about four drinks in 2 hours for women or five drinks in 2 hours for men (https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/moderate-binge-drinking). It should be noted that, for most teens, drinking four or five drinks can produce a BAC well beyond 0.08%. When typical body weights of adolescents are taken into consideration, the number of drinks needed to reach a BAC of 0.08% is closer to three standard drinks within a 2-hour period for girls ages 9 to 17 and boys ages 9 to 13, four drinks for boys ages 14 to 15, and five drinks for boys ages 16 to 17.[20] Thus,

it is likely that studies that assess binge drinking among adolescents by using the criteria of four or more drinks for girls and five or more for boys, or in some cases a five-drink threshold for both males and females,[21] underestimate the extent of potentially dangerous alcohol consumption, particularly among young females.

Alcohol consumption, including binge drinking, declined significantly among adolescents since the beginning of the new millennium. Between 2002 and 2018, past-month alcohol use by adolescents ages 12 to 17 decreased from 18% to 9% and binge drinking declined from 11% to 5%.[19] The declines in drinking were much larger for young males than for young females, leading to significant narrowing of long-established gender differences in alcohol use among adolescents. Until recently, by 10th grade, young males reported higher levels of alcohol use and binge drinking than females. By 12th grade, the differences were quite large and remained so throughout adulthood. These gender differences are disappearing and have reversed for some measures. According to data from the Monitoring the Future (MTF) study, in 1991, 46% of males and 40% of females in 10th grade reported drinking in the past month. By 2018, levels declined significantly for both and the gender gap reversed, with 22% of females reporting alcohol use in the past month compared to 17% of males.[22] Among 12th graders, in 1991, 58% of males and 49% of females drank in the month before the survey. In 2018, past-month alcohol use was equally prevalent among males (30%) and females (30%). Gender differences in self-reported past-month drunkenness among 12th graders also narrowed considerably between 1991 (37% males, 25% females) and 2018 (19% males, 16% females), as shown in Figure 2.

Smaller declines in alcohol use and drunkenness by girls are troubling for several reasons. Evidence suggests that levels of anxiety and depression are increasing among adolescents, particularly females,[16,23] and it appears that females, in general, are more likely than males to drink to cope.[24,25] Drinking to cope is associated with faster progression of alcohol use and a higher incidence of alcohol-related harms.[26] The percentage of adolescents who report drinking alone on their last drinking occasion also is increasing, and more so for girls than boys.[6] In a longitudinal study, more episodes of drinking alone during adolescence predicted a larger number of AUD symptoms during emerging adulthood.[27]

Roughly 1 in 9 students, including 10% of females and 13% of males, drop out of school by 12th grade. Compared to teens who stay in school, those who drop out are more likely to drink and/or use other drugs. In 2014, approximately 1 in 3 (32%) students who dropped out (37% males, 26% females) reported binge drinking compared with 1 in 5 (26% males, 16% females) 12th-grade students in school.[28] Males and females who drop out also are more likely to smoke cigarettes, use marijuana, and misuse prescription medications.[6] Effective prevention strategies are needed to address alcohol and other drug use in this population.

EMERGING ADULTS

Over the past few decades, alcohol use declined among emerging adults, although the declines were smaller than those seen among adolescents.[21] Gender gaps narrowed as well. Roughly 40% of people ages 18 to 24 are enrolled in college. Historically, male college students were more likely to drink and did so more heavily than female college students, and college students drank far more than their peers not enrolled in college. Gender differences among college students have disappeared for some measures. For instance, in 1953, 80% of males and 49% of females in college reported having been drunk at some point in their lives.[29] In 2014, 69% of both males and females in college reported having been drunk at some point in their lives.[30] Differences in alcohol use among college students and their non-college peers are shrinking as well. According to data from the MTF study, between 1980 and 2018, the prevalence of binge drinking—in this

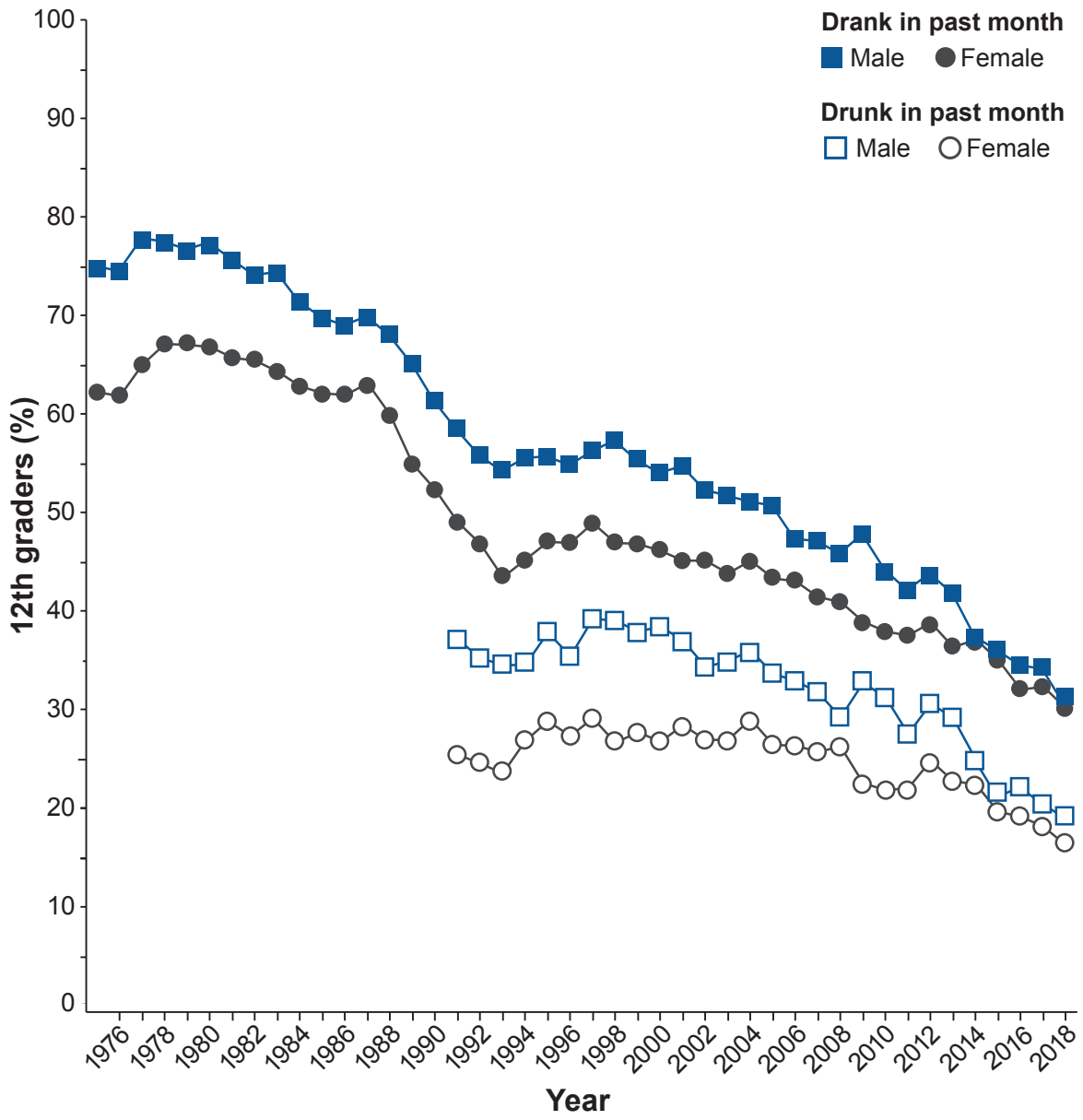

Figure 2 Past-month alcohol use from 1975 to 2018 and past-month drunkenness from 1991 to 2018 among 12th graders. Alcohol use and drunkenness declined more for young males than for young females, leading to disappearing gender gaps in 12th grade. *Source:* Adapted from Johnston, 2019.[22]

case having five or more drinks on an occasion in the previous 2 weeks for both males and females—declined among males in college from 52% to 32% and among males not in college from 54% to 25%.[21] The declines were smaller for females. The prevalence declined for females in college from 36% to 27% and for females not in college from 29% to 25%. For past-month alcohol use and reports of being drunk, the gender gaps reversed, with females both in and outside of college exceeding the levels among their male counterparts (see Figure 3).[22] In 2018, 61% of females in college and 51% of females not in college reported past-month drunkenness, compared to 58% of males in college and 50% not in college. These shifts are remarkable given the long history of heavier alcohol use among young adult males than females.

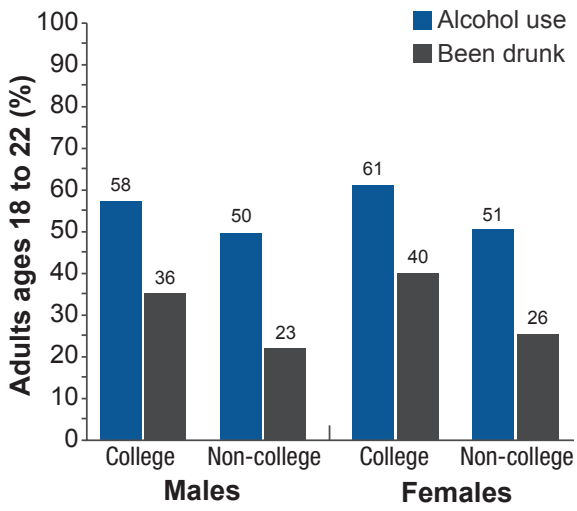

Figure 3 Past-month alcohol use and drunkenness among emerging adults (ages 18 to 22) based on college status. Both measures are declining more for emerging adult males than for emerging adult females, leading to disappearing gender gaps. *Source:* Adapted from Schulenberg et al., 2019.[21]

ADULTS

Despite declines in alcohol use among adolescents and emerging adults, the prevalence of alcohol use, binge drinking, and the number of drinking days in the past month increased among all females age 12 and older between 2002 and 2012.[5] These measures did not increase among males, leading to narrowing gender gaps. Figure 1 shows narrowing gender gaps in past-month alcohol use and past-year AUD—according to criteria for alcohol abuse and alcohol dependence in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV). An examination of alcohol measures among adults age 18 and older in six national surveys showed increases in past-year alcohol use and binge drinking among females between 2000 and 2016, with no increases for males.[15] The prevalence of alcohol consumption and binge drinking did not increase for young adults ages 18 to 29, but increased for all adults age 30 and older, with the biggest increases occurring among people beyond age 50.

Several studies suggest that alcohol use and related harms are increasing among older people as the baby boomer cohort (now ages 55 to 75) ages. As with adults as a whole, the increases in alcohol use among older drinkers have been larger for women than for men.[14,31,32] Between 2005 and 2014, past-month binge drinking among adults age 50 and older increased more for women (6% to 9%) than for men (20% to 22%).[31] During that time period, the prevalence of past-year AUD also increased more for women age 50 and older (1.3% to 2.4%) than for men in that age group (5.0% to 5.1%). Similarly, data from the National Health Interview Surveys suggest that, between 1997 and 2014, the prevalence of past-month drinking among adults aged 60 and older increased more for women than for men, and the prevalence of binge drinking in this age group increased for women only.[32] Consistent with narrowing gender gaps in alcohol use among older drinkers, between 2006 and 2014, the rates of emergency department (ED) visits related to both acute and chronic alcohol consumption increased more for women than men among those ages 55 to 64.[8]

SEXUAL ORIENTATION

Sexual orientation influences drinking patterns and alcohol-related outcomes for males and females.[33-35] In the 2018 NSDUH, past-month binge drinking (four or more drinks for females and five or more drinks for males) was reported by 26% of respondents who identified as heterosexual, 33% who identified as lesbian or gay, and 37% who identified as bisexual.[6] Data from the National Epidemiologic Survey on Alcohol and Related Conditions III suggest that lesbians and bisexual women are twice as likely as heterosexual women to engage in binge drinking each year (lesbian 49%, bisexual 59%, heterosexual 26%)[35] (see Table 2). Lesbians and bisexual women also are more likely than heterosexual women to consume 12 or more drinks on an occasion—three times the standard binge threshold for women—in the past year (lesbian, 8%; bisexual, 8%; heterosexual, 3%). Consuming 12 or more drinks is potentially lethal.

Table 2 Binge Drinking Levels in the Past Year Among Women and Men Based on Sexual Identity, National Epidemiologic Survey on Alcohol and Related Conditions III, 2012–2013

	Women (%)			Men (%)		
Binge Level*	**Heterosexual**	**Lesbian**	**Bisexual**	**Heterosexual**	**Gay**	**Bisexual**
4+/5+	26.3	48.6	58.5	39.3	46.5	47.0
8+/10+	7.2	20.7	21.1	18.4	17.8	26.4
12+/15+	2.9	8.2	7.8	7.1	8.2	11.0

***Binge drinking:** Defined as four or more drinks on an occasion for females and five or more drinks on an occasion for males (4+/5+).
Source: Adapted from Fish, 2019.[35]

In a study based on data from the 2000 National Alcohol Survey, lesbians were nearly 11 times more likely, and bisexual women eight times more likely, than heterosexual women to report negative social consequences from drinking.[34,36] Among emerging adults ages 18 to 25, 8% of heterosexual women reached criteria for DSM-IV AUD in the previous year, compared to 15% of lesbians and 10% of bisexual women.[6] Alcohol use does not decline as much with age among sexual minority women relative to heterosexual women.[37] Overall, the influence of sexual orientation on alcohol use and related outcomes appears to be greater among women than among men.[38,39]

PREGNANCY

In 1973, a paper by Jones and Smith detailed a syndrome involving facial dysmorphology, growth retardation, and central nervous system dysfunction in children exposed to alcohol in the womb.[40] Since then, our understanding of the effects of alcohol on embryonic and fetal development has advanced greatly, yet alcohol use during pregnancy remains a significant public health concern. An examination of data from the Behavioral Risk Factor Surveillance Survey suggests that from 2015 to 2017, 12% of pregnant women drank alcohol and 4% engaged in binge drinking in the previous month.[41] The average frequency of binge drinking was five times per month and the average number of drinks per binge was six.

A report using data from NSDUH suggests that past-month alcohol use did not decline between 2002 and 2017 for non-pregnant women ages 18 to 44 (from 57% to 58%) but did decline for pregnant women in this age group (from 13% to 10%).[42] Between 2002 and 2014, past-month binge drinking—in this case, five or more drinks on an occasion—increased for non-pregnant women (24.9% to 26.6%) but declined for pregnant women (4.7% to 2.9%).[42] Risk factors associated with alcohol use or binge drinking during pregnancy include the use of other substances, meeting DSM-IV criteria for AUD, depression, and being unmarried. An examination of NSDUH data averaged between 2001 and 2011 suggests that alcohol use during pregnancy tends to decline abruptly after the first month as women discover they are pregnant. Among pregnant women, 42% reported drinking in the first month, declining to 17% in the second month and 8% in the third month. For binge drinking, prevalence declined from 20% in the first month of pregnancy to 9% in the second month and 3% in the third month.[43] Monthly declines were much smaller for women

who met criteria for DSM-IV alcohol dependence in the previous year.

Despite declines in drinking during pregnancy, the fact that roughly 1 in 10 pregnant women still drink each month is concerning.[44] A recent estimate suggests that the prevalence of fetal alcohol spectrum disorder (FASD) in the United States is 1% to 5%.[45] A prospective study of roughly 31,000 women found that birth weight in newborns was reduced even when the mother's alcohol intake was limited to an average of one drink per day (14 grams of alcohol).[46] Drinking even 3.5 standard U.S. servings of alcohol (14 grams each) per week is associated with lower IQ scores in offspring at age 8, particularly if they have one of four genetic variants in alcohol-metabolizing genes.[47] Alcohol exposure during the first trimester appears to be particularly detrimental, but even low to moderate levels of alcohol exposure throughout pregnancy are associated with morphological, cognitive, and motor deficits.[44,48] It should be noted that recent studies raise the possibility that alcohol use by the father before conception also might influence fetal development and later alcohol use.[49]

HEALTH EFFECTS

As patterns of alcohol use by girls and women changed over the past few decades, so did our knowledge about the potential health consequences faced by female drinkers. Research suggests that, although women tend to drink less than men, a risk-severity paradox occurs wherein women suffer greater harms than men at lower levels of alcohol exposure.[50] For instance, men in the military drink more heavily than women in the military, yet women are at greater risk of DSM-IV alcohol dependence and lost productivity.[51] The number of drinks needed to feel drunk is one-third lower among women (four drinks) than men (seven drinks), probably relating to lower average body weights and less total body water in women.[52] Despite drinking less often and less heavily than males, roughly similar percentages of female and male drinkers in college report having experienced at least one alcohol-induced memory blackout in the past 2 weeks (10% females, 9% males),[53] in the past 6 months (22% females, 17% males),[54] and in the past year (29.2% females, 28.8% males).[55] Females with AUD perform more poorly than males with AUD on a variety of cognitive tasks, even with fewer years of AUD.[56] Research suggests that women have faster progression of AUD than men and are at greater risk than men for alcohol-induced hangovers, liver inflammation, cardiovascular diseases, and certain cancers.[11,57-60] Compared with their male counterparts, women with alcoholic liver disease have a more rapid progression to fibrosis that persists after abstinence from alcohol.[61] The Million Women Study in the United Kingdom, which included more than 28,000 women with breast cancer, suggests that every 10 grams of alcohol consumed per day (less than one standard 14-gram U.S. serving) was associated with a 12% increase in the risk of breast cancer.[62] Because women reach higher blood alcohol levels than do men of comparable weight, their body tissues are exposed to more alcohol and acetaldehyde, a toxic metabolite of alcohol, with each drink.[63]

MEDICAL EMERGENCIES AND DEATHS

Long-standing gender differences in alcohol-related medical emergencies and deaths are narrowing. Alcohol-related hospitalizations and ED visits increased over the past few decades, and rates increased more for women.[8,10,64] Although men still account for the majority of these events, women are catching up. For instance, between 2006 and 2014, the number of ED visits involving alcohol increased from 2,132,645 to 3,366,477 for men (a 58% increase) and from 947,173 to 1,609,320 for women (a 70% increase).[8]

Between 1999 and 2017, nearly 1 million people died from alcohol-related injuries, overdoses, and diseases in the United States.[64] The number of such deaths more than doubled from 35,914 per

year to 72,558 per year, and the rate increased 51%, from 17 to 26 per 100,000. Males accounted for the majority (76%) of alcohol-related deaths over the years (721,587 males, 223,293 females). However, a steeper increase was observed for females (136% in numbers, 85% in age-adjusted rates) than for males (93% in numbers and 39% in rates). Over the years, rates of alcohol-related deaths were highest for males and females in the age range of 45 to 74, but the biggest increase in rates occurred among young adults ages 25 to 34 for both genders. Deaths related to injuries and overdoses increased significantly for females ages 16 to 20 but did not change for males. Although alcohol-related mortality increased each year for non-Hispanic White males and females, there were initial declines early on for several groups. By the end of the study period, deaths were increasing in all racial and ethnic groups for both males and females in nearly every age group.

DRIVING UNDER THE INFLUENCE

Driving under the influence of alcohol (DUI) declined over the past few decades, but the rates of decline were greater for males than females.[65] For instance, Schwartz and Davaran reported that, between 1990 and 2007, rates of arrests for DUI declined by 32% for males (from 2,019 to 1,033 per 100,000) but by only 5% for females (from 306 to 275 per 100,000).[66] The authors suggested that the smaller decline among females might be partly related to changes in DUI enforcement practices. Schwartz observed a similar narrowing of the gender gap in DUI arrests due to steeper declines for males than females between 1982 and 2004.[67] Reilly et al. reported that the percentage of DUI arrests involving female drivers increased in California from 11% in 1989 to 24% in 2012.[68] Further, the percentage of female clients attending a DUI program in southern California increased from 28% in 2009 to 31% in 2014. Among male drivers who died in car crashes, the percentage of crashes in which the driver had a BAC of 0.08% or greater decreased from 25% in 2008 to 21% in 2017. In contrast, there was a small increase in the percentage of female drivers in fatal crashes with BACs greater than 0.08%, from 13% to 14%.[69] Overall, it appears that differences in the prevalence of DUI arrests and fatalities between males and females are becoming smaller.[70]

HARMS TO OTHERS

Alcohol consumption by an individual often leads to harms to others, also known as secondhand harms.[12,71,72] Traffic crash injuries and fatalities are well-known secondhand harms caused by another person's alcohol use, but there are more. A recent study by Nayak and colleagues utilized data from the 2015 National Alcohol's Harms to Others Survey, which asked respondents about secondhand harms such as having property vandalized or damaged, being harassed or assaulted, or experiencing financial troubles.[12] The findings suggest that roughly 1 in 5 adults in the United States experiences harm due to someone else's alcohol use each year. This includes 21% of adult women and 23% of adult men. Women and men under age 25, those who were unmarried, and those who drank excessively, were more likely to report experiencing secondhand harms. Women more often than men reported harm related to aggression on the part of an alcohol-consuming spouse, partner, ex-partner, or family member. Men were more likely to report harm because of a stranger's drinking. Additional research on secondhand harms from alcohol use could be helpful for elucidating gender differences in the risk for alcohol-related consequences.

SUMMARY

For at least a century, differences in the prevalence and amount of alcohol consumption between males and females in the United States have been narrowing.[73-76] As a result, so have rates of alcohol-related harms, including DUIs, ED visits, hospitalizations, and deaths. Although men still

account for more total alcohol consumption and the negative outcomes that follow, the gaps are slowly disappearing. In fact, among adolescents and emerging adults, females are now more likely to report drinking and getting drunk in the past month than their male peers for the first time since researchers began measuring such behaviors.

Importantly, it is not the case that women in the U.S. are simply drinking more like men. Instead, women and men appear to be moving toward one another in terms of drinking patterns and harms. Among adolescents and emerging adults, narrowing gaps are being driven primarily by faster declines in alcohol use by males than females. Among adults, gaps are narrowing primarily because women are drinking more while men are either drinking less or maintaining their levels.

Knowledge of the unique risks that alcohol poses for women—including an increased likelihood of memory blackouts and hangovers and a faster progression of liver disease and AUD—makes recent increases in alcohol use by women more concerning.[77] Although alcohol use by pregnant women has declined, research regarding the impact of prenatal alcohol exposure has accelerated and suggests that relatively small amounts of alcohol can produce detectable changes in morphology and deficits in cognitive and motor function. It is important to consider the unique factors that might influence alcohol use among women, and the unique direct and secondhand health effects that alcohol poses for women, when developing prevention strategies to address alcohol use and related harms.

Financial Disclosure
The author declares no competing financial interests.

References

1. World Health Organization. Global status report on alcohol and health 2018. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.
2. Wilsnack RW, Wilsnack SC, Kristjanson AF, et al. Gender and alcohol consumption: Patterns from the multinational GENACIS project. *Addiction.* 2009;104(9):1487-1500. https://doi.org/10.1111/j.1360-0443.2009.02696.x.
3. Ritchie H, Roser M. Alcohol consumption. Published online at OurWorldInData.org. 2020. Retrieved from: https://ourworldindata.org/alcohol-consumption [Online Resource].
4. Wilsnack RW, Vogeltanz ND, Wilsnack SC, et al. Gender differences in alcohol consumption and adverse drinking consequences: Cross-cultural patterns. *Addiction.* 2000;95:251-265. https://doi.org/10.1046/j.1360-0443.2000.95225112.x.
5. White A, Castle IP, Chen CM, et al. Converging patterns of alcohol use and related outcomes among females and males in the United States, 2002 to 2012. *Alcohol Clin Exp Res.* 2015;39:1712-1726. https://doi.org/10.1111/acer.12815.
6. Substance Abuse and Mental Health Services Administration. Results from the 2018 National Survey on Drug Use and Health: Detailed tables. 2019. https://www.samhsa.gov/data/.
7. Schwartz J, Davaran A. Enforcement following 0.08% BAC law change: Sex-specific consequences of changing arrest practices? *Addict Behav.* 2013;38:2506-2512. https://doi.org/10.1016/j.addbeh.2013.04.004.
8. White AM, Slater ME, Ng G, et al. Trends in alcohol-related emergency department visits in the United States: Results from the Nationwide Emergency Department Sample, 2006 to 2014. *Alcohol Clin Exp Res.* 2018;42:352-359. https://doi.org/10.1111/acer.13559.
9. White AM, Hingson RW, Pan IJ, et al. (2011). Hospitalizations for alcohol and drug overdoses in young adults ages 18-24 in the United States, 1999–2008: Results from the Nationwide Inpatient Sample. *J Stud Alcohol Drugs.* 2011;72(5):774-786. https://doi.org/10.15288/jsad.2011.72.774.
10. Yoon YH, Chen CM. *Surveillance Report #114. Trends in Alcohol-Related Morbidity Among Community Hospital Discharges, United States, 2000–2017.* Bethesda, MD: National Institute on Alcohol Abuse and Alcoholism, 2018. Available at: https://pubs.niaaa.nih.gov/publications/surveillance114/Cirr17.htm
11. Centers for Disease Control and Prevention. Alcohol Related Disease Impact (ARDI) application, 2019. Available at www.cdc.gov/ARDI. Accessed August 3, 2020.
12. Nayak MB, Patterson D, Wilsnack SC, et al. Alcohol's secondhand harms in the United States: New data on prevalence and risk factors. *J Stud Alcohol Drugs.* 2019;80(3):273-281. https://doi.org/10.15288/jsad.2019.80.273.
13. Stanesby O, Callinan S, Graham K, et al. Harm from known others' drinking by relationship proximity to the harmful drinker and gender: A meta-analysis across 10 countries. *Alcohol Clin Exp Res.* 2018;42(9):1693-1703. https://doi.org/10.1111/acer.13828.
14. Slade T, Chapman C, Swift W, et al. Birth cohort trends in the global epidemiology of alcohol use and alcohol-related harms in men and women: Systematic review and metaregression. *BMJ Open.* 2016;6(10):e011827. https://doi.org/10.1136/bmjopen-2016-011827.
15. Grucza RA, Sher KJ, Kerr WC, et al. Trends in adult alcohol use and binge drinking in the early 21st-century United States: A meta-analysis of 6 national survey series. *Alcohol Clin Exp Res.* 2018;42(10):1939-1950. https://doi.org/10.1111/acer.13859.

16. Keyes KM, Jager J, Mal-Sarkar T, et al. Is there a recent epidemic of women's drinking? A critical review of national studies. *Alcohol Clin Exp Res.* 2019;43:1344-1359. https://doi.org/10.1111/acer.14082.
17. Patton GC, Olsson CA, Skirbekk V, et al. Adolescence and the next generation. *Nature.* 2018;554:458-466. https://doi.org/10.1038/nature25759.
18. Cheng HG, Anthony JC. Male-female differences in the onset of heavy drinking episode soon after first full drink in contemporary United States: From early adolescence to young adulthood. *Drug Alcohol Depend.* 2018;190:159-165. https://doi.org/10.1016/j.drugalcdep.2017.12.035.
19. Substance Abuse and Mental Health Services Administration, Public Online Data Analysis System (PDAS) (2019). National Survey on Drug Use and Health, 2018 (NSDUH-2018-DS0001). Available at: https://pdas.samhsa.gov/#/survey/NSDUH-2018-DS0001/.
20. Donovan JE. Estimated blood alcohol concentrations for child and adolescent drinking and their implications for screening instruments. *Pediatrics.* 2009;123(6):e975-e981. https://doi.org/10.1542/peds.2008-0027.
21. Schulenberg JE, Johnston LD, O'Malley PM, et al. *Monitoring the Future National Survey Results on Drug Use, 1975-2018: Volume II, College Students and Adults Ages 19–60.* Ann Arbor, MI: Institute for Social Research, The University of Michigan; 2019. Available at http://monitoringthefuture.org/pubs.html#monographs.
22. Johnston LD, Miech RA, O'Malley PM, et al. *Demographic Subgroup Trends Among Adolescents in the Use of Various Licit and Illicit Drugs, 1975–2018* (Monitoring the Future Occasional Paper No. 92). Ann Arbor, MI: Institute for Social Research, The University of Michigan; 2019. Available at: http://monitoringthefuture.org/pubs/occpapers/mtf-occ92.pdf.
23. Mojtabai R, Olfson M, Han B. National trends in the prevalence and treatment of depression in adolescents and young adults. *Pediatrics.* 2016;138(6):e20161878. https://doi.org/10.1542/peds.2016-1878.
24. Kuntsche E, Knibbe R, Gmel G, et al. Why do young people drink? A review of drinking motives. *Clin Psychol Rev.* 2005;25(7):841-861. https://doi.org/10.1016/j.cpr.2005.06.002.
25. Peltier MR, Verplaetse TL, Mineur YS, et al. Sex differences in stress-related alcohol use. *Neurobiol Stress.* 2019;10:100149. https://doi.org/10.1016/j.ynstr.2019.100149.
26. Merrill JE, Wardell JD, Read JP. Drinking motives in the prospective prediction of unique alcohol-related consequences in college students. *J Stud Alcohol Drugs.* 2014;75(1):93-102. https://doi.org/10.15288/jsad.2014.75.93.
27. Creswell KG, Chung T, Clark DB, et al. Solitary alcohol use in teens is associated with drinking in response to negative affect and predicts alcohol problems in young adulthood. *Clin Psychol Sci.* 2014;2(5):602-610. https://doi.org/10.1177/2167702613512795.
28. Tice P, Lipari RN, Van Horn SL. *Substance Use Among 12th Grade Aged Youths, by Dropout Status.* The CBHSQ Report: August 15, 2017. Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration.
29. Straus R, Bacon SD. *Drinking in College*. New Haven, CT: Yale University Press; 1953.
30. Johnston LD, O'Malley PM, Bachman JG, et al. *Monitoring the Future National Survey Results on Drug Use, 1975-2014: Volume II, College Students and Adults Ages 19-55.* Ann Arbor, MI: Institute for Social Research, University of Michigan; 2015.
31. Han BH, Moore AA, Sherman S, et al. Demographic trends of binge alcohol use and alcohol use disorders among older adults in the United States, 2005–2014. *Drug Alcohol Depend.* 2017;170:198-207. https://doi.org/10.1016/j.drugalcdep.2016.11.003.
32. Breslow RA, Castle IP, Chen CM, et al. Trends in alcohol consumption among older Americans: National Health Interview Surveys, 1997 to 2014. *Alcohol Clin Exp Res.* 2017;41(5), 976-986. https://doi.org/10.1111/acer.13365.
33. Dermody SS, Marshal MP, Cheong J, et al. Longitudinal disparities of hazardous drinking between sexual minority and heterosexual individuals from adolescence to young adulthood. *J Youth Adolesc.* 2014;43(1):30-39. https://doi.org/10.1007/s10964-013-9905-9.
34. Hughes TL, Wilsnack SC, Kantor LW. The influence of gender and sexual orientation on alcohol use and alcohol-related problems: Toward a global perspective. *Alcohol Res.* 2016;38(1):121-132.
35. Fish JN. Sexual orientation-related disparities in high-intensity binge drinking: Findings from a nationally representative sample. *LGBT Health.* 2019;6(5):242-249. https://doi.org/10.1089/lgbt.2018.0244.
36. Drabble L, Midanik LT, Trocki K. Reports of alcohol consumption and alcohol-related problems among homosexual, bisexual, and heterosexual respondents: Results from the 2000 National Alcohol Survey. *J Stud Alcohol.* 2005;66(1):111-120. https://doi.org/10.15288/jsa.2005.66.111.
37. Veldhuis CB, Talley AE, Hancock DW, et al. Alcohol use, age, and self-rated mental and physical health in a community sample of lesbian and bisexual women. *LGBT Health.* 2017;4(6):419-426. https://doi.org/10.1089/lgbt.2017.0056.
38. Fish JN, Hughes TL, Russell ST. Sexual identity differences in high-intensity binge drinking: Findings from a US national sample. *Addiction.* 2018;113(4):749-758. https://doi.org/10.1111/add.14041.
39. Fish JN, Schulenberg JE, Russell ST. Sexual minority youth report high-intensity binge drinking: The critical role of school victimization. *J Adolesc Health.* 2019;64(2):186-193. https://doi.org/10.1016/j.jadohealth.2018.07.005.
40. Jones KL, Smith DW. Recognition of the fetal alcohol syndrome in early infancy. *Lancet.* 1973;302(7836):999-1001. https://doi.org/10.1016/s0140-6736(73)91092-1.
41. Denny CH, Acero CS, Naimi TS, et al. Consumption of alcohol beverages and binge drinking among pregnant women aged 18–44 years — United States, 2015–2017. *MMWR Morb Mortal Wkly Rep.* 2019;68(16):365-368. https://doi.org/10.15585/mmwr.mm6816a1.
42. Hasin DS, Shmulewitz D, Keyes K. Alcohol use and binge drinking among U.S. men, pregnant and non-pregnant women ages 18–44: 2002–2017. *Drug Alcohol Depend.* 2019;205:107590. https://doi.org/10.1016/j.drugalcdep.2019.107590.
43. Alshaarawy O, Breslau N, Anthony JC. Monthly estimates of alcohol drinking during pregnancy: United States, 2002-2011. *J Stud Alcohol Drugs.* 2016;77(2):272-276. https://doi.org/10.15288/jsad.2016.77.272.
44. Charness ME, Riley EP, Sowell ER. Drinking during pregnancy and the developing brain: Is any amount safe? *Trends Cogn Sci.* 2016;20(2):80-82. https://doi.org/10.1016/j.tics.2015.09.011.
45. May PA, Chambers CD, Kalberg WO, et al. Prevalence of fetal alcohol spectrum disorders in 4 US communities. *JAMA.* 2018;319(5):474-482. https://doi.org/10.1001/jama.2017.21896.
46. Mills JL, Graubard BI, Harley EE, et al. Maternal alcohol consumption and birth weight. How much drinking during pregnancy is safe? *JAMA.* 1984;252(14):1875-1879.

47. Lewis SJ, Zuccolo L, Davey Smith G, et al. Fetal alcohol exposure and IQ at age 8: Evidence from a population-based birth-cohort study. *PLoS One.* 2012;7(11):e49407. https://doi.org/10.1371/journal.pone.0049407.
48. Mamluk L, Edwards HB, Savović J, et al. Low alcohol consumption and pregnancy and childhood outcomes: Time to change guidelines indicating apparently 'safe' levels of alcohol during pregnancy? A systematic review and meta-analyses. *BMJ Open.* 2017;7(7):e015410. https://doi.org/10.1136/bmjopen-2016-015410.
49. Chastain LG, Sarkar DK. Alcohol effects on the epigenome in the germline: Role in the inheritance of alcohol-related pathology. *Alcohol.* 2017;60:53-66. https://doi.org/10.1016/j.alcohol.2016.12.007.
50. Foster KT, Hicks BM, Durbin CE, et al. The gender risk-severity paradox for alcohol use disorder from adolescence through young adulthood. *Emerg Adulthood.* 2018;6(6):375-386. https://doi.org/10.1177/2167696817740453.
51. Brown JM, Bray RM, Hartzell MC. A comparison of alcohol use and related problems among women and men in the military. *Mil Med.* 2010;175(2):101-107. https://doi.org/10.7205/milmed-d-09-00080.
52. Kerr WC, Greenfield TK, Midanik LT. How many drinks does it take you to feel drunk? Trends and predictors for subjective drunkenness. *Addiction.* 2006;101(10):1428-1437. https://doi.org/10.1111/j.1360-0443.2006.01533.x.
53. White A, Hingson R. The burden of alcohol use: Excessive alcohol consumption and related consequences among college students. *Alcohol Res.* 2013;35(2):201-218.
54. Hingson R, Zha W, Simons-Morton B, et al. Alcohol-induced blackouts as predictors of other drinking related harms among emerging young adults. *Alcohol Clin Exp Res.* 2016;40(4):776-784. https://doi.org/10.1111/acer.13010.
55. American College Health Association. *American College Health Association-National College Health Assessment II: Reference Group Executive Summary Spring 2019.* Silver Spring, MD: American College Health Association; 2019. https://www.acha.org/documents/ncha/NCHA-II_SPRING_2019_US_REFERENCE_GROUP_EXECUTIVE_SUMMARY.pdf.
56. Nixon SJ, Prather R, Lewis B. Sex differences in alcohol-related neurobehavioral consequences. *Handb Clin Neurol.* 2014;125:253-272. https://doi.org/10.1016/B978-0-444-62619-6.00016-1.
57. Nolen-Hoeksema S. Gender differences in risk factors and consequences for alcohol use and problems. *Clin Psychol Rev.* 2004;24(8):981-1010. https://doi.org/10.1016/j.cpr.2004.08.003.
58. van Lawick van Pabst AE, Devenney LE, Verster JC. Sex differences in the presence and severity of alcohol hangover symptoms. *J Clin Med.* 2019;8(6):867. 10.3390/jcm8060867. Correction published in *J Clin Med.* 2019;26;8(9). https://doi.org/10.3390/jcm8091308.
59. Vatsalya V, Stangl BL, Schmidt VY, et al. Characterization of hangover following intravenous alcohol exposure in social drinkers: Methodological and clinical implications. *Addict Biol.* 2018;23(1):493-502. https://doi.org/10.1111/adb.12469.
60. Kirpich IA, McClain CJ, Vatsalya V, et al. Liver injury and endotoxemia in male and female alcohol-dependent individuals admitted to an alcohol treatment program. *Alcohol Clin Exp Res.* 2017;41(4):747-757. https://doi.org/10.1111/acer.13346.
61. Guy J, Peters MG. Liver disease in women: The influence of gender on epidemiology, natural history, and patient outcomes. *Gastroenterol Hepatol (N Y).* 2013;9(10):633-639.
62. Allen NE, Beral V, Casabonne D, et al., on behalf of the Million Women Study Collaborators. Moderate alcohol intake and cancer incidence in women. *J Natl Cancer Inst.* 2009;101(5):296-305. https://doi.org/10.1093/jnci/djn514.
63. Gochfeld M. Sex differences in human and animal toxicology. *Toxicol Pathol.* 2017;45(1):172-189. https://doi.org/10.1177/0192623316677327.
64. White AM, Castle IP, Hingson RW, et al. Using death certificates to explore changes in alcohol-related mortality in the United States, 1999 to 2017. *Alcohol Clin Exp Res.* 2020;44(1):178-187. https://doi.org/10.1111/acer.14239.
65. Vaca FE, Romano E, Fell JC. Female drivers increasingly involved in impaired driving crashes: Actions to ameliorate the risk. *Acad Emerg Med.* 2014;21(12):1485-1493. https://doi.org/10.1111/acem.12542.
66. Schwartz J, Davaran A. Enforcement following 0.08% BAC law change: Sex-specific consequences of changing arrest practices? *Addict Behav.* 2013;38(10):2506-2512. https://doi.org/10.1016/j.addbeh.2013.04.004.
67. Schwartz J. Gender differences in drunk driving prevalence rates and trends: A 20-year assessment using multiple sources of evidence. *Addict Behav.* 2008;33(9):1217-1222. https://doi.org/10.1016/j.addbeh.2008.03.014.
68. Reilly K, Woodruff SI, Hohman M, et al. Gender differences in driving under the influence (DUI) program client characteristics: Implications for treatment delivery, *Women Health.* 2019;59(2):132-144. https://doi.org/10.1080/03630242.2018.1434589.
69. National Center for Statistics and Analysis. *Alcohol-impaired driving: 2017 data* (Traffic Safety Facts. Report No. DOT HS 812 630). Washington, DC: National Highway Traffic Safety Administration; 2018.
70. Insurance Institute for Highway Safety. *Fatality Facts, 2018.* Gender. https://www.iihs.org/topics/fatality-statistics/detail/gender. 2018.
71. Karriker-Jaffe KJ, Room R, Giesbrecht N, et al. Alcohol's harm to others: Opportunities and challenges in a public health framework. *J Stud Alcohol Drugs.* 2018;79(2):239-243. https://doi.org/10.15288/jsad.2018.79.239.
72. Quigg Z, Bellis MA, Grey H, et al. Alcohol's harms to others in Wales, United Kingdom: Nature, magnitude and associations with mental well-being. *Addict Behav Rep.* 2019;9:100162. https://doi.org/10.1016/j.abrep.2019.100162.
73. Wilsnack RW, Wilsnack SC, Gmel G, et al. Gender differences in binge drinking. *Alcohol Res.* 2018;39(1):57-76.
74. Keyes KM, Grant BF, Hasin DS. Evidence for a closing gender gap in alcohol use, abuse, and dependence in the United States population. *Drug Alcohol Depend.* 2008;93(1-2):21-29. https://doi.org/10.1016/j.drugalcdep.2007.08.017.
75. Keyes KM, Li G, Hasin DS. Birth cohort effects and gender differences in alcohol epidemiology: A review and synthesis. *Alcohol Clin Exp Res.* 2011;35(12):2101-2112. https://doi.org/10.1111/j.1530-0277.2011.01562.x.
76. Keyes KM, Miech R. Age, period, and cohort effects in heavy episodic drinking in the US from 1985 to 2009. *Drug Alcohol Depend.* 2013;132(1-2):140-148. https://doi.org/10.1016/j.drugalcdep.2013.01.019.
77. McCaul ME, Roach D, Hasin DS, et al. Alcohol and women: A brief overview. *Alcohol Clin Exp Res.* 2019;43(5):774-779. https://doi.org/10.1111/acer.13985.

ALCOHOL RESEARCH
Current Reviews

Alcohol Res. 2020;40(2):02 • https://doi.org/10.35946/arcr.v40.2.02

Published: 23 July 2020

The Endocrine System and Alcohol Drinking in Females

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Sexually dimorphic effects of alcohol exposure throughout life have been documented in clinical and preclinical studies. In the past, rates of alcohol use disorder (AUD) were higher in men than in women, but over the past 10 years, the difference between sexes in prevalence of AUD and binge drinking has narrowed. Recent evidence adds to historical data regarding the influence of sex steroids on alcohol drinking and the interaction with stress-related steroids. This review considers the contribution of the endocrine system to alcohol drinking in females, with a focus on the hypothalamic pituitary gonadal axis and the hypothalamic pituitary adrenal axis and their reciprocal interactions. Emphasis is given to preclinical studies that examined genomic and rapid membrane effects of estrogen, progesterone, glucocorticoids, and GABAergic neurosteroids for their effects on alcohol drinking and models of relapse. Pertinent comparisons to data in males highlight divergent effects of sex and stress steroids on alcohol drinking and emphasize the importance of considering sex in the development of novel pharmacotherapeutic targets for the treatment of AUD. For instance, pharmacological strategies targeting the corticotropin releasing factor and glucocorticoid receptor systems may be differentially effective in males and females, whereas strategies to enhance GABAergic neurosteroids may represent a biomarker of treatment efficacy in both sexes.

KEY WORDS: estrogen; ethanol; glucocorticoid; neurosteroid; progesterone; stress

INTRODUCTION

Alcohol use disorder (AUD), a diagnosis that combines criteria for alcohol abuse and alcohol dependence from the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders into a single disorder in the 5th edition,[1] negatively influences health and is the third-leading preventable cause of death in the United States.[2] According to the 2015 National Survey on Drug Use and Health, the prevalence of binge drinking, which is the consumption of an excessive amount of alcohol in a short period of time, and of heavy alcohol use was similar in males and females.[2] Likewise, a recent meta-analysis confirmed a greater increase in alcohol use and binge drinking in women versus men over the past 16 years,[3] representing a narrowing of the historically higher

AUD rate in males. It has been suggested that the increased rate of AUD among women may be due to stress or to drinking to regulate a negative affect.[4-6]

As elegantly reviewed by Rachdaoui and Sarkar, acute and chronic alcohol administration disrupts functioning of the endocrine system, which is a complex system of glands that work in conjunction with the nervous system to maintain homeostasis.[7] Glands of the endocrine system produce and secrete hormones into the circulation, which can have long-lasting as well as rapid actions. Hormones affect physiological functions such as metabolism, reproduction, growth, and development, and they facilitate the ability to respond to changes in the environment and to stress.[7-8] Additionally, gonadal sex steroid hormones exert organizational (permanent) and activational (transient) effects on the brain to regulate sexual differentiation, secondary sex characteristics, and sex differences in behavior.[4,9-11] Gonadal steroids also influence the stress response that is mediated by the hypothalamic-pituitary-adrenal (HPA) axis, and elevated stress hormones affect the reproductive or hypothalamic-pituitary-gonadal (HPG) axis.[8] Finally, sex and stress hormones influence alcohol consumption and behavior in models of addiction.[4-5,10,12] As a result, it should be considered that alcohol consumption can influence the endocrine system and the reciprocal interaction between the stress and reproductive axes and that gonadal and stress steroid hormones can influence alcohol drinking and addiction-related behaviors.

This review highlights preclinical research on the contribution of gonadal and stress steroids to alcohol drinking in females. It focuses on the HPG and HPA axes and describes how endogenous fluctuations in steroid hormones as well as exogenous administration influence alcohol drinking and other pertinent addiction-related phenotypes. In addition to a discussion of how classical steroid responses are mediated by genomic effects via intracellular receptors, this review considers rapid steroid responses via membrane receptors and the interaction with neurotransmitter systems. Relevant comparisons to results in males bolster the emerging evidence for sex differences in steroid hormone and stress effects on alcohol drinking behavior and addiction-related phenotypes. These comparisons emphasize the importance of considering sex in the development of novel pharmacotherapies for the treatment of AUD.

OVERVIEW OF THE HPG AND HPA AXES

The HPG axis is the neuroendocrine axis important for reproduction, whereas the HPA axis is the neuroendocrine axis important for the stress response. As depicted in Figure 1, both the HPG and HPA axes are regulated by steroid hormone feedback and reciprocal interactions between steroids in each axis.

The HPG axis comprises the hypothalamus, pituitary, and gonads. Hypothalamic nuclei (e.g., in the preoptic area) release gonadotropin-releasing hormone (GnRH) into the portal vasculature to stimulate the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary (see Figure 1). Circulating LH and FSH act on the gonads to stimulate the production and release of estrogen and progesterone from the ovary and of testosterone from the testis.[7,13] In females, FSH stimulates follicle development in the ovary and the secretion of estradiol, which promotes a surge in LH and FSH. LH stimulates ovulation and the subsequent secretion of progesterone. These overall effects of estradiol are similar across species, but phases of the 28- to 30-day menstrual cycle in primates and the 4- to 5-day estrous cycle in rodents are not completely analogous (see the box **Phases of Primate Menstrual and Rodent Estrous Cycles**). Additionally, steroid hormone feedback loops regulate HPG axis function at the level of the hypothalamus and anterior pituitary. Testosterone inhibits GnRH, LH, and FSH through negative feedback, whereas estradiol and progesterone can exert both negative (inhibitory) and positive (stimulatory) feedback actions, depending on the stage of the ovarian cycle (see Figure 1).

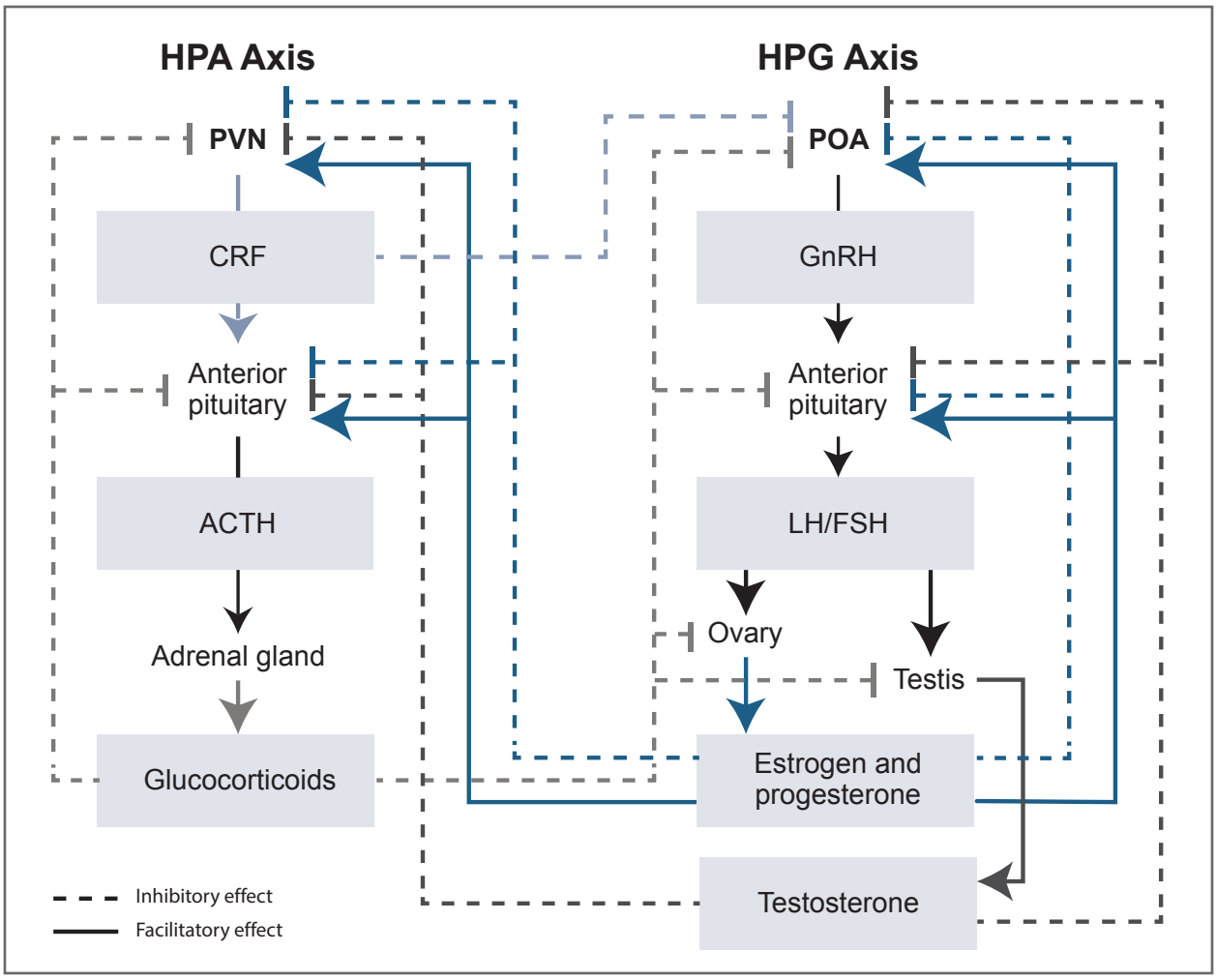

Figure 1 Simplified diagram of the reciprocal interaction between the HPA axis and the HPG axis. Solid lines with arrows depict facilitatory effects. Dashed lines with block symbols depict inhibitory or negative feedback effects. Gonadal steroids are involved in the regulation of the HPA axis at the level of the PVN and the anterior pituitary. Specifically, testosterone has negative feedback effects at the PVN and the anterior pituitary, and estrogen and progesterone can have either a facilitatory or an inhibitory effect at the PVN and the anterior pituitary. Stress steroids can regulate the HPG axis at the level of the hypothalamic POA, anterior pituitary, and gonads (ovaries or testes). Glucocorticoids (corticosterone in rodents, cortisol in humans and monkeys) exert negative feedback at each level of the HPG axis, and CRF exerts negative feedback at the POA. Upstream regulatory centers for each axis are not shown. Also shown is the negative feedback exhibited by glucocorticoids within the HPA axis, the negative feedback exhibited by testosterone within the HPG axis, and the negative and positive feedback exhibited by estrogen and progesterone within the HPG axis. *Note:* ACTH, adrenocorticotropic hormone; CRF, corticotropin releasing factor; FSH, follicle stimulating hormone; GnRH, gonadotropin releasing hormone; HPA, hypothalamic-pituitary-adrenal; HPG, hypothalamic-pituitary-gonadal; LH, luteinizing hormone; POA, preoptic area; PVN, paraventricular nucleus. *Source:* Modified from a figure by Oyola and Handa.[8]

Responses to stress are mediated by the HPA axis and the sympathetic autonomic response. Short-term activation of the HPA axis produces beneficial effects, whereas chronic activation can result in deleterious effects.[14] Neurons in the paraventricular nucleus (PVN) of the hypothalamus are responsible for the secretion of corticotropin releasing factor (CRF) and arginine vasopressin into the portal system, and CRF causes the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary. ACTH stimulates the biosynthesis and release of glucocorticoids from the adrenal cortex.[13] Negative feedback of glucocorticoids at the level of the

Phases of Primate Menstrual and Rodent Estrous Cycles*	
Primate (Human and Monkey)	**Rodent (Rat and Mouse)**
The average length of the menstrual cycle is 28 to 30 days.	The average length of the estrous cycle is 4 to 5 days.
Follicular phase: As the ovarian follicle develops, estradiol is secreted. Menstruation overlaps with the beginning of the follicular phase.	**Metestrus/diestrus phase:** As the ovarian follicle develops, estradiol is secreted.
Periovulatory phase: A rapid estradiol increase triggers an LH surge, which produces ovulation.	**Proestrus/estrus phase:** A rapid estradiol increase triggers an LH surge, which stimulates progesterone release and produces ovulation.
Luteal phase: The corpus luteum releases high levels of estradiol and progesterone. Menstruation occurs at the end of the luteal phase as hormone levels fall.	**No equivalent phase:** Female rodents do not have a functional corpus luteum.

*Adapted from a table by Becker and Koob.[4] *Note:* LH, luteinizing hormone.

anterior pituitary and PVN inhibits CRF, arginine vasopressin, and ACTH production and helps maintain optimal glucocorticoid levels (Figure 1).

An additional consideration is that the HPA and HPG axes have reciprocal interactions in terms of steroid hormone feedback, as depicted in Figure 1.[8] For example, glucocorticoids exhibit negative feedback of the HPG axis at the level of the hypothalamus, anterior pituitary, and gonads. As a result, a chronic elevation of glucocorticoids can result in suppressed HPG axis function. Likewise, gonadal steroids may influence HPA axis function, as evidenced by the effects of testosterone, progesterone, and estrogen at the level of the PVN and anterior pituitary.[13] For example, basal and stress-induced increases in glucocorticoids are greater in female than in male rodents. Evidence from studies that used gonadectomy and hormone replacement suggests that testosterone exerts an inhibitory influence on HPA axis activity in male rodents, whereas estrogen primarily produces a facilitatory effect on HPA axis activity in female rodents. Some of the differing results for estrogen on HPA axis function may be due in part to the opposing actions of two types of estrogen receptors.[13]

STEROID HORMONE RECEPTORS AND CIRCUITRY IMPORTANT FOR STRESS AND DRINKING

Steroid hormones produce effects through several mechanisms. First, steroid hormones bind to their classical intracellular receptors, which act as ligand-activated transcription factors to alter gene expression and produce long-lasting actions.[13] Progestins, such as progesterone and dihydroprogesterone, bind to two progesterone receptor isoforms: A and B.[15] Estrogens, such as 17beta-estradiol, bind to two distinct receptor subtypes: estrogen receptor-alpha and estrogen receptor-beta.[13,16] Androgens, such as testosterone and dihydrotestosterone, bind to androgen receptors.[13] Glucocorticoids, such as corticosterone in rodents and cortisol in humans and monkeys, bind to mineralocorticoid receptors (type I) and glucocorticoid receptors (type II).[13] Endogenous glucocorticoids have higher affinity for mineralocorticoid receptors than for glucocorticoid receptors.[13]

Second, through classical and nonclassical receptors located in the cell membrane, steroids have rapid effects that influence second-messenger

pathways and ion channel function.[16-22] Finally, steroid hormone derivatives can rapidly alter ion channel function via allosteric interactions with ligand-gated ion channels.[23-26] For example, the progesterone derivative allopregnanolone and the deoxycorticosterone derivative tetrahydrodeoxycorticosterone (THDOC) are very potent positive allosteric modulators of gamma-aminobutyric acid$_A$ (GABA$_A$) receptors and can rapidly alter neuronal inhibition. Rapid actions at the cell membrane gave rise to the terms "neuroactive steroids" and "neurosteroids" (Refer to the Finn and Jimenez article on neurosteroid networks for more information about neurosteroid synthesis and pathways.)[24] Thus, steroid hormones and their derivatives can influence brain function and behavior through classic genomic actions and rapid membrane effects.

Neuroanatomical overlap occurs between gonadal and adrenal steroid hormone receptors within the hypothalamic (the PVN) and extra-hypothalamic (e.g., in the amygdala and the bed nucleus of the stria terminalis) stress circuitry (see Figure 2). Overlap also occurs within components of the mesocorticolimbic circuitry (e.g., in the medial prefrontal cortex, nucleus accumbens, ventral tegmental area, and hippocampus). Ultimately, this overlap can affect output of the PVN (i.e., the stress response) and alcohol drinking. Figure 2 shows simplified circuitry of

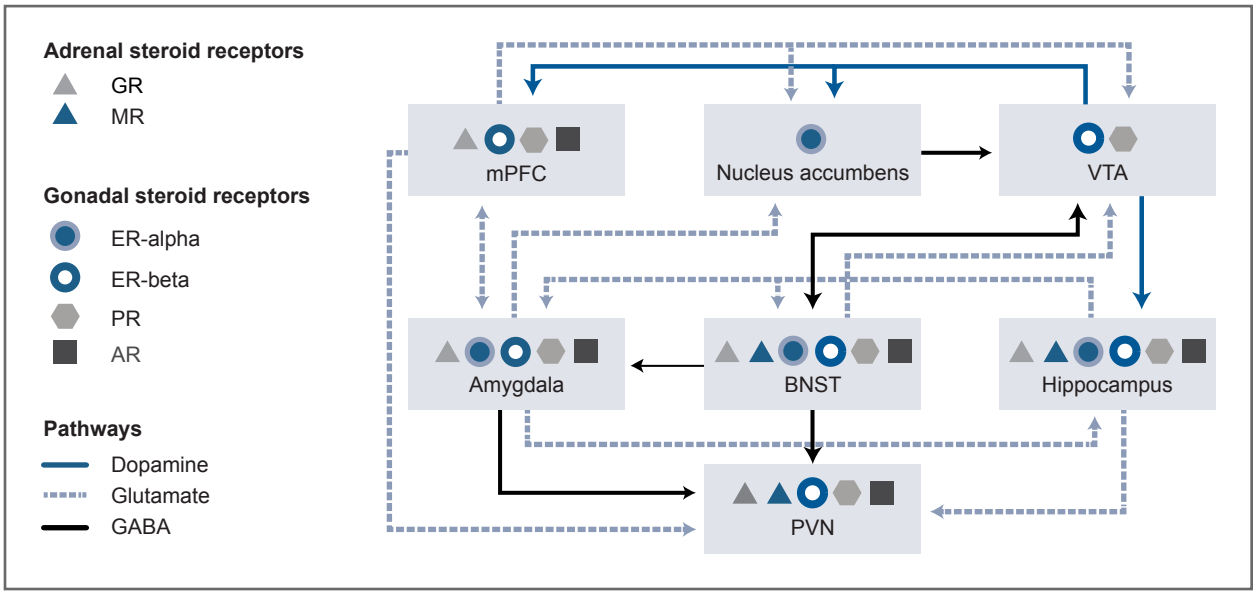

Figure 2 Simplified stress and mesocorticolimbic circuitry, including inputs to the HPA axis and the distribution of gonadal and adrenal steroid receptors. Rapid steroid actions at associated receptors and neurosteroid actions at GABA$_A$ receptors represent additional mechanisms for fine-tuning central nervous system excitability. Gonadal and adrenal steroid receptors have considerable overlap in expression within the hypothalamic (PVN) and extrahypothalamic (e.g., amygdala, BNST) stress circuitry, as well as among components of the mesocorticolimbic (e.g., mPFC, nucleus accumbens, VTA, and hippocampus) circuitry, which ultimately can affect output of the PVN (i.e., the stress response) and alcohol drinking. This simplified circuitry shows GABAergic (red), glutamatergic (green), and dopaminergic (blue) projections within the brain regions that input to the PVN, either directly or indirectly through an inhibitory projection from the peri-PVN (which contains ER-alpha and GR, not shown). The brain regions involved and the overall influence on the output of the PVN (and HPA axis activity) depend on the stressor modality, the level of acute or chronic alcohol consumption, and the various steroid and neurosteroid levels and actions at their associated receptors. *Note:* AR, androgen receptor; BNST, bed nucleus of the stria terminalis; ER-alpha, estrogen receptor-alpha; ER-beta, estrogen receptor-beta; GABA, gamma-aminobutyric acid; GR, glucocorticoid receptor; HPA, hypothalamic-pituitary-adrenal; mPFC, medial prefrontal cortex; MR, mineralocorticoid receptor; PR, progesterone receptor (both isoforms); PVN, paraventricular nucleus; VTA, ventral tegmental area. *Source:* Circuitry[13,24] and steroid receptor distribution[13,15,21,33-36] are modified from other sources.

glutamatergic, GABAergic, and dopaminergic projections in brain regions important for responses to stress and alcohol drinking behavior. These responses to stress and alcohol drinking behavior may be modulated by steroid actions at receptors localized within the brain regions.

For example, the brain regions involved and the overall influence on PVN output depends on the stress, on various steroid hormone levels and actions at associated receptors,[8,13] and on $GABA_A$ receptor–active neurosteroid levels and actions at $GABA_A$ receptors.[24] Alcohol's ability to activate the HPA axis relies on activation of the PVN.[27] Synaptic connections within the PVN are primarily GABAergic and glutamatergic.[28,29] As a result, glutamatergic afferents in the forebrain that increase GABA release in the PVN, and upstream GABAergic projection neurons that activate the PVN, produce tonic inhibition of the PVN.[30]

Additionally, stress-induced elevations in $GABA_A$ receptor–active neurosteroids can modulate PVN activity, given that physiological concentrations of allopregnanolone (i.e., 10 nM to 100 nM) inhibit output of PVN neurons (i.e., CRF release) via a potentiation of $GABA_A$ receptors. [31,32] A neurosteroid-induced inhibition of CRF release likely represents another mechanism for terminating the stress response.

Another consideration is that alcohol-induced alterations to neurotransmission within the circuitry depicted in Figure 2 can be modulated by steroid hormone and neurosteroid levels. For instance, estradiol and progesterone can rapidly affect dopamine signaling via actions at their respective steroid receptors, functional coupling between estrogen receptors (both alpha and beta) and metabotropic glutamate receptors (Group I or Group II) can activate distinct signaling pathways, and neurosteroids can rapidly increase $GABA_A$ receptor–mediated signaling.[21,23,24,33-36] Thus, rapid steroid actions at associated receptors and neurosteroid actions at $GABA_A$ receptors are other mechanisms for fine-tuning central nervous system excitability.

STEROID HORMONE EFFECTS ON DRINKING AND OTHER ADDICTION-RELATED BEHAVIORS

Investigations of sex differences in drug misuse and self-administration behavior have gained momentum, particularly after 2015, when the National Institutes of Health announced a policy of including sex as a biological variable. Clinical and preclinical alcohol research offers many examples of sex differences, given that alcohol exposure can produce sexually dimorphic effects throughout life. Discussion of all these studies is beyond the focus of this review, but several excellent reviews describe sex differences in the effects of alcohol exposure across development. Reviews have summarized findings from prenatal[37] and adolescent[38-41] alcohol exposure, as well as from exposure during adulthood.[4,7] Marked sex differences in self-administration patterns have been well-documented and observed at every stage of the course of drug exposure, from acquisition to maintenance to relapse, although more evidence has been reported for psychostimulants than for alcohol.[42,43]

In general, results from preclinical alcohol models indicate that females acquire self-administration of alcohol more rapidly and consume larger alcohol doses during maintenance phases than males, but females exhibit a reduced severity in somatic and negative affective symptoms of alcohol withdrawal than males.[4] Although the potential role of organizational steroid effects in controlling sex differences in alcohol responses cannot be ruled out, this review focuses primarily on the effects, during adulthood, of estrogen, progesterone, and neuroactive metabolites on alcohol drinking and pertinent addiction-related phenotypes in females.

Gonadal Steroids

In a variety of models of alcohol access, preclinical research in rodents documents that females consume larger doses of alcohol than males. This sex difference appears to be partly due to

a facilitatory effect of estrogen in females and an inhibitory effect of testosterone in males.[4,44] In female rodents, the estrous cycle phase had minimal effects on alcohol drinking or operant self-administration.[45] Reduced self-administration of alcohol was observed in females during proestrus and estrus only when their cycles had been experimentally synchronized (the effect was not observed in randomly cycling females that were not synchronized). Likewise, microanalysis of alcohol drinking patterns revealed increased frequency of bouts but less alcohol consumed within each bout during proestrus,[46] suggesting subtle differences in the pattern of alcohol drinking across the estrous cycle. In several models, more recent evidence confirmed that the phase of estrous cycle did not significantly influence alcohol drinking, including binge drinking,[47] escalated drinking among dependent animals,[48] self-administration of alcohol,[49] or cue plus yohimbine-induced reinstatement of alcohol-seeking.[49]

In contrast to studies of rodents, a recent, longitudinal study of female rhesus monkeys with systematic and extensive hormonal monitoring of menstrual cycle phase across 15 months of active alcohol drinking determined that the monkeys drank more alcohol during the luteal versus the follicular phase and drank the most alcohol during the late luteal phase, when progesterone declines rapidly.[50] These results from a nonhuman, primate model of self-administration of alcohol were the first to show that typical menstrual cycle–related fluctuations in progesterone, especially during the late luteal phase, modulated alcohol drinking. Previous studies that used less accurate characterization of menstrual cycles and differing histories of alcohol intake revealed inconsistent effects of the menstrual cycle on alcohol drinking. Therefore, Dozier and colleagues' method of extensive menstrual cycle characterization during periods of active drinking[50] likely was necessary to show the significant menstrual cycle–related fluctuation in alcohol drinking.

The results by Dozier and colleagues are consistent with clinical studies in which increases in premenstrual distress and negative affective states in women were positively correlated with greater alcohol drinking during the late luteal phase.[4,51] Thus, existing data support the conclusion that typical hormonal fluctuations during the menstrual cycle, but not during the estrous cycle, can influence alcohol drinking. These differences may reflect hormonal changes during the menstrual cycle that are distinct from those in the estrous cycle,[51] because rodents have no equivalent luteal phase (see the box **Phases of Primate Menstrual and Rodent Estrous Cycles**).

Despite minimal effects of the estrous cycle phase on alcohol drinking, several lines of evidence in studies of rodents indicate that the hormonal milieu contributes to sex differences in models of alcohol drinking behavior and alcohol reward. First, development of the four core genotype (FCG) mouse model has enabled researchers to examine the sex chromosome complement (XX versus XY) and the gonadal phenotype (testes versus ovaries) and their independent contributions to sex differences.[52] This model produces four different progeny, each with a different combination of sex chromosomes and gonadal sex: XXF (XX gonadal females), XXM (XX gonadal males), XYF (XY gonadal females), and XYM (XY gonadal males). Use of the FCG model determined that gonadal phenotype predicted self-administration of alcohol, independent of the sex chromosome complement.[53] That is, gonadal females consumed more alcohol than gonadal males.

Second, several studies that used gonadectomy and hormone replacement found that when compared with intact female rats, female rats with gonadectomy drank significantly less alcohol.[54,55] After the gonadectomized rats received estradiol replacement, the low levels of alcohol drinking increased significantly to baseline levels. Also, in female mice, gonadectomy significantly reduced binge drinking from the high levels of consumption among intact females to levels of consumption equivalent to that of intact males.[47] The lower levels of binge drinking among female mice with gonadectomy increased significantly following replacement with 17beta-estradiol.[47]

Similarly, gonadectomy in male and female rats produced shifts in operant alcohol self-administration toward the pattern of the opposite sex (i.e., reduced for females and increased for males).[49] In these rats, estradiol replacement in females with gonadectomy significantly increased self-administration of alcohol, and testosterone replacement in males with gonadectomy significantly decreased self-administration of alcohol. However, in rodent males, the suppressive effect of testosterone on alcohol drinking contrasts with fairly consistent clinical reports that found positive associations between blood or salivary testosterone levels and alcohol drinking among human adolescent and adult males.[10]

Third, in studies that used conditioned place preference as a measure of alcohol reward, only intact female rats exhibited conditioned place preference to an intermediate alcohol dose.[56] Intact male rats and female rats with gonadectomy (males with gonadectomy were not tested) did not exhibit the preference for the drug paired side of the testing chamber. Subsequent studies in female mice determined that in females with gonadectomy, 17beta-estradiol facilitated alcohol-induced conditioned place preference due to activation of both estrogen receptor-alpha and estrogen receptor-beta.[57]

The facilitatory effects of estradiol on alcohol drinking and a measure of alcohol reward may be due, in part, to estradiol's rapid enhancement of dopaminergic signaling.[36] In the prefrontal cortex, the ability of a low dose of alcohol (0.5 g/kg) to enhance extracellular dopamine levels in female rats during estrus was eliminated by gonadectomy and restored by estradiol treatment.[58] In the striatum, the well-documented ability of estradiol to enhance dopaminergic signaling in females was hypothesized to be associated with effects of estradiol on membrane-localized estrogen receptor-alpha and estrogen receptor-beta that were functionally coupled to metabotropic glutamate receptors.[34,36] Collectively, research confirms that within each sex, activational effects of gonadal steroids can modulate alcohol drinking behavior.

The organizational effect of testosterone-derived estrogen, which causes sex-specific differentiation of the mammalian brain,[9,52,59] during a critical period of brain development, also influences alcohol drinking. Early work found that neonatal exposure to estrogen among female rats, which conferred a male phenotype on a genetically female brain, produced levels of alcohol drinking that were lower than levels in intact females but similar to levels in intact males.[60]

More recent work has determined that gonadectomy alone in male and female rats shifted self-administration of alcohol toward the pattern of the opposite sex, but it did not eliminate the sex difference.[49] Females with gonadectomy still self-administered more alcohol than males with gonadectomy. Likewise, during tests of alcohol-seeking (cue plus yohimbine-induced reinstatement), intact females engaged in active lever presses more than intact males. Females with gonadectomy still had more lever presses than males with gonadectomy, and lever presses were not altered by steroid replacement (i.e., estradiol in females and testosterone in males). These results suggest that in addition to the contribution of the activational effects of gonadal steroids on alcohol drinking in males and females, permanent factors, such as sex chromosomes and the organizational effects of gonadal steroids, contribute to sex differences in alcohol-drinking and alcohol-seeking behaviors.

Use of the FCG model also determined that independent of gonadal phenotype, the sex chromosome complement mediates habitual responding for alcohol reinforcement after moderate instrumental training.[53] Specifically, XY mice (XYM and XYF) were insensitive to alcohol devaluation, a procedure that established conditioned taste aversion by pairing alcohol consumption with lithium chloride injections. Both valued (no conditioned taste aversion) and devalued (with conditioned taste aversion) XY mice responded similarly, indicating that XY mice were responding in a habitual manner. XX mice (XXM and XXF) were sensitive to alcohol devaluation (devalued XX mice responded less

than valued XX mice), indicating that XX mice retained goal-directed responding.[53]

Given that AUD involves a transition from casual to habitual use, as well as a transition from ventral striatal circuitry including the prefrontal cortex to a more dorsal circuit involving the dorsolateral striatum,[61] the results from Barker and colleagues[53] suggest that sex chromosomes mediate sex differences in habit formation for alcohol, and they may underlie sex differences in alcohol-induced neuroadaptation. Additional studies are necessary to disentangle the contribution of sex chromosomes and the organizational effects of gonadal steroids on alcohol-motivated behavior.

Neurosteroids

Studies have examined whether manipulation in levels of the progesterone derivative allopregnanolone, which is a potent, positive allosteric modulator of $GABA_A$ receptors,[23-26] alters alcohol drinking and alcohol's subjective effects. In general, females have higher endogenous allopregnanolone levels than males. Allopregnanolone levels in females fluctuate across the estrous and menstrual cycles and increase during pregnancy in a time-dependent manner that is related to fluctuations in endogenous progesterone.[25,62,63] The majority of studies, which were conducted in male rodents, consistently have shown that allopregnanolone, after systemic and intracerebroventricular administration, exerts a biphasic effect (i.e., increases with low physiological doses and decreases with supraphysiological doses) on alcohol drinking and operant self-administration.[64]

In contrast, research has shown that allopregnanolone does not alter alcohol drinking in female mice (see Figure 3).[65] Administration of the 5alpha-reductase inhibitor finasteride to mice, which decreased endogenous $GABA_A$ receptor–active neurosteroids such as allopregnanolone,[65] produced a decrease in the acquisition and maintenance phases of self-administration of alcohol in males, with females, again, being less sensitive to these modulatory effects.[66-68] A priming dose of allopregnanolone promoted reinstatement of alcohol-seeking behavior in male mice and rats,[69,70] but similar studies in females have not been conducted.

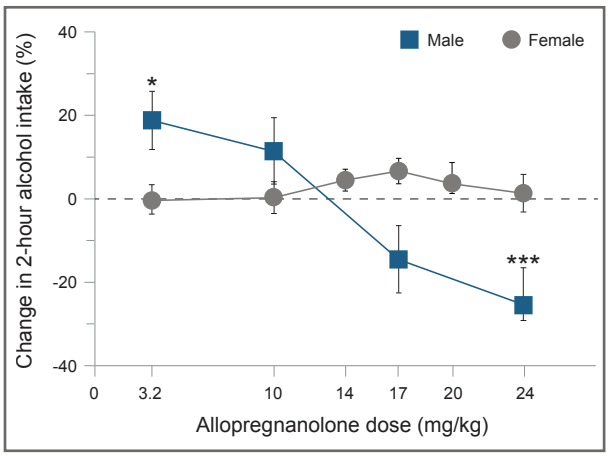

Figure 3 Sex differences in the modulatory effect of allopregnanolone on limited-access alcohol drinking in mice. Dose response is shown as a percentage of change from baseline values (vehicle treatments). The graph depicts the means and standard errors for 18 male and 24 female C57BL/6J mice. The dashed line represents the baseline values. *Note:* $*p \leq 0.05$; $***p \leq 0.001$ versus respective vehicle treatment (20% beta-cyclodextrin). *Source:* Adapted from Finn DA, Beckley EH, Kaufman KR, et al.[64]

Finally, evidence also suggests that allopregnanolone and its 5beta-isomer, pregnanolone, like alcohol, possess positive motivational effects, as demonstrated by conditioned place preference among male mice,[71] preference for drinking steroids versus water in male mice and rats,[72,73] and intravenous self-administration in four rhesus monkeys, with the highest self-administration of pregnanolone in the one female versus the three male monkeys.[74] Both allopregnanolone and pregnanolone produced potent, alcohol-like, discriminative stimulus effects in male and female cynomolgus monkeys.[75] Also, during the luteal phase of the menstrual cycle, when endogenous allopregnanolone levels were highest, female cynomolgus monkeys were more sensitive to the discriminative stimulus effects of alcohol and

to the alcohol-like effects of allopregnanolone.[76] Collectively, these results suggest that GABAergic neurosteroid levels may enhance the reinforcing effects of alcohol, and that in rodents, sensitivity to neurosteroid effects differs by sex.

A comparison of results in female mice and monkeys suggests that female monkeys are more sensitive to allopregnanolone's modulatory effects on alcohol drinking behavior. However, the relative insensitivity in female mice contrasts with the enhanced sensitivity to the anticonvulsant effect of allopregnanolone and THDOC during alcohol withdrawal in female rats and in female mice that have a low withdrawal phenotype.[77-79]

Based on evidence that local allopregnanolone metabolism in hippocampal subregions significantly altered $GABA_A$ receptor–mediated inhibition,[80] a sex difference in allopregnanolone metabolism in discrete brain regions in mice possibly contributes to low sensitivity to allopregnanolone's modulatory effects on alcohol drinking. Belelli and Herd used the 3alpha-hydroxysteroid dehydrogenase (3alpha-HSD) inhibitor indomethacin to inhibit oxidation of allopregnanolone to dihydroprogesterone, which increased local allopregnanolone levels and enhanced $GABA_A$ receptor–mediated inhibition.[80] Early work indicated that female rats, when compared with males, had about twice the activity of 3alpha-HSD from rat-liver cytosol, and that this sex difference was induced by ovarian estrogen.[81] So, in female rodents, more 3alpha-HSD activity within neurocircuitry fundamental to the regulatory processes underlying alcohol intake possibly contributes to insensitivity to the effects of allopregnanolone on alcohol drinking. Consistent with this idea, administration of allopregnanolone and indomethacin in female mice did not alter alcohol drinking when administered separately but produced a significant decrease in alcohol drinking when administered in combination (see Figure 4, DA Finn and MM Ford, unpublished data, May 2013).

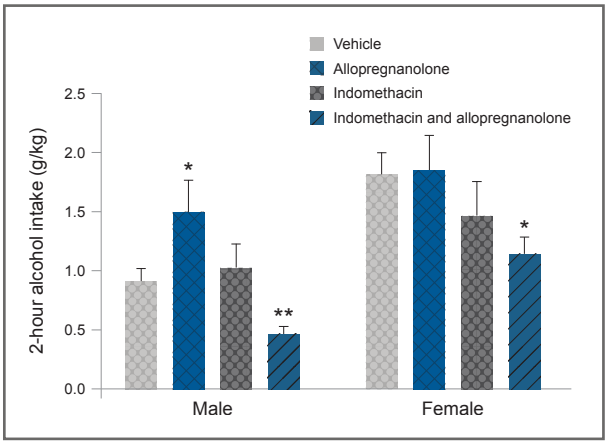

Figure 4 Modulatory effect of a combination of allopregnanolone and indomethacin in male and female mice. Female mouse insensitivity to allopregnanolone's modulatory effect on limited-access alcohol drinking was overcome by administering 0.1 mg/kg indomethacin along with 10 mg/kg allopregnanolone. Indomethacin blocks the oxidation of allopregnanolone and thereby enhances allopregnanolone's effect on $GABA_A$ receptor–mediated inhibition. The graph depicts the means and standard errors for 10 male and 10 to 11 female C57BL/6J mice. *Note*: $*p \leq 0.05$; $**p \leq 0.01$ versus respective vehicle treatment (20% beta-cyclodextrin). *Source:* DA Finn and MM Ford, unpublished data, May 2013.

Another strategy for avoiding potential confounds of rapid allopregnanolone metabolism is use of a synthetic allopregnanolone analog, such as ganaxolone.[82] Ganaxolone has a similar pharmacological profile to allopregnanolone, but it has an additional 3beta-methyl group that protects the steroid from metabolic attack at the 3alpha-position and extends the half-life about three to four times longer than that of allopregnanolone. In male rodents, ganaxolone produced a biphasic effect on alcohol drinking and self-administration when administered systemically[83-85] or bilaterally into the nucleus accumbens shell.[86] Systemic ganaxolone also promoted reinstatement of alcohol-seeking,[87] These effects of ganaxolone on alcohol drinking and seeking were similar to those observed following allopregnanolone administration. Preliminary results suggest that ganaxolone also

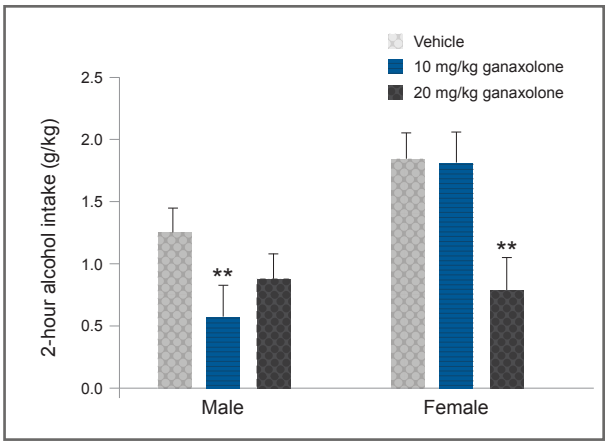

Figure 5 Sex differences in the modulatory effect of the synthetic neurosteroid ganaxolone in mice. Ganaxolone significantly decreased limited-access alcohol drinking in males and females. To significantly suppress alcohol drinking, female mice required a higher dose (20 mg/kg) than male mice (10 mg/kg). The graph depicts the means and standard errors for 10 male and 10 to 11 female C57BL/6J mice. *Note:* **$p \leq 0.01$ versus respective vehicle treatment (20% beta-cyclodextrin). *Source:* DA Finn and MM Ford, unpublished data, April 2013.

significantly reduces alcohol drinking in female mice, although a higher dose was required to produce a comparable reduction to that observed in male mice (see Figure 5, DA Finn and MM Ford, unpublished data, April 2013).

The U.S. Food and Drug Administration recently approved the allopregnanolone analog brexanolone for treatment of postpartum depression. In addition, ganaxolone is in phase 2 clinical trials for treatment of various disorders, such as postpartum depression, treatment-resistant depression, post-traumatic stress disorder (PTSD), and epilepsy. Allopregnanolone analogs and strategies to stabilize allopregnanolone levels also are being examined in clinical trials for the treatment of various central nervous system disorders.[88] Collectively, evidence suggests that targeting neurosteroid synthesis or use of neurosteroid analogs such as ganaxolone may represent innovative therapies for the treatment of AUD in males and females.[26]

EFFECTS OF CHRONIC ALCOHOL USE ON GONADAL STEROID LEVELS

Alcohol misuse and AUD produce significant hormonal disruptions in the endocrine system.[7] For sex steroids, the majority of evidence in rodents and humans suggests that chronic alcohol exposure significantly increases estradiol levels in both males and females, produces a slight or significant decrease in progesterone levels in both males and females, decreases testosterone levels in males, and produces a transient increase in testosterone levels in females. Additional work found that chronic exposure to alcohol vapor to induce dependence significantly increased testosterone levels in female mice and suggested that the increased testosterone levels in dependent female mice contributed to an observed estrous cycle disruption (i.e., prolonged diestrus).[89]

Thus, the HPG dysfunction that occurs in people with AUD can be associated with deleterious effects on reproduction in both males and females. However, some preclinical studies suggest that 6 weeks of binge drinking by female rodents[47] or 15 months of active drinking by female monkeys[50] did not significantly alter the estrous or menstrual cycles, respectively, in terms of overall cycle length or the length of specific cycle phases. Fifteen months of active drinking also did not alter progesterone or estradiol levels in the female monkeys.[50] The method of chronic alcohol exposure and resulting blood alcohol concentrations, which are considerably higher for vapor exposure (e.g., 200 mg%) than for drinking models (e.g., 80 mg% to 100 mg%), may contribute to the differences among studies with regard to whether chronic alcohol exposure disrupted the estrous or menstrual cycle.

EFFECTS OF CHRONIC ALCOHOL USE ON NEUROSTEROID LEVELS

Preclinical models of chronic alcohol drinking and vapor exposure both produce significant alterations in neurosteroid levels. Most of the evidence supports changes to allopregnanolone levels in plasma and in discrete brain regions.[24] The majority of available data are from studies in male rodents and monkeys. The results consistently show that chronic alcohol drinking and vapor exposure significantly decrease plasma allopregnanolone levels during acute withdrawal, a finding in harmony with the limited results reported for males and females with AUD.

In a small cohort of females with AUD, a significant reduction in allopregnanolone, progesterone, and estradiol levels was detected upon detoxification, and levels recovered to baseline values after 4 months of abstinence.[90] In contrast, chronic alcohol drinking did not significantly alter serum allopregnanolone levels in female monkeys,[50] nor did withdrawal from chronic alcohol vapor exposure alter plasma allopregnanolone levels in female mice (DA Finn and JP Jensen, unpublished data, Feb 2019 and Nov 2019).

Regarding brain regional changes, chronic alcohol exposure and withdrawal significantly decreased allopregnanolone levels in the amygdala of male monkeys and in the nucleus accumbens, ventral tegmental area, and medial prefrontal cortex of male rodents, with divergent changes reported in hippocampal subregions in male rodents.[24] However, preliminary results in female mice suggest that withdrawal from chronic alcohol exposure did not significantly alter cortical or hippocampal allopregnanolone levels (DA Finn and JP Jensen, unpublished data, Feb 2020 and Mar 2020).

Collectively, preclinical results in male rodents and monkeys suggest that independent adrenal and brain region regulation of neurosteroid synthesis occurs after chronic alcohol exposure and withdrawal. More preclinical research in females is necessary, but the available preclinical results suggest that females may be protected from chronic alcohol–induced suppression of allopregnanolone synthesis. Given the preclinical evidence that severity of alcohol withdrawal is reduced in females versus males,[4] and that allopregnanolone has anticonvulsant, anxiolytic, and antidepressant properties,[24] females may have the ability to maintain endogenous allopregnanolone levels after chronic alcohol exposure. This maintenance, versus the suppression seen in males, may contribute to the female phenotype for reduced severity and duration of alcohol withdrawal.

STRESS STEROIDS AND ALCOHOL-RELATED BEHAVIOR

Clinical studies provide evidence for a positive association between stress and alcohol drinking and other phases of AUD, including evidence of stress as a trigger of alcohol relapse.[91] Additionally, males and females have different sensitivities to alcohol and stress.[4-6] Acute stress exposure and alcohol intoxication both activate the HPA axis, and the HPA and HPG interact reciprocally (Figure 1).[8] Therefore, sex differences in HPA axis responsivity following acute stress or acute alcohol intoxication (i.e., enhanced elevation in glucocorticoids in females versus males) are not surprising. Discussion of all studies on this topic is beyond the scope of this review, but other reviews provide more detail.[5,8,13,92]

Preclinical studies demonstrate conflicting evidence regarding the influence of various stressors on alcohol drinking in rodents, and sex- and stress-related alterations in drinking vary with the stress model used.[5,93] However, a few examples of results show a sex difference in the relationship between corticosterone levels and alcohol drinking or alcohol-seeking.

First, studies have shown that exposure to predator odor stress (PS), which is considered a traumatic stress and used as a model of PTSD, significantly increases alcohol drinking and self-administration in rodents.[94] Evidence supports greater PS-enhanced drinking among female

versus male mice.[93,95] Plasma corticosterone levels following PS exposure have been shown to be significantly higher in female versus male mice when mice were naïve and also when the mice had a history of alcohol drinking.[93,95] Also, investigators have reported a significant positive correlation between plasma corticosterone levels and alcohol intake on the first day after PS exposure. When all mice were considered, the goodness of fit of the regression line ($R^2 = 0.26$, $p < 0.05$) indicated that the variation in PS-induced corticosterone levels accounted for 26% of the variance in alcohol drinking on the day after PS exposure. The relationship was stronger in females ($R^2 = 0.42$, $p < 0.05$), confirming that the amount of HPA axis activation after PS exposure significantly influenced alcohol drinking the following day.[93]

Second, studies examining cue plus yohimbine-induced reinstatement of alcohol-seeking in male and female rats determined that active lever presses during the reinstatement tests were significantly higher in females versus males.[96] During the reinstatement testing for female rats only, corticosterone and estradiol levels were significantly, positively correlated with active lever presses.[96]

Third, in mice deficient in beta-endorphin (knockout mice), a peptide that regulates HPA axis activity via mu opioid receptor–mediated inhibition, the females had elevated basal levels of anxiety, plasma corticosterone, and CRF in the extended amygdala when they were compared with female wild-type mice.[97] High binge alcohol intake in the female beta-endorphin knockout mice normalized their high levels of basal anxiety, corticosterone, and CRF. This relationship was not observed for the male beta-endorphin knockout mice when they were compared with wild-type mice.

Fourth, in mice with a history of alcohol drinking and exposure to PS, the PS-induced increase in plasma corticosterone was significantly lower in male mice, and tended to be lower in female mice, versus respective naïve mice.[95] This result is consistent with evidence that AUD in humans and alcohol dependence in rodents can lead to a dampened neuroendocrine state in terms of HPA axis responsivity.[7] Collectively, the results suggest that overlapping stress and gonadal steroids, as well as sex differences in HPA axis responsivity, contribute to sex differences in alcohol drinking, alcohol-seeking, and interaction with stress.

Preclinical studies also demonstrate cellular and molecular sex differences in stress response systems.[5,8,13,92] Both glucocorticoid receptors and CRF_1 receptors are being pursued as potential targets for AUD pharmacotherapies, but preclinical data in support of these targets have been generated primarily in males.[98] Recent work in male and female mice found that a history of alcohol drinking and intermittent PS exposure produced sexually divergent and brain region differences in protein levels for glucocorticoid receptors and CRF_1 receptors.[95] Increased cortical glucocorticoid receptor levels and hippocampal CRF_1 receptor levels were only found in female mice. These findings are consistent with evidence for impaired glucocorticoid negative feedback resulting from inhibition of glucocorticoid receptor translocation and evidence for increased CRF_1 receptor signaling and decreased CRF_1 receptor internalization in female versus male rodents.[92]

Collectively, an increased endocrine response to stress and alcohol consumption in females may result from sex differences that occur at the molecular and systems level. The sex differences in CRF_1 receptor and glucocorticoid receptor protein levels described above suggest that sexually divergent mechanisms may contribute to HPA axis dysregulation following a history of alcohol drinking and repeated stress exposure. As a result, pharmacological strategies targeting the CRF_1 receptor and glucocorticoid receptor systems may be differentially effective in males versus females.

EFFECTS OF STRESS ON NEUROSTEROID LEVELS

Exposure to stress[31] and models of acute alcohol intoxication[24,99] also significantly increase levels of $GABA_A$ receptor–active neurosteroids, although some species differences in the effects of alcohol

administration on neurosteroid levels have been reported.[100] In addition, most of these studies were conducted in males. In male rats, alcohol's steroidogenic effect was shown to be regulated by an alcohol-induced increase in ACTH release and by de novo synthesis of adrenal steroidogenic acute regulatory protein.[101] Chronic alcohol exposure blunts alcohol's steroidogenic effect on neurosteroid levels, but administration of ACTH restores the steroidogenic effect.[102] Although comparable studies have not been conducted in females, limited data have indicated that CRF and ACTH tests in women significantly increase serum allopregnanolone, progesterone, and dehydroepiandrosterone levels.[63] Studies also have reported that binge alcohol intoxication in male and female adolescent humans significantly increased serum allopregnanolone levels.[103,104]

Preclinical studies found that exposure to various stressors significantly increased plasma allopregnanolone levels in male and female mice that had been consuming alcohol for weeks,[93] whereas weeks of alcohol consumption alone (i.e., without stress exposure) significantly increased brain allopregnanolone levels in male mice but not in female mice.[62] Thus, data available for females suggest that stress and activation of the HPA axis increases neurosteroid levels, whereas acute alcohol administration produces inconsistent effects. Additional studies in females are necessary to determine whether an alcohol-induced steroidogenic effect can exert a protective effect against further alcohol drinking, as has been proposed for males.[99]

Two studies with small cohorts of male and female patients with co-occurring AUD and cocaine use disorder found that progesterone administration decreased cue-induced craving and cortisol responses.[105] The male and female subjects with the highest allopregnanolone levels after progesterone administration showed the greatest reductions in craving,[106] with no sex differences in these relationships. Consequently, despite no direct data on neurosteroid treatment in patients with AUD, strategies to enhance levels of $GABA_A$ receptor–active neurosteroids, such as allopregnanolone, may represent a biomarker of treatment efficacy among men and women.[5,91]

CONCLUSION

The current review considered the contribution of the endocrine system to alcohol drinking and addiction-related behaviors in females, with a focus on the HPG and HPA axes and their reciprocal interactions. The majority of results from preclinical models indicate that females acquire self-administration of alcohol more rapidly and consume higher alcohol doses during maintenance phases than males. However, aspects of alcohol withdrawal, especially somatic and some negative affective symptoms, are less severe in females than in males. Some of these behavioral differences are due to the organizational and activational effects of gonadal steroids.

Numerous studies that used gonadectomy and steroid replacement documented that gonadal steroids have activational effects and that these activational effects contribute to the higher alcohol drinking, self-administration, and responding during reinstatement tests of alcohol-seeking in females versus males. However, additional studies determined that permanent factors, such as sex chromosomes and the organizational effects of gonadal steroids, also can contribute to sex differences in alcohol drinking and alcohol-seeking. For example, elegant studies that used the FCG mouse model determined that the sex chromosome complement mediated habitual responding for alcohol reinforcement. Additional studies are necessary to distinguish how sex chromosomes and the organizational effects of gonadal steroids contribute to alcohol-motivated behavior.

Sex steroids also influence the stress response, and elevated glucocorticoids can suppress HPG axis function (Figure 1). In addition to the facilitatory and inhibitory feedback mechanisms within and between the HPA and HPG axes, steroid hormones and their derivatives (e.g., neurosteroids) can influence brain function and behavior through classic genomic actions and rapid membrane effects at receptors localized

within brain regions important for stress responses and for alcohol-related behaviors (Figure 2). For example, ovarian steroids can modulate dopamine signaling and distinct signaling pathways through actions at their membrane receptors, and neurosteroids can rapidly increase $GABA_A$ receptor–mediated signaling. These effects represent another way that steroids and neurosteroids modulate alcohol-drinking and -seeking behaviors.

Likewise, sex steroids modulate PVN output (e.g., the stress response). Estrogen has a facilitatory effect, and testosterone has an inhibitory effect. These effects are consistent with enhanced HPA axis responsivity and elevated glucocorticoids in females versus males. In both sexes, a neurosteroid-induced inhibition of CRF release via enhancement of GABAergic inhibition likely is a mechanism for terminating the stress response.

Another consideration is that the well-documented effects of chronic alcohol use and exposure on steroid levels provides another level of complexity toward understanding the influence of gonadal and stress steroids on alcohol-related behaviors.

Evidence for a positive association between stress and alcohol drinking is strong in clinical studies and mixed in preclinical studies. However, stress is a potent trigger of alcohol relapse in clinical studies and of alcohol-seeking in preclinical studies. HPA axis responsivity is enhanced in females versus males. So, it is interesting that only female rodents exhibited positive correlations between corticosterone levels following stress and stress-enhanced drinking as well as between corticosterone and estradiol levels and lever presses during cue- and stress-induced reinstatement tests of alcohol-seeking. In addition to the facilitatory effect of estrogen on the HPA axis, these sex differences could be due, in part, to impaired glucocorticoid receptor negative feedback and increased CRF_1 receptor signaling in female rodents.

Both glucocorticoid receptors and CRF_1 receptors are being pursued as potential targets for treatment of AUD, but most preclinical and clinical data examining medications that target these receptor systems have used male subjects. The few clinical studies that included female subjects were underpowered to examine for sex effects. In the single study conducted with females—who had anxiety and AUD—the CRF_1 receptor antagonist verucerfont reduced HPA responsivity without altering measures of alcohol craving.[91] Considering the preclinical data indicating that CRF_1 receptor antagonists effectively reduce escalation in alcohol drinking in dependent male rodents, it is not known whether verucerfont would reduce measures of alcohol drinking in females with AUD.

Regarding glucocorticoid receptor antagonists, the mixed glucocorticoid receptor and progesterone receptor antagonist mifepristone (also known as RU-486) significantly reduced measures of alcohol craving and alcohol consumption in participants with AUD.[5] These participants were predominantly male (the mifepristone treatment group was 82% male). Because of its progesterone receptor antagonism, mifepristone is used in females to terminate pregnancy. Thus, use of mifepristone in females may be confounded by its mixed pharmacological properties, with the progesterone receptor antagonism producing more serious side effects in females versus males.

More selective glucocorticoid receptor antagonists, such as CORT113176, are being pursued, but data for females are not available. Preliminary data in mice selectively bred for a high binge drinking phenotype determined that CORT113176 significantly decreased binge drinking in both male and female mice, and that female mice were more sensitive to the effect.[107]

Pharmacological strategies targeting the CRF_1 receptor and glucocorticoid receptor systems may be differentially effective in males versus females, and new strategies targeting these systems could have greater specificity for females.[92] For example, inhibiting molecules that facilitate the transport of glucocorticoid receptors to their classical intracellular receptor might normalize high glucocorticoid levels in females. Likewise,

compounds that target the CRF_1 receptor and shift signaling away from pathways that enhance CRF_1 receptor signaling might make females more resilient to stress-induced hyperarousal.[92]

Strategies targeting $GABA_A$ receptor–active neurosteroids or their biosynthesis may represent an approach to effectively treat AUD in males and females. Results from preclinical models suggest that chronic alcohol drinking or the induction of dependence in females does not significantly alter allopregnanolone levels, as is seen in males. These results are consistent with the idea that the ability of females to maintain endogenous levels of a GABAergic neurosteroid following chronic alcohol exposure may contribute to the reduced severity of their alcohol withdrawal phenotype. Alternately, strategies to enhance neurosteroid synthesis may exert a protective effect against further alcohol drinking in females, as has been proposed for males.[99]

Neurosteroid analogs with a longer half-life than allopregnanolone show promise as another effective strategy. For instance, brexanolone was recently approved for the treatment of postpartum depression. Currently, ganaxolone also is in clinical trials for treatment of postpartum depression, as well as for treatment-resistant depression, PTSD, and epilepsy. Preclinical results indicate that ganaxolone significantly reduces alcohol drinking in male and female mice (Figure 5, DA Finn and MM Ford, unpublished data, April 2013). Thus, neurosteroid analogs may be effective at reducing alcohol drinking in individuals with co-occurring AUD and depression or co-occurring AUD and PTSD, or in individuals with AUD who drink to alleviate stress and negative affect.

Finally, use of progesterone as a "prodrug" to increase allopregnanolone levels has been an effective strategy to decrease cue-induced craving and cortisol responses in small cohorts of male and female patients with co-occurring AUD and cocaine use disorder.[105,106] The greatest reduction in craving was observed in male and female participants who had the highest allopregnanolone levels after progesterone administration.[105,106] Thus, strategies to use allopregnanolone analogs with longer half-lives, or to stabilize or enhance levels of $GABA_A$ receptor–active neurosteroids such as allopregnanolone, may represent new efficacious treatments for both males and females with AUD.

Collectively, the importance of arriving at a more complete understanding of the neuroendocrine mechanisms underlying sex differences is clear, as treatment strategies and their effectiveness may revolve around sex differences in the endogenous steroid and neurosteroid environments and in sexually divergent downstream signaling mechanisms. In addition, variations in neurosteroid physiology also may help explain individual differences in susceptibility to AUD, vulnerability to relapse, and the negative health consequences of alcohol intake.

Acknowledgments

This article was supported by the National Institute on Alcohol Abuse and Alcoholism grant R01AA012439, U.S. Department of Veterans Affairs grant BX002966, and resources and facilities at the Veterans Affairs Portland Health Care System.

Financial disclosure

The author declares no competing financial interests.

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References

1. National Institute on Alcohol Abuse and Alcoholism. *Alcohol Use Disorder: A Comparison Between DSM-IV and DSM-5*. 2016. https://www.niaaa.nih.gov/publications/brochures-and-fact-sheets/alcohol-use-disorder-comparison-between-dsm.
2. National Institute on Alcohol Abuse and Alcoholism. *Alcohol Facts and Statistics*. 2018. http://www.niaaa.nih.gov/publications/brochures-and-fact-sheets/alcohol-facts-and-statistics. Accessed August 22, 2019.
3. Grucza RA, Sher JK, Kerr WC, et al. Trends in adult alcohol use and binge drinking in the early 21st-century United States: A meta-analysis of 6 national survey series. *Alcohol Clin Exp Res*. 2018;42(10):1939-1950. https://doi.org/10.1111/acer.13859.
4. Becker JB, Koob GF. Sex differences in animal models: Focus on addiction. *Pharmacol Rev.* 2016;68(2):242-263. https://doi.org/10.1124/pr.115.011163.

5. Logrip ML, Milivojevic V, Bertholomey ML, et al. Sexual dimorphism in the neural impact of stress and alcohol. *Alcohol.* 2018;72:49-59. https://doi.org/10.1016/j.alcohol.2018.02.002.
6. Peltier MR, Verplaetse TL, Mineur YS, et al. Sex differences in stress-related alcohol use. *Neurobiol Stress.* February 2019:10:100149. https://doi.org/10.1016/j.ynstr.2019.100149.
7. Rachdaoui N, Sarkar DK. Pathophysiology of the effects of alcohol abuse on the endocrine system. *Alcohol Res.* 2017;38(2):255-276. PMID: 28988577.
8. Oyola MG, Handa RJ. Hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal axes: Sex differences in regulation of stress responsivity. *Stress.* 2017;20(5):476-494. https://doi.org/10.1080/10253890.2017.1369523.
9. Arnold AP, Gorski RA. Gonadal steroid induction of structural sex differences in the central nervous system. *Ann Rev Neurosci.* 1984;7:413-442. https://doi.org/10.1146/annurev.ne.07.030184.002213.
10. Erol A, Ho AMC, Winham SJ, et al. Sex hormones in alcohol consumption: A systematic review of evidence. *Addiction Biol.* 2019;24(2):157-169. https://doi.org/10.1111/adb.12589.
11. McCarthy MM, Arnold AP, Ball GF, et al. Sex differences in the brain: The not so inconvenient truth. *J Neurosci.* 2012;32(7):2241-2247. https://doi.org/10.1523/JNEUROSCI.5372-11.2012.
12. Lenz B, Müller CP, Stoessel C, et al. Sex hormone activity in alcohol addiction: Integrating organizational and activational effects. *Prog Neurobiology.* 2012;96(1):136-163. https://doi.org/10.1016/j.pneurobio.2011.11.001.
13. Handa RJ, Weiser MJ. Gonadal hormones and the hypothalamic-pituitary-adrenal axis. *Front Neuroendocrinol.* 2014;35(2):197-220. https://doi.org/10.1016/j.yfrne.2013.11.001.
14. McEwen BS, Bowles NP, Gray JD, et al. Mechanisms of stress in the brain. *Nat Neurosci.* 2015;18(10):1353-1363. https://doi.org/10.1038/nn.4086.
15. Brinton RD, Thompson RF, Foy MR, et al. Progesterone receptors: Form and function in brain. *Front Neuroendocrinol.* 2008;29(2):313-339. https://doi.org/10.1016/j.yfrne.2008.02.001.
16. Vasudevan N, Pfaff DW. Non-genomic actions of estrogens and their interaction with genomic actions in the brain. *Front Neuroendocrinol.* 2008;29(2):238-257. https://doi.org/10.1016/j.yfrne.2007.08.003.
17. Di S, Maxson MM, Franco A, et al. Glucocorticoids regulate glutamate and GABA synapse-specific retrograde transmission via divergent nongenomic signaling pathways. *J Neurosci.* 2009;29(2):393-401. https://doi.org/10.1523/JNEUROSCI.4546-08.2009.
18. Foradori CD, Weiser MJ, Handa RJ. Non-genomic actions of androgens. *Front Neuroendocrinol.* 2008;29(2):169-181. https://doi.org/10.1016/j.yfrne.2007.10.005.
19. Kelly MJ, Rønnekleiv OK. Minireview: Neural signaling of estradiol in the hypothalamus. *Mol Endocrinol.* 2015;29(5):645-657. https://doi.org/10.1210/me.2014-1397.
20. Meitzen J, Mermelstein PG. Estrogen receptors stimulate brain region specific metabotropic glutamate receptors to rapidly initiate signal transduction pathways. *J Chem Neuroanat.* 2011;42(4):236-241. https://doi.org/10.1016/j.jchemneu.2011.02.002.
21. Schumacher M, Mattern C, Ghoumari A, et al. Revisiting the roles of progesterone and allopregnanolone in the nervous system: Resurgence of progesterone receptors. *Prog Neurobiol.* 2014;113:6-39. https://doi.org/10.1016/j.pneurobio.2013.09.004.
22. Stahn C, Buttergereit F. Genomic and nongenomic effects of glucocorticoids. *Nat Clin Pract Rheumatol.* 2008;4(10):525-533. https://doi.org/10.1038/ncprheum0898.
23. Belelli D, Lambert JJ. Neurosteroids: Endogenous regulators of the $GABA_A$ receptor. *Nat Rev Neurosci.* 2005;6(7):565-575. https://doi.org/10.1038/nrn1703.
24. Finn DA, Jimenez VA. Dynamic adaptation in neurosteroid networks in response to alcohol. *Handb Exp Pharmacol.* 2018;248:55-78. https://doi.org/10.1007/164_2017_82.
25. Paul SM, Purdy RH. Neuroactive steroids. *FASEB J.* 1992;6(6):2311-2322. https://doi.org/10.1096/fasebj.6.6.1347506.
26. Porcu P, Barron AM, Frye CA, et al. Neurosteroidogenesis today: Novel targets for neuroactive steroid synthesis and action and their relevance for translational research. *J Neuroendocrinol.* 2016;28(2):12351. https://doi.org/10.1111/jne.12351.
27. Lee S, Selvage D, Hansen K, et al. Site of action of acute alcohol administration in stimulating the rat hypothalamic-pituitary-adrenal axis: Comparison between the effect of systemic and intracerebroventricular injection of this drug on pituitary and hypothalamic responses. *Endocrinology.* 2004;145(10):4470-4479. https://doi.org/10.1210/en.2004-0110.
28. Miklós IH, Kovács KJ. GABAergic innervation of corticotropin-releasing hormone (CRH)-secreting parvocellular neurons and its plasticity as demonstrated by quantitative immune-electron microscopy. *Neuroscience.* 2002;113(3):581-592. https://doi.org/10.1016/S0306-4522(02)00147-1.
29. van den Pol AN, Wuarin JP, Dudek FE. Glutamate, the dominant excitatory transmitter in neuroendocrine regulation. *Science.* 1990;250(4985):1276-1278. https://doi.org/10.1126/science.1978759.
30. Cullinan WE, Ziegler DR, Herman JP. Functional role of local GABAergic influences on the HPA axis. *Brain Struct Funct.* 2008;213(1-2):63-72. https://doi.org/10.1007/s00429-008-0192-2.
31. Barbaccia ML, Serra M, Purdy RH, et al. Stress and neuroactive steroids. *Int Rev Neurobiol.* 2001;46:243-272. https://doi.org/10.1016/S0074-7742(01)46065-X.
32. Gunn BG, Brown AR, Lambert JJ, et al. Neurosteroids and $GABA_A$ receptor interactions: A focus on stress. *Front Neurosci.* 2011;5:131. https://doi.org/10.3389/fnins.2011.00131.
33. Creutz LM, Kritzer MF. Estrogen receptor-beta immunoreactivity in the midbrain of adult rats: Regional, subregional, and cellular localization in the A10, A9, and A8 dopamine cell groups. *J Comp Neurol.* 2002;446(3):288-300. https://doi.org/10.1002/cne.10207.
34. Tonn Eisinger KR, Gross KS, Head BP, et al. Interactions between estrogen receptors and metabotropic glutamate receptors and their impact on drug addiction in females. *Horm Behav.* 2018;104:130-137. https://doi.org/10.1016/j.yhbeh.2018.03.001.
35. Willing J, Wagner CK. Progesterone receptor expression in the developing mesocortical dopamine pathway: Importance for complex cognitive behavior in adulthood. *Neuroendocrinology.* 2016;103(3-4):207-222. https://doi.org/10.1159/000434725.
36. Yoest KE, Quigley JA, Becker JB. Rapid effects of ovarian hormones in dorsal striatum and nucleus accumbens. *Horm Behav.* 2018;104:119-129. https://doi.org/10.1016/j.yhbeh.2018.04.002.
37. Weinberg J, Sliwowska JH, Lan N, et al. Prenatal alcohol exposure: Foetal programming, the hypothalamic-pituitary-adrenal axis and sex differences in outcome. *J Neuroendocrinol.* 2008;20(4):470-488. https://doi.org/10.1111/j.1365-2826.2008.01669.x.
38. Dees WL, Hiney JK, Srivastava VK. Alcohol and puberty. *Alcohol Res.* 2017;38(2):277-282.
39. Kuhn C. Emergence of sex differences in the development of substance use and abuse during adolescence. *Pharmacol Ther.* 2015;153:55-78. https://doi.org/10.1016/j.pharmthera.2015.06.003.

40. Spear L. Adolescent alcohol exposure: Are there separable vulnerable periods within adolescence? *Physiol Behav.* 2015;148:122-130. https://doi.org/10.1016/j.physbeh.2015.01.027.
41. Witt ED. Puberty, hormones, and sex differences in alcohol abuse and dependence. *Neurotoxicol Teratol.* 2007;29(1):81-95. https://doi.org/10.1016/j.ntt.2006.10.013.
42. Becker JB, Hu M. Sex differences in drug abuse. *Front Neuroendocrinol.* 2008;29(1):36-47. https://doi.org/10.1016/j.yfrne.2007.07.003.
43. Carroll ME, Anker JJ. Sex differences and ovarian hormones in animal models of drug dependence. *Horm Behav.* 2010;58(1):44-56. https://doi.org/10.1016/j.yhbeh.2009.10.001.
44. Guizzetti M, Davies DL, Egli M, et al. Sex and the lab: An alcohol-focused commentary on the NIH initiative to balance sex in cell and animal studies. *Alcohol Clin Exp Res.* 2016;40(6):1182-1191. https://doi.org/10.1111/acer.13072.
45. Roberts AJ, Smith AD, Weiss F, et al. Estrous cycle effects on operant responding for ethanol in female rats. *Alcohol Clin Exp Res.* 1998;22(7):1564-1569. https://doi.org/10.1111/j.1530-0277.1998.tb03950.x.
46. Ford MM, Eldridge JC, Samson HH. Microanalysis of ethanol self-administration: Estrous cycle phase-related changes in consumption patterns. *Alcohol Clin Exp Res.* 2002;26(5):635-643. https://doi.org/10.1111/j.1530-0277.2002.tb02585.x.
47. Satta R, Hilderbrand ER, Lasek AW. Ovarian hormones contribute to high levels of binge-like drinking by female mice. *Alcohol Clin Exp Res.* 2018;42(2):286-294. https://doi.org/10.1111/acer.13571.
48. Priddy BM, Carmack SA, Thomas LC, et al. Sex, strain, and estrous cycle influences on alcohol drinking in rats. *Pharmacol Biochem Behav.* 2017;152:61-67. https://doi.org/10.1016/j.pbb.2016.08.001.
49. Bertholomey ML, Torregrossa MM. Gonadal hormones affect alcohol drinking, but not cue plus yohimbine-induced alcohol seeking, in male and female rats. *Physiol Behav.* 2019;203:70-80. https://doi.org/10.1016/j.physbeh.2017.10.025.
50. Dozier BL, Stull CA, Baker EJ, et al. Chronic ethanol drinking increases during the luteal menstrual cycle phase in rhesus monkeys: Implication of progesterone and related neurosteroids. *Psychopharmacology.* 2019;236(6):1817-1828. https://doi.org/10.1007/s00213-019-5168-9.
51. Hudson A, Stamp JA. Ovarian hormones and propensity to drug relapse: A review. *Neurosci Biobehav Rev.* 2011;35(3):427-436. https://doi.org/10.1016/j.neubiorev.2010.05.001.
52. Arnold AP, Chen X. What does the "four core genotypes" mouse model tell us about sex differences in the brain and other tissues? *Front Neuroendocrinol.* 2009;30(1):1-9. https://doi.org/10.1016/j.yfrne.2008.11.001.
53. Barker JM, Torregrossa MM, Arnold AP, et al. Dissociation of genetic and hormonal influence on sex differences in alcoholism-related behaviors. *J Neurosci.* 2010;30(27):9140-9144. https://doi.org/10.1523/JNEUROSCI.0548-10.2010.
54. Ford MM, Eldridge JC, Samson HH. Ethanol consumption in the female Long-Evans rat: A modulatory role of estradiol. *Alcohol.* 2002;26(2):103-113. https://doi.org/10.1016/S0741-8329(01)00203-8.
55. Ford MM, Eldridge JC, Samson HH. Determination of an estradiol dose-response relationship in the modulation of ethanol intake. *Alcohol Clin Exp Res.* 2004;28(1):20-28. https://doi.org/10.1097/01.ALC.0000108647.62718.5A.
56. Torres OV, Walker EM, Beas BS, et al. Female rats display enhanced rewarding effects of ethanol that are hormone dependent. *Alcohol Clin Exp Res.* 2014;38(1):108-115. https://doi.org/10.1111/acer.12213.
57. Hilderbrand ER, Lasek AW. Estradiol enhances ethanol reward in female mice through activation of ERα and ERβ. *Horm Behav.* 2018;98:159-164. https://doi.org/10.1016/j.yhbeh.2018.01.001.
58. Dazzi L, Seu E, Cherchi G, et al. Estrous cycle-dependent changes in basal and ethanol-induced activity of cortical dopaminergic neurons in the rat. *Neuropsychopharmacology.* 2007;32(4):892-901. https://doi.org/10.1038/sj.npp.1301150.
59. Patchev VK, Hayashi S, Orikasa C, et al. Implications of estrogen-dependent brain organization for gender differences in hypothalamic-pituitary-adrenal regulation. *FASEB J.* 1995;9(5):419-423. https://doi.org/10.1096/fasebj.9.5.7896013.
60. Almeida OFX, Shoaib M, Deicke J, et al. Gender differences in ethanol preference and ingestion in rats. The role of the gonadal steroid environment. *J Clin Invest.* 1998;101(12):2677-2685. https://doi.org/10.1172/JCI1198.
61. Everitt BJ, Robbins TW. Neural systems of reinforcement for drug addiction: From actions to habits to compulsion. *Nat Neurosci.* 2005;8(11):1481-1489. https://doi.org/10.1038/nn1579.
62. Finn DA, Sinnott RS, Ford MM, et al. Sex differences in the effect of ethanol injection and consumption on brain allopregnanolone levels in C57BL/6 mice. *Neuroscience.* 2004;123(4):813-819. https://doi.org/10.1016/j.neuroscience.2003.11.017.
63. Genazzani AR, Petraglia F, Bernardi F, et al. Circulating levels of allopregnanolone levels in humans: Gender, age, and endocrine influences. *J Clin Endocrinol Metab.* 1998;83:2099-2103. https://doi.org/10.1210/jcem.83.6.4905.
64. Finn DA, Beckley EH, Kaufman KR, et al. Manipulation of GABAergic steroids: Sex differences in the effects on alcohol drinking- and withdrawal-related behaviors. *Horm Behav.* 2010;57(1):12-22. https://doi.org/10.1016/j.yhbeh.2009.07.002.
65. Finn DA, Beadles-Bohling AS, Beckley EH, et al. A new look at the 5α-reductase inhibitor finasteride. *CNS Drug Rev.* 2006;12(1):53-76. https://doi.org/10.1111/j.1527-3458.2006.00053.x.
66. Ford MM, Nickel JD, Finn DA. Treatment with and withdrawal from finasteride alters ethanol intake patterns in male C57BL/6J mice: Potential role of endogenous neurosteroids? *Alcohol.* 2005;37:25-33. https://doi.org/10.1016/j.alcohol.2005.11.002.
67. Ford MM, Beckley EH, Nickel JD, et al. Ethanol intake patterns in female mice: Influence of allopregnanolone and the inhibition of its synthesis. *Drug Alcohol Depend.* 2008;97(1-2):73-85. https://doi.org/10.1016/j.drugalcdep.2008.03.021.
68. Ford MM, Yoneyama N, Strong MN, et al. Inhibition of 5α-reduced steroid biosynthesis impedes acquisition of ethanol self-administration in male C57BL/6J mice. *Alcohol Clin Exp Res.* 2008;32(8):1408-1416. https://doi.org/10.1111/j.1530-0277.2008.00718.x.
69. Finn DA, Mark GP, Fretwell AM, et al. Reinstatement of ethanol and sucrose seeking by the neurosteroid allopregnanolone in C57BL/6 mice. *Psychopharmacology.* 2008;201(3):423-433. https://doi.org/10.1007/s00213-008-1303-8.
70. Nie H, Janak PH. Comparison of reinstatement of ethanol- and sucrose-seeking by conditioned stimuli and priming injections of allopregnanolone after extinction in rats. *Psychopharmacology.* 2003;168:222-228. https://doi.org/10.1007/s00213-003-1468-0.
71. Finn DA, Phillips TJ, Okorn DM, et al. Rewarding effect of the neuroactive steroid 3α-hydroxy-5α-pregnan-20-one in mice. *Pharmacol Biochem Behav.* 1997;56(2):261-264. https://doi.org/10.1016/S0091-3057(96)00218-3.
72. Finn DA, Roberts AJ, Long S, et al. Neurosteroid consumption has anxiolytic effects in mice. *Pharmacol Biochem Behav.* 2003;76(3-4):451-462. https://doi.org/10.1016/j.pbb.2003.09.004.

73. Sinnott RS, Mark GP, Finn DA. Reinforcing effect of the neurosteroid allopregnanolone in rats. *Pharmacol Biochem Behav.* 2002;72(4):923-929. https://doi.org/10.1016/S0091-3057(02)00776-1.
74. Rowlett JK, Winger G, Carter RB, et al. Reinforcing and discriminative stimulus effects of the neuroactive steroids pregnanolone and Co 8-7071 in rhesus monkeys. *Psychopharmacology.* 1999;145(2):205-212. https://doi.org/10.1007/s002130051050.
75. Grant KA, Helms CM, Rogers LSM, et al. Neuroactive steroid stereospecificity of ethanol-like discriminative stimulus effects in monkeys. *J Pharmacol Exp Ther.* 2008;326(1):354-361. https://doi.org/10.1124/jpet.108.137315.
76. Grant KA, Azarov A, Shively CA, et al. Discriminative stimulus effects of ethanol and 3α-hydroxy-5α-pregnan-20-one in relation to menstrual cycle phase in cynomolgus monkeys (Macaca fascicularis). *Psychopharmacology.* 1997;130(1):59-68. https://doi.org/10.1007/s002130050211.
77. Beckley EH, Fretwell AM, Tanchuck MA, et al. Decreased anticonvulsant efficacy of allopregnanolone during ethanol withdrawal in female Withdrawal Seizure-Prone vs. Withdrawal Seizure-Resistant mice. *Neuropharmacology.* 2008;54(2):365-374. https://doi.org/10.1016/j.neuropharm.2007.10.006.
78. Devaud LL, Purdy RH, Morrow AL. The neurosteroid, 3α-hydroxy-5α-pregnan-20-one, protects against bicuculline-induced seizures during ethanol withdrawal in rats. *Alcohol Clin Exp Res.* 1995;19(2):350-355. https://doi.org/10.1111/j.1530-0277.1995.tb01514.x.
79. Devaud LL, Fritschy J-M, Morrow AL. Influence of gender on chronic ethanol-induced alterations in $GABA_A$ receptors in rats. *Brain Res.* 1998;796(1-2):222-230. https://doi.org/10.1016/S0006-8993(98)00357-6.
80. Belelli D, Herd MB. The contraceptive agent Provera enhances $GABA_A$ receptor-mediated inhibitory neurotransmission in the rat hippocampus: Evidence for endogenous neurosteroids? *J Neurosci.* 2003;23(31):10013-10020. https://doi.org/10.1523/JNEUROSCI.23-31-10013.2003.
81. Smithgall TE, Penning TM. Sex differences in indomethacin-sensitive 3α-hydroxysteroid dehydrogenase of rat liver cytosol. *Cancer Res.* 1985;45(10):4946-4949.
82. Carter RB, Wood PL, Wieland S, et al. Characterization of the anticonvulsant properties of ganaxolone (CCD 1042; 3α-hydroxy-3β-methyl-5α-pregnan-20-one), a selective, high-affinity, steroid modulator of the g-aminobutyric acidA receptor. *J Pharmacol Exp Ther.* 1997;280(3):1284-1295.
83. Besheer J, Lindsay TG, O'Buckley TK, et al. Pregnenolone and ganaxolone reduce operant ethanol self-administration in alcohol-preferring P rats. *Alcohol Clin Exp Res.* 2010;34(12):2044-2052. https://doi.org/10.1111/j.1530-0277.2010.01300.x.
84. Ramaker MJ, Ford MM, Fretwell AM, et al. Alteration of ethanol drinking in mice via modulation of the $GABA_A$ receptor with ganaxolone, finasteride, and gaboxadol. *Alcohol Clin Exp Res.* 2011;35(11):1994-2007. https://doi.org/10.1111/j.1530-0277.2011.01551.x.
85. Ramaker MJ, Strong MN, Ford MM, et al. The effect of ganaxolone and THIP on operant and limited access ethanol self-administration. *Neuropharmacology.* 2012;63(4):555-564. https://doi.org/10.1016/j.neuropharm.2012.05.007.
86. Ramaker MJ, Strong-Kaufman MN, Ford MM, et al. Effect of nucleus accumbens shell infusions of ganaxolone or gaboxadol on ethanol consumption in mice. *Psychopharmacology.* 2015;232(8):1415-1426. https://doi.org/10.1007/s00213-014-3777-x.
87. Ramaker MJ, Strong MN, Ford MM, et al. Differences in the reinstatement of ethanol seeking with ganaxolone and gaboxadol. *Neuroscience.* 2014;272:180-187. https://doi.org/10.1016/j.neuroscience.2014.04.065.
88. Reddy DS, Estes WA. Clinical potential of neurosteroids for CNS disorders. *Trends Pharmacol Sci.* 2016;37(7):543-561. https://doi.org/10.1016/j.tips.2016.04.003.
89. Forquer MR, Hashimoto JG, Roberts ML, et al. Elevated testosterone in females reveals a robust sex difference in altered androgen levels during chronic alcohol withdrawal. *Alcohol.* 2011;45(2):161-171. https://doi.org/10.1016/j.alcohol.2010.08.013.
90. Hill M, Popov P, Havlíková H, et al. Altered profiles of serum neuroactive steroids in premenopausal women treated for alcohol addiction. *Steroids.* 2005;70(8):515-524. https://doi.org/10.1016/j.steroids.2005.02.013.
91. Blaine SK, Sinha R. Alcohol, stress, and glucocorticoids: From risk to dependence and relapse in alcohol use disorders. *Neuropharmacology.* 2017;122:136-147. https://doi.org/10.1016/j.neuropharm.2017.01.037.
92. Bangasser DA, Valentino RJ. Sex differences in stress-related psychiatric disorders: Neurobiological perspectives. *Front Neuroendocrinol.* 2014;35(3):303-319. https://doi.org/10.1016/j.yfrne.2014.03.008.
93. Cozzoli DK, Tanchuck-Nipper MA, Kaufman MN, et al. Environmental stressors influence limited-access ethanol consumption by C57BL/6J mice in a sex-dependent manner. *Alcohol.* 2014;48(8):741-754. https://doi.org/10.1016/j.alcohol.2014.07.015.
94. Gilpin NW, Weiner JL. Neurobiology of comorbid post-traumatic stress disorder and alcohol-use disorder. *Genes Brain Behav.* 2017;16(1):15-43. https://doi.org/10.1111/gbb.12349.
95. Finn DA, Helms ML, Nipper MA, et al. Sex differences in the synergistic effect of prior binge drinking and traumatic stress on subsequent ethanol intake and neurochemical responses in adult C57BL/6J mice. *Alcohol.* 2018;71:33-45. https://doi.org/10.1016/j.alcohol.2018.02.004.
96. Bertholomey ML, Nagarajan V, Torregrossa MM. Sex differences in reinstatement of alcohol seeking in response to cues and yohimbine in rats with and without a history of adolescent corticosterone exposure. *Psychopharmacology.* 2016;233(12):2277-2287. https://doi.org/10.1007/s00213-016-4278-x.
97. Nentwig TB, Wilson DE, Rhinehart EM, et al. Sex differences in binge-like EtOH drinking, corticotropin-releasing hormone and corticosterone: Effects of β-endorphin. *Addict Biol.* 2019;24(3):447-457. https://doi.org/10.1111/adb.12610.
98. Egli M. Advancing pharmacotherapy development from preclinical animal studies. *Handb Exp Pharmacol.* 2018;248:537-578. https://doi.org/10.1007/164_2017_85.
99. Morrow AL, Porcu P, Boyd KN, et al. Hypothalamic-pituitary-adrenal axis modulation of GABAergic neuroactive steroids influences ethanol sensitivity and drinking behavior. *Dialogues Clin Neurosci.* 2006;8(4):463-477.
100. Porcu P, O'Buckley TK, Alward SE, et al. Differential effects of ethanol on serum GABAergic 3α,5α/3α,5β neuroactive steroids in mice, rats, cynomolgus monkeys, and humans. *Alcohol Clin Exp Res.* 2010;34(3):432-442. https://doi.org/10.1111/j.1530-0277.2009.01123.x.
101. Boyd KN, Kumar S, O'Buckley TK, et al. Ethanol induction of steroidogenesis in rat adrenal and brain is dependent upon pituitary ACTH release and de novo adrenal StAR synthesis. *J Neurochem.* 2010;112(3):784-796. https://doi.org/10.1111/j.1471-4159.2009.06509.x.

102. Boyd KN, Kumar S, O'Buckley TK, et al. Chronic ethanol exposure produces tolerance to elevations in neuroactive steroids: Mechanisms and reversal by exogenous ACTH. *J Neurochem.* 2010;115:142-152. https://doi.org/10.1111/j.1471-4159.2010.06904.x.
103. Torres JM, Ortega E. Alcohol intoxication increases allopregnanolone levels in female adolescent humans. *Neuropsychopharmacology.* 2003;28(6):1207-1209. https://doi.org/10.1038/sj.npp.1300170.
104. Torres JM, Ortega E. Alcohol intoxication increases allopregnanolone levels in male adolescent humans. *Psychopharmacology.* 2004;172(3):352-355. https://doi.org/10.1007/s00213-003-1662-0.
105. Fox HC, Sofuoglu M, Morgan PT, et al. The effects of exogenous progesterone on drug craving and stress arousal in cocaine dependence: Impact of gender and cue type. *Psychoneuroendocrinology.* 2013;38(9):1532-1544. https://doi.org/10.1016/j.psyneuen.2012.12.022.
106. Milivojevic V, Fox HC, Sofuoglu M, et al. Effects of progesterone stimulated allopregnanolone on craving and stress response in cocaine dependent men and women. *Psychoneuroendocrinology.* 2016;65:44-53. https://doi.org/10.1016/j.psyneuen.2015.12.008.
107. Savarese AM, Ozburn AR, Metten P, et al. Targeting the glucocorticoid receptor reduces binge-like drinking in High Drinking in the Dark (HDID-1) mice. *Alcohol Clin Exp Res.* 2020;44(5):1025-1036. https://doi.org/10.1111/acer.14318.

ALCOHOL RESEARCH
Current Reviews

Alcohol Res. 2020;40(2):03 • https://doi.org/10.35946/arcr.v40.2.03

Published: 10 September 2020

Alcohol's Unique Effects on Cognition in Women: A 2020 (Re)view to Envision Future Research and Treatment

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Alcohol use and misuse is increasing among women. Although the prevalence of drinking remains higher in men than women, the gender gap is narrowing. This narrative review focuses on the cognitive sequelae of alcohol consumption in women. Studies of acute alcohol effects on cognition indicate that women typically perform worse than men on tasks requiring divided attention, memory, and decision-making. Beneficial effects of moderate alcohol consumption on cognition have been reported; however, a number of studies have cautioned that other factors may be driving that association. Although chronic heavy drinking affects working memory, visuospatial abilities, balance, emotional processing, and social cognition in women and men, sex differences mark the severity and specific profile of functional deficits. The accelerated or compressed progression of alcohol-related problems and their consequences observed in women relative to men, referred to as "telescoping," highlights sex differences in the pharmacokinetics, pharmacodynamics, cognitive, and psychological consequences of alcohol. Brain volume deficits affecting multiple systems, including frontolimbic and frontocerebellar networks, contribute to impairment. Taken together, sex-related differences highlight the complexity of this chronic disease in women and underscore the relevance of examining the roles of age, drinking patterns, duration of abstinence, medical history, and psychiatric comorbidities in defining and understanding alcohol-related cognitive impairment.

KEY WORDS: alcohol; women; cognition; acute consumption; AUD; recovery

INTRODUCTION

Alcohol use and misuse have increased among women over the past 2 decades,[1] with an estimated 5.3 million women age 18 and older meeting criteria for alcohol use disorder (AUD) in the United States in 2018 (https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/alcohol-use-disorders). The rate of AUD in women increased 84% over the past decade in comparison with a 35% increase in men.[2] Although the prevalence of men who drink is still higher than that of women, the gender gap is narrowing.[2-4] Of note, prevalence of drinking and binge drinking, defined by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) as four or more alcoholic beverages on the same occasion for women, rose in older women (age 60 and older)[5,6] compared with previously reported levels.

Commensurate with the rising rates of women with AUD should be enhanced efforts to examine sex differences related to consequences of alcohol consumption. Most of the earliest reports of the untoward consequences of alcohol focused on men and suffered from lack of statistical power to identify sex-related differences because of small numbers of female participants or unequal sample sizes between the sexes, raising limits on generalizability to women.[7] Despite this bias, appreciation of sex differences in alcohol-related factors and consequences is not new. Indeed, Lisansky addressed the importance of examining alcohol factors uniquely related to women more than a half century ago.[8] What is new, however, is greater insistence in research studies and clinical applications for systematic investigations to address sex-related differences in alcohol consumption, antecedent factors of drinking, and alcohol-related consequences. As a result of this mandate, work over the past decade has made it amply apparent that men and women differ in alcohol-related risks, health and cognitive consequences, and factors related to successful abstinence and sobriety.[9]

This narrative review focuses on the cognitive sequelae of alcohol use in women, including deficits associated with acute consumption, moderate drinking, at-risk or hazardous drinking, and chronic excessive drinking. (See the box **Effects of Alcohol Consumption on Women and Factors That Influence Research Outcomes**.) Over the years, nomenclature regarding alcohol misuse has changed based on scientific understanding of the disease—for example, "alcohol abuse" and "alcohol dependence" in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) evolved into "alcohol use disorder" by the fifth edition (DSM-5). Although anachronistic for studies predating DSM-5 nomenclature, the term "AUD" is used throughout this review when referring to individuals who met criteria for an alcohol misuse-related diagnosis at the time of assessment.

SEX DIFFERENCES IN ALCOHOL METABOLISM AND THE CONSTRUCT OF "TELESCOPING"

Alcohol is metabolized at different rates in men and women,[10] and these sex differences in the pharmacokinetics of alcohol are biologically founded. Particularly notable is sexual dimorphism of body composition. Compared with men, women generally have less body water and a higher proportion of fat, which does not absorb alcohol, resulting in higher blood alcohol concentration (BAC) levels, even when the amount of alcohol consumed is adjusted for body weight. In addition, women tend to have lower levels of gastric alcohol dehydrogenase, the enzyme that breaks down ethanol into its metabolites. Thus, BAC levels rise faster and stay elevated longer in women than men.[3] It has been speculated that these sex-related pharmacokinetic differences underlie why women can develop health-related consequences, including cirrhosis of the liver, earlier in their disease and after lower total lifetime alcohol consumption than men.[7,11]

"Telescoping" describes the accelerated or compressed progression of the landmark events of AUD (e.g., age at first drink, age when started

Effects of Alcohol Consumption on Women and Factors That Influence Research Outcomes

What We Know

Acute alcohol consumption

Deficits reported in women

- Divided attention
- Psychomotor speed
- Working memory
- Short-term memory
- Set-shifting
- Decision-making

Moderate drinking

Modest beneficial effects

- Better overall cognitive ability
- Slower rate of cognitive decline in aging

Increased risk of

- Breast cancer
- Gastrointestinal disorders
- Infectious diseases

Chronic excessive alcohol consumption

Telescoping

Compared with men:

- Women have shorter intervals between landmark events from the inception of drinking to entering treatment.
- Women experience medical and health-related problems earlier, even when duration and amount of alcohol consumed are comparable between the sexes.
- Women exhibit different patterns and severity of cognitive compromise, some modulated by sex-related emotional and social factors.

Factors That Influence Research Outcomes

* Differences in task demands
* Heterogeneity of response to alcohol
* Small sample sizes
* Differences in study inclusion and exclusion criteria
* Cross-sectional vs. longitudinal study
* Important to control for variables such as
  - Age
  - Education
  - Socioeconomic status (SES)
  - Depression/anxiety symptoms
  - Smoking status
  - Drinking patterns
  - Alcohol-related pharmacokinetics
  - Hormonal differences
  - Nutritional status
  - Comorbid medical conditions
    - HIV
    - Hepatitis C
    - Non-alcohol substance misuse
    - Psychiatric conditions
    - Chronic pain

having problems related to alcohol, age when first entered treatment) in women compared with men.[12,13] Initial studies addressing telescoping focused on duration of time from onset of drinking to time to enter alcohol treatment or time to develop medical problems (e.g., hepatic disease). Early studies reported that women initiate hazardous drinking—drinking that puts a person at heightened risk of developing AUD—at a later age than men, although they enter alcohol treatment earlier in their disease than men.[14,15] Women also were reported to be more susceptible and to experience alcohol-related medical problems after a shorter time of chronic heavy drinking[12] and lower lifetime consumption compared with men.[16] Indeed, there is evidence that women are at heightened risk of alcohol-related heart disease.[3] Taken together, there is increasing support for this phenomenon as it pertains to the physiological and health-related consequences of alcohol in women.[3,17]

Telescoping has been invoked in studies examining the timing and severity of cognitive deficits associated with chronic heavy drinking in women compared with men.[7,18] Demonstration of a shorter duration from drinking to detectable cognitive deficits in women, however, has received mixed support, with some studies supporting the concept of telescoping of select cognitive processes,[18] whereas other studies do not.[19,20] Additional research is needed to examine the temporal sequencing, pattern, and severity of cognitive deficits in women and men in relation to landmark events associated with alcohol consumption. Inconsistency among studies examining the temporal sequence of events related to AUD in men and women could be due in part to methodological or even geographical factors, including accuracy of self-report and factors that mediate and moderate a woman's decision to seek sobriety-related or health-related treatment, such as ease or availability of treatment and help with family responsibilities.[21]

ALCOHOL'S EFFECTS ON COGNITION IN WOMEN

Acute Alcohol Consumption

An early study directly compared the acute effects of alcohol on men and women who were social drinkers without an alcohol misuse diagnosis and reported that, after moderate levels of alcohol consumption (BAC = .04%), women scored lower than men on a short-term memory task.[22] In a study examining divided attention and balance (sway) in light drinkers (12 men—average absolute ethanol intake in the 30 days prior to testing was 7.9 g/kg (range: 5.6-10.0 g/kg), 12 women—7.38 g/kg (range: 5.01-10.23 g/kg); ages 18 to 24), it was reported that the women scored significantly lower on divided attention than the men only at higher alcohol levels (BAC = .06%) and not lower levels (BAC = .03%) or for placebo.[23] Sex-related differences were not observed in sway at any BAC level. Data summarized from seven experiments examining the effects of moderate alcohol dose (0.65 g/kg) in participants with no self-reported history of substance use disorder (ages 21 to 35) on driving performance indicated that these young social drinking women showed greater deficits in memory recall, divided attention, and motor skills than did young social drinking men who did not have AUD.[24] In that review, all driving-related measures were impaired for both men and women after alcohol consumption compared with their nondrinking performance, with women demonstrating a larger decline in performance after drinking than men. These studies provide support for the notion that women may be more vulnerable than men to the cognitive effects of acute intoxication.[16]

By contrast, other studies have failed to find sex differences in relation to acute alcohol consumption. Accordingly, a study assessing 11 men and 13 women found no significant sex differences in performance on cognitive tests including assessment of divided attention, short-term memory, and rotary pursuit at moderate levels of acute consumption, blood alcohol levels (BALs) of .054% for men and .062% for women. BALs were measured at 20-minute intervals after the first drink by using a gas chromatographic intoximeter, and BALs were statistically controlled for in between-group analyses.[25] Additionally, although both men and women were impaired, no sex differences were reported in a study that assessed flight simulation performance in general aviation pilots ages 21 to 40 at moderately high BALs (12 women = .084%, 11 men = .087%), levels exceeding legal limits of intoxication in the United States (BAL = .08%).[26]

Age can moderate the effects of acute alcohol consumption on cognition.[27,28] A double-blind, placebo-controlled factorial design study assessing psychomotor, set-shifting, and working memory processes in community-dwelling social drinkers who had never met criteria for an alcohol misuse diagnosis (15 men, 24 women; ages 55 to 70) at low (breath alcohol concentration [BrAC] = .04%) and moderate (BrAC = .065%) levels of acute alcohol administration reported age-related deficits compared with 51 younger community-dwelling moderate drinkers (31 men, 20 women; ages 25 to 35). Both the younger and older adult groups exhibited some beneficial effect of low-dose alcohol compared with placebo on a simple psychomotor sequencing task (Trail Making Test, Part A). At the higher dose level (BrAC = .065%), however, only the older adults were impaired on a more complex psychomotor task requiring sequencing and working memory (Trail Making Test, Part B).[28] Cognitive efficiency, the ability to perform quickly and accurately, was most compromised in the moderate-dosage group of older adults, regardless of sex.[28]

An examination of acute alcohol effects on cognition failed to identify sex differences in tests of set shifting, psychomotor speed, or working memory in non-problem drinking older adults (26 men, 36 women; ages 55 to 70) randomly assigned to one of three dose conditions: placebo; low dose (BrAC = .040%); and moderate dose (BrAC = .065%).[29] The authors concluded that sub-intoxicating doses of alcohol do not differentially affect healthy, older, moderate-drinking men and women.

Taken together, studies that find sex-related differences on cognitive effects of acute alcohol consumption report that women tended to perform worse than men on higher-order cognitive tasks requiring divided attention, working memory, and decision-making, as opposed to less complex tasks such as reaction time or psychomotor measures.[9] Inconsistency of findings across studies is likely due to a number of factors including subject selection, task demands, and heterogeneity of response to alcohol.

Acute Cognitive Effects of Binge Drinking and Blackouts

Binge drinking can produce blackouts, defined by periods of amnesia (the inability to transfer information from short-term to long-term memory) experienced while an individual is apparently conscious and able to engage in activities such as walking, talking, and driving.[30-32] Rapid increase of BAC is a major risk factor for a blackout, with BAC levels of .22% having upward of a 50% chance of producing a blackout.[33] In young adults, blackouts are a common consequence of binge drinking.[34] Of 2,140 young adults 1 year post high school, 68% reported consuming alcohol at some point in their lifetime, and 20% of that group reported a blackout in the past 6 months.[34] The occurrence of blackouts was as prevalent among young women (17%) as men (22%) in this cohort. Blackouts have been associated with poor decision-making and impulsivity, and they increase the vulnerability of both women and men to unlawful, regrettable, and dangerous interpersonal and social situations. It has been speculated that blackouts could be more predictive than level of consumption of alcohol-related harms.[34]

AUD and Chronic Excessive Consumption

DSM-5 conceptualizes AUD as a chronic relapsing disease, where an individual continues to drink despite knowing that one's current drinking pattern is likely to lead to untoward medical, personal, and social consequences.[35] The diagnosis of AUD is based on a severity continuum ranging from mild to moderate to severe, depending on the number of diagnostic criteria met, which include but are not limited to drinking more than intended, having difficulty refraining from drinking, drinking that interferes with work and family responsibilities, cravings, tolerance, and withdrawal. The AUD continuum differs from the previous diagnostic classification system, DSM-IV-TR,[36] which made a categorical distinction between alcohol abuse and alcohol dependence. Studies investigating the effects of chronic heavy drinking on cognitive processes in women with an alcohol-related diagnosis defined by either DSM system often have reported deficits in line with those in men with an alcohol-related diagnosis, but a number of studies also have reported differences in the cognitive effects of alcohol based on sex, described next.[37-39]

Based on rigorous, quantitative assessments, cognitive deficits associated with chronic heavy drinking in women have been reported since the early 1980s.[19,40] One of the earliest studies compared 33 recently sober women (10 to 23 days since last drink) with 44 age- and education-matched control women on a number of cognitive and motor domains. Impairments were observed in visuospatial processing (block design), psychomotor speed (trail making), information processing (digit symbol substitution), and memory (verbal and visual recognition and recall).[18] The authors of this study noted that the women with AUD displayed significant cognitive and motor deficits, yet had a notably shorter drinking history than participants in previously reported studies that included men with AUD.[18] Indeed, even after statistically controlling for differences in drinking histories between men and women—duration of hazardous drinking in men was more than twice that of women (13 years vs. 6 years, respectively)—and then separately matching men and women on age and years of problem drinking, the study found that women still scored significantly lower than men on tests of memory recall and psychomotor speed.[14] However, it has been cautioned that, given the cross-sectional

nature of the study, it could not be determined whether cognitive deficits in the women were a risk factor for or a consequence of drinking.[14]

The pattern and extent of cognitive and motor deficits across six domains (i.e., executive functions, short-term memory and fluency, declarative memory, visuospatial abilities, upper-limb motor ability, postural stability) were examined in 43 recently sober (average duration, 3.6 months; range 2 to 15 months) women with AUD ages 28 to 63.[41] Compared with 47 no- to low-drinking control women matched on education and scores standardized on age, the women with AUD demonstrated deficits in verbal and nonverbal working memory, visuospatial abilities, and postural stability (balance and gait), with relative sparing of executive functions, declarative memory, and upper limb strength and speed.[41] By comparison, an earlier study examining the pattern and extent of cognitive deficits in 71 recently (1 month) sober men with AUD—compared with 74 healthy control men—reported deficits in executive function, visuospatial abilities, and gait and balance in men with AUD.[42] Taken together, these studies demonstrated that both women and men with AUD showed impairment on visuospatial processes; however, compared with nondrinking, sex-matched control participants, only the women were impaired on tasks of short-term memory, and only the men exhibited executive function deficits.

In a more recent cross-sectional study of 164 older DSM-IV alcohol-dependent participants (62 women, 102 men; age 62.6 ± 6.4 years), women performed better than men on mental flexibility as assessed by the Trail Making Test.[43] By contrast, men performed better than women on a test of visual processing assessed with a figure recognition task. Despite impairment in men and women, sex differences were not forthcoming on ability to overcome cognitive interference assessed with the Stroop Color and Word Test.[43]

Taken together, chronic excessive drinking in women is associated with myriad cognitive deficits, overlapping but not identical to the pattern of deficits observed in men. Although some evidence indicates that women develop cognitive deficits earlier in their disease or at lower lifetime consumption rates than men, its generalizability has not been clearly established.

POTENTIAL BENEFITS ASSOCIATED WITH MODERATE DRINKING

Despite the association of chronic excessive drinking with cognitive and motor deficits, much has been made about the potential beneficial health effects associated with moderate drinking—notably decreased risk of cardiovascular disease, better overall cognitive ability, and a slower rate of cognitive decline associated with normal aging.[44-47] Moderate drinking is generally defined as no more than one standard drink (14 grams of 95% alcohol) per day for women and two standard drinks per day for men. The pattern of performance from no drinking to excessive drinking has often been denoted as a U-shaped curve[48,49] or a J-shaped curve[50] with amount drunk modifying performance level.

Even moderate levels of alcohol consumption, however, have been associated with an increased risk of breast cancer, liver-related diseases, and cardiomyopathy in women (https://www.niaaa.nih.gov/publications/brochures-and-fact-sheets/women-and-alcohol), as well as infectious diseases, gastrointestinal disorders, and alcohol-related injuries.[51] In addition, for older women (particularly those age 60 and older), interactions between alcohol consumption at any level and aging, age-related disease, and drugs commonly prescribed to older people (including antibiotics, antidepressants, anxiolytics, and warfarin) can be hazardous.[52] Indeed, in addition to comorbid use of other drugs and medical comorbidities, AUD in older women often presents with complex clinical issues including untreated or undertreated depression and anxiety, which can exacerbate problems related to consumption and consequences of alcohol, family responsibilities, and feelings of guilt and shame surrounding their drinking. Although concern for older women in relation to

alcohol consumption is not new,[53] there remains a dearth of literature addressing the complexity of the factors associated with AUD in the elderly. With such a range of medical and mental health problems in this subpopulation, personalized treatment plans taking into account the entire picture and not just problem drinking are needed if abstinence and recovery are to be successful.[52]

An early study examining sex differences in 1,389 low to moderate drinkers (574 men, 815 women; ages 59 to 71) reported that women who were light (fewer than two drinks daily) to moderate (two or three but fewer than four drinks daily) drinkers performed better on set shifting, as assessed by the Trail Making Test, Part B, than women who reported abstaining from alcohol.[48] This beneficial effect of light to moderate drinking was not observed for men. These authors reiterated the importance of controlling for variables such as age, education, income, depressive symptoms, and smoking status in studies examining sex-related cognitive differences in relation to alcohol.

More recently, a longitudinal study of 818 older adults (age 65 and older; 139 moderate drinkers and 679 nondrinkers) found that although moderate alcohol use (defined as one to 14 drinks per week; average number of drinks per week in this cohort = 5.02 $\pm$ 3.79 *SD*) was related to higher baseline cognitive performance, no relation was observed on rate of change over time (spanning 7 years) across cognitive domains.[54] These authors highlighted the importance of future research focusing on the influence of demographic, genetic, and lifestyle factors on the variability observed in moderate drinking in relation to cognition. Indeed, another study cautioned that studies reporting beneficial effects of moderate drinking may have included an inappropriate selection of reference groups and little control for confounders.[55] The authors of this study found a beneficial dose-response relation only for women drinkers age 65 and older, with no measurable benefit of moderate drinking in other age-sex groups.

Another longitudinal study examined the relation between cognitively healthy longevity—defined as living to age 85 without cognitive impairment, as assessed by the Mini-Mental State Examination—and amount and frequency of alcohol intake in 1,344 older community-dwelling adults (728 women and 616 men; ages 55 to 84) and found a beneficial effect of regular, moderate drinking.[44] Indeed, individuals who reported drinking at moderate to heavy levels—up to three standard drinks per day for women on a near-daily basis—had twofold higher odds of living to age 85 without cognitive impairment compared with nondrinkers.[44] Nonetheless, another study of nondemented autonomously living octogenarians reported that older women who drank moderately did not appear to benefit at the same level as older men who drank moderately when it came to cognitive performance.[56] Indeed, only a relatively modest benefit in verbal memory for short stories was observed in women compared with men with moderate-level drinking. Sex differences were speculated to be due to myriad factors including drinking patterns and alcohol-related pharmacokinetics.

ALCOHOL CONSUMPTION AND RISK OF DEMENTIA

It is projected that the U.S. population age 65 and older will nearly double, from 48 million currently to 88 million by 2050 (https://www.nih.gov/news-events/news-releases/worlds-older-population-grows-dramatically). With an ever-increasing aging population, it is imperative to understand the effects of chronic excessive drinking on the structure and function of the aging brain and the moderating and mediating effects of age-related medical and psychiatric conditions, interactions with medications, and life-related stressors.

A meta-analytic study assessing risk of dementia in relation to alcohol consumption reported a modest U-shaped relation.[57] Results highlighted that moderate alcohol consumption, defined as fewer than 12.5 g/day (about one standard drink), was associated with a reduced risk of dementia, whereas drinking to excess (defined as $\geq$ 23 standard drinks per week) was associated with a significantly greater risk of dementia

compared with light drinking. The lowest risk of dementia was associated with drinking 6 g/day of alcohol, and wine was reported to be selectively associated with protective effects.

Another study—which included 2,874 women (of 9,087 total participants) with an average length of follow-up of 23 years—reported that abstainers and those who drank heavily (defined as more than 14 standard drinks per week) had a greater risk of dementia, determined from electronic health records.[58] These authors speculated that nondrinkers and those who drink excessively may be at higher risk of cardiometabolic disease including diabetes and hypertension, which, in turn, is associated with an increased risk of dementia.

At-risk drinking in the elderly is a timely issue. One study noted that 12% of older women (age 60 and older) reported drinking in excess of the recommended guidelines of no more than one standard drink a day or seven standard drinks per week but without meeting diagnostic criteria for AUD.[52] Without proper screening and intervention, these older adult women may be at particular risk for alcohol-related health and cognitive problems including dementia.

EMOTIONAL PROCESSING AND SOCIAL COGNITION IN WOMEN WITH AUD

Over the past decade, emotional processing and social cognition have become a focus of addiction research, highlighting the relevance of one's abilities to identify and respond to emotional and social cues in interpersonal interactions at home, at work, and with friends. Sex differences outside of AUD typically note better performance in women than men in decoding emotional facial expression and in performing tasks of social cognition such as the Reading the Mind in the Eyes Test or the Faux Pas Recognition Test.[59-63] Taken together, these findings suggest a potential resilience to social cognition disorders in women. This section reviews whether AUD disrupts this protective factor as a whole or interferes with selective processes.

AUD is associated with difficulties in components of emotion processing and social cognition, notably alexithymia, issues in decoding others' emotions, inferring others' mental states or feelings (i.e., Theory of Mind [ToM] deficit), and experiencing empathy.[64] Factors contributing to deficits in emotional processing and social cognition include an increased risk of personal, social, and work problems as well as poor initiation of action to achieve abstinence in AUD.[65] Vulnerability to emotional decoding and social cognition impairment in women with AUD may trigger an additional burden in their emotional and interpersonal interactions, thereby increasing relapse risk. Despite known sex differences in the severity of brain compromise and cognitive impairment in AUD,[66] the literature on sex differences in emotional processing and social cognition in AUD is scant.

Alexithymia is a multidimensional personality construct that comprises four core characteristics: (1) difficulty identifying feelings in oneself and differentiating feelings from the physical sensation of emotional arousal, (2) difficulty describing feelings to others, (3) restricted imaginative processes featured by limited fantasy life, and (4) an externally oriented style of thinking.[67] Alexithymia is commonly assessed by the Toronto Alexithymia Scale-20 (TAS-20), a self-report questionnaire, exploring three factors: difficulty identifying feelings, difficulty describing feelings, and externally oriented thinking (i.e., tendency to focus attention outside of oneself).[68] Higher prevalence of alexithymia in women with AUD than in men with AUD has been observed, especially on the global TAS-20 score and its "difficulty identifying feelings" factor.[69] Interestingly, alexithymia factors can play a moderator role in the relations between depressive mood and craving for alcohol in recently detoxified individuals with AUD.[70] In particular, women with AUD who reported difficulty describing feelings were at higher risk for craving when experiencing depressed mood, which is

consistent with the hypothesis that relapse would be more frequently associated with negative affect in women than men.[71]

Emotion decoding skills are crucial when assessing one's immediate social environment, providing valuable information regarding others' internal affective state, enabling behavioral adaptation according to others' thoughts and intentions, and facilitating social interactions in daily life. Contradictory findings on sex differences have been reported in studies that assessed decoding of emotional facial expressions (EFE) in AUD. Although no evidence of sex differences was found in recently detoxified individuals,[72,73] vulnerability to alcohol-related EFE recognition deficits was reported in recently detoxified women.[74,75] Lack of consistency between studies could be related to the small sample sizes of women (fewer than 15 women), which may not be representative of the population of women with AUD. Elsewhere, assessment with the social cognition module of the Wechsler Advanced Clinical Solutions revealed significant impairment in recognizing affect from facial expression in long-term abstinent men but not in long-term abstinent women.[76] Although the women did not differ from their sex-matched controls, better identification of emotional facial expressions was related to longer length of abstinence.

ToM refers to the ability to attribute mental states to oneself and others, and to understand that others' mental states might differ from those of oneself.[77] ToM enables individuals to predict, anticipate, and interpret the behavior of others and facilitates appropriate social interactions.[78] Large effect sizes were identified in two recent meta-analyses for deficits in ToM in AUD.[79,80] In support of the vulnerability hypothesis of emotional and social functioning impairment in women with AUD, a meta-analysis indicated that the effect size was modulated by sex, such that increasing the percentage of men in the treatment group decreased the effect size—results suggesting that "AUD is more likely to be associated with affective ToM deficits in females."[80(p 413)]

SEX DIFFERENCES IN ALCOHOL EFFECTS ON BRAIN STRUCTURE AND FUNCTION

Three decades of magnetic resonance imaging (MRI) studies describe patterns of brain structural abnormalities characteristic of chronic, heavy drinking.[81,82] Despite the rich literature on neuroimaging in AUD, the mainstay of studies does not address sex differences. The focus of this section is on the research in women with AUD and starts with studies using conventional structural MRI to quantify regional brain volumes; also summarized are studies using magnetic resonance diffusion tensor imaging to assess the microstructural integrity of white matter fibers and finally functional MRI done in the task activation state.

Structural MRI

Individuals with AUD but without neurological complications generally show ventricular expansion and shrinkage of selective cerebellar lobules and regions of the cerebral cortex. Volume deficits in cerebellar and cortical regions generally extend to gray and white matter macrostructure and microstructure. Whole-brain analyses support the profile of widespread damage to gray matter structures, including the frontal cortex, thalamus, insula, hippocampus, and cerebellum, as well as white matter regions including the cerebellar peduncles, pons, corpus callosum, and periventricular area.[83-87] The exploration of specific brain damage in women with AUD has been limited by an inclusion bias of men in most studies and by the lack of methodological consideration of sex differences with respect to an appropriate control group matched in sex and other relevant factors to the clinical group. The few neuroimaging studies considering differences between men and women on alcohol-related brain structural changes have generated conflicting results.

A number of cross-sectional studies investigating brain macrostructural abnormalities and alcohol misuse have reported no sex differences in brain volumes.[85,88] However, other

studies have reported inconsistent findings including greater vulnerability in men than women,[89,90] greater susceptibility to structural abnormalities in women than men,[91,92] and sex-related differences in the pattern and severity of regional brain volumetric deficits.[66] A study using a longitudinal design tested for, but did not find, sex differences on brain volumes related to chronic heavy drinking.[93]

Hippocampal volume deficits were identified in individuals with moderate alcohol consumption (fewer than 14 standard drinks per week for women, fewer than 21 standard drinks per week for men) in a study of 527 community-dwelling men and women who did not have AUD (mean age = 43 $\pm$ 5.4 years). This dose-dependent relation between alcohol consumption (i.e., alcohol units/week) over 30 years and hippocampal shrinkage, however, was significant only for men and not for women.[49] A lack of effect in women may be attributed to inadequate statistical power given the smaller number of women (n = 103) than men (n = 424) in the study and the fact that few women in the study were categorized as unsafe drinkers (n = 14 women reported drinking more than 14 standard drinks per week). In addition, no demonstrable beneficial effect was observed with light alcohol consumption compared with abstinence on brain structure and function. The authors cautioned that the protective effect reported in association with moderate drinking in other studies may be due to confounding variables, such as socioeconomic status or IQ. Beneficial effects, defined as a reduction of age-related decline in brain volume, also were not observed in a study of nondependent (DSM-IV) drinking men and women, with a relation between greater amount of alcohol consumed and smaller total brain volume, which was more pronounced in women than men.[94]

Diffusion Tensor Imaging (DTI)

This neuroimaging approach enables examination of the integrity of the microstructure of white matter, which comprises linearly organized fiber tracts that connect proximal and distal gray matter regions (that is, brain structures composed of neurons). Fiber integrity is measured in terms of fractional anisotropy (FA), typically higher in fibers with a homogeneous or linear structure such as healthy white matter, and bulk mean diffusivity of water movement for which higher values reflect diminished integrity or edematous tissue. In men with AUD, the greatest microstructural white matter abnormalities are reported in the corpus callosum, but for women with AUD, these abnormalities are greatest in the centrum semiovale.[95] In other cross-sectional DTI studies, when matched for alcohol history variables, women with AUD showed more signs of white matter degradation than men with AUD in several fiber bundles, suggesting an enhanced risk for alcohol-related degradation in selective white matter systems.[96] By contrast, no evidence for alcohol-related sex differences was forthcoming in DTI metrics for six anatomically defined transcallosal white matter fiber bundles.[97]

Potential sex differences in brain structural recovery with abstinence require further investigation. Contradictory results based on relations with length of abstinence[66,98] showed stronger positive association between length of sobriety and white matter volumes in women with AUD than in men with AUD within the first year of abstinence.[66] By contrast, positive associations between length of sobriety and white matter volumes were observed in men with AUD but not in women with AUD after 1 year of abstinence, suggesting faster white matter recovery in women.

Another DTI study reported relations between longer duration of abstinence and higher FA of the callosal white matter in men with AUD, but not in women with AUD.[98] The authors suggested better callosal white matter recovery with abstinence in men, especially when men with shorter length of abstinence showed lower FA than recently abstinent women, but the opposite pattern was observed for longer duration of abstinence. Moreover, recent neuroimaging investigations found sex interactions displaying opposite patterns. Compared with control men, men with AUD had smaller volumes in the reward network

and lower FA in select white matter tracts. By contrast, women with AUD had larger volumes in the reward system and higher FA in the same white matter tracts compared with control women.[98-100] These authors suggested that this opposite pattern in brain structural abnormalities between men and women with AUD might reflect a sex-specific phenotype related to dissimilarities in neuroanatomical and neurobehavioral expressions as risk factors or in sex-based motivation to seek alcohol.

Functional MRI

The literature investigating sex-related effects on brain functioning in AUD with functional MRI (fMRI) is scarce and is sampled next. A task-activated fMRI study revealed lower brain activation in the prefrontal and parietal cortices during a spatial working memory task in 10 women with AUD compared to 10 healthy women controls.[101] During high-risk decisions to drink, control women activated the default mode network, whereas women with AUD simultaneously activated the reward, cognitive control, and default mode networks. These results suggest that risky decisions to drink could be associated with difficulties to switch between different neural networks in women with AUD, potentially due to dysfunction in the anterior insula.[102]

A small fMRI study of airplane pilots—individuals with AUD (8 women, 6 men) and healthy controls (9 women, 5 men)—revealed an interactive effect of AUD and sex on brain activation during negative and positive facial affective processing, such that men with AUD demonstrated higher brain activation than control men, whereas women with AUD showed lower brain activation than control women.[103] By contrast, an fMRI study conducted in long-term abstinent individuals with AUD reported sex-related differences in the pattern of brain responsivity to emotional stimuli, with lower activation in the rostral middle and superior frontal cortex, precentral gyrus, and inferior parietal cortex in men with AUD than in control men, whereas higher activation in superior frontal and supramarginal cortices were observed in women with AUD compared to control women.[104] As suggested, these specificities in brain reactivity between men and women during emotional processing may reflect sex-related differences in the emotional mechanisms leading to the development of AUD.

Taken together, these studies demonstrate the relation between chronic heavy drinking and structural and functional brain abnormalities in men and women; however, due to their cross-sectional nature, these studies cannot determine whether AUD-related brain dysmorphology was caused by drinking, was pre-existing, or both. Prospective longitudinal studies—such as the National Institutes of Health/NIAAA-supported National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA)[105] and the Collaborative Studies on the Genetics of Alcoholism (COGA)[106]—study adolescents before they initiate appreciable drinking. Assessing children as young as age 8, the Adolescent Brain Cognitive Development (ABCD) Study is a longitudinal prospective study[107] that aims to identify the antecedent and resultant effects of alcohol and to track the drinking patterns that contribute to deviations from normal neurodevelopmental growth trajectories in cerebral[108] and cerebellar[109] volumes starting in preadolescence. These studies also will provide information that can address questions of specific sex-related risk factors that contribute to excessive drinking behavior and underlie differential prodromal brain abnormalities between men and women with AUD.

RECOVERY OF COGNITIVE ABILITIES WITH SUSTAINED ABSTINENCE

On an optimistic note, potential for recovery of selective cognitive deficits including memory and psychomotor abilities can occur with sustained abstinence. Functions that appear more resistant to recovery include visuospatial skills and gait and balance stability, which often endure

even with long-term abstinence.[110-113] Cognitive impairment has been associated with higher rate of relapse and lower motivation to initiate and maintain abstinence.[114]

One of the earliest studies examining recovery of cognitive function with abstinence included both short-term abstinent (1 month, $n = 40$) and long-term abstinent (4 years, $n = 40$) women.[115] This study indicated differential recovery among cognitive processes, with long-term sober women showing improvement on complex tasks of abstraction, assessed with the Halstead Category Test, whereas perceptuomotor ability, assessed with the Digit Symbol Test and the Trail Making Test, Part A, was more resistant to recovery. Critically, it was the subset of women who resumed drinking after baseline assessment that accounted for the greatest deficits at baseline compared with the subset of alcoholic women who remained sober. These authors highlighted the possibility that heterogeneity within their cohort could partly be explained by difference in posttreatment drinking (resumers vs. abstainers) and by differential premorbid "at-risk" variables in women compared with men with AUD.

Follow-up of a cohort of women with AUD at 3 to 6 years post–baseline testing after an average of 3 months of sobriety[41] reported recovery of nonverbal short-term memory and psychomotor speed.[111] Postural instability, however, was still noted, even after this extended length of abstinence. These studies highlight the selectivity of dissociable cognitive and motor processes in terms of time course and extent of recovery with abstinence.

An investigation of cognitive recovery after 6-week sobriety in a controlled environment after being in a residential treatment unit reported that a slightly lower percentage of women than men (41% vs. 46%) showed recovery on a general cognitive measure.[116] These authors speculated that the timeline of recovery and factors promoting recovery may differ between men and women and highlighted the relevance of examining the effect of sex on remediation and extent and the timeline of recovery of component cognitive processes.

FACTORS THAT MODERATE OR MEDIATE COGNITIVE AND MOTOR PERFORMANCE IN WOMEN WITH AUD

Hormonal differences between men and women and within cohorts of women have been hypothesized to at least partially underlie sex differences reported in AUD, although studies to establish this relation have been inconsistent and inconclusive.[9,117] Only limited evidence suggests that phase of menstrual cycle accounts for a significant amount of the variability in behavioral response to alcohol, with a number of studies finding that phase of menstrual cycle had no significant effects on alcohol consumption in women.[117,118] In addition, no differences among menstrual phases in alcohol pharmacokinetics have been forthcoming.[119]

Other factors speculated to moderate or mediate cognitive performance between alcoholic men and women or to underlie the heterogeneity among women with AUD are (1) age and aging effects and their interaction with alcohol; (2) alcohol consumption variables including age of AUD onset, amount drunk in one's lifetime, quantity and pattern of binge events, family history of alcohol misuse, and number and severity of withdrawals; (3) nutritional status including thiamine and other vitamin B deficiencies; (4) existence of comorbid medical and health conditions including HIV, hepatitis C, and chronic pain; (5) other drug use (including prescription and illicit); and (6) psychiatric symptoms and disorders.[37,65,120]

Research strongly supports the notion that whether one maintains sobriety or relapses into drinking, even when drinking does not meet AUD criteria, may moderate the extent and rate of cognitive and motor recovery in AUD. Attention has been paid recently to the history of trauma and chronic pain and their relation to initiation and maintenance of hazardous drinking in women and bidirectional effects of alcohol on these factors.[120,121]

Pain, for example, may be both a risk factor and a consequence of excessive drinking.[121,122] Although alcohol can reduce and even quell pain in some individuals when alcohol is initially used, over time increasing amounts of alcohol are needed to achieve pain relief, with the paradoxical effect that alcohol consumption exacerbates pain intensity. In a study of 451 treatment-seeking participants with an alcohol misuse diagnosis in residential treatment, women were more likely to report significant recurrent pain, more concurrent chronic pain conditions, and greater pain severity than men.[122] Taken together, these studies highlight the relevance of including effective pain management in initiation and maintenance of abstinence, particularly in women.

LIMITATIONS OF STUDIES

Limitations commonly noted in studies on the cognitive effects associated with chronic excessive drinking include the fact that most of the data pertaining to alcohol consumption variables, including pattern, severity, and amount, are obtained through self-report. Structured follow-back interviews likely aid accuracy of documentation but are subject to memory distortion. Differences in subject inclusion and exclusion criteria and task demands make it difficult to generalize across studies; standardization of participant characteristics and tests would allow meta-analyses across data. Additionally, the dearth of longitudinal reports limits the ability to determine whether a deficit was pre-existing or caused by alcohol misuse or to document the temporal sequence of cognitive declines and recovery in relation to the dynamic nature of alcohol use.

Additional limitations relevant to review of studies on moderate alcohol consumption and cognition and women include inclusion of "sick quitters" in the group of abstainers—that is, individuals who no longer drink because of previous alcohol misuse.[51] Efforts were taken to include studies where this was not a clear issue. Further, this review only included studies assessing sex differences and not gender differences, per se.

TREATMENT IMPLICATIONS AND CONCLUSION

There is a growing appreciation of direct comparisons between men and women in the examination of alcohol's effects on brain structure and function and the identification of factors contributing to alcohol-related cognitive impairment, including those that affect personal, social, and professional lives. Of course, regardless of sex, assessment of cognitive deficits is relevant to treatment plans, as it has been documented that efficacy of treatment with a heavy cognitive behavioral therapy component may be best delayed until recovery of the cognitive processes relevant to task demands.[123]

Highlighting the cognitive effects of acute, moderate, at-risk, and excessive drinking in women speaks to the urgency of screening, treating, and monitoring women who report patterns of possible alcohol misuse, even if diagnostic criteria for AUD are not met.[124] Young adults should be educated on the cognitive effects of binge and intensive drinking for both the short term and the long term.[125] Older adult women need to be educated on how alcohol interacts with age-related biological changes, comorbid medical conditions related to aging, and medications.

Longitudinal studies that examine the pattern and extent of cognitive and motor deficits associated with chronic heavy drinking and the factors that play a role in initiation and maintenance of alcohol misuse will continue to have both theoretical and clinical implications, steering specialized treatment for women with AUD and informing practice and policy. Heterogeneity among women with AUD highlights the complexity of this chronic disease and underscores the relevance of examining the effects of demographic factors, especially age and aging factors, and disease-related variables, notably

pattern of drinking and duration of abstinence, in identifying the cognitive effects of alcohol and its biological underpinnings.

Acknowledgment

This study was funded by National Institutes of Health grants AA010723, AA017923, AA005965, AA017347, and AA021697.

Financial Disclosure

The authors declare no competing financial interests.

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References

1. Grucza RA, Sher KJ, Kerr WC, et al. Trends in adult alcohol use and binge drinking in the early 21st-century United States: A meta-analysis of 6 national survey series. *Alcohol Clin Exp Res.* 2018;42(10):1939-1950. https://doi.org/10.1111/acer.13859.
2. Grant BF, Chou SP, Saha TD, et al. Prevalence of 12-month alcohol use, high-risk drinking, and DSM-IV alcohol use disorder in the United States, 2001–2002 to 2012–2013: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *JAMA Psychiatry.* 2017;74(9):911-923. https://doi.org/10.1001/jamapsychiatry.2017.2161.
3. McCaul ME, Roach D, Hasin DS, et al. Alcohol and women: A brief overview. *Alcohol Clin Exp Res.* 2019;43(5):774-779. https://doi.org/10.1111/acer.13985.
4. Slade T, Chapman C, Swift W, et al. Birth cohort trends in the global epidemiology of alcohol use and alcohol-related harms in men and women: Systematic review and metaregression. *BMJ Open*. 2016;6(10):e011827. https://doi.org/10.1136/bmjopen-2016-011827.
5. Breslow RA, Castle IP, Chen CM, et al. Trends in alcohol consumption among older Americans: National Health Interview Surveys, 1997 to 2014. *Alcohol Clin Exp Res*. 2017;41(5):976-986. https://doi.org/10.1111/acer.13365.
6. Han BH, Moore AA, Ferris R, et al. Binge drinking among older adults in the United States, 2015 to 2017. *J Am Geriatr Soc*. 2019; 67(10):2139-2144. https://doi.org/10.1111/jgs.16071.
7. Nolen-Hoeksema S. Gender differences in risk factors and consequences for alcohol use and problems. *Clin Psychol Rev*. 2004;24(8):981-1010. https://doi.org/10.1016/j.cpr.2004.08.003.
8. Lisansky ES. Alcoholism in women: Social and psychological concomitants. I. Social history data. *Q J Stud Alcohol*. 1957;18(4):588-623. https://doi.org/10.15288/qjsa.1957.18.588.
9. Nixon SJ, Prather R, Lewis B. Sex differences in alcohol-related neurobehavioral consequences. *Handb Clin Neurol*. 2014;125:253-272. https://doi.org/10.1016/B978-0-444-62619-6.00016-1.
10. Thomasson HR. Gender differences in alcohol metabolism. Physiological responses to ethanol. *Recent Dev Alcohol*. 1995;12:163-179. https://doi.org/10.1007/0-306-47138-8_9.
11. Erol A, Karpyak VM. Sex and gender-related differences in alcohol use and its consequences: Contemporary knowledge and future research considerations. *Drug Alcohol Depend*. 2015;156:1-13. https://doi.org/10.1016/j.drugalcdep.2015.08.023.
12. Ashley MJ, Olin JS, le Riche WH, et al. Morbidity in alcoholics. Evidence for accelerated development of physical disease in women. *Arch Intern Med*. 1977;137(7):883-887.
13. Piazza NJ, Vrbka JL, Yeager RD. Telescoping of alcoholism in women alcoholics. *Int J Addict*. 1989;24(1):19-28. https://doi.org/10.3109/10826088909047272.
14. Acker C. Neuropsychological deficits in alcoholics: The relative contributions of gender and drinking history. *Br J Addict*. 1986;81(3):395-403. https://doi.org/10.1111/j.1360-0443.1986.tb00346.x.
15. Randall CL, Roberts JS, Del Boca FK, et al. Telescoping of landmark events associated with drinking: A gender comparison. *J Stud Alcohol*. 1999;60(2):252-260. https://doi.org/10.15288/jsa.1999.60.252.
16. Mumenthaler MS, Taylor JL, O'Hara R, et al. Gender differences in moderate drinking effects. *Alcohol Res Health*. 1999;23(1):55-64.
17. Foster KT, Hicks BM, Iacono WG, et al. Alcohol use disorder in women: Risks and consequences of an adolescent onset and persistent course. *Psychol Addict Behav*. 2014;28(2):322-335. https://doi.org/10.1037/a0035488.
18. Acker C. Performance of female alcoholics on neuropsychological testing. *Alcohol Alcohol*. 1985;20(4):379-386.
19. Silberstein JA, Parsons OA. Neuropsychological impairment in female alcoholics: Replication and extension. *J Abnorm Psychol*. 1981;90(2):179-182. https://doi.org/10.1037//0021-843x.90.2.179.
20. Sullivan EV, Rohlfing T, Pfefferbaum A. Pontocerebellar volume deficits and ataxia in alcoholic men and women: No evidence for "telescoping." *Psychopharmacology (Berl)*. 2010;208(2):279-290. https://doi.org/10.1007/s00213-009-1729-7.
21. Ait-Daoud N, Blevins D, Khanna S, et al. Women and addiction. *Psychiatr Clin North Am.* 2017;40(2):285-297. https://doi.org/10.1016/j.psc.2017.01.005.
22. Jones BM, Jones MK. Alcohol and memory impairment in male and female social drinkers. In: Birnbaum IM, Parker ES, eds. *Alcohol and Human Memory*. Hillsdale, NJ: Lawrence Erlbaum; 1977:127-138.
23. Mills KC, Bisgrove EZ. Body sway and divided attention performance under the influence of alcohol: Dose-response differences between males and females. *Alcohol Clin Exp Res*. 1983;7(4):393-397. https://doi.org/10.1111/j.1530-0277.1983.tb05492.x.
24. Miller MA, Weafer J, Fillmore MT. Gender differences in alcohol impairment of simulated driving performance and driving-related skills. *Alcohol Alcohol*. 2009;44(6):586-593. https://doi.org/10.1093/alcalc/agp051.
25. Niaura RS, Nathan PE, Frankenstein W, et al. Gender differences in acute psychomotor, cognitive, and pharmacokinetic response to alcohol. *Addict Behav*. 1987;12(4):345-356. https://doi.org/10.1016/0306-4603(87)90048-7.
26. Taylor JL, Dolhert N, Friedman L, et al. Alcohol elimination and simulator performance of male and female aviators: A preliminary report. *Aviat Space Environ Med*. 1996;67(5):407-413.
27. Lewis B, Boissoneault J, Gilbertson R, et al. Neurophysiological correlates of moderate alcohol consumption in older and younger social drinkers. *Alcohol Clin Exp Res*. 2013;37(6):941-951. https://doi.org/10.1111/acer.12055.

28. Boissoneault J, Sklar A, Prather R, et al. Acute effects of moderate alcohol on psychomotor, set shifting, and working memory function in older and younger social drinkers. *J Stud Alcohol Drugs*. 2014;75(5):870-879. https://doi.org/10.15288/jsad.2014.75.870.
29. Hoffman LA, Sklar AL, Nixon SJ. The effects of acute alcohol on psychomotor, set-shifting, and working memory performance in older men and women. *Alcohol*. 2015;49(3):185-191. https://doi.org/10.1016/j.alcohol.2015.02.001.
30. Goodwin DW. Alcohol amnesia. *Addiction*. 1995;90(3):315-317.
31. Bjork JM, Gilman JM. The effects of acute alcohol administration on the human brain: insights from neuroimaging. *Neuropharmacology*. 2014;84:101-110. https://doi.org/10.1016/j.neuropharm.2013.07.039.
32. White AM. What happened? Alcohol, memory blackouts, and the brain. *Alcohol Res Health*. 2003;27(2):186-196.
33. Perry PJ, Argo TR, Barnett MJ, et al. The association of alcohol-induced blackouts and grayouts to blood alcohol concentrations. *J Forensic Sci*. 2006;51(4):896-899. https://doi.org/10.1111/j.1556-4029.2006.00161.x.
34. Hingson R, Zha W, Simons-Morton B, et al. Alcohol-induced blackouts as predictors of other drinking related harms among emerging young adults. *Alcohol Clin Exp Res*. 2016;40(4):776-784. https://doi.org/10.1111/acer.13010.
35. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Association; 2013. https://doi.org/10.1176/appi.books.9780890425596.
36. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th, Text Revision ed. Washington, DC: American Psychiatric Association; 2000.
37. Oscar-Berman M, Valmas MM, Sawyer KS, et al. Profiles of impaired, spared, and recovered neuropsychologic processes in alcoholism. *Handb Clin Neurol*. 2014;125:183-210. https://doi.org/10.1016/b978-0-444-62619-6.00012-4.
38. Parsons OA. Intellectual impairment in alcoholics: Persistent issues. *Acta Med Scand Suppl*. 1987;717:33-46. https://doi.org/10.1111/j.0954-6820.1987.tb13040.x.
39. Fama R, Sullivan EV. Alcohol. In: Allen DN, Woods SP, eds. *Neuropsychological Aspects of Substance Use Disorders: Evidence-Based Perspectives*. New York, NY: Oxford University Press; 2013.
40. Fabian MS, Parsons OA, Silberstein JA. Impaired perceptual—cognitive functioning in women alcoholics. Cross-validated findings. *J Stud Alcohol.* 1981;42(3):217-229. https://doi.org/10.15288/jsa.1981.42.217.
41. Sullivan EV, Fama R, Rosenbloom MJ, et al. A profile of neuropsychological deficits in alcoholic women. *Neuropsychology*. 2002;16(1):74-83. https://doi.org/10.1037/0894-4105.16.1.74.
42. Sullivan EV, Rosenbloom MJ, Pfefferbaum A. Pattern of motor and cognitive deficits in detoxified alcoholic men. *Alcohol Clin Exp Res*. 2000;24(5):611-621. https://doi.org/10.1111/j.1530-0277.2000.tb02032.x.
43. Van den Berg JF, Dogge B, Kist N, et al. Gender differences in cognitive functioning in older alcohol-dependent patients. *Subst Use Misuse*. 2017;52(5):574-580. https://doi.org/10.1080/10826084.2016.1245341.
44. Richard EL, Kritz-Silverstein D, Laughlin GA, et al. Alcohol intake and cognitively healthy longevity in community-dwelling adults: The Rancho Bernardo Study. *J Alzheimers Dis*. 2017;59(3):803-814. https://doi.org/10.3233/jad-161153.
45. Peters R, Peters J, Warner J, et a;. Alcohol, dementia and cognitive decline in the elderly: a systematic review. *Age Ageing*. 2008;37(5):505-512. https://doi.org/10.1093/ageing/afn095.
46. Sun Q, Townsend MK, Okereke OI, et al. Alcohol consumption at midlife and successful ageing in women: A prospective cohort analysis in the Nurses' Health Study. *PLoS Med*. 2011;8(9):e1001090. https://doi.org/10.1371/journal.pmed.1001090.
47. Ilomaki J, Jokanovic N, Tan EC, et al. Alcohol consumption, dementia and cognitive decline: An overview of systematic reviews. *Curr Clin Pharmacol*. 2015;10(3):204-212. https://doi.org/10.2174/1574884710031508201455 39.
48. Dufouil C, Ducimetiere P, Alperovitch A. Sex differences in the association between alcohol consumption and cognitive performance. EVA Study Group. Epidemiology of Vascular Aging. *Am J Epidemiol*. 1997;146(5):405-412. https://doi.org/10.1093/oxfordjournals.aje.a009293.
49. Topiwala A, Allan CL, Valkanova V, et al. Moderate alcohol consumption as risk factor for adverse brain outcomes and cognitive decline: Longitudinal cohort study. *BMJ*. 2017;357:j2353. https://doi.org/10.1136/bmj.j2353.
50. Andréasson S. Alcohol and J-shaped curves. *Alcohol Clin Exp Res*. 1998;22(7 Suppl):359S-64S. https://doi.org/10.1097/00000374-199807001-00013.
51. Roerecke M, Rehm J. Alcohol intake revisited: Risks and benefits. *Curr Atheroscler Rep*. 2012;14(6):556-562. https://doi.org/10.1007/s11883-012-0277-5.
52. Blow FC. Treatment of older women with alcohol problems: Meeting the challenge for a special population. *Alcohol Clin Exp Res*. 2000;24(8):1257-1266. https://doi.org/10.1111/j.1530-0277.2000.tb02092.x.
53. Droller H. Some aspects of alcoholism in the elderly. *Lancet*. 1964;2(7351):137-139. https://doi.org/10.1016/s0140-6736(64)90143-6.
54. Herring D, Paulson D. Moderate alcohol use and apolipoprotein E-4 (ApoE-4): Independent effects on cognitive outcomes in later life. *J Clin Exp Neuropsychol*. 2018;40(4):326-337. https://doi.org/10.1080/13803395.2017.1343803.
55. Knott CS, Coombs N, Stamatakis E, et al. All cause mortality and the case for age specific alcohol consumption guidelines: Pooled analyses of up to 10 population based cohorts. *BMJ*. 2015;350:h384. https://doi.org/10.1136/bmj.h384.
56. Wardzala C, Murchison C, Loftis JM, et al. Sex differences in the association of alcohol with cognitive decline and brain pathology in a cohort of octogenarians. *Psychopharmacology (Berl)*. 2018;235(3):761-770. https://doi.org/10.1007/s00213-017-4791-6.
57. Xu W, Wang H, Wan Y, et al. Alcohol consumption and dementia risk: A dose-response meta-analysis of prospective studies. *Eur J Epidemiol*. 2017;32(1):31-42. https://doi.org/10.1007/s10654-017-0225-3.
58. Sabia S, Fayosse A, Dumurgier J, et al. Alcohol consumption and risk of dementia: 23 year follow-up of Whitehall II cohort study. *BMJ*. 2018;362:k2927. https://doi.org/10.1136/bmj.k2927.
59. Kret ME, De Gelder B. A review on sex differences in processing emotional signals. *Neuropsychologia*. 2012;50(7):1211-1221. https://doi.org/10.1016/j.neuropsychologia.2011.12.022.
60. McClure EB. A meta-analytic review of sex differences in facial expression processing and their development in infants, children, and adolescents. *Psychol Bull*. 2000;126(3):424-453. https://psycnet.apa.org/doi/10.1037/0033-2909.126.3.424.
61. Ahmed FS, Miller SL. Executive function mechanisms of theory of mind. *J Autism Dev Disord*. 2011;41(5):667-678. https://doi.org/10.1007/s10803-010-1087-7.
62. Wacker R, Bolte S, Dziobek I. Women know better what other women think and feel: Gender effects on mindreading across the adult life span. *Front Psychol*. 2017;8:1324. https://doi.org/10.3389/fpsyg.2017.01324.

63. Kirkland R, Peterson E, Baker C, et al. Meta-analysis reveals adult female superiority in "reading the mind in the eyes test". *N Am J Psychol.* 2013;15(1):121-146.
64. Le Berre AP. Emotional processing and social cognition in alcohol use disorder. *Neuropsychology*. 2019;33(6):808-821. https://doi.org/10.1037/neu0000572.
65. Le Berre AP, Fama R, Sullivan EV. Executive functions, memory, and social Cognitive deficits and recovery in chronic alcoholism: A critical review to inform future research. *Alcohol Clin Exp Res*. 2017;41(8):1432-1443. https://doi.org/10.1111/acer.13431.
66. Ruiz SM, Oscar-Berman M, Sawyer KS, et al. Drinking history associations with regional white matter volumes in alcoholic men and women. *Alcohol Clin Exp Res*. 2013;37(1):110-122. https://doi.org/10.1111/j.1530-0277.2012.01862.x.
67. Sifneos PE. The prevalence of 'alexithymic' characteristics in psychosomatic patients. *Psychother Psychosom*. 1973;22(2):255-262. https://doi.org/10.1159/000286529.
68. Bagby RM, Taylor GJ, Parker JD. The twenty-item Toronto Alexithymia Scale—II. Convergent, discriminant, and concurrent validity. *J Psychosom Res*. 1994;38(1):33-40.
69. Craparo G, Ardino V, Gori A, et al. The relationships between early trauma, dissociation, and alexithymia in alcohol addiction. *Psychiatry Investig*. 2014;11(3):330-335. https://doi.org/10.4306/pi.2014.11.3.330.
70. Luminet O, Cordovil de Sousa Uva M, Fantini C, et al. The association between depression and craving in alcohol dependency is moderated by gender and by alexithymia factors. *Psychiatry Res*. 2016;239:28-38. https://doi.org/10.1016/j.psychres.2016.02.062.
71. Zywiak WH, Westerberg VS, Connors GJ, et al. Exploratory findings from the reasons for drinking questionnaire. *J Subst Abuse Treat*. 2003;25(4):287-292. https://doi.org/10.1016/s0740-5472(03)00118-1.
72. Philippot P, Kornreich C, Blairy S, et al. Alcoholics' deficits in the decoding of emotional facial expression. *Alcohol Clin Exp Res*. 1999;23(6):1031-1038. https://doi.org/10.15288/jsa.2001.62.533.
73. Foisy ML, Kornreich C, Petiau C, et al. Impaired emotional facial expression recognition in alcoholics: Are these deficits specific to emotional cues? *Psychiatry Res*. 2007;150(1):33-41. https://doi.org/10.1016/j.psychres.2005.12.008.
74. Lewis B, Price JL, Garcia CC, et al. Emotional face processing among treatment-seeking individuals with alcohol use disorders: Investigating sex differences and relationships with interpersonal functioning. *Alcohol Alcohol*. 2019;54(4):361-369. https://doi.org/10.1093/alcalc/agz010.
75. Frigerio E, Burt DM, Montagne B, et al. Facial affect perception in alcoholics. *Psychiatry Res*. 2002;113(1-2):161-171. https://doi.org/10.1016/s0165-1781(02)00244-5.
76. Valmas MM, Mosher RS, Gansler DA, et al. Social cognition deficits and associations with drinking history in alcoholic men and women. *Alcohol Clin Exp Res*. 2014;38(12):2998-3007. https://doi.org/10.1111/acer.12566.
77. Premack D, Woodruff G. Does the chimpanzee have a theory of mind? *Behav Brain Sci*. 1978;1:515-526. https://doi.org/10.1017/S0140525X00076512.
78. Frith CD, Frith U. Interacting minds—a biological basis. *Science*. 1999;286(5445):1692-1695. https://doi.org/10.1126/science.286.5445.1692.
79. Bora E, Zorlu N. Social cognition in alcohol use disorder: a meta-analysis. *Addiction*. 2017;112(1):40-48. https://doi.org/10.1111/add.13486.
80. Onuoha RC, Quintana DS, Lyvers M, et al. A meta-analysis of theory of mind in alcohol use disorders. *Alcohol Alcohol*. 2016;51(4):410-415. https://doi.org/10.1093/alcalc/agv137.
81. Zahr NM, Pfefferbaum A. Alcohol's effects on the brain: Neuroimaging results in humans and animal models. *Alcohol Res*. 2017;38(2):183-206.
82. Le Berre AP, Laniepce A, Segobin S, et al. Alcohol use disorder. In: Alosco MSR, ed. *The Oxford Handbook of Adult Cognitive Disorders*. New York, NY: Oxford University Publishing; 2019:307-337.
83. Chanraud S, Martelli C, Delain F, et al. Brain morphometry and cognitive performance in detoxified alcohol-dependents with preserved psychosocial functioning. *Neuropsychopharmacology*. 2007;32(2):429-438. https://doi.org/10.1038/sj.npp.1301219.
84. Jang DP, Namkoong K, Kim JJ, et al. The relationship between brain morphometry and neuropsychological performance in alcohol dependence. *Neurosci Lett*. 2007;428(1):21-26. https://doi.org/10.1016/j.neulet.2007.09.047.
85. Mechtcheriakov S, Brenneis C, Egger K, et al. A widespread distinct pattern of cerebral atrophy in patients with alcohol addiction revealed by voxel-based morphometry. *J Neurol Neurosurg Psychiatry.* 2007;78(6):610-614. https://doi.org/10.1136/jnnp.2006.095869.
86. Pfefferbaum A, Rosenbloom MJ, Sassoon SA, et al. Regional brain structural dysmorphology in human immunodeficiency virus infection: Effects of acquired immune deficiency syndrome, alcoholism, and age. *Biol Psychiatry*. 2012;72(5):361-370. https://doi.org/10.1016/j.biopsych.2012.02.018.
87. Le Berre AP, Pitel AL, Chanraud S, et al. Chronic alcohol consumption and its effect on nodes of frontocerebellar and limbic circuitry: Comparison of effects in France and the United States. *Hum Brain Mapp*. 2014;35(9):4635-4653. https://doi.org/10.1002/hbm.22500.
88. Demirakca T, Ende G, Kammerer N, et al. Effects of alcoholism and continued abstinence on brain volumes in both genders. *Alcohol Clin Exp Res*. 2011;35(9):1678-1685. https://doi.org/10.1111/j.1530-0277.2011.01514.x.
89. Pfefferbaum A, Rosenbloom M, Deshmukh A, et al. Sex differences in the effects of alcohol on brain structure. *Am J Psychiatry*. 2001;158(2):188-197. https://doi.org/10.1176/appi.ajp.158.2.188.
90. Fein G, Shimotsu R, Chu R, et al. Parietal gray matter volume loss is related to spatial processing deficits in long-term abstinent alcoholic men. *Alcohol Clin Exp Res*. 2009;33(10):1806-1814. https://doi.org/10.1111/j.1530-0277.2009.01019.x.
91. Agartz I, Shoaf S, Rawlings RR, et al. CSF monoamine metabolites and MRI brain volumes in alcohol dependence. *Psychiatry Res Neuroimaging*. 2003;122(1):21-35. https://doi.org/10.1016/s0925-4927(02)00084-7.
92. Hommer D, Momenan R, Kaiser E, et al. Evidence for a gender-related effect of alcoholism on brain volumes. *Am J Psychiatry*. 2001;158(2):198-204. https://doi.org/10.1176/appi.ajp.158.2.198.
93. Sullivan EV, Zahr NM, Sassoon SA, et al. The role of aging, drug dependence, and hepatitis C comorbidity in alcoholism cortical compromise. *JAMA Psychiatry*. 2018;75(5):474-483. https://doi.org/10.1001/jamapsychiatry.2018.0021.
94. Paul CA, Au R, Fredman L, et al. Association of alcohol consumption with brain volume in the Framingham study. *Arch Neurol*. 2008;65(10):1363-1367. https://doi.org/10.1001/archneur.65.10.1363.
95. Pfefferbaum A, Sullivan EV. Microstructural but not macrostructural disruption of white matter in women with chronic alcoholism. *Neuroimage*. 2002;15(3):708-718. https://doi.org/10.1006/nimg.2001.1018.

96. Pfefferbaum A, Rosenbloom MJ, Rohlfing T, et al. Degradation of association and projection white matter systems in alcoholism detected with quantitative fiber tracking. *Biol Psychiatry*. 2009;65(8):680-690. https://doi.org/10.1016/j.biopsych.2008.10.039.
97. Pfefferbaum A, Rosenbloom MJ, Fama R, et al. Transcallosal white matter degradation detected with quantitative fiber tracking in alcoholic men and women: Selective relations to dissociable functions. *Alcohol Clin Exp Res*. 2010;34(7):1201-1211. https://doi.org/10.1111/j.1530-0277.2010.01197.x.
98. Sawyer KS, Maleki N, Papadimitriou G, et al. Cerebral white matter sex dimorphism in alcoholism: A diffusion tensor imaging study. *Neuropsychopharmacology*. 2018;43(9):1876-1883. https://doi.org/10.1038/s41386-018-0089-6.
99. Sawyer KS, Oscar-Berman M, Barthelemy OJ, et al. Gender dimorphism of brain reward system volumes in alcoholism. *Psychiatry Res Neuroimaging*. 2017;263:15-25. https://doi.org/10.1016/j.pscychresns.2017.03.001.
100. Rivas-Grajales AM, Sawyer KS, Karmacharya S, et al. Sexually dimorphic structural abnormalities in major connections of the medial forebrain bundle in alcoholism. *Neuroimage Clin*. 2018;19:98-105. https://doi.org/10.1016/j.nicl.2018.03.025.
101. Tapert SF, Brown GG, Kindermann SS, et al. fMRI measurement of brain dysfunction in alcohol-dependent young women. *Alcohol Clin Exp Res*. 2001;25(2):236-245. https://doi.org/10.1111/j.1530-0277.2001.tb02204.x.
102. Arcurio LR, Finn PR, James TW. Neural mechanisms of high-risk decisions-to-drink in alcohol-dependent women. *Addict Biol*. 2015;20(2):390-406. https://doi.org/10.1111/adb.12121.
103. Padula CB, Anthenelli RM, Eliassen JC, et al. Gender effects in alcohol dependence: An fMRI pilot study examining affective processing. *Alcohol Clin Exp Res*. 2015;39(2):272-281. https://doi.org/10.1111/acer.12626.
104. Sawyer KS, Maleki N, Urban T, et al. Alcoholism gender differences in brain responsivity to emotional stimuli. *Elife*. 2019;8: e41723. https://doi.org/10.7554/elife.41723.
105. Brown SA, Brumback T, Tomlinson K, et al. The National Consortium on Alcohol and NeuroDevelopment in Adolescence (NCANDA): A multisite study of adolescent development and substance use. *J Stud Alcohol Drugs*. 2015;76(6):895-908. https://doi.org/10.15288/jsad.2015.76.895.
106. Begleiter H, Reich T, Hesselbrock V. The collaborative study on the genetics of alcoholism. *Alcohol Health Res World*. 1995;19:228-236.
107. Bjork JM, Straub LK, Provost RG, et al. The ABCD study of neurodevelopment: Identifying neurocircuit targets for prevention and treatment of adolescent substance abuse. *Curr Treat Options Psychiatry*. 2017;4(2):196-209. https://doi.org/10.1007/s40501-017-0108-y.
108. Pfefferbaum A, Kwon D, Brumback T, et al. Altered brain developmental trajectories in adolescents after initiating drinking. *Am J Psychiatry*. 2018;175(4):370-380. https://doi.org/10.1176/appi.ajp.2017.17040469.
109. Sullivan EV, Brumback T, Tapert SF, et al. Disturbed cerebellar growth trajectories in adolescents who initiate alcohol drinking. *Biol Psychiatry*. 2020;87(7):632-644.
110. Nixon SJ, Lewis B. Cognitive training as a component of treatment of alcohol use disorder: A review. *Neuropsychology*. 2019;33(6):822-841. https://doi.org/10.1037/neu0000575.
111. Rosenbloom MJ, Pfefferbaum A, Sullivan EV. Recovery of short-term memory and psychomotor speed but not postural stability with lone-term sobriety in alcoholic women. *Neuropsychology*. 2004;18:589-597. https://doi.org/10.1037/0894-4105.18.3.589.
112. Stavro K, Pelletier J, Potvin S. Widespread and sustained cognitive deficits in alcoholism: A meta-analysis. *Addict Biol*. 2013;18(2):203-213. https://doi.org/10.1111/j.1369-1600.2011.00418.x.
113. Fein G, Greenstein D. Gait and balance deficits in chronic alcoholics: No improvement from 10 weeks through 1 year abstinence. *Alcohol Clin Exp Res*. 2013;37(1):86-95. https://doi.org/10.1111/j.1530-0277.2012.01851.x.
114. Rolland B, D'Hondt F, Montegue S, et al. A patient-tailored evidence-based approach for developing early neuropsychological training programs in addiction settings. *Neuropsychol Rev*. 2019;29(1):103-115. https://doi.org/10.1007/s11065-018-9395-3.
115. Fabian MS, Parsons OA. Differential improvement of cognitive functions in recovering alcoholic women. *J Abnorm Psychol*. 1983;92(1):87-95. https://doi.org/10.1037//0021-843x.92.1.87.
116. Luquiens A, Rolland B, Pelletier S, et al. Role of patient sex in early recovery from alcohol-related cognitive impairment: Women penalized. *J Clin Med*. 2019;8(6):790. https://doi.org/10.3390/jcm8060790.
117. Evans SM, Levin FR. Response to alcohol in women: Role of the menstrual cycle and a family history of alcoholism. *Drug Alcohol Depend*. 2011;114(1):18-30. https://doi.org/10.1016/j.drugalcdep.2010.09.001.
118. Lammers SM, Mainzer DE, Breteler MH. Do alcohol pharmacokinetics in women vary due to the menstrual cycle? *Addiction*. 1995;90(1):23-30.
119. Holdstock L, de Wit H. Effects of ethanol at four phases of the menstrual cycle. *Psychopharmacology (Berl)*. 2000;150(4):374-382. https://doi.org/10.1007/s002130000461.
120. Maleki N, Tahaney K, Thompson BL, et al. At the intersection of alcohol use disorder and chronic pain. *Neuropsychology*. 2019;33(6):795-807. https://doi.org/10.1037/neu0000558.
121. Egli M, Koob GF, Edwards S. Alcohol dependence as a chronic pain disorder. *Neurosci Biobehav Rev*. 2012;36(10):2179-2192. https://doi.org/10.1016/j.neubiorev.2012.07.010.
122. Boissoneault J, Lewis B, Nixon SJ. Characterizing chronic pain and alcohol use trajectory among treatment-seeking alcoholics. *Alcohol*. 2019;75:47-54. https://doi.org/10.1016/j.alcohol.2018.05.009.
123. Bates ME, Buckman JF, Nguyen TT. A role for cognitive rehabilitation in increasing the effectiveness of treatment for alcohol use disorders. *Neuropsychol Rev*. 2013;23(1):27-47. https://doi.org/10.1007/s11065-013-9228-3.
124. Lewis B, Garcia CC, Nixon SJ. Drinking patterns and adherence to "low-risk" guidelines among community-residing older adults. *Drug Alcohol Depend.* 2018;187:285-291. https://doi.org/10.1016/j.drugalcdep.2018.02.031.
125. Vinader-Caerols C, Talk A, Montanes A, et al. Differential effects of alcohol on memory performance in adolescent men and women with a binge drinking history. *Alcohol Alcohol.* 2017;52:610-616. https://doi.org/10.1093/alcalc/agx040.

ALCOHOL RESEARCH
Current Reviews

Alcohol Res. 2020;40(2):04 • https://doi.org/10.35946/arcr.v40.2.04

Published: 8 October 2020

Sex Differences in the Neurobiology of Alcohol Use Disorder

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Sex differences may play a critical role in modulating how chronic or heavy alcohol use impacts the brain to cause the development of alcohol use disorder (AUD). AUD is a multifaceted and complex disorder driven by changes in key neurobiological structures that regulate executive function, memory, and stress. A three-stage framework of addiction (binge/intoxication; withdrawal/negative affect; preoccupation/anticipation) has been useful for conceptualizing the complexities of AUD and other addictions. Initially, alcohol drinking causes short-term effects that involve signaling mediated by several neurotransmitter systems such as dopamine, corticotropin releasing factor, and glutamate. With continued intoxication, alcohol leads to dysfunctional behaviors that are thought to be due in part to alterations of these and other neurotransmitter systems, along with alterations in neural pathways connecting prefrontal and limbic structures. Using the three-stage framework, this review highlights examples of research examining sex differences in drinking and differential modulation of neural systems contributing to the development of AUD. New insights addressing the role of sex differences in AUD are advancing the field forward by uncovering the complex interactions that mediate vulnerability.

KEY WORDS: alcohol use disorder; animal models; sex differences; stress; adolescence; alcohol; brain

BACKGROUND

Addiction is a chronic relapsing disorder characterized by continued substance misuse despite harmful consequences. Alcohol use disorder (AUD) is specific to the maladaptive consumption of alcohol.[1,2] The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), published by the American Psychiatric Association, describes AUD by mild, moderate, and severe subclassifications depending on the number of criteria met for the diagnosis.[3] These criteria

include symptoms of (1) compulsive excessive drinking; (2) persistent desire to consume alcohol and unsuccessful efforts to quit; (3) increased time spent in activities necessary to obtain, consume, and recover from alcohol; (4) craving or strong desire to consume alcohol; (5) recurrent use of alcohol that disrupts obligations such as work, school, or home; (6) continued use of alcohol despite persistent social or interpersonal problems; (7) important social, recreational, or occupational activities are reduced; (8) drinking persists in situations that cause harm to the individual or others; (9) consumption persists despite knowledge of the detrimental effects caused by alcohol; (10) tolerance for alcohol by having a diminished effect with the same amount or needing increased amounts for the same effect; and (11) symptoms of alcohol withdrawal. Mild AUD meets two or three of the criteria, moderate AUD meets four or five of the criteria, and severe AUD meets six or more of the 11 total criteria. The severity diagnosis for AUD could be useful for determining distinct neurobiological profiles that may be associated with mild, moderate, and severe AUD. Importantly, preclinical and clinical studies that include sex as a biological factor in experimental design will be essential to fully understand these complex neurobiological mechanisms.

OVERVIEW

The goal of this review is to discuss AUD using the three-stage framework of addiction—binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation[4]—to highlight examples of sex differences in drinking and related behaviors and to describe some of the neurobiological systems underlying AUD. There has been a recent upsurge in clinical studies in humans and experimental studies in animals in which females are included in the experimental design to elucidate the role of sex in the transition from alcohol use, to alcohol misuse, and ultimately to AUD. Sex differences may influence the three phases of addiction and consequently impact AUD risk differently in men and women.[5] The approach of considering sex as a biological factor in study design has gained even more traction because the gap between men and women in the prevalence of AUD has been closing in the past few years.[6,7]

This review focuses primarily on preclinical animal studies using self-administration procedures to elicit alcohol exposure and/or to measure drinking behaviors to allow for more direct comparison to key findings about drinking behaviors in humans. Preclinical drinking models are summarized in other reviews.[8-12] This article also considers the implications of sex on the onset of drinking, the exacerbation of the negative consequences of drinking, and the increased cue-induced relapse in more advanced stages of AUD. Overall, by presenting examples of studies that address sex differences within these stages, this review aims to show the dynamic role sex differences may have on vulnerability to the development of AUD, to generate enthusiasm for studying sex differences in preclinical and clinical alcohol research, and to advance our understanding and treatment of AUD.

BINGE/INTOXICATION STAGE

In this phase, individuals consume enough alcohol to induce intoxication and cause impairment of physical and mental abilities. An example of this is binge drinking—the excessive consumption of alcohol that results in blood alcohol levels of 0.08 gram percent (g/dL) or higher—typically reached by consumption of five or more drinks in men and four or more drinks in women within a 2-hour period.[12-15] When individuals first start binge drinking, they may not experience any physiological or emotional changes of withdrawal when the alcohol wears off; however, this changes over time.

AUD Prevalence and Age at Drinking Onset

The lifetime prevalence of AUD is 29% in the United States, with a higher prevalence in men than women.[2] In the United States, 33% of men and 17% of women binge drink at least once a month, and longitudinal studies suggest that this gap is narrowing due to a decline in frequency

among men.[15] Sex differences in AUD prevalence may relate to the age at drinking onset or an individual's first experiences with drinking alcohol—especially if alcohol consumption is high enough to elicit intoxication.[16,17] The lifetime risk of AUD quadruples when drinking begins on or before age 14 versus age 18,[18] and the factors motivating individuals to first start drinking and to drink heavily differ with sex.[16,17]

Higher risk-taking tendencies can lead to early-onset use and subsequent alcohol misuse—especially in males.[17] Adolescent boys reported "risk taking" and "curiosity" as motivators for drinking alcohol, whereas this was not the case in adolescent girls.[17] Adolescent boys also have higher levels of impulsivity and sensation seeking compared to adolescent girls.[19] Likewise, men have lower aversion to risk in a social context compared to women, which may lead men to engage in more risk-taking behaviors.[20] Interestingly, a significant positive relationship between sensation seeking and alcohol-related risks such as driving under the influence has been observed in women, but not men.[19] This suggests that women with high sensation-seeking tendencies may have an increased chance of causing harm to themselves and others after drinking alcohol compared to men with the same sensation-seeking tendencies. Alcohol-induced increases in risk-taking behavior also have been shown to differ by sex in rodents, with adolescent male rats engaging in higher risk-taking behavior after drinking alcohol compared to adolescent female rats.[21]

Another reason that individuals may drink alcohol is for its acute anxiolytic, or anxiety-reducing, properties. Experimenter-administered alcohol intoxication can temporarily reduce anxiety-like behavior in rodents.[22] Adolescent girls are more likely than adolescent boys to report drinking alcohol to alleviate stress, social isolation, and psychological distress.[23] Similarly, female mice are more sensitive to the anxiolytic effects of experimenter-administered alcohol compared to males, indexed by increased time spent in the open arms of an elevated plus maze.[24] Notably, the anxiety-reducing properties of alcohol are short-lived, experienced only during and immediately following alcohol drinking. As discussed later, and previously reviewed,[25] there is a rebounding effect during the withdrawal phase after alcohol wears off, and the degree of negative affect and altered stress hormone levels experienced at that time differs with sex.

Overall, these studies suggest that sex plays a distinct role in the motivating factors leading to drinking initiation. Risk-taking behaviors are more likely to influence adolescent boys to consume alcohol, whereas adolescent girls are more likely to consume alcohol due to its anxiety-reducing properties. Understanding the factors underlying early alcohol drinking onset may produce better strategies to prevent and dissuade alcohol consumption in adolescence and may help create specialized alternatives to alleviate the need for this coping mechanism.

Frontal Lobe Development and Early-Onset Drinking

Drinking during adolescence has been shown to lead to higher levels of drinking in adulthood in both male and female mice.[26] Heightened levels of risky behavior, such as binge drinking, during adolescence is thought to occur, at least in part, because the frontal lobes are still undergoing significant development during this time. Through its connections to other cortical regions and subcortical limbic structures, the prefrontal cortex coordinates higher executive function and behavior including decision making, stress responses, working memory, and attention.[9,27-29] The anterior cingulate cortex is one of the medial prefrontal regions that is negatively impacted by alcohol drinking, with more pronounced effects in adolescent male rodents and young men compared to adolescent female rodents and young women.[30-32]

Imaging studies in humans show other prefrontal regions are also altered with alcohol drinking in adolescence and early adulthood. The dorsolateral prefrontal cortex is thinner in younger adults who frequently engage in heavy drinking (≥5 drinks) compared to controls, and the magnitude of this effect is more robust in young

adult men compared to young adult women.[32] Binge drinking is associated with lower cortical volume and thickness in adolescent boys versus higher cortical volume and thickness in adolescent girls.[33-35] Notably, alcohol-naïve adolescent boys and girls with a family history of AUD have thinner orbitofrontal cortices compared to age-matched adolescents without a family history of AUD, indicating that some cortical differences precede alcohol misuse.[36] Considering these findings altogether, it is conceivable that an underdeveloped prefrontal cortex may promote early-onset of alcohol drinking, which could further delay or perturb this development—especially in boys and young men—and increase their lifetime risk of developing AUD.

Gonadal Hormones and Dopamine

Reward comprises learning (cue associations), hedonic ("liking"), and motivational ("wanting") components.[37] Conditioned stimuli are initially associated with a reward, but can become motivational cues on their own, incentivizing both appetitive approach and consummatory behavior.[37,38] Female rats show more appetitive approach, measured by the total number of head entries into a dipper access area (dipper approaches) and have higher levels of lever presses (active lever approaches) to obtain the alcohol reward.[39] Consummatory behavior, measured by the number of dipper presentations into the access area (reinforcers delivered) is also higher in female rats compared to male rats.[39] This is consistent with other rodent studies showing that females consume more alcohol relative to body weight and engage in higher levels of cue-mediated alcohol-seeking behaviors compared to males.[40-42]

The mesocorticolimbic dopamine pathway may contribute to sex differences in appetitive and consummatory behaviors, given its essential role in conditioning and associative learning of environmental and physiological cues that predict alcohol reward availability.[39,43-45] Alcohol binge drinking activates cells in the ventral tegmental area (VTA) of the mesocorticolimbic dopamine pathway.[45-47] This midbrain structure is the origin of dopaminergic cells that project to the ventral striatum (nucleus accumbens), frontal cortex, and amygdala. Rats will press a lever to self-administer alcohol directly into the VTA, but a higher dose of alcohol is needed for reinforcement of this behavior in males compared to females.[48,49] Moreover, a prior history of adolescent intermittent alcohol exposure leads to heightened sensitivity to the rewarding properties of alcohol in both sexes, indexed by a leftward shift in alcohol dose-response curves in rats.[48] In humans, a familial history of AUD is associated with an exaggerated ventral striatum dopamine response to the expectation of alcohol.[50] Although this study did not find a sex difference in this dopamine response, perhaps a larger number of subjects would be needed to detect a subtle, but statistically significant, difference in this measure in men and women.[50] Nevertheless, it is important to consider how dopamine contributes to sex differences in AUD vulnerability, given the role dopaminergic cells in the VTA play in reinforcement learning and in expectation of alcohol availability.

The interaction between gonadal hormones and dopamine may provide insight into the molecular mechanisms underlying sex differences in the rewarding properties of alcohol.[51,52] Estradiol enhances the stimulating effect of alcohol on VTA dopamine neurons.[51] In vitro extracellular recordings of dopaminergic neurons have been conducted using VTA slices obtained from female mice under the following hormonal conditions: no estradiol (ovariectomized and vehicle-treated) or low circulating levels of estradiol (gonadally intact mice in estrus) versus moderate (gonadally intact mice in diestrus II) or high (ovariectomized mice treated with proestrus-like levels of estradiol benzoate) circulating levels of estradiol.[51] Alcohol increased excitation of VTA dopamine neurons in brain slices from mice of all hormonal conditions, but the effects were most robust when estradiol levels were moderate or high.

Lastly, in vitro treatment with ICI 182,780—an antagonist of estrogen receptor subtypes alpha and beta (ERα and ERβ, respectively)—attenuated alcohol-induced excitation of VTA dopamine

neurons in mice with moderate levels of estradiol (diestrus II); this suggests that estradiol's modulation of dopamine sensitivity to alcohol may be occurring through its acute interaction with ERα and/or ERβ subtype in the VTA slice. The acute interaction between estradiol and its receptors appears to depend on moderate or high estradiol levels, as the ERα/ERβ antagonist did not measurably attenuate alcohol-induced increases in dopamine firing under conditions of low estradiol (estrus).

Through its effects on mesocorticolimbic dopamine, estradiol appears to mediate association-based learning and the rewarding properties of alcohol in context, which could ultimately promote drinking. Indeed, estradiol-treated ovariectomized mice show both increased dopamine signaling in the VTA in response to alcohol and increased preference of an alcohol context compared to vehicle-treated ovariectomized mice.[53] The preference for an alcohol-paired context suggests that estradiol enhances the rewarding effects of alcohol.[53] Estradiol also increases alcohol consumption in these mice and inhibition of either ERα or ERβ blocks this effect, suggesting that co-activation of both receptor subtypes is dependent on estradiol.[53]

Progesterone and its metabolites also have been implicated in the modulation of mesocorticolimbic dopamine neurons in response to alcohol.[54] A study in male rats showed that progesterone increases the dopamine extracellular concentration in the medial prefrontal cortex after an experimenter delivered administration of alcohol, inducing a 55% increase compared to controls.[54] Alcohol intake also increases brain concentrations of allopregnanolone (3a-hydroxy-5a-pregnan-20-one)—a neuroactive metabolite of progesterone.[55] Nonhuman primate research in females shows that drinking levels increase when serum levels of estradiol and progesterone and its metabolites are higher (i.e., during the luteal phase compared to the follicular phase of the menstrual cycle).[56] Within the luteal phase the highest drinking occurred on the declining phase of the progesterone peak, with a trend of a positive correlation between serum allopregnanolone levels and alcohol intake.[56] Progesterone and neuroactive steroids could be modifying drinking behavior through effects on mesocorticolimbic dopaminergic neurons involved in reward processing, but more research is needed to understand sex differences in these effects.[54]

Sensitivity to the Aversive Consequences of Drinking

Binge drinking can cause injuries and other adverse outcomes, with high-intensity (extreme binge) drinking (10 or more drinks in men, eight or more drinks in women) resulting in more severe consequences such as blackouts, alcohol overdose, and even death.[57] Some of the short-term aversive consequences of alcohol intoxication can help curtail continued alcohol consumption; yet, these are more subdued during adolescence, and in males in particular.[57] Adolescent boys are less prone to the negative effects of alcohol after a binge-drinking episode, taking less time to recover from alcohol intoxication compared to adolescent girls.[23] Similar trends of decreased sensitivity to the aversive properties of alcohol have been reported in male rodents, but this varies with age, species, and other factors.[58-61] Nevertheless, reduced sensitivity to the aversive properties of alcohol may contribute to higher levels of binge and extreme binge drinking in adolescent boys compared to adolescent girls, which ultimately could lead to differential risk of AUD in adulthood.[57]

WITHDRAWAL/NEGATIVE AFFECT STAGE

After repeated episodes of binge drinking, individuals can begin to experience a negative affective state when alcohol is withdrawn voluntarily or involuntarily. This includes dysregulated stress hormone levels, dysphoria, anxiety, depression, and irritability—a symptomology thought to be due in part to adaptations in stress-related neural pathways.[9,62,63] Experiencing these aversive symptoms when alcohol wears off can set up a strong cyclical pattern of negative reinforcement in

which individuals learn that if they consume alcohol again, they can "feel normal"—at least temporarily.

Negative Affective State During Alcohol Withdrawal

Chronic heavy alcohol consumption eventually can lead to severe AUD. A hallmark feature of AUD is the negative emotional and physiological state that arises when alcohol wears off.[64] Individuals may experience a combination of various symptoms ranging from dizziness to headaches, irritability, anxiety, dysphoria, sleep disturbances, and hypersensitivity to pain.[3] As mentioned above, it has been proposed that alcohol dependence arises because individuals go through repeated cycles in which alcohol consumption serves to mediate the effects of withdrawal, acting as a negative reinforcer.[5,25,45,65,66] A negative reinforcer is a driving force that—with the removal of an aversive stimulus such as negative affective state during withdrawal—promotes a specific behavioral response such as drinking relapse.[65]

Individuals with AUD report having negative and unpleasant feelings during withdrawal, such as low self-concept, neuroticism, depression, and hostility—all of which predict alcohol craving.[67,68] Behavioral assays also have been developed to assess a negative affective state experienced during withdrawal in animals. In addition to the traditional assays such as the elevated plus maze and open field, the frequency of ultrasonic vocalizations also can be measured to assess anxiety-like symptoms of negative affect that are experienced early after withdrawal from chronic alcohol exposure in rodents.[69,70] A recent study used this measure to examine sex differences in withdrawal-induced negative affect in rats that were exposed to 6 weeks of intermittent alcohol.[71] The researchers found that male rats increased the frequency of vocalizations during acute withdrawal, whereas female rats did not.[71] A difference in withdrawal sensitivity may incentivize continued heavy alcohol use to a greater degree in males compared to females, thus putting them at a higher risk of AUD.

Male rats and mice show a more pronounced display of negative affective-like behaviors and neuroactivity after withdrawal from chronic alcohol exposure compared to female rats and mice.[71-75] Alterations in glutamate signaling from the stria terminalis projecting into the basolateral amygdala are thought to mediate these behavioral differences.[73,76] Shorter duration of exposure to chronic intermittent alcohol vapor intoxication and withdrawal cycles was sufficient to detect these synaptic alterations in male rats versus female rats.[73] Furthermore, a translational study using magnetic resonance spectroscopy showed that rats exposed to chronic intermittent alcohol vapors and people diagnosed with AUD have increased glutamatergic neurotransmission during acute alcohol withdrawal compared to their respective controls.[77]

Dysregulation of Stress Hormones

Withdrawal from alcohol is associated with a dysregulation of stress hormones. The hypothalamic pituitary adrenal (HPA) axis governs the neuroendocrine response to stress by releasing corticotropin-releasing factor (CRF) from the hypothalamus, which activates the release of the adrenocorticotropic hormone (ACTH) from the anterior pituitary, resulting in the release of the glucocorticoids from the adrenal glands (cortisol in primates and corticosterone in rodents).

Studies in humans show that, compared to men, women had lower ACTH and cortisol levels under baseline (resting) conditions in the morning, but were more sensitive to peripheral stimulation of the HPA axis as indexed by the dexamethasone/CRF test.[78] In contrast, men showed a greater response than women to the centrally acting citalopram stimulation test.[78] This test measures the extent to which a selective serotonin-reuptake inhibitor acts specifically on the hypothalamus to initiate a stress response. Compared to women, men also exhibited greater activation in response to stress of corticolimbic structures including the medial prefrontal cortex, the extended amygdala and posterior insula, and the hippocampus.[79] In rodents, HPA activity is higher in females under basal (stress-free) conditions and in response

to an acute stress challenge.[25,80-82] In rodents, stress experienced in utero can exaggerate these sex differences even more by enhancing HPA responses in females and dampening it in males.[83]

In male rats, dampened HPA responsivity has been observed after withdrawal from chronic intermittent alcohol vapor exposure, and to a lesser extent following chronic alcohol drinking alone.[84] Although sex differences in corticosterone responsivity were not directly tested, corticosterone responsivity appears to differ 24 hours into withdrawal from chronic alcohol drinking and following predator order stress in male and female mice.[81] Studies in nonhuman primates and rodents have confirmed that alcohol drinking acutely elevates blood levels of ACTH and glucocorticoids.[81,84-86] It is thought that repeated cycles of intoxication and withdrawal eventually desensitize this system, resulting in neuroendocrine tolerance to alcohol.[9,87]

Dysregulation of the HPA axis is thought to result from alcohol-induced neuroadaptive changes within this neuroendocrine axis itself.[84] Glucocorticoid receptor signaling is required for the development of dependence, but it remains unknown whether the accompanying neuroendocrine tolerance contributes functionally to escalated drinking after dependence.[9,88] In addition to the HPA axis, there are neuroadaptive changes in other stress regulatory pathways as well such as the prefrontal cortex, bed nucleus of the stria terminalis, and central amygdala.[9,47,88-91]

Stress can increase alcohol drinking, but this depends on sex, age, and the type of stress exposure.[81,92] Adult female rodents show higher drinking compared to adult males, relative to body weight, and predator odor stress has been shown to elevate drinking in male rodents to the level of drinking observed in females.[40,80] In one study, adult mice had 3 weeks of intermittent binge drinking using the scheduled high alcohol consumption (SHAC) procedure, followed by 1 month of abstinence, and then were tested for alcohol drinking before and following 2 weeks of intermittent predator odor stress (dirty bedding from rats).[81] Among male mice with a prior history of binge drinking, 2 weeks of stress elicited the greatest increase in drinking relative to baseline. This stress effect was found in female mice only when the baseline drinking was stratified into two subgroups: low versus high levels of drinking. Only females that had originally exhibited low drinking levels showed the increase in drinking in response to stress.[81] Female mice that initially exhibited high drinking did not show a further elevation, possibly due to a ceiling effect.

Another study of mice used the "Drinking in the Dark" (DID) binge drinking procedure for 2 weeks followed by 11 days of unpredictable, chronic, mild stress.[93] Afterwards, alcohol drinking was measured with a two-bottle choice of 20% versus 40% v/v alcohol test. Stress increased alcohol binge drinking in both sexes, but this effect was exacerbated even more in male mice with a previous history of drinking prior to stress.[93]

The studies discussed above and others[94] suggest that males may be more susceptible to alcohol withdrawal; however, early-onset drinking can interact with these factors and drive up vulnerability in females. Five days of exposure to restraint stress increased alcohol drinking in adolescent female rats, but decreased drinking in adolescent male and adult female rats.[92] This suggests a heightened sensitivity to stress in adolescence that may have a particularly detrimental impact in females. In support of this, adolescent-onset binge drinking increased anxiety-like behavior early in withdrawal in female mice, and this persisted into abstinence.[95] Likewise, acute stress elicited a negative affective state in the novelty-induced suppression of feeding task in adult female mice with a history of adolescent alcohol exposure.[76] A history of adolescent binge drinking and intermittent alcohol vapor exposure led to a negative affective-like state in the elevated plus maze task and fear conditioning response in male mice, but it did not emerge until later in abstinence.[96]

The neural systems implicated in the interactive effects of stress and alcohol include not only structures of extended amygdala, but also brain regions thought to be involved in the third stage of AUD (preoccupation/anticipation).[73,86,97-100] For

example, a history of prior binge drinking and exposure to predator odor stress dysregulates protein levels of stress-related receptors, and does so in a sex-specific manner.[81] After chronic drinking, there is a measurable increase in glucocorticoid receptors in the prefrontal cortex and hippocampus, and CRF receptor 1 in the hippocampus of female mice, but not male mice.[81] These neuroadaptive changes in stress-regulatory circuits could persist well beyond withdrawal and underlie some of the psychological components that predict craving and relapse.[67]

PREOCCUPATION/ ANTICIPATION STAGE

Prolonged heavy alcohol use leads to a state of a constant preoccupation with alcohol and compulsive drinking despite negative consequences.[88,101,102] This craving can continue into abstinence for months or years, making it difficult to abstain from alcohol altogether or to shift to a healthier level of drinking.[103]

Sensitivity to Alcohol-Related Cues

After long bouts of abstinence, alcohol-related cues can trigger incentive salience, which heightens cravings and precipitates relapse.[37,104,105] Men in particular exhibit higher levels of alcohol craving than do women,[106] and cravings are associated with increased activity in the striatum in men, but not in women.[79] Cue-induced reinstatement procedures are useful for studying the underlying neurobiological mechanisms by which alcohol-related cues promote craving and relapse during abstinence.[107] Like humans, male rodents appear more susceptible to relapse than females.[108] Brain-derived neurotrophic factor (BDNF) may play a role in mediating this sex difference.

In mice, male offspring of alcohol-exposed fathers have high *Bdnf* gene expression in the VTA and low alcohol drinking behavior; this effect was not observed in female offspring.[109] Conversely, genetic manipulation to reduce BDNF protein levels to 50% in female rats resulted in a heightened, male-like, response to alcohol cues.[108] This genetic manipulation had no effect in males. Others have found a sex difference in tropomyosin receptor kinase B (TrkB) signaling in *Bdnf* +/– mice, with males showing higher TrkB phosphorylation than females in the prefrontal cortex and striatum.[110] Consequently, BDNF signaling is presumed to mediate cravings in response to alcohol cues and this increased sensitivity to alcohol-related cues could put males at higher risk of relapse even after long periods of abstinence.

Compulsive Alcohol Drinking After Chronic Use

As discussed earlier, multiple cycles of binge intoxication followed by withdrawal can transition individuals from light to moderate drinking to severe AUD.[5,25,45,66] At this point, heavy drinking can become more compulsive.[111] Compulsive alcohol use is inflexible and persists despite negative consequences or despite devaluation of the rewarding effects of alcohol. This type of drinking is characteristic of physical and motivational/emotional dependence on alcohol.[88,112]

One strategy used to measure inflexible drinking is the assessment of a persistent motivation to drink despite increasing the response requirement to obtain alcohol. In animal studies, this can be tested by training subjects to press a lever or nose poke for alcohol in operant boxes.[9] The number of responses to get the reward can be changed using fixed ratio or progressive ratio schedules of reinforcement in operant alcohol self-administration studies. Fixed ratio is the number of presses necessary for reward delivery, increasing the response requirement for the reward. This challenge measures compulsive-like behavior that is characteristic of addiction, in which individuals go to extreme lengths to obtain the drug on which they are dependent. Progressive ratio takes this a step further and increases the response requirement for reward delivery. In humans, a progressive ratio trial of intravenous alcohol self-administration showed that women increased their work effort to obtain alcohol after resumption following 2 weeks of abstinence, whereas men decreased this effort.[113] Male rats exposed to alcohol vapors to produce

dependence display increased compulsive-like behavior and increased intake on both fixed and progressive ratio schedules.[88] However, progressive ratio tests in Long Evans rats suggest there is no sex difference in motivation for alcohol, at least following extinction and reinstatement of alcohol self-administration.[114] Comprehensive studies are needed to assess compulsive drinking behaviors and relapse after prolonged abstinence in both nondependent and dependent animals to better understand sex differences in AUD.

Alcohol solutions also can be manipulated to devalue reward and to test for signs of inflexible drinking. One approach to devaluing alcohol is the addition of an unpleasant substance to change the flavor of alcohol by adding the bitter taste of quinine hydrochloride dihydrate or lithium chloride.[111] Female mice have been shown to be more resistant to devaluation by quinine than males, and this sex difference was not attributable to differences in sensitivity to quinine.[115] Nevertheless, sex differences in sensitivity to alcohol reward devaluation may be temperament- or species-specific, as male and female Long Evans rats reduce drinking levels to the same extent following alcohol devaluation.[114,116] In addition to alcohol adulteration, more sophisticated procedures derived from behavioral economics can be used to manipulate the value of the reward by changing the alcohol reinforcer magnitude, availability of alternative reinforcers, and delay discounting.[117,118]

Another approach used to test for inflexible drinking is to measure shock-resistant alcohol intake.[112,119] Rodent and human studies use these procedures to measure compulsive alcohol drinking despite negative consequences (e.g., foot shock or electric shock to the wrist, respectively). In rats, when one of eight alcohol-seeking responses are paired with foot shock, half of the alcohol-dependent male rats exhibit shock-resistant alcohol intake.[120] Male alcohol-preferring rats that received an intermittent foot shock in response to alcohol seeking separated behaviorally into three distinct subgroups: (1) compulsive rats that continued alcohol seeking despite punishment, (2) noncompulsive rats that diminished their alcohol-seeking responses, and (3) an intermediate group that only partially suppressed their alcohol-seeking behavior.[119] These two studies did not elucidate a sex difference as neither included female rats in the study design.[119,120] Heavy alcohol use in men and women is associated with risky and inflexible drinking, with men and women with AUD making more attempts to obtain aversion-paired rewards compared to individuals without AUD.[121,122] Furthermore, higher connectivity between the anterior insula and the nucleus accumbens is associated with increased compulsive-like behavior.[122]

Altogether, these studies suggest that inflexible drinking promotes heavy and continued use of alcohol and, consequently, may lead to further neuroadaptations in the brain. However, some of the devaluation strategies show limited evidence of sex differences. The inclusion of female subjects in these studies to directly compare the effects is vital to evaluate the role of sex in compulsive-like drinking under these different paradigms.

Chronic Alcohol Use and Corticolimbic Circuitry

Deficits in executive function can result from early-onset drinking or chronic heavy use, and this may lead to a higher chance of relapse following abstinence.[123] Some of these effects may be due to alterations in connectivity between prefrontal cortices and subcortical structures that are involved in reward processing.[5,124] The medial prefrontal cortex, anterior insula, and striatum are more active and have stronger connections in men and women with AUD compared to controls.[125] This could result in more subcortical control over decision-making processes based on reward reactivity rather than executive control.[125]

With long-term abstinence in both men and women, there is increased resting-state connectivity to brain regions that control executive function and decreased connectivity within reward processing regions.[126] Connectivity between the nucleus accumbens and the orbitofrontal cortex has been observed to be stronger in individuals with a familial history of AUD compared to individuals without this predisposition.[127] These studies suggest that chronic

exposure to alcohol leads to reduced function of the prefrontal cortex, which, when combined with a stronger influence of striatal control over decision-making, can increase the risk of relapse.[125,127]

Animal studies have advanced our understanding of neural connectivity at the axonal and microstructural level, giving insight into the mechanisms by which prefrontal function improves across development and can be impaired after alcohol exposure. During adolescent development in rats, prefrontal axons undergo robust increases in myelin ensheathment, which corresponds with a twofold increase in neuronal transmission speed.[128] Binge drinking during adolescence is also associated with altered neurodevelopmental trajectories including poor frontal white matter integrity in adolescent boys and girls.[129,130]

Longitudinal studies show that white matter growth is attenuated in the frontal lobes in humans who started drinking during adolescence—an effect that was comparable in both sexes.[131,132] The abnormal microstructural development of white matter in the frontostriatal region relates to binge drinking during adolescence and poorer cognitive function.[133,134] Likewise, animal studies show that voluntary alcohol exposure during adolescence decreases the density of myelinated axons in the anterior cingulate subregion of the medial prefrontal cortex, with higher adolescent drinking levels predicting lower working memory performance later in adulthood.[30] Reduced myelin density was not observed in female rats after adolescent binge drinking,[31] which corresponds with another study in mice showing that high doses of alcohol reduce myelin genes to a lesser extent in adolescent females compared to males.[135]

Despite more robust effects in males, examination of myelinated axons at the microstructural level shows that alcohol alters the nodal domain in both male and female rats.[31] The nodes of Ranvier are the ion channel–rich gaps between myelin sheaths on the prefrontal axons, and reduced length-to-width nodal ratios were detected in male and female rats following adolescent binge drinking.[31] In males, the decrease in nodal ratio was due to an increase in nodal diameter after the exposure, whereas in females it was due to a decrease in the nodal length. In both cases, these microstructural alterations have potential to negatively impact the speed and integrity of neural transmission, which is essential for effective communication within and between cortical and subcortical structures.[31] Altogether these studies show alcohol affects cortical circuits that are important for executive functioning and behavioral control, and does so to a greater extent in males than in females.

Administration of extreme binge-like doses of alcohol damages the hippocampus and prefrontal cortex, and impairs memory in rats.[136-138] While damage within the prefrontal cortex was similar in both sexes[138] the severe damage to the dentate gyrus of the hippocampus was greater in females compared to males.[136] The dentate gyrus is a subregion of the hippocampus where new granule neurons are normally produced for the formation of new memories; however, alcohol impairs cell proliferation and reduces the number of granule neurons in this region and does so to a greater extent in females.[136] This damage is associated with a reduction of trophic support molecules and the heightened vulnerability in female rats appears to be due to more robust downregulation of BDNF, insulin-like growth factor 1 (IGF-1), and cyclic adenosine monophosphate (AMP) response element-binding protein (CREB) signaling cascades.[136] These results are consistent with human studies in which the hippocampus was shown to be particularly vulnerable to the effects of alcohol binge drinking.[124,139] Self-administration studies in rodents suggest that even much lower levels of alcohol (low-binge) can decrease neurogenesis and hippocampal size,[140] with reports of alcohol drinking reducing neurogenesis to a greater extent in females compared to males[141] or similarly in both sexes.[142] Hippocampal damage after alcohol drinking in rodents corresponds with significant cognitive and memory dysfunction, especially when the alcohol exposure occurs during adolescence.[26,137,143] Thus, early-onset drinking and chronic heavy alcohol use may eventually lead to sustained hippocampal damage

to a greater extent in female rodents, which in conjunction with prefrontal dysfunction, could interfere with the ability to regulate reactivity to stress and alcohol-related cues that promote craving and relapse.

CONCLUSIONS AND CLINICAL IMPLICATIONS

The preclinical and clinical studies outlined in the current review show sex differences in behavioral risk factors and neural systems implicated in AUD, as summarized in Table 1 and Figure 1. This approach of incorporating sex differences in research studies has enhanced understanding of the complex mechanisms driving alcohol-related behaviors that lead to AUD. An increasing body of evidence shows sex differences in factors contributing to AUD vulnerability during the onset of alcohol drinking and later in the development of severe AUD and relapse following abstinence (see Table 1 for details).

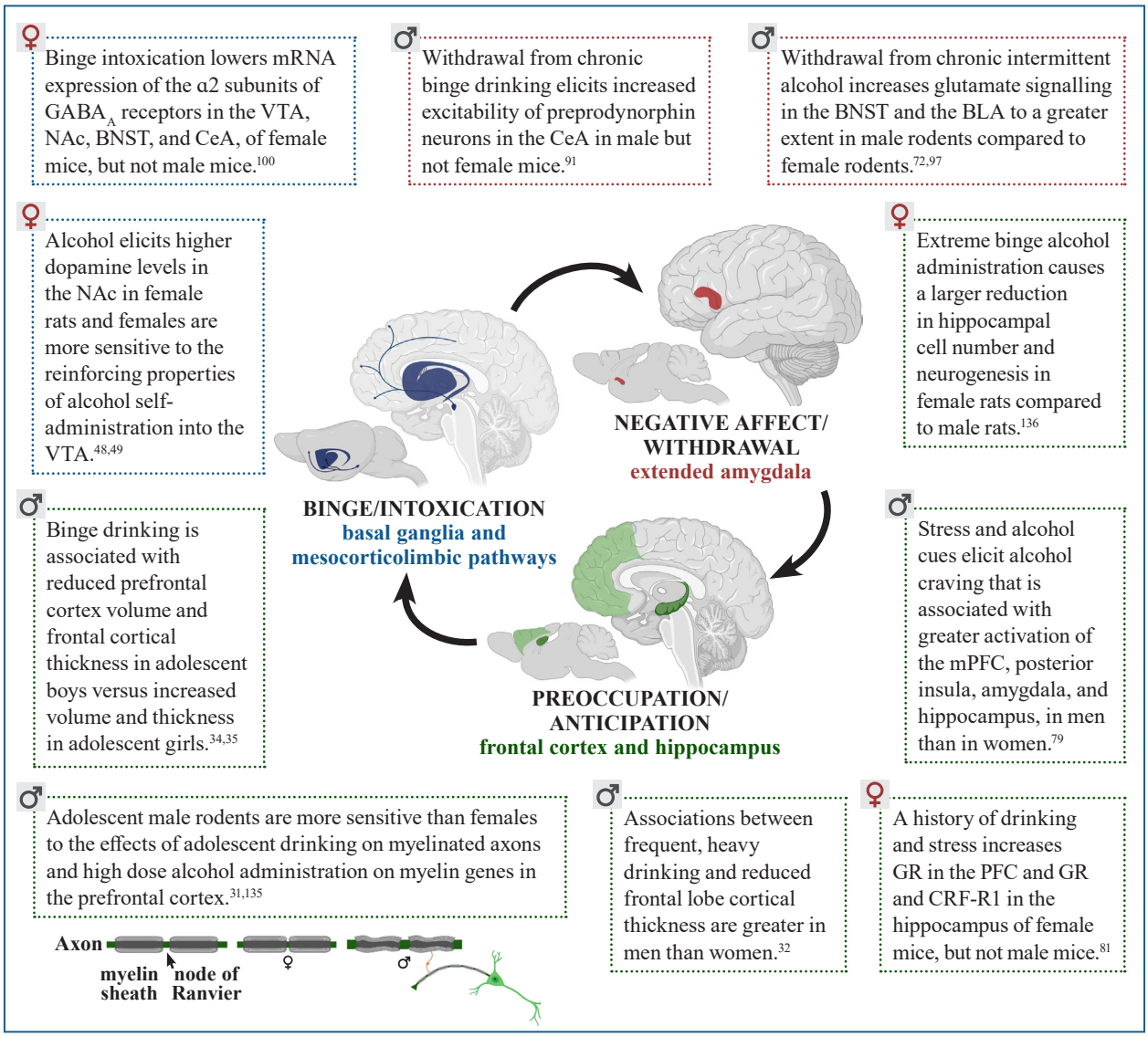

Figure 1 Sex differences in the effects of alcohol on the interacting brain systems associated with the three stages of addiction. *Note:* BLA, basolateral amygdala; BNST, bed nucleus of the stria terminalis; CeA, central amygdala; CRF-R1, corticotropin-releasing factor receptor 1; GABA$_A$ receptors, gamma-aminobutyric acid type A receptors; GR, glucocorticoid receptors; mPFC, medial prefrontal cortex; mRNA, messenger RNA; NAc, nucleus accumbens; PFC, prefrontal cortex; VTA, ventral tegmental area. Created with BioRender.

Table 1 Sex Differences in Behaviors Associated With the Three Stages of Addiction

Binge/Intoxication	
Risk factors that promote early-onset drinking	Impulsivity, a risk factor for adolescent drinking, is higher in adolescent boys compared to girls.[19]
	Drinking to alleviate psychological distress is higher in adolescent girls compared to boys.[23]
Alcohol drinking behavior	Prevalence of binge drinking is higher in adolescent boys compared to girls.[15]
	Appetitive approach in response to a dipper presentation is greater in female rats than male rats.[39]
	Acute alcohol injection increases preference to a large/uncertain reward (a measure of risk-taking behavior) in males, with no preference shown in females.[21]
Withdrawal/Negative Affect	
Alcohol drinking behavior	Restraint stress increases drinking in adolescent female rats, but decreases drinking in adolescent male rats.[92]
	A prior history of adolescent binge drinking augments drinking levels later in adulthood in female mice, but not in male mice.[81]
	Female mice drink more alcohol under baseline conditions in adulthood, but a history of binge drinking and chronic unpredictable stress or predator odor can elevate drinking in male mice to the level of females.[81]
Effects of alcohol withdrawal on negative affect	Adolescent girls report more negative mood states following recent heavy episodic drinking than do adolescent boys.[23]
	A history of adolescent binge drinking elicits active coping responses to stress in female mice vs. passive coping responses to stress in male mice (indexed by less time vs. more time immobile in the forced swim test).[95,96]
	Frequency of ultrasonic vocalizations, a measure of anxiety-like behavior, is increased following withdrawal from chronic intermittent alcohol vapors in male rats, but not females.[69-71]
Preoccupation/Anticipation	
Alcohol drinking behavior	Men exhibit higher levels of alcohol craving in response to cues than women do.[106]
	Women increased work effort in a progressive ratio trial following resumption after 2 weeks of abstinence. Men showed a decrease in effort.[113]
	Relapse-like behavior in response to alcohol availability is higher in male rats compared to female rats.[108]
	Female mice have a higher degree of aversion-resistant drinking than male mice.[115]

Adolescent drinking in the context of stress, negative affect, and increased cue-reactivity is greater in females. Males show vulnerability with regard to higher levels of impulsivity and, compared to females, they are less sensitive to the aversive effects of intoxication, making males less likely to stop drinking. Sex also was found to be a predictor of the negative impact that chronic alcohol use has on the brain (see Figure 1 for details). Males show more severe reductions in cortical thickness and reduced myelinated fiber density in the prefrontal cortex, whereas females show more robust decreases in neurogenesis in the hippocampus in response to alcohol. Sex can specifically influence the effects of alcohol in the brain in the context of intoxication, withdrawal, and cravings, leading to a robust vulnerability to AUD. Overall, these findings show that sex differences in humans and animal models of AUD are also dependent on the unique physiological characteristics of the stages of addiction. Effects of alcohol can be mediated by sex in different directions, by increasing or decreasing vulnerability to AUD depending on

the specific factor being considered. This complex shifting of vulnerability mediated by sex calls for a comprehensive approach toward studying AUD and other addictions.

A number of other health consequences endured after chronic heavy alcohol use are greater in women compared to men. Women with AUD experience higher risks of developing cancers, alcohol-related liver injury, and cardiovascular disease compared to men with AUD despite comparable levels of drinking.[7,25,144-150] Specifically, binge drinking shows an increase of mortality, including cancer-related mortality, and people with AUD have a threefold increase of death and a higher risk of digestive diseases, dementia, cancer, and liver disease. Women with AUD show higher risk of liver disease-related mortality, with 71% of mortality in women compared to 64% in men.[146] Sex differences in the effects of alcohol drinking may be explained in part by the role of gonadal steroid hormones in modulating a variety of functions in the brain. These functions include regulation of hypothalamus-driven social behavior;[151] cognition, memory, and learning driven by the hippocampus and the prefrontal cortex;[152] amygdala-mediated stress responses;[25,153] dopamine-mediated reward;[51] and synaptic plasticity.[154] Moreover, alcohol binge drinking in women can dysregulate the menstrual cycle,[155] which can affect endogenous steroid hormone levels.[156-159]

New diagnostic neuroimaging approaches are being explored to improve the assessment of AUD severity and circumvent limitations of the more traditional methods such as the Alcohol Use Disorders Identification Test (AUDIT) self-report questionnaire. A metabiological study recently reported that resting state connectivity functional magnetic imaging can be useful for assessing AUD.[160] Specifically, differential functional connectivity between the prefrontal cortex and the reward-related areas predicted the severity of AUD with accuracy that surpassed other functional magnetic resonance imaging, structural magnetic resonance imaging, combined magnetic resonance imaging features, or demographic features. The usefulness of these new diagnostic approaches exemplifies the great urgency for more inclusion of female subjects in preclinical AUD studies in humans and animal models. With heightened attention to detail in experimental design and increased consideration of sex/gender differences in interpretation of research findings, we can enhance our understanding of the neurobiological mechanisms underlying AUD to improve diagnosis and treatment in the future.

Acknowledgments

The authors thank Dr. Said Akli, Lynn Bengston, Andrea Silva-Gotay, and Barbara de Oliveira for their valuable assistance in the critical reading of this manuscript. Funding that made this review possible comes from the National Institute on Alcohol Abuse and Alcoholism grant R01AA024774 to Dr. Heather N. Richardson and the National Institutes of Health Postbaccalaureate Research Education Program grant NIH R25GM08624 that funded the participation of Annabelle Flores-Bonilla in the program.

Financial Disclosures

The authors declare no competing financial interests.

References

1. Alcohol-Related Emergency Department Visits and Hospitalizations and Their Co-Occurring Drug-Related, Mental Health, and Injury Conditions in the United States: Findings From the 2006-2010 Nationwide Emergency Department Sample (NEDS) and Nationwide Inpatient Sample (NIS). *Alcohol Epidemiologic Data Reference Manual,* Volume 9, September 2013, NIH Publication No. 13-8000. https://pubs.niaaa.nih.gov/publications/manual.htm.
2. Grant BF, Goldstein RB, Saha TD, et al. Epidemiology of DSM-5 alcohol use disorder results from the National Epidemiologic Survey on Alcohol and Related Conditions III. *JAMA Psychiatry*. 2015;72(8):757-766. https://doi.org/10.1001/jamapsychiatry.2015.0584.
3. American Psychiatric Association (APA). *Diagnostic and Statistical Manual of Mental Disorders.* 5th ed. Washington, DC: APA; 2013. https://doi.org/10.1176/appi.books.9780890425596.
4. Volkow ND, Koob GF, McLellan AT. Neurobiologic advances from the brain disease model of addiction. *N Engl J Med*. 2016;374(4):363-371. https://doi.org/10.1056/NEJMra1511480.

5. Becker JB, Perry AN, Westenbroek C. Sex differences in the neural mechanisms mediating addiction: A new synthesis and hypothesis. *Biol Sex Differ*. 2012;3(1):1-35. https://doi.org/10.1186/2042-6410-3-14.
6. Grant BF, Chou SP, Saha TD, et al. Prevalence of 12-month alcohol use, high-risk drinking, and DSM-IV alcohol use disorder in the United States, 2001-2002 to 2012-2013. Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *JAMA Psychiatry.* 2017;74(9):911-923. https://doi.org/10.1001/jamapsychiatry.2017.2161.
7. White AJ, DeRoo LA, Weinberg CR, et al. Lifetime alcohol intake, binge drinking behaviors, and breast cancer risk. *Am J Epidemiol*. 2017;186(5):541-549. https://doi.org/10.1093/aje/kwx118.
8. June HL, Gilpin NW. Operant self-administration models for testing the neuropharmacological basis of ethanol consumption in rats. *Curr Protoc Neurosci*. 2010;50(1):9.12.1-9.12.26. https://doi.org/10.1002/0471142301.ns0912s51.
9. Lu YL, Richardson HN. Alcohol, stress hormones, and the prefrontal cortex: A proposed pathway to the dark side of addiction. *Neuroscience*. 2014;277:139-151. https://doi.org/10.1016/j.neuroscience.2014.06.053.
10. Becker JB, Koob GF. Sex differences in animal models: Focus on addiction. *Pharmacol Rev.* 2016;68(2):242-263. https://doi.org/10.1124/pr.115.011163.
11. Becker HC. Animal models of alcohol withdrawal. *Alcohol Res Health.* 2000; 24(2):105-113.
12. Hilderbrand ER, Lasek AW. Studying sex differences in animal models of addiction: An emphasis on alcohol-related behaviors. *ACS Chem Neurosci*. 2018;9(8):1907-1916. https://doi.org/10.1021/acschemneuro.7b00449.
13. National Institute on Alcohol Abuse and Alcoholism (NIAAA). NIAAA Council approves definition of binge drinking. *NIAAA Newsletter.* 2004;3:3. https://pubs.niaaa.nih.gov/publications/Newsletter/winter2004/Newsletter_Number3.pdf.
14. Substance Abuse and Mental Health Services Administration (SAMHSA). *2018 National Survey on Drug Use and Health: Methodological Summary and Definitions.* Rockville, MD: Center for Behavioral Health Statistics and Quality, SAMHSA; 2019. Retrieved from https://www.samhsa.gov/data/.
15. SAMHSA. *Results from the 2014 National Survey on Drug Use and Health (NSDUH): Detailed Tables.* Table 2.46B — Alcohol Use, Binge Alcohol Use, and Heavy Alcohol Use in the Past Month among Persons Aged 18 or Older, by Demographic Characteristics: Percentages, 2013 and 2014 and Table 2.79B – Alcohol Use, Binge Alcohol Use, and Heavy Alcohol Use in the Past Month among Persons Aged 12 to 20, by Demographic Characteristics: Percentages, 2013 and 2014. Rockville, MD: Center for Behavioral Health Statistics and Quality, SAMHSA; 2015. Retrieved from https://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs2014/NSDUH-DetTabs2014.htm.
16. SAMHSA. *Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings*. NSDUH Series H-46, HHS Publication No. (SMA) 13-4795. Rockville, MD: SAMHSA, 2013. Retrieved from https://www.samhsa.gov/data/sites/default/files/NSDUHresults2012/NSDUHresults2012.pdf.
17. Kuntsche E, Müller S. Why do young people start drinking? Motives for first-time alcohol consumption and links to risky drinking in early adolescence. *Eur Addict Res*. 2012;18(1):34-39. https://doi.org/10.1159/000333036.
18. Chou SP, Pickering RP. Early-onset of drinking as a risk factor for lifetime alcohol-related problems. *Br J Addict*. 1992;87(8):1199-1204. https://doi.org/10.1111/j.1360-0443.1992.tb02008.x.
19. Navas JF, Martín-Pérez C, Petrova D, et al. Sex differences in the association between impulsivity and driving under the influence of alcohol in young adults: The specific role of sensation seeking. *Accid Anal Prev*. 2019;124:174-179. https://doi.org/10.1016/j.aap.2018.12.024.
20. Friedl A, Pondorfer A, Schmidt U. Gender differences in social risk taking. *J Econ Psychol*. 2020;77:1-17. https://doi.org/10.1016/j.joep.2019.06.005.
21. Wallin-Miller KG, Chesley J, Castrillon J, et al. Sex differences and hormonal modulation of ethanol-enhanced risk taking in rats. *Drug Alcohol Depend*. 2017;174:137-144. https://doi.org/10.1016/j.drugalcdep.2017.01.023.
22. Morales-Mulia M. Intra-accumbal orexin-1 receptor inhibition prevents the anxiolytic-like effect of ethanol and leads to increases in orexin-A content and receptor expression. *Pharmacol Biochem Behav*. 2019;185. https://doi.org/10.1016/j.pbb.2019.172761.
23. Bekman NM, Winward JL, Lau LL, et al. The impact of adolescent binge drinking and sustained abstinence on affective state. *Alcohol Clin Exp Res*. 2013;37(8):1432-1439. https://doi.org/10.1111/acer.12096.
24. Tanchuck-Nipper MA, Ford MM, Hertzberg A, et al. Sex differences in ethanol's anxiolytic effect and chronic ethanol withdrawal severity in mice with a null mutation of the 5α-reductase type 1 gene. *Behav Genet*. 2015;45(3):354-367. https://doi.org/10.1007/s10519-014-9691-5.
25. Peltier MR, Verplaetse TL, Mineur YS, et al. Sex differences in stress-related alcohol use. *Neurobiol Stress*. 2019;10:100149. https://doi.org/10.1016/j.ynstr.2019.100149.
26. Younis RM, Wolstenholme JT, Bagdas D, et al. Adolescent but not adult ethanol binge drinking modulates ethanol behavioral effects in mice later in life. *Pharmacol Biochem Behav*. 2019;184. https://doi.org/10.1016/j.pbb.2019.172740.
27. Seamans JK, Floresco SB, Phillips AG. Functional differences between the prelimbic and anterior cingulate regions of the rat prefrontal cortex. *Behav Neurosci*. 1995;109(6):1063-1073. https://doi.org/10.1037//0735-7044.109.6.1063.
28. Kaping D, Vinck M, Hutchison RM, et al. Specific contributions of ventromedial, anterior cingulate, and lateral prefrontal cortex for attentional selection and stimulus valuation. *PLoS Biol*. 2011;9(12). https://doi.org/10.1371/journal.pbio.1001224.
29. Stephens DN, Duka T. Cognitive and emotional consequences of binge drinking: Role of amygdala and prefrontal cortex. *Philos Trans R Soc Lond B Biol Sci*. 2008;363(1507):3169-3179. https://doi.org/10.1098/rstb.2008.0097.
30. Vargas WM, Bengston L, Gilpin NW, et al. Alcohol binge drinking during adolescence or dependence during adulthood reduces prefrontal myelin in male rats. *J Neurosci*. 2014;34(44):14777-14782. https://doi.org/10.1523/jneurosci.3189-13.2014.
31. Tavares ER, Silva-Gotay A, Riad WV, et al. Sex differences in the effect of alcohol drinking on myelinated axons in the anterior cingulate cortex of adolescent rats. *Brain Sci*. 2019;9(7):167. https://doi.org/10.3390/brainsci9070167.
32. Morris VL, Owens MM, Syan SK, et al. Associations between drinking and cortical thickness in younger adult drinkers: Findings from the Human Connectome Project. *Alcohol Clin Exp Res*. 2019;43(9):1918-1927. https://doi.org/10.1111/acer.14147.
33. Pfefferbaum A, Rohlfing T, Pohl KM, et al. Adolescent development of cortical and white matter structure in the NCANDA sample: Role of sex, ethnicity, puberty, and alcohol drinking. *Cereb Cortex*. 2016;26(10):4101-4121. https://doi.org/10.1093/cercor/bhv205.

34. Squeglia LM, Sorg SF, Schweinsburg AD, et al. Binge drinking differentially affects adolescent male and female brain morphometry. *Psychopharmacology (Berl)*. 2012;220(3):529-539. https://doi.org/10.1007/s00213-011-2500-4.
35. Kvamme TL, Schmidt C, Strelchuk D, et al. Sexually dimorphic brain volume interaction in college-aged binge drinkers. *Neuroimage Clin*. 2015;10:310-317. https://doi.org/10.1016/j.nicl.2015.12.004.
36. Henderson KE, Vaidya JG, Kramer JR, et al. Cortical thickness in adolescents with a family history of alcohol use disorder. *Alcohol Clin Exp Res.* 2018;42(1):89-99. https://doi.org/10.1111/acer.13543.
37. Berridge KC, Robinson TE. Parsing reward. *Trends Neurosci*. 2003;26(9):507-513. https://doi.org/10.1016/S0166-2236(03)00233-9.
38. Samson HH, Slawecki CJ, Sharpe AL, et al. Appetitive and consummatory behaviors in the control of ethanol consumption: A measure of ethanol seeking behavior. *Alcohol Clin Exp Res*. 1998;22(8):1783-1787.
39. Nieto SJ, Kosten TA. Female Sprague-Dawley rats display greater appetitive and consummatory responses to alcohol. *Behav Brain Res*. 2017;327:155-161. https://doi.org/10.1016/j.bbr.2017.03.037.
40. Lancaster FE, Spiegel KS. Sex differences in pattern of drinking. *Alcohol.* 1992;9(5):415-420. https://doi.org/10.1016/0741-8329(92)90041-8.
41. Crabbe JC, Metten P, Rhodes JS, et al. A line of mice selected for high blood ethanol concentrations shows drinking in the dark to intoxication. *Biol Psychiatry*. 2009;65(8):662-670. https://doi.org/10.1016/j.biopsych.2008.11.002.
42. Cofresí RU, Monfils MH, Chaudhri N, et al. Cue-alcohol associative learning in female rats. *Alcohol*. 2019;81:1-9. https://doi.org/10.1016/j.alcohol.2019.03.003.
43. Diana M, Rossetti ZL, Gessa G. Rewarding and aversive effects of ethanol: Interplay of GABA, glutamate and dopamine. *Alcohol Alcohol Suppl.* 1993;2:315-319.
44. Berridge KC, Robinson TE, Aldridge JW. Dissecting components of reward: 'Liking', 'wanting', and learning. *Curr Opin Pharmacol*. 2009;9(1):65-73. https://doi.org/10.1016/j.coph.2008.12.014.
45. Mason BJ. Emerging pharmacotherapies for alcohol use disorder. *Neuropharmacology*. 2017;122:244-253. https://doi.org/10.1016/j.neuropharm.2017.04.032.
46. Karkhanis AN, Huggins KN, Rose JH, et al. Switch from excitatory to inhibitory actions of ethanol on dopamine levels after chronic exposure: Role of kappa opioid receptors. *Neuropharmacology*. 2016;110(Pt A):190-197. https://doi.org/10.1016/j.neuropharm.2016.07.022.
47. Blaine SK, Sinha R. Alcohol, stress, and glucocorticoids: From risk to dependence and relapse in alcohol use disorders. *Neuropharmacology*. 2017;122:136-147. https://doi.org/10.1016/j.neuropharm.2017.01.037.
48. Hauser SR, Knight CP, Truitt WA, et al. Adolescent intermittent ethanol increases the sensitivity to the reinforcing properties of ethanol and the expression of select cholinergic and dopaminergic genes within the posterior ventral tegmental area. *Alcohol Clin Exp Res*. 2019;43(9):1937-1948. https://doi.org/10.1111/acer.14150.
49. Blanchard BA, Glick SD. Sex differences in mesolimbic dopamine responses to ethanol and relationship to ethanol intake in rats. *Recent Dev Alcohol*. 1995;12:231-241. https://doi.org/10.1007/0-306-47138-8_15.
50. Kegeles LS, Horga G, Ghazzaoui R, et al. Enhanced striatal dopamine release to expectation of alcohol: A potential risk factor for alcohol use disorder. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2018;3(7):591-598. https://doi.org/10.1016/j.bpsc.2018.03.018.
51. Vandegrift BJ, You C, Satta R, et al. Estradiol increases the sensitivity of ventral tegmental area dopamine neurons to dopamine and ethanol. *PLoS One*. 2017;12(11):1-18. https://doi.org/10.1371/journal.pone.0187698.
52. Nimitvilai S, Lopez MF, Woodward JJ. Effects of monoamines on the intrinsic excitability of lateral orbitofrontal cortex neurons in alcohol-dependent and non-dependent female mice. *Neuropharmacology*. 2018;137:1-12. https://doi.org/10.1016/j.neuropharm.2018.04.019.
53. Hilderbrand ER, Lasek AW. Estradiol enhances ethanol reward in female mice through activation of ERα and ERβ. *Horm Behav*. 2018;98:159-164. https://doi.org/10.1016/j.yhbeh.2018.01.001.
54. Dazzi L, Serra M, Seu E, et al. Progesterone enhances ethanol-induced modulation of mesocortical dopamine neurons: Antagonism by finasteride. *J Neurochem*. 2002;83(5):1103-1109. https://doi.org/10.1046/j.1471-4159.2002.01218.x.
55. Morrow AL, VanDoren MJ, Penland SN, et al. The role of GABAergic neuroactive steroids in ethanol action, tolerance and dependence. *Brain Res Rev*. 2001;37(1-3):98-109. https://doi.org/10.1016/s0165-0173(01)00127-8.
56. Dozier BL, Stull CA, Baker EJ, et al. Chronic ethanol drinking increases during the luteal menstrual cycle phase in rhesus monkeys: Implication of progesterone and related neurosteroids. *Psychopharmacology (Berl)*. 2019;236(6):1817-1828. https://doi.org/10.1007/s00213-019-5168-9.
57. Chung T, Creswell KG, Bachrach R, et al. Adolescent binge drinking. *Alcohol Res*. 2018;39(1):5-15.
58. Glover EJ, McDougle MJ, Siegel GS, et al. Role for the rostromedial tegmental nucleus in signaling the aversive properties of alcohol. *Alcohol Clin Exp Res*. 2016;40(8):1651-1661. https://doi.org/10.1111/acer.13140.
59. Morales M, Schatz KC, Anderson RI, et al. Conditioned taste aversion to ethanol in a social context: Impact of age and sex. *Behav Brain Res*. 2014;261:323-327. https://doi.org/10.1016/j.bbr.2013.12.048.
60. Spear LP. Adolescent neurodevelopment. *J Adolesc Health*. 2013;52(2 Suppl 2):S7-S13. https://doi.org/10.1016/j.jadohealth.2012.05.006.
61. Spear LP. Adolescents and alcohol: Acute sensitivities, enhanced intake, and later consequences. *Neurotoxicol Teratol*. 2014;41:51-59. https://doi.org/10.1016/j.ntt.2013.11.006.
62. Koob GF. Alcoholism: Allostasis and beyond. *Alcohol Clin Exp Res.* 2003;27(2):232-243. https://doi.org/10.1097/01.alc.0000057122.36127.c2.
63. Becker HC. Alcohol dependence, withdrawal, and relapse. *Alcohol Res Health*. 2008;31(4):348-361.
64. Koob GF, Volkow ND. Neurobiology of addiction: A neurocircuitry analysis. *Lancet Psychiatry*. 2016;3(8):760-773. https://doi.org/10.1016/s2215-0366(16)00104-8.
65. George O, Koob G, Vendruscolo L. Negative reinforcement via motivational withdrawal is the driving force behind the transition to addiction. *Psychopharmacology.* 2014;231(19): 3911-3917.
66. Koob GF. Addiction is a reward deficit and stress surfeit disorder. *Front Psychiatry*. 2013;4:72. https://doi.org/10.3389/fpsyt.2013.00072.

67. Pombo S, Luísa Figueira M, Walter H, et al. Motivational factors and negative affectivity as predictors of alcohol craving. *Psychiatry Res*. 2016;243:53-60. https://doi.org/10.1016/j.psychres.2016.02.064.
68. Sinha R, Fox HC, Hong KA, et al. Enhanced negative emotion and alcohol craving, and altered physiological responses following stress and cue exposure in alcohol dependent individuals. *Neuropsychopharmacology*. 2009;34(5):1198-1208. https://doi.org/10.1038/npp.2008.78.
69. Knapp DJ, Duncan GE, Crews FT, et al. Induction of Fos-like proteins and ultrasonic vocalizations during ethanol withdrawal: Further evidence for withdrawal-induced anxiety. *Alcohol Clin Exp Res*. 1998;22(2):481-493.
70. Williams AM, Reis DJ, Powell AS, et al. The effect of intermittent alcohol vapor or pulsatile heroin on somatic and negative affective indices during spontaneous withdrawal in Wistar rats. *Psychopharmacology (Berl)*. 2012;223(1):75-88. https://doi.org/10.1007/s00213-012-2691-3.
71. Henricks AM, Berger AL, Lugo JM, et al. Sex- and hormone-dependent alterations in alcohol withdrawal-induced anxiety and corticolimbic endocannabinoid signaling. *Neuropharmacology*. 2017;124:121-133. https://doi.org/10.1016/j.neuropharm.2017.05.023.
72. Morales M, McGinnis MM, McCool BA. Chronic ethanol exposure increases voluntary home cage intake in adult male, but not female, Long-Evans rats. *Pharmacol Biochem Behav*. 2015;139:67-76. https://doi.org/10.1016/j.pbb.2015.10.016.
73. Morales M, McGinnis MM, Robinson SL, et al. Chronic intermittent ethanol exposure modulation of glutamatergic neurotransmission in rat lateral/basolateral amygdala is duration-, input-, and sex-dependent. *Neuroscience*. 2018;371:277-287. https://doi.org/10.1016/j.neuroscience.2017.12.005.
74. Jury NJ, DiBerto JF, Kash TL, et al. Sex differences in the behavioral sequelae of chronic ethanol exposure. *Alcohol*. 2017;58:53-60. https://doi.org/10.1016/j.alcohol.2016.07.007.
75. Crowley NA, Magee SN, Feng M, et al. Ketamine normalizes binge drinking-induced defects in glutamatergic synaptic transmission and ethanol drinking behavior in female but not male mice. *Neuropharmacology*. 2019;149:35-44. https://doi.org/10.1016/j.neuropharm.2019.02.003.
76. Kasten CR, Carzoli KL, Sharfman NM, et al. Adolescent alcohol exposure produces sex differences in negative affect-like behavior and group I mGluR BNST plasticity. *Neuropsychopharmacology*. 2020;45(8):1306-1315. https://doi.org/10.1038/s41386-020-0670-7.
77. Hermann D, Weber-Fahr W, Sartorius A, et al. Translational magnetic resonance spectroscopy reveals excessive central glutamate levels during alcohol withdrawal in humans and rats. *Biol Psychiatry*. 2012;71(11):1015-1021. https://doi.org/10.1016/j.biopsych.2011.07.034.
78. Anthenelli RM, Heffner JL, Blom TJ, et al. Sex differences in the ACTH and cortisol response to pharmacological probes are stressor-specific and occur regardless of alcohol dependence history. *Psychoneuroendocrinology*. 2018;94:72-82. https://doi.org/10.1016/j.psyneuen.2018.05.007.
79. Seo D, Jia Z, Lacadie CM, et al. Sex differences in neural responses to stress and alcohol context cues. *Hum Brain Mapp*. 2011;32(11):1998-2013. https://doi.org/10.1002/hbm.21165.
80. Cozzoli DK, Tanchuck-Nipper MA, Kaufman MN, et al. Environmental stressors influence limited-access ethanol consumption by C57BL/6J mice in a sex-dependent manner. *Alcohol*. 2014;48(8):741-754. https://doi.org/10.1016/j.alcohol.2014.07.015.
81. Finn DA, Helms ML, Nipper MA, et al. Sex differences in the synergistic effect of prior binge drinking and traumatic stress on subsequent ethanol intake and neurochemical responses in adult C57BL/6J mice. *Alcohol*. 2018;71:33-45. https://doi.org/10.1016/j.alcohol.2018.02.004.
82. Kudielka BM, Kirschbaum C. Sex differences in HPA axis responses to stress: A review. *Biol Psychol*. 2005;69(1):113-132. https://doi.org/10.1016/j.biopsycho.2004.11.009.
83. Richardson HN, Zorrilla EP, Mandyam CD, et al. Exposure to repetitive versus varied stress during prenatal development generates two distinct anxiogenic and neuroendocrine profiles in adulthood. *Endocrinology*. 2006;147(5):2506-2517. https://doi.org/10.1210/en.2005-1054.
84. Richardson HN, Lee SY, O'Dell LE, et al. Alcohol self-administration acutely stimulates the hypothalamic-pituitary-adrenal axis, but alcohol dependence leads to a dampened neuroendocrine state. *Eur J Neurosci*. 2008;28(8):1641-1653. https://doi.org/10.1111/j.1460-9568.2008.06455.x.
85. Jimenez VA, Grant KA. Studies using macaque monkeys to address excessive alcohol drinking and stress interactions. *Neuropharmacology*. 2017;122:127-135. https://doi.org/10.1016/j.neuropharm.2017.03.027.
86. Nentwig TB, Wilson DE, Rhinehart EM, et al. Sex differences in binge-like EtOH drinking, corticotropin-releasing hormone and corticosterone: Effects of β-endorphin. *Addict Biol*. 2019;24(3):447-457. https://doi.org/10.1111/adb.12610.
87. Stephens MAC, Wand G. Stress and the HPA axis: Role of glucocorticoids in alcohol dependence. *Alcohol Res*. 2012;34(4):468-483.
88. Vendruscolo LF, Barbier E, Schlosburg JE, et al. Corticosteroid-dependent plasticity mediates compulsive alcohol drinking in rats. *J Neurosci*. 2012;32(22):7563-7571. https://doi.org/10.1523/jneurosci.0069-12.2012.
89. Marcinkiewcz CA, De La Rosa GB, Dorrier CE, et al. Sex-dependent modulation of anxiety and fear by 5-HT_{1A} receptors in the bed nucleus of the stria terminalis. *ACS Chem Neurosci*. 2019;10(7):3154-3166. https://doi.org/10.1021/acschemneuro.8b00594.
90. Torruella-Suárez ML, Vandenberg JR, Cogan ES, et al. Manipulations of central amygdala neurotensin neurons alter the consumption of ethanol and sweet fluids in mice. *J Neurosci*. 2020;40(3):632-647. https://doi.org/10.1523/jneurosci.1466-19.2019.
91. Bloodgood DW, Hardaway JA, Stanhope CM, et al. Kappa opioid receptor and dynorphin signaling in the central amygdala regulates alcohol intake. *Mol Psychiatry*. 2020. https://doi.org/10.1038/s41380-020-0690-z.
92. Wille-Bille A, Ferreyra A, Sciangula M, et al. Restraint stress enhances alcohol intake in adolescent female rats but reduces alcohol intake in adolescent male and adult female rats. *Behav Brain Res*. 2017;332:269-279. https://doi.org/10.1016/j.bbr.2017.06.004.
93. Quadir SG, Guzelian E, Palmer MA, et al. Complex interactions between the subject factors of biological sex and prior histories of binge-drinking and unpredictable stress influence behavioral sensitivity to alcohol and alcohol intake. *Physiol Behav*. 2019;203:100-112. https://doi.org/10.1016/j.physbeh.2017.08.002.
94. Yu W, Hwa LS, Makhijani VH, et al. Chronic inflammatory pain drives alcohol drinking in a sex-dependent manner for C57BL/6J mice. *Alcohol*. 2019;77:135-145. https://doi.org/10.1016/j.alcohol.2018.10.002.

95. Szumlinski KK, Coelho MA, Lee KM, et al. DID it or DIDn't it? Exploration of a failure to replicate binge-like alcohol-drinking in C57BL/6J mice. *Pharmacol Biochem Behav*. 2019;178:3-18. https://doi.org/10.1016/j.pbb.2018.12.002.
96. Lee KM, Coehlo MA, Solton NR, et al. Negative affect and excessive alcohol intake incubate during protracted withdrawal from binge-drinking in adolescent, but not adult, mice. *Front Psychol*. 2017;8:1128. https://doi.org/10.3389/fpsyg.2017.01128.
97. Carzoli KL, Sharfman NM, Lerner MR, et al. Regulation of NMDA receptor plasticity in the BNST following adolescent alcohol exposure. *Front Cell Neurosci*. 2019;13:440. https://doi.org/10.3389/fncel.2019.00440.
98. Rhinehart EM, Nentwig TB, Wilson DE, et al. Sex and β-endorphin influence the effects of ethanol on limbic *Gabra2* expression in a mouse binge drinking model. *Front Genet.* 2018;9:567. https://doi.org/10.3389/fgene.2018.00567.
99. Gilpin NW, Karanikas CA, Richardson HN. Adolescent binge drinking leads to changes in alcohol drinking, anxiety, and amygdalar corticotropin releasing factor cells in adulthood in male rats. *PLoS One*. 2012;7(2). https://doi.org/10.1371/journal.pone.0031466.
100. Logrip ML, Oleata C, Roberto M. Sex differences in responses of the basolateral-central amygdala circuit to alcohol, corticosterone and their interaction. *Neuropharmacology*. 2017;114:123-134. https://doi.org/10.1016/j.neuropharm.2016.11.021.
101. Siciliano CA, Karkhanis AN, Holleran KM, et al. Cross-species alterations in synaptic dopamine regulation after chronic alcohol exposure. *Handb Exp Pharmacol*. 2018;248:213-238. https://doi.org/10.1007/164_2018_106.
102. Breese GR, Sinha R, Heilig M. Chronic alcohol neuroadaptation and stress contribute to susceptibility for alcohol craving and relapse. *Pharmacol Ther*. 2011;129(2):149-171. https://doi.org/10.1016/j.pharmthera.2010.09.007.
103. Witkiewitz K, Falk DE, Litten RZ, et al. Maintenance of World Health Organization risk drinking level reductions and posttreatment functioning following a large alcohol use disorder clinical trial. *Alcohol Clin Exp Res*. 2019;43(5):979-987. https://doi.org/10.1111/acer.14018.
104. Berridge KC, Robinson TE. What is the role of dopamine in reward: Hedonic impact, reward learning, or incentive salience? *Brain Res Rev*. 1998;28(3):309-369. https://doi.org/10.1016/s0165-0173(98)00019-8.
105. Barker JM, Taylor JR. Sex differences in incentive motivation and the relationship to the development and maintenance of alcohol use disorders. *Physiol Behav*. 2019;203:91-99. https://doi.org/10.1016/j.physbeh.2017.09.027.
106. Wang W, Zhornitsky S, Le TM, et al. Cue-elicited craving, thalamic activity, and physiological arousal in adult non-dependent drinkers. *J Psychiatr Res*. 2019;116:74-82. https://doi.org/10.1016/j.jpsychires.2019.06.005.
107. Nall RW, Craig AR, Browning KO, et al. Longer treatment with alternative non-drug reinforcement fails to reduce resurgence of cocaine or alcohol seeking in rats. *Behav Brain Res*. 2018;341:54-62. https://doi.org/10.1016/j.bbr.2017.12.020.
108. Hogarth SJ, Jaehne EJ, van den Buuse M, et al. Brain-derived neurotrophic factor (BDNF) determines a sex difference in cue-conditioned alcohol seeking in rats. *Behav Brain Res*. 2018;339:73-78. https://doi.org/10.1016/j.bbr.2017.11.019.
109. Finegersh A, Homanics GE. Paternal alcohol exposure reduces alcohol drinking and increases behavioral sensitivity to alcohol selectively in male offspring. *PLoS One*. 2014;9(6). https://doi.org/10.1371/journal.pone.0099078.
110. Hill RA, van den Buuse M. Sex-dependent and region-specific changes in TrkB signaling in BDNF heterozygous mice. *Brain Res.* 2011;1384:51-60. https://doi.org/10.1016/j.brainres.2011.01.060.
111. Hopf FW, Lesscher HMB. Rodent models for compulsive alcohol intake. *Alcohol*. 2014;48(3):253-264. https://doi.org/10.1016/j.alcohol.2014.03.001.
112. Goltseker K, Hopf FW, Barak S. Advances in behavioral animal models of alcohol use disorder. *Alcohol*. 2019;74:73-82. https://doi.org/10.1016/j.alcohol.2018.05.014.
113. Plawecki MH, White K, Kosobud AEK, et al. Sex differences in motivation to self-administer alcohol after 2 weeks of abstinence in young-adult heavy drinkers. *Alcohol Clin Exp Res*. 2018;42(10):1897-1908. https://doi.org/10.1111/acer.13860.
114. Randall PA, Stewart RT, Besheer J. Sex differences in alcohol self-administration and relapse-like behavior in Long-Evans rats. *Pharmacol Biochem Behav*. 2017;156:1-9. https://doi.org/10.1016/j.pbb.2017.03.005.
115. Fulenwider HD, Nennig SE, Price ME, et al. Sex differences in aversion-resistant ethanol intake in mice. *Alcohol Alcohol*. 2019;54(4):345-352. https://doi.org/10.1093/alcalc/agz022.
116. Radke AK, Quinn JJ, Held IT, et al. Additive influences of acute early life stress and sex on vulnerability for aversion-resistant alcohol drinking. *Addict Biol*. 2019:e12829. https://doi.org/10.1111/adb.12829.
117. Mackillop J. The behavioral economics and neuroeconomics of alcohol use disorders. *Alcohol Clin Exp Res*. 2016;40(4):672-685. https://doi.org/10.1111/acer.13004.
118. Benson TA, Little CS, Henslee AM, et al. Effects of reinforcer magnitude and alternative reinforcer delay on preference for alcohol during a multiple-choice procedure. *Drug Alcohol Depend*. 2009;100(1-2):161-163. https://doi.org/10.1016/j.drugalcdep.2008.09.005.
119. Giuliano C, Peña-Oliver Y, Goodlett CR, et al. Evidence for a long-lasting compulsive alcohol seeking phenotype in rats. *Neuropsychopharmacology*. 2018;43(4):728-738. https://doi.org/10.1038/npp.2017.105.
120. Seif T, Chang S, Simms JA, et al. Cortical activation of accumbens hyperpolarization-active NMDARs mediates aversion-resistant alcohol intake. *Nat Neurosci*. 2013;16(8):1094-1100. https://doi.org/10.1038/nn.3445.
121. Rossiter S, Thompson J, Hester R. Improving control over the impulse for reward: Sensitivity of harmful alcohol drinkers to delayed reward but not immediate punishment. *Drug Alcohol Depend.* 2012;125(1-2):89-94. https://doi.org/10.1016/j.drugalcdep.2012.03.017.
122. Grodin EN, Sussman L, Sundby K, et al. Neural correlates of compulsive alcohol seeking in heavy drinkers. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2018;3(12):1022-1031. https://doi.org/10.1016/j.bpsc.2018.06.009.
123. Campbell E, Flannagan J, Walker L, et al. Anterior insular cortex is critical for the propensity to relapse following punishment-imposed abstinence of alcohol seeking. *J Neurosci.* 2019;39(6):1977-1087. https://doi.org/10.1523/JNEUROSCI.1596-18.2018.
124. Dir AL, Bell RL, Adams ZW, et al. Gender differences in risk factors for adolescent binge drinking and implications for intervention and prevention. *Front Psychiatry*. 2017;8:289. https://doi.org/10.3389/fpsyt.2017.00289.

125. Galandra C, Basso G, Manera M, et al. Abnormal fronto-striatal intrinsic connectivity reflects executive dysfunction in alcohol use disorders. *Cortex*. 2019;115:27-42. https://doi.org/10.1016/j.cortex.2019.01.004.
126. Camchong J, Stenger VA, Fein G. Resting-state synchrony in short-term versus long-term abstinent alcoholics. *Alcohol Clin Exp Res*. 2013;37(5):794-803. https://doi.org/10.1111/acer.12037.
127. Cservenka A, Casimo K, Fair DA, et al. Resting state functional connectivity of the nucleus accumbens in youth with a family history of alcoholism. *Psychiatry Res Neuroimaging*. 2014;221(3):210-219. https://doi.org/10.1016/j.pscychresns.2013.12.004.
128. McDougall S, Riad WV, Silva-Gotay A, et al. Myelination of axons corresponds with faster transmission speed in the prefrontal cortex of developing male rats. *eNeuro*. 2018;5(4). https://doi.org/10.1523/eneuro.0203-18.2018.
129. McQueeny T, Schweinsburg BC, Schweinsburg AD, et al. Altered white matter integrity in adolescent binge drinkers. *Alcohol Clin Exp Res*. 2009;33(7):1278-1285.
130. Pfefferbaum A, Kwon D, Brumback T, et al. Altered brain developmental trajectories in adolescents after initiating drinking. *Am J Psychiatry*. 2018;175(4):370-380. https://doi.org/10.1176/appi.ajp.2017.17040469.
131. Squeglia LM, Tapert SF, Sullivan EV, et al. Brain development in heavy-drinking adolescents. *Am J Psychiatry*. 2015;172(6):531-542. https://doi.org/10.1176/appi.ajp.2015.14101249.
132. Luciana M, Collins PF, Muetzel RL, et al. Effects of alcohol use initiation on brain structure in typically developing adolescents. *Am J Drug Alcohol Abuse*. 2013;39(6):345-355. https://doi.org/10.3109/00952990.2013.837057.
133. Jones SA, Nagel BJ. Altered frontostriatal white matter microstructure is associated with familial alcoholism and future binge drinking in adolescence. *Neuropsychopharmacology*. 2019;44(6):1076-1083. https://doi.org/10.1038/s41386-019-0315-x.
134. Bava S, Jacobus J, Thayer RE, et al. Longitudinal changes in white matter integrity among adolescent substance users. *Alcohol Clin Exp Res*. 2013;37(Suppl.1):E181-E189. https://doi.org/10.1111/j.1530-0277.2012.01920.x.
135. Wolstenholme JT, Mahmood T, Harris GM, et al. Intermittent ethanol during adolescence leads to lasting behavioral changes in adulthood and alters gene expression and histone methylation in the PFC. *Front Mol Neurosci*. 2017;10:307. https://doi.org/10.3389/fnmol.2017.00307.
136. Maynard ME, Barton EA, Robinson CR, et al. Sex differences in hippocampal damage, cognitive impairment, and trophic factor expression in an animal model of an alcohol use disorder. *Brain Struct Funct*. 2018;223(1):195-210. https://doi.org/10.1007/s00429-017-1482-3.
137. Vetreno RP, Crews FT. Binge ethanol exposure during adolescence leads to a persistent loss of neurogenesis in the dorsal and ventral hippocampus that is associated with impaired adult cognitive functioning. *Front Neurosci*. 2015;9:35. https://doi.org/10.3389/fnins.2015.00035.
138. West RK, Maynard ME, Leasure JL. Binge ethanol effects on prefrontal cortex neurons, spatial working memory and task-induced neuronal activation in male and female rats. *Physiol Behav.* 2018;188:79-85. https://doi.org/10.1016/j.physbeh.2018.01.027.
139. McClintick JN, McBride WJ, Bell RL, et al. Gene expression changes in the ventral hippocampus and medial prefrontal cortex of adolescent alcohol-preferring (P) rats following binge-like alcohol drinking. *Alcohol*. 2018;68:37-47. https://doi.org/10.1016/j.alcohol.2017.09.002.
140. Richardson HN, Chan SH, Crawford EF, et al. Permanent impairment of birth and survival of cortical and hippocampal proliferating cells following excessive drinking during alcohol dependence. *Neurobiol Dis*. 2009;36(1):1-10. https://doi.org/10.1016/j.nbd.2009.05.021.
141. Anderson ML, Nokia MS, Govindaraju KP, et al. Moderate drinking? Alcohol consumption significantly decreases neurogenesis in the adult hippocampus. *Neuroscience*. 2012;224:202-209. https://doi.org/10.1016/j.neuroscience.2012.08.018.
142. He J, Overstreet DH, Crews FT. Abstinence from moderate alcohol self-administration alters progenitor cell proliferation and differentiation in multiple brain regions of male and female P rats. *Alcohol Clin Exp Res*. 2009;33(1):129-138. https://doi.org/10.1111/j.1530-0277.2008.00823.x.
143. Broadwater MA, Liu W, Crews FT, et al. Persistent loss of hippocampal neurogenesis and increased cell death following adolescent, but not adult, chronic ethanol exposure. *Dev Neurosci*. 2014;36(3-4):297-305. https://doi.org/10.1159/000362874.
144. Mann K, Ackermann K, Croissant B, et al. Neuroimaging of gender differences in alcohol dependence: Are women more vulnerable? *Alcohol Clin Exp Res*. 2005;29(5):896-901. https://doi.org/10.1097/01.alc.0000164376.69978.6b.
145. Åberg F, Helenius-Hietala J, Puukka P, et al. Binge drinking and the risk of liver events: A population-based cohort study. *Liver Int*. 2017;37(9):1373-1381. https://doi.org/10.1111/liv.13408.
146. Schwarzinger M, Thiébaut SP, Baillot S, et al. Alcohol use disorders and associated chronic disease - A national retrospective cohort study from France. *BMC Public Health*. 2017;18(1):43. https://doi.org/10.1186/s12889-017-4587-y.
147. Hydes TJ, Burton R, Inskip H, et al. A comparison of gender-linked population cancer risks between alcohol and tobacco: How many cigarettes are there in a bottle of wine? *BMC Public Health*. 2019;19(1):316. https://doi.org/10.1186/s12889-019-6576-9.
148. Wilsnack RW, Wilsnack SC, Gmel G, et al. Gender differences in binge drinking. *Alcohol Res*. 2018;39(1):57-76.
149. Kerr-Corrêa F, Igami TZ, Hiroce V, et al. Patterns of alcohol use between genders: A cross-cultural evaluation. *J Affect Disord*. 2007;102(1-3):265-275. https://doi.org/10.1016/j.jad.2006.09.031.
150. Erol A, Karpyak VM. Sex and gender-related differences in alcohol use and its consequences: Contemporary knowledge and future research considerations. *Drug Alcohol Depend*. 2015;156:1-13. https://doi.org/10.1016/j.drugalcdep.2015.08.023.
151. Choleris E, Galea LAM, Sohrabji F, et al. Sex differences in the brain: Implications for behavioral and biomedical research. *Neurosci Biobehav Rev.* 2018 ;85:126-145. https://doi.org/10.1016/j.neubiorev.2017.07.005.
152. Hamson DK, Roes MM, Galea LAM. Sex hormones and cognition: Neuroendocrine influences on memory and learning. *Compr Physiol*. 2016;6(3):1295-1337. https://doi.org/10.1002/cphy.c150031.
153. Law AJ, Pei Q, Feldon J, et al. Gene expression in the anterior cingulate cortex and amygdala of adolescent marmoset monkeys following parental separations in infancy. *Int J Neuropsychopharmacol*. 2009;12(6):761-772. https://doi.org/10.1017/s1461145708009723.
154. Hyer MM, Phillips LL, Neigh GN. Sex differences in synaptic plasticity: Hormones and beyond. *Front Mol Neurosci*. 2018;11:266. https://doi.org/10.3389/fnmol.2018.00266.
155. Becker U, Tønnesen H, Kaas-Claesson N, et al. Menstrual disturbances and fertility in chronic alcoholic women. *Drug Alcohol Depend*. 1989;24(1):75-82. https://doi.org/10.1016/0376-8716(89)90012-4.

156. Reichman ME, Judd JT, Longcope C, et al. Effects of alcohol consumption on plasma and urinary hormone concentrations in premenopausal women. *J Natl Cancer Inst*. 1993;85(9):722-727. https://doi.org/10.1093/jnci/85.9.722.
157. Martel MM, Eisenlohr-Moul T, Roberts B. Interactive effects of ovarian steroid hormones on alcohol use and binge drinking across the menstrual cycle. *J Abnorm Psychol.* 2017;126(8):1104-1113. https://doi.org/10.1037/abn0000304.
158. Emanuele MA, Wezeman F, Emanuele NV. Alcohol's effects on female reproductive function. *Alcohol Res Health*. 2002;26(4):274-281.
159. Erol A, Ho AM, Winham SJ, et al. Sex hormones in alcohol consumption: A systematic review of evidence. *Addict Biol*. 2019;24(2):157-169. https://doi.org/10.1111/adb.12589.
160. Fede SJ, Grodin EN, Dean SF, et al. Resting state connectivity best predicts alcohol use severity in moderate to heavy alcohol users. *Neuroimage Clin*. 2019;22:101782. https://doi.org/10.1016/j.nicl.2019.101782.

ALCOHOL RESEARCH
Current Reviews

Alcohol Res. 2020;40(2):05 • https://doi.org/10.35946/arcr.v40.2.05

Published: 20 August 2020

The Role of Stress, Trauma, and Negative Affect in Alcohol Misuse and Alcohol Use Disorder in Women

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Recent evidence indicates that the United States is facing a public health crisis of alcohol misuse and alcohol use disorder (AUD), which has been fueled in part by dramatic rises in binge and heavy drinking and prevalence of AUD in women. Historically, alcohol misuse and AUD have been more prevalent in men than in women. However, recent evidence on data from the past decade shows increases in AUD prevalence rates that are associated with substantially higher binge and heavy drinking and AUD prevalence in women compared to men. This paper first addresses the key roles of stress, trauma, childhood maltreatment, negative affect, and mood and anxiety disorders; sex differences in the presentation of these psychosocial and psychological factors; and their contributions to alcohol misuse, escalation to binge and heavy drinking, and transition to AUD in women. Also examined are potential central and peripheral biological mechanisms by which stressors and traumatic experiences, as well as chronic stress states—including depression and anxiety—may facilitate differential pathways to alcohol misuse, escalation, and transition to AUD in women. Finally, this paper discusses major gaps in the literature on sex differences in these areas as well as the need for greater research on sex-specific pathways to alcohol misuse and transition to AUD, so as to support a more comprehensive understanding of AUD etiology and for the development of new strategies for prevention and treatment of alcohol misuse and AUD in women.

KEY WORDS: girls and women; sex differences; early trauma; child maltreatment; alcohol craving

INTRODUCTION

There has been a global increase in alcohol misuse and rates of alcohol use disorder (AUD) over the last two decades.[1] Recent substantial increases in the United States come from dramatic rises in the prevalence of alcohol misuse and AUD in women relative to men (women, 84% increase; men, 35% increase).[2] This dramatic rise stems from increases in hazardous and binge drinking in girls during adolescence as well as in women.[3] Even though alcohol misuse and AUD are more prevalent in men than in women, there are no sex differences in prevalence of alcohol use during adolescence.[4] These increases are especially alarming given the fact that women tend to experience greater alcohol-related health problems than do men.[5] This article focuses on the roles of stress, trauma, childhood maltreatment, negative affect, and mood and anxiety disorders and their contributions to the increases in alcohol misuse, escalation of binge and heavy drinking, and transition to AUD in women. Although there are likely additional genetic and social factors and related mechanisms that may contribute to specific risks of binge drinking and AUD in women, a review of this literature is beyond the scope of this review. Rather, this article focuses on the psychosocial and biological processes by which stress, trauma, negative affect, and mood and anxiety disorders increase the risk of binge and heavy drinking, AUD, and relapse.

PSYCHOSOCIAL FACTORS INVOLVED IN THE ONSET AND PREVALENCE OF AUD IN WOMEN

Women in the United States are largely overrepresented in stress-related psychopathology rates,[6] and stress along with drug-related environmental cues are among the most important risk factors driving alcohol seeking, maintenance, and relapse.[7] Studies suggest that men and women differ in risk trajectories for the development of AUD and in AUD-related health consequences.[8] For example, women are more likely than men to experience certain types of stressors, such as sexual trauma,[9] and higher levels of stress have been shown to increase alcohol misuse and AUD vulnerability.[10] Also, women demonstrate a significantly "more rapid and risk-oriented path to compulsive drug seeking,"[11] pointing to a significant need to understand sex differences in risk for AUD development and maintenance in order to develop novel prevention and treatment approaches for AUD in women.

Psychosocial Factors of Early Trauma, Maltreatment, and Adversity

Early trauma, maltreatment, and cumulative adversity are psychosocial stress factors that have long been associated with alcohol misuse, development of AUD, AUD maintenance, and relapse.[10] Both boys and girls face physical and emotional abuse and neglect, sexual abuse, and cumulative adversity stemming from specific adverse childhood experiences such as substance use and mental health problems in the home, parental discord, and divorce, which are each associated with greater alcohol initiation in childhood.[12] However, girls and women face significantly higher rates of childhood sexual abuse and violent victimization.[13] Notably, higher rates of sexual abuse and violent victimization, especially in girls and women, are factors that produce the highest odds ratios for association with heavy drinking, drinking to cope with negative affect, and development of AUD.[10,12,14]

Sex Differences in Stress Factors, Early Onset Alcohol Misuse, and AUD

An extensive number of studies point to a positive association between negative affect, trauma, adversity, and chronic stress and vulnerability in developing AUD. Recent studies have shown that girls who report a history of abuse before adulthood are more vulnerable to developing AUD.[15] Other studies have found that adolescents who face a number of negative life events show increased levels of drug use (and misuse)

compared to those who do not face these adverse events.[7,10] Exposure to early life stress may be especially harmful for women, who are exposed to more high-impact trauma (e.g., sexual abuse) than men are, and at a younger age.[16] Thus, early trauma and chronic adversity both may increase vulnerability to alcohol use initiation, as well as maintenance, especially in girls. However, it is important to consider estimation biases, as women may be more likely to endorse stressful life events; thus, the contribution of these factors to binge drinking and AUD risk among women may be influenced by such estimation biases.

A study by Cheng and Anthony conducted between 2006 and 2014 assessed the dates of first full drink and first heavy drinking episode in around 33,000 females and males (ages 12 to 21) in the United States who had their first heavy drinking episode within the past 24 months.[15] Their findings revealed that, among adolescents who started to drink between ages 11 and 14, females progressed to a heavy drinking episode more quickly than males. This suggests that when drinking starts before age 15, females are at greater risk than males of progressing to a heavy drinking episode. When considered with the information that girls are more likely than boys to suffer sexual abuse before age 18, these findings raise the possibility that sexual abuse and other trauma, and victimization-related increases may contribute to increased risk of alcohol misuse and development of AUD in women.[17] However, the specific contribution of these factors to the development of AUD in women needs to be further explored.

PSYCHOLOGICAL ASPECTS OF STRESS AND TRAUMA EFFECTS ON AUD IN WOMEN

Experiencing stress, trauma, and adversity activates psychological processes of cognitive, affective, and behavioral emotion regulation and self-control to cope with and adapt to such negative life circumstances. During adolescence and young adulthood, emotion regulation becomes particularly relevant because of the rapid brain changes in regions associated with regulating emotion, stress, reward, and higher-order cognitive functioning; such changes underlie the significant biological and psychological changes that boys and girls undergo throughout adolescent development.[18] Alcohol experimentation occurs frequently during adolescence and young adulthood, and there is a higher risk for the development of AUD or substance use disorder during this time.[19] Findings indicate that exposure to early trauma and life stressors is associated with greater difficulties in emotional experiences, behavioral control, executive function, and decision-making, which contribute to behavioral control of alcohol intake, and thus could be one pathway that contributes to early onset of alcohol intake and risk of alcohol and substance use disorders.[12,19] Discussed below are the sex differences and impact of negative affect, mood and anxiety symptoms, and post-traumatic stress disorder (PTSD) and their contribution to development of binge and heavy drinking and AUD in women.

Negative Affect and Alcohol Intake

Negative affect is broadly defined as a state of emotional distress, and is associated with unpleasant feelings, such as anxiety, fear, anger, irritability, and sadness. Repeated and cumulative exposure to stress, trauma, adversity, and maltreatment is associated with greater levels of negative affect, anxiety, and depressed mood. Past literature suggests that women report more negative affect compared to men,[20] and higher negative affect has been linked to greater emotion dysregulation and associated with affective, anxiety, and substance use disorders.[10,21] A previous experimental study exposed healthy social drinkers to emotional stress, alcohol cues, and a control neutral relaxing cue using a personalized guided imagery method that individually calibrates stress imagery so as to

remove any provocation-related bias between men and women.[22] Results indicated that men and women were similar in cue-induced craving ratings. However, women reported greater stress-provoked sadness, anxiety, and body sensations compared to men (see Figure 1). These data indicate sex differences in stress and negative affect responses in women versus men, separate from alcohol motivation.

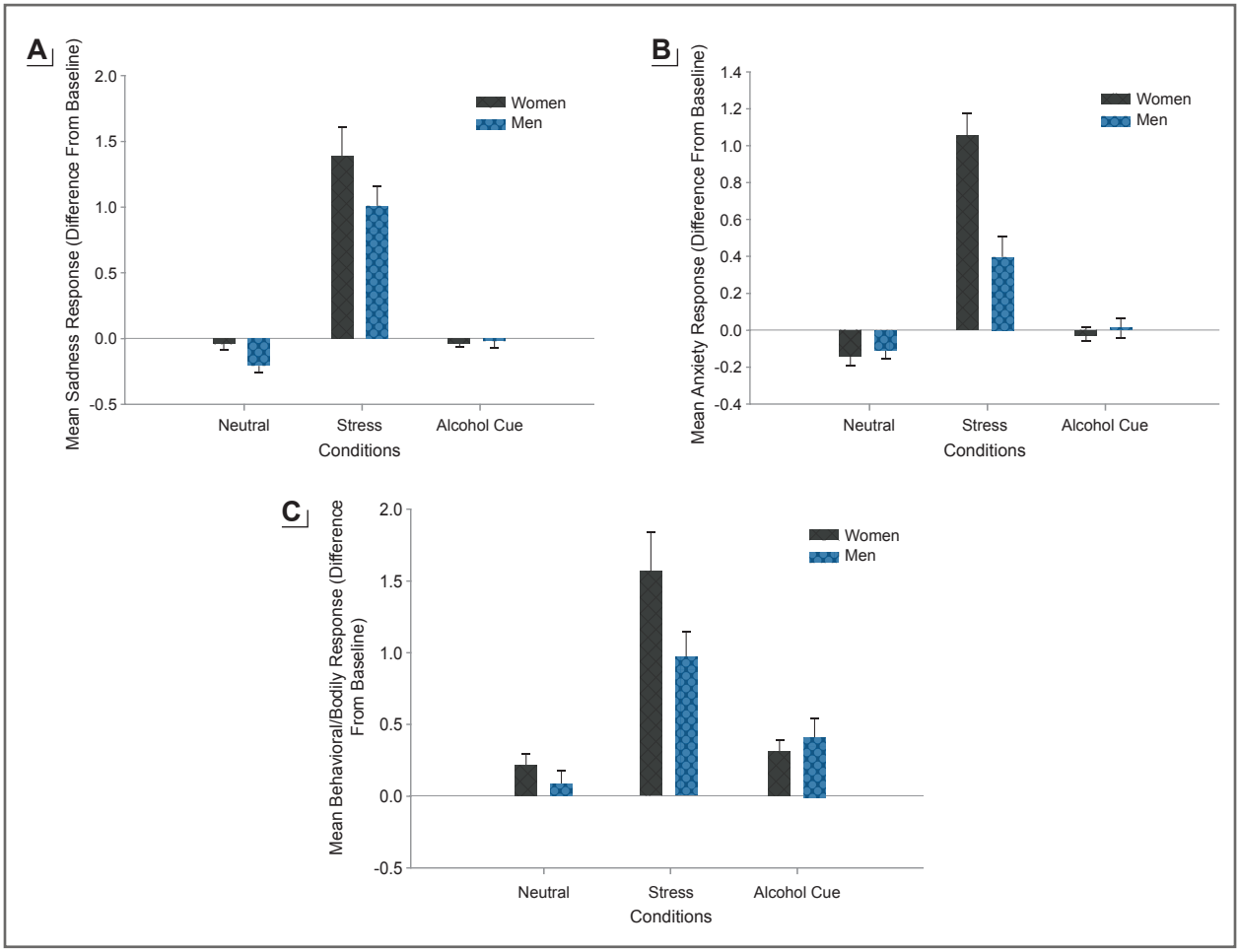

Figure 1 Gender differences in socially drinking volunteers' average subjective responses to individually calibrated exposure to stress, alcohol cue, and neutral-relaxing control provocation conditions, assessed repeatedly over time in an experimental study. *Figure 1a:* Average subjective sadness response over time to neutral, stress, and alcohol cue conditions by gender (in stress: women > men, $p = .01$). *Figure 1b:* Average subjective anxiety response over time to neutral, stress, and alcohol cue conditions by gender (in stress: women > men, $p < .0001$). *Figure 1c:* Average observed nonverbal behavioral and body responses to neutral, stress, and alcohol cue conditions by gender (in stress: women > men, $p = .04$). *Source:* Reproduced with permission from Chaplin et al. 2008.[22] Copyright © 2008 Research Society on Alcoholism and the International Society for Biomedical Research on Alcoholism. Published by Wiley-Blackwell. All rights reserved.

Higher levels of negative affect have specifically been linked to initiation and relapse in alcohol and other substance use disorders.[23] In adolescents, negative affect is strongly associated with the onset of drinking and alcohol misuse, and higher levels of negative affect are also associated with greater child maltreatment, victimization, and adversity.[23] Girls show greater negative affect such as sadness in response to early life stress than boys,[19] similar to findings for adults (and as shown in Figure 1). A number of studies have shown that emotional stress and negative

affect also elicit significant alcohol craving,[10] and negative affect and anxiety are key symptoms of alcohol withdrawal that are further exacerbated by exposure to alcohol cues.[7] Such a link between stress and negative affect and alcohol motivation highlights the need to assess sex differences and women-specific vulnerability in processes underlying the association between stress and negative affect and alcohol intake, alcohol misuse, and risk of AUD.

Negative affect becomes an important component in the development of AUD in women because past literature has documented that, while men tend to consume alcohol to enhance positive feelings,[24] women more frequently consume alcohol in response to negative emotions.[11,25] Much like the association between early trauma and substance use, negative affect, such as temperamental negative mood, has also been associated with the development and maintenance of substance use disorders.[11] Negative emotions, drinking to regulate negative affect, and stress are among the factors associated with increasing rates of AUD in women.[11] Furthermore, studies have also shown that, in addition to trauma, abuse, and chronic stress, negative affect is predictive of alcohol misuse and addiction vulnerability.[10] Thus, temperamental negative emotionality, which is often documented as higher in women and is linked to substance use vulnerability, may place women at a higher risk of subsequent alcohol and substance misuse, but its specific role in women's substance misuse needs further investigation.

Sex Differences in Anxiety and Depression

Gender gaps in rates of mental illnesses tend to emerge and/or widen during puberty and have been associated with the rise of different sex steroid hormones in boys and girls that occurs during this period. Before puberty, boys and girls have similar rates of depression; however, soon after puberty, depression becomes twice as prevalent in girls than in boys until late adulthood.[26] This is also true of other mental conditions such as anxiety disorders.[18] Adult women report more mental health problems than men,[21] with women with AUD reporting greater mental health problems than women without AUD. In fact, affective disorders have been shown to be the most commonly comorbid psychiatric disorders in individuals with substance use disorder, including AUD.[10] Even though there exists a representation and estimation bias of women in epidemiological mental health studies, a better understanding of sex-based differences in mental health is crucial to understanding specific risk factors in the development of AUD in women.

Stress is significantly associated with affective and anxiety disorders, raising the issue of whether these disorders contribute to the association between stress and AUD.[11] Research has shown that individuals with anxiety disorders who reported drinking to cope with their anxiety symptoms drank more alcohol and had a higher rate of DSM-IV alcohol dependence than those who did not report drinking to lessen their symptoms.[27] There are higher rates of AUD in those with PTSD than in those without PTSD,[28] and PTSD precedes AUD more often in women than in men.[29] Both stress and trauma exposure experimentally increase alcohol craving,[30] and women with both PTSD and AUD report higher levels of trauma, anxiety, and mood symptoms than men.[31] Furthermore, studies have found that co-occurring AUD, mood and anxiety disorders, and PTSD are associated with higher relapse rates than AUD without such comorbidity.[32,33] Women present different biological, psychological, and physiological effects of alcohol misuse that are crucial to the maintenance of their alcohol use.[5,11] For this reason, sex differences in mental health not only are relevant in the development of AUD, but also need further consideration, especially with regard to prognosis and treatment outcome. Due to the differential physiological and subjective effects of alcohol use in women,[5] AUD symptoms and progression of disease are accelerated in women, including progression to comorbidities of AUD with other psychopathology such as depression, phobias, and other anxiety and affective illnesses.[11,21]

BIOLOGICAL FACTORS INVOLVED IN THE ONSET AND PREVALENCE OF AUD IN WOMEN

Exposure to stressful and traumatic events as well as chronic adverse environments trigger a biological stress response characterized by neural, physiological (autonomic), hormonal (hypothalamic-pituitary-adrenal [HPA] axis), and immune response changes to support resilient, adaptive coping.[10] However, uncontrollable events, repeated or chronic stress, and trauma disrupt these responses, thereby breaking down the adaptive nature of stress responses.[10] This results in allostasis and maladaptive psychological and behavioral responses that put an individual at risk for neuropsychiatric illnesses, including AUD.[10] Well-documented sex differences start in childhood and continue throughout the life span in these physiological, hormonal, and immune responses, and in the disruption and adaptations that occur as a result of childhood trauma, chronic adversity, and repeated stress experiences.[10,11,21] Findings from the authors of this paper and other studies have shown that repeated stress and childhood trauma result in sex-specific adaptations in the autonomic, HPA axis, and immune responses, which have not been well addressed in the literature on risk of AUD.[10,11] For example, girls and women with childhood maltreatment show a blunted HPA axis stress response,[10] but those without trauma histories and with high negative affect and mood disorders have a hyperreactive HPA axis response to stress.[10] Changes such as a hyporeactive HPA axis response to acute stress are associated with greater risk of alcohol misuse and AUD, as documented in large longitudinal studies tracking adolescents through young adulthood.[14] Thus, these youth may seek out substances to normalize their lower basal level of arousal.

Other studies document the highly sexually dimorphic stress response, represented by girls and women showing a higher autonomic, catecholaminergic, and immune response to stress, whereas boys and men show greater glucocorticoid and HPA axis responses to acute stress.[11] Recent findings also document that increased exposure to childhood victimization results in higher C-reactive protein levels in girls but not boys,[34] suggesting more stress-related immune compromise and susceptibility in girls relative to boys. In addition, the HPA axis and the autonomic pathways—including the sympathetic and parasympathetic components that coordinate the peripheral biological stress response—show significant dysregulation associated with early life trauma as well as childhood maltreatment, with sex differences in the extent and nature of dysregulation.[10,35] However, specific data on sex differences are not entirely clear. Chronic stress and comorbid mood and anxiety disorders are also associated with altered stress responses,[21] with higher stress responses in women with mood disorders and without childhood maltreatment, but also blunted stress responses in women who misuse alcohol or who have AUD.[11,36] These findings highlight that a critical aspect of the biological stress response is the associated plasticity in peripheral and central stress biology associated with repeated stress, trauma, and adversity. The sex-specific nature of the stress response also results in sex-specific adaptations and allostatic responses to repeated or chronic stress, adversity, and early life trauma and maltreatment.[35] The effects on alcohol motivation and intake of such changes in the stress response are discussed below.

Alcohol Effects on Stress, Negative Affect, and Motivation for Drinking

Alcohol consumption dramatically affects human physiology, and repeated high-intensity use and misuse is associated with significant neuroadaptations and breakdown of the brain and peripheral systems that coordinate stress, emotion, and reward regulation.[36] Growing evidence suggests that these adaptations promote a feedforward development of compulsive motivation for alcohol use and misuse.[10,21,33] Not only does alcohol stimulate striatal dopaminergic pathways, but it also directly stimulates the HPA axis and affects glucocorticoid receptors in extrahypothalamic, limbic, forebrain, and medial

prefrontal cortex (mPFC) circuits associated with the development and progression of AUD.[36] Alcohol-associated neuroadaptations in HPA axis responses to stress and alcohol cues may serve as psychobiological markers of the cycle of recurring alcohol consumption.[36] Sex differences in individuals with AUD in the phasic response to stress and in basal tonic levels of HPA axis and the peripheral catecholamines have also been documented.[11] For example, women with AUD show lower tonic adrenocorticotropic hormone (ACTH) levels but higher norepinephrine (NE) levels relative to men, but also higher relative stress-induced ACTH response and more blunted stress-induced NE response relative to men[11] (see Figure 2). Thus, neuroadaptations resulting from alcohol consumption (acute and chronic) may facilitate the risk for AUD susceptibility and maintenance in a sex-specific manner.

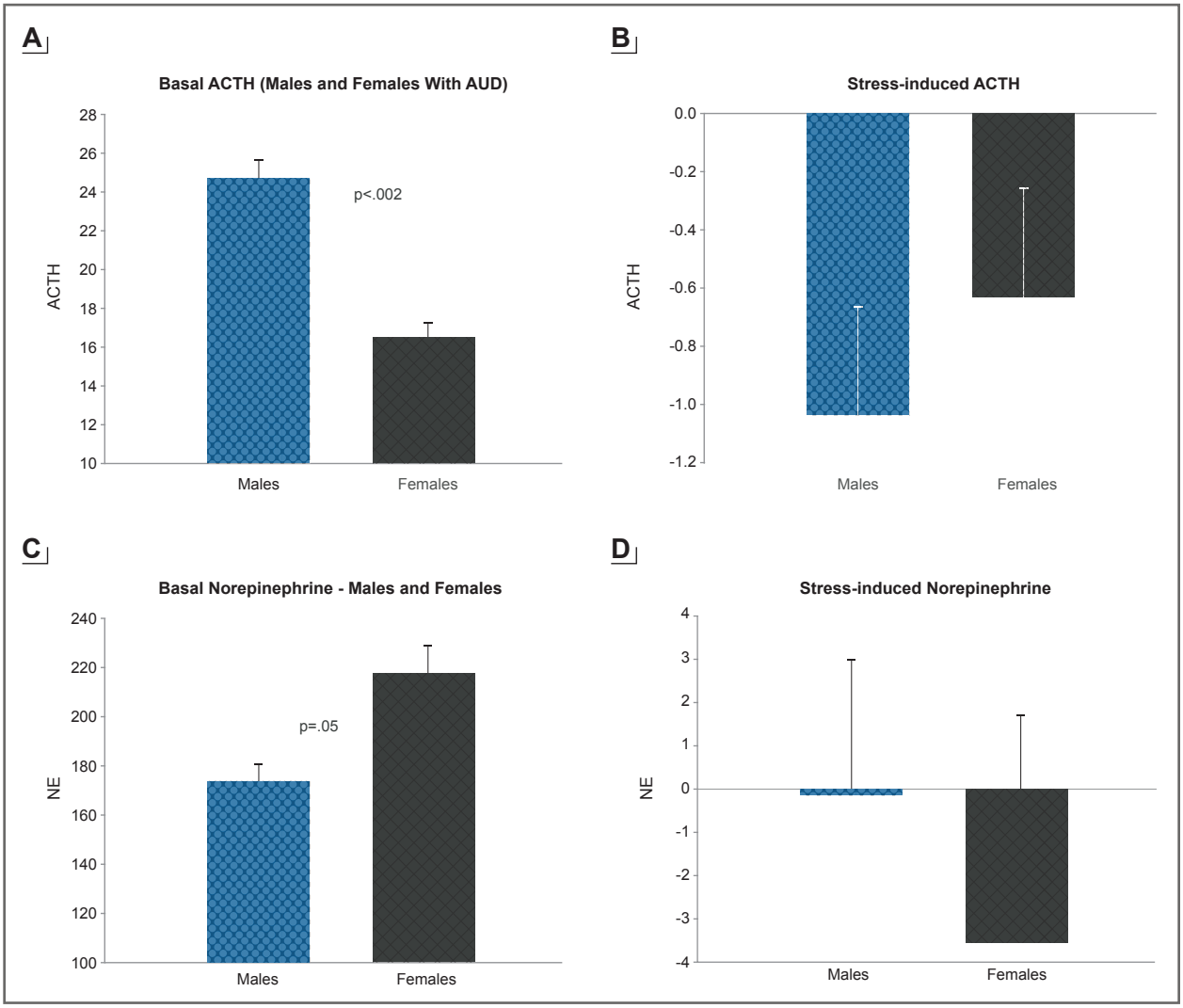

Figure 2 Gender differences in ACTH and NE in men and women with alcohol use disorder (AUD) participating in a laboratory experiment with exposure to individually calibrated stress, alcohol cue, and neutral relaxing imagery on 3 separate days, one condition per day. *Figure 2a and Figure 2b:* ACTH differences between males and females with AUD at baseline (a) and following stress exposure (b) relative to their neutral response. Attenuation of the diurnal drop is shown in females (Stress > Neutral, $p = .0009$) but not in males. *Figure 2c and Figure 2d:* NE differences between males and females with AUD at baseline (a) and following stress exposure (b) relative to their neutral response. Attenuation of the diurnal drop is shown in males, but not in females (Neutral > Stress, $p < .0001$). *Note:* ACTH, adrenocorticotropic hormone; NE, norepinephrine.

Following acute, moderate exposure to alcohol or stress, dopaminergic, hypothalamic autonomic, and catecholaminergic pathways have the opportunity to return to their basal states after activation. With alcohol misuse, binge or heavy drinking, and chronic alcohol use, large-scale adaptations and allostatic overload to neuroendocrine regulation circuits occur. These physiological changes have been associated with the transition from controlled to compulsive alcohol seeking in humans.[36] In fact, in binge and heavy drinkers, a neuroendocrine tolerance to stress and alcohol consumption is observed. For example, a blunted cortisol response to alcohol is observed among individuals with a history of binge or heavy drinking relative to moderate drinkers.[37] This blunted response to alcohol in those with a history of binge or heavy drinking is identified as neuroendocrine tolerance. Recent findings indicate that, in binge or heavy drinkers, blunted cortisol responses and higher subjective craving are each associated with greater amounts of alcohol intake in the laboratory.[37] It is important to note that the sample had a majority of men, and sex differences in these effects have yet to be explored. Thus, although binge and heavy alcohol use and associated adaptations in stress biology appear to be involved in the development of neuroendocrine tolerance and in the resulting increases in compulsive motivation,[36,37] neither sex differences in the alcohol-related neuroendocrine tolerance nor the possible sex differences on its effects on alcohol motivation and intake have been explored thus far.

Alcohol and Stress Interactions on Peripheral and Central Nervous System Responses and Sex Differences

Sex differences have been found in pharmacokinetics and pharmacodynamics of alcohol[38] as well as in neuroanatomy and chemistry.[24] Blood alcohol levels rise faster and stay elevated for longer in women than in men. Sex hormones affect the neural pathways and influence neurotransmitter activity, which affects an individual's physiological and behavioral responses to drugs.[24] For example, even though men show stronger activation of the brain reward system in response to alcohol than do women,[24] the female brain suffers more damage and inflammation from alcohol withdrawal.[39] Important to the current discussion, alcohol stimulates the biological stress pathways in similar ways to psychological stress and trauma.[36] Similarly, significant adaptations and changes occur as a function of repeated and binge alcohol use in these biological stress pathways, and stress and alcohol misuse may act synergistically to modify HPA as well as autonomic and neural responses to stress and alcohol, which may in turn drive greater craving and compulsive seeking for alcohol.[10,36]

A number of studies have linked greater stress reactivity in plasma/salivary cortisol responses as a risk factor for comorbidity of mood disorders and AUD.[40] Research has also shown that blunted salivary cortisol response to stress is a risk factor for AUD development in at-risk children with a family history of substance misuse or substance use disorder.[41] There also may be significant variation in these responses as assessed by concentrations in plasma/serum for ACTH, plasma/serum and saliva for cortisol, salivary alpha-amylase (a measure of autonomic adrenergic arousal), and physiological assessments of heart rate and heart rate variability, as a function of extent of chronic stress or trauma exposure.[10,42] Specifically, one study evaluated at-risk prepubertal boys (ages 10 to 12) with fathers with substance use disorder and found that high-risk boys secreted significantly less salivary cortisol in response to an anticipated stressor compared to controls.[41] These findings were corroborated by another study using a stress task in adolescents, which documented that blunted physiological and emotional responses to stress in adolescents were related to greater risk of alcohol and substance use.[43] In a larger cohort that also evaluated sex differences in adolescents ages 14 to 17 who were prenatally exposed to cocaine relative to nonexposed youth, elevated basal salivary concentrations of cortisol were found in the at-risk group relative to nonexposed youth.[44] In contrast, at-risk youth exhibited a blunted salivary cortisol response to a social stressor compared to controls.[44] Furthermore, sex differences were

found in prediction of future substance use: for girls, self-reported sadness in response to the social stressor predicted future drug use, whereas for boys, blunted salivary alpha-amylase (an autonomic nervous system measure) in response to the same social stressor predicted future drug use.[44] These results suggest that distinct physiological and emotional stress responses among boys and girls are associated with different risk profiles for future drug use.

In another series of studies, impaired neuroendocrine responses to alcohol and to stress have also been associated with an increased motivation for binge or heavy drinking, thereby serving as a potential risk marker for the progression from heavy drinking to DSM-IV alcohol dependence.[45] In a large population-based study where children were followed longitudinally between ages 14 and 20, the age at which the first alcoholic drink was consumed varied as a function of cortisol levels, and blunted cortisol responses to stress were associated with greater risk of alcohol misuse.[46] Furthermore, among heavy- and light-drinking adults who were exposed to an oral alcohol challenge and followed for 6 years, heavy drinkers showed greater sensitivity to stimulating effects and lower sensitivity to the sedative effects of alcohol compared to light drinkers.[45] Moreover, heavy drinkers demonstrated lower salivary cortisol release in response to the alcohol challenge and, 6 years later, presented with a greater number of AUD symptoms than did light drinkers.[45] These findings suggest that alcohol and stress significantly impact the psychological and biological stress responses—altering affect, mood, and anxiety as well as biological stress responses. However, a significant gap remains in understanding sex differences in these effects given that differences by gender have not been well studied in the literature.

One of the effects of acute administration of alcohol is the activation of both reward and stress pathways in the brain. The mesocorticolimbic dopaminergic system, involved in reward processing, is activated alongside the corticotropin-releasing factor (CRF)-HPA axis and the autonomic nervous system pathways involved in stress responses. Activation of these central pathways results in increased levels of ACTH and cortisol, as well as changes in heart rate, blood pressure, and skin conductance responses.[10] Withdrawal and abstinence following chronic alcohol use also are associated with dysfunctional sympathetic and parasympathetic responses, highlighting the effect of alcohol misuse on these peripheral stress pathways; as shown in Figure 2, there are sex differences in these alcohol-related adaptations of the stress pathways.

Even though acute administration of drugs, such as alcohol, may increase mesolimbic dopamine levels, sustained alcohol misuse downregulates the mesolimbic dopamine pathways and thus decreases basal dopamine levels.[10] Using brain imaging, research has shown that there are fewer dopamine D2 receptors and less dopamine transmission in frontal regions and in the ventral striatum area of individuals with AUD during withdrawal.[10] Furthermore, dopamine response to drugs is sex-specific, with men showing greater dopamine release than women.[47] Prolonged exposure to drugs, such as alcohol, results in altered and blunted neurochemical responses to drugs as well as to stress. Behavioral sensitization to drugs and stress can also be observed and is associated with CRF and noradrenergic effects on dopaminergic (and non-dopaminergic) pathways and with synaptic alterations in the ventral tegmental area, amygdala, nucleus accumbens, and mPFC.[10] More importantly, sex differences in both stress and reward circuitry have been reported using functional magnetic resonance imaging (fMRI) research, where responses to stress and to alcohol cues relative to neutral cues show a differential profile in men who drink socially versus women who drink socially[48] (see Figure 3). Furthermore, although striatal activation during alcohol cue exposure was associated with alcohol craving, this effect was seen in men only and not in women, and different prefrontal regions were associated with stress-induced anxiety in men and women (see Figure 4). These data suggest that central brain pathways differentially modulate stress and alcohol motivation responses in men and women who drink socially and point to a significant need to

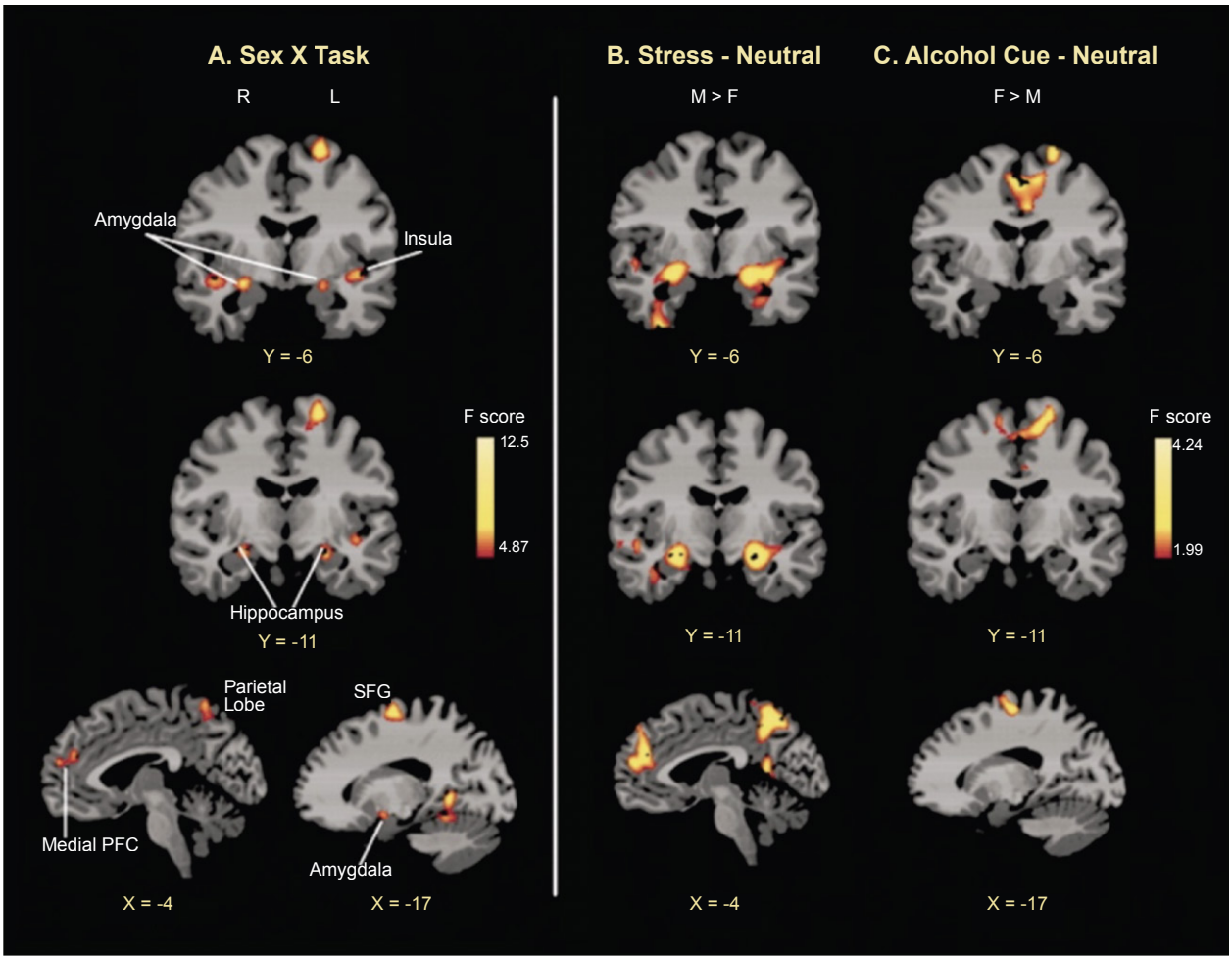

Figure 3 Whole-brain voxel-based functional magnetic resonance imaging (fMRI) showing a sex × condition interaction and corresponding activations in the stress-neutral and alcohol cue-neutral contrasts for males (M) and females (F) who drink socially. **A**: The sex × condition interaction effect was significant in regions of the superior and middle frontal gyrus (SFG/MFG), medial prefrontal cortex (mPFC, dorsomedial and ventromedial), rostral anterior cingulate cortex, emotion limbic regions (posterior insula, putamen, amygdala, hippocampus, and parahippocampal gyrus), temporal lobe, and visuomotor perception areas (parietal lobe, occipital lobe, and cerebellum) ($p < 0.01$ whole-brain familywise error [FWE] rate corrected). To elucidate the source of the interaction, male versus female contrasts were conducted for (**B**) stress relative to neutral, and (**C**) alcohol cue relative to neutral brain responses at the $p < .05$ whole-brain FWE corrected. Significantly, greater M > F stress-induced activity in the mPFC and limbic regions was observed. Alcohol cue-induced activity in the SFG/MFG was significantly higher in women than in men. No differences in F > M for the stress-neutral and in M > F contrast for the alcohol cue-neutral survived whole-brain correction. Coordinates are given in Montreal Neurological Institute space. *Note:* F, female; L, left; M, male; mPFC, medial prefrontal cortex; R, right. *Source:* Reproduced with permission from Seo et al., 2011.[49]

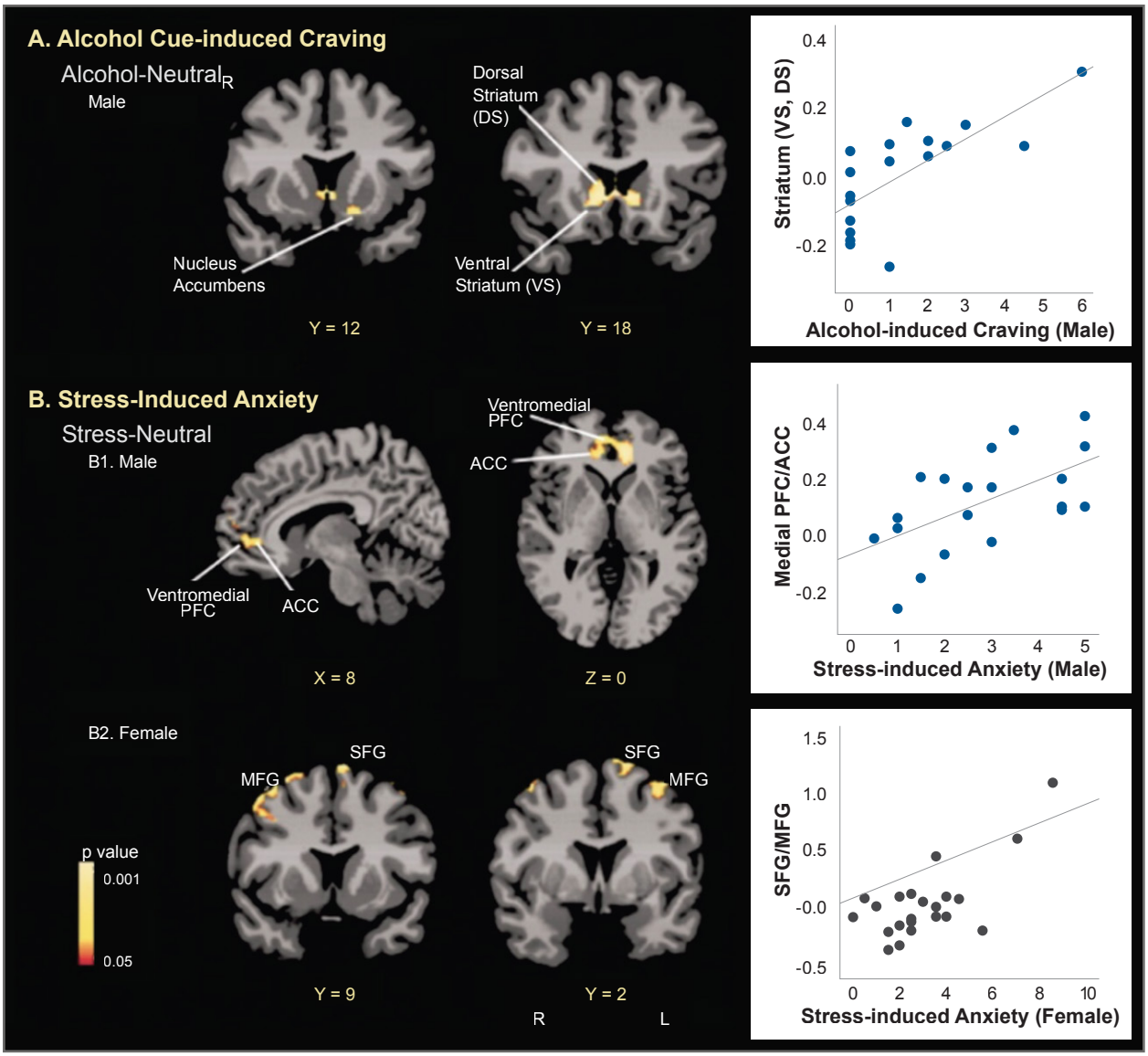

Figure 4 In men and women who drink socially, whole brain voxel-based correlation and corresponding scatter plots for (A) alcohol cue-induced craving ratings with neural responses during alcohol cue versus neutral cue exposure in males as well as (B) stress-induced anxiety ratings with neural response during stress versus neutral cue exposure in males and females ($p < .05$, whole-brain familywise error rate [FWE] corrected). **A**: In males, elevated alcohol craving ratings were associated with increased activity in the striatum cluster ($r = .74$) that encompassed ventral and dorsal striatum, including the left nucleus accumbens (X = −13, Y = 12, Z = −12). **B1**: In males, enhanced stress-induced anxiety ratings were associated with increased brain activity in a medial prefrontal cortex cluster that included the ACC, ventromedial PFC, and medial PFC ($r = .59$). **B2**: In females, stress-induced anxiety ratings were positively correlated with bilateral brain activity in superior/middle frontal gyrus (winsorized $r = 0.62$). Coordinates are given in Montreal Neurological Institute space. *Note:* ACC, anterior cingulated cortex; L, left; MFG, middle frontal gyrus; PFC, prefrontal cortex; R, right; SFG, superior frontal gyrus. *Source:* Reproduced with permission from Seo et al., 2011.[49] Copyright © 2010 Wiley-Liss, Inc. All rights reserved.

understand the neurobiology of binge drinking and chronic alcohol misuse in women.

STRESS NEUROCIRCUITRY, EMOTION REGULATION, AND ALCOHOL CRAVING

Previous human research indicates that trauma, adversity, and chronic stress alter the activity and structure of the prefrontal cortical, limbic, and striatal brain networks involved in regulating stress and emotions as well as reward and higher cognitive or executive control functions.[10] These brain circuits also show significant sexual dimorphism, suggesting a need to explore the role of sex differences in their structure and function in critical regulation and coping functions for stress, trauma, and self-control over alcohol intake. These functions can include the regulation of distress and emotions, such as controlling and inhibiting impulses, refocusing and shifting attention, employing working memory, monitoring conflict and behavior, linking behaviors to possible future consequences, and demonstrating flexible consideration of alternatives for response selection and decision-making.[10]

Recent evidence from human brain structural and magnetic resonance imaging shows that recent life stressors (e.g., death in family, divorce, relationships ending, being assaulted, financial crises, robberies), trauma (physical, emotional, or sexual abuse), and chronic stress (subjective experience of continual stressors or ongoing life problems) are associated with lower gray matter volume in medial prefrontal, amygdala, hippocampus, and insula regions of the brain.[50,51] Similarly, recent life stress and acute stress exposure (such as those listed above) may decrease responses in the prefrontal regions (such as the dorsolateral prefrontal cortex and ventromedial prefrontal cortex) associated with working memory, reward processing, and resilient coping.[52] Such changes in the neural circuits underlying emotion and reward dysregulation may promote risky alcohol use (e.g., binge drinking), emotional eating, and frequency of arguments and fights.[52] Furthermore, these circuits are sexually dimorphic in their responses to stress and anxiety, where differential brain regions are associated with stress-induced anxiety in men versus women[52] (see Figure 5). As anxiety and stress responses are associated with alcohol motivation and increased alcohol use, sex differences in the neurocircuits that respond to and regulate stress and anxiety suggest that there are also sex differences in the brain regions that drive stress-induced alcohol craving and intake. However, there is a need for examining this association in a sex-specific manner in future research.

Across at-risk children and adults with exposure to stress, trauma, or in utero substance use, sex-specific brain changes in emotion and reward regions are associated with risk of alcohol misuse and AUD.[53] A study of prenatally cocaine-exposed and non-exposed adolescents (ages 14 to 17) found lower gray matter volume in limbic and frontal regions of the brain as assessed by MRI and whole-brain voxel-based morphometry in the at-risk prenatally exposed relative to non–cocaine-exposed adolescent controls.[53] In addition, lower gray matter volume in these brain regions was associated with initiation of tobacco, alcohol, and cannabis use.[53] Furthermore, sex-specific effects were found in adults who misuse cocaine and alcohol, with women showing lower gray matter volume in emotional-limbic regions of the insula, amygdala, and hippocampus, and men showing lower gray matter volume in the midcingulate and frontal regions.[54] These data suggest that changes in brain volume may serve as biological risk markers for alcohol misuse, AUD, and substance use. Indeed, low behavioral and cognitive control are linked to lower prefrontal and insular cortex volume, and high activation of limbic-emotional and striatal-motivation brain regions under stress suggest one specific pattern underlying risk of addictive behaviors where there is a decreased ability to control rewarding behaviors.[10] Thus, cortico-striatal reward and motivational brain pathways appear to be key targets of disrupted

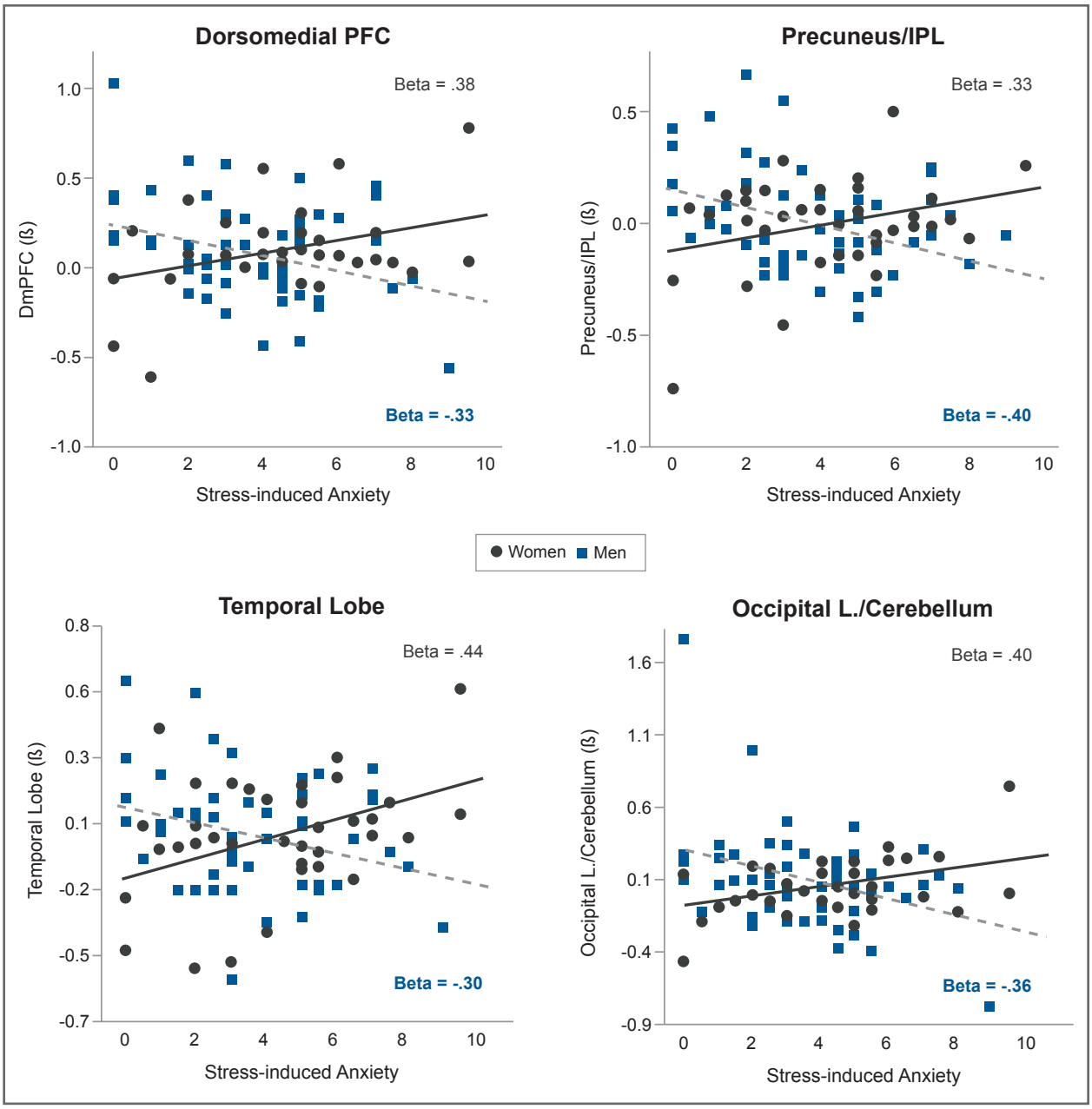

Figure 5 Scatter plots and regression lines for stress-induced anxiety ratings with neural responses during stress relative to neutral-relaxing exposure for specific regions of interest (ROIs). Simple effects in ROIs from whole-brain regression of significant regions from the gender-by-anxiety interaction effects analyses are shown separately in men and women. Stress-induced anxiety predicted brain responses to stress differentially by gender. The plots show (A) positive (women [W]) and negative (men [M]) associations between stress-induced anxiety ratings and activity in the dorsomedial prefrontal cortex (PFC) (W: β = .38; M: β = −.33), precuneus and inferior parietal lobe (W: β = .33; M: β = −.40), middle/inferior temporal gyrus (W: β = .44; M: β = −.30), and occipital lobe and cerebellum (W: β = .40; M: β = −.36). Beta (β) indicates the standardized coefficient. There were no outliers in any of these brain regions for both men and women. *Note:* DmPFC, dorsomedial prefrontal cortex; IPL, inferior parietal lobe; Occipital L., occipital lobe. *Source:* Reproduced with permission from Seo et al., 2017.[48] Copyright © 1999-2020 Wiley-Liss, Inc. All rights reserved.

central stress and emotional responses, suggesting a potentially important sex-specific mechanism by which stress may affect susceptibility to alcohol misuse and AUD vulnerability. As these pathways are sex-specific, the stress- and alcohol-related adaptations also occur in a sex-specific manner, resulting in sex differences in the biological pathways of risk for AUD. However, there is a desperate need for research to elucidate these sex-specific changes and risk factors for AUD.

TRANSITION TO ADDICTION

Women report different motives for alcohol use than men,[10,11] and are more likely to self-medicate their emotional distress, negative affect stemming from high stress, and mood and anxiety disorders.[10,11] As outlined above, sex differences in addiction vulnerabilities set women at a disadvantage related to exposure to and risk of alcohol misuse, maintenance, and relapse.[11] As described in the previous sections, some research has documented sex-based differences in neuroendocrine stress and reward pathways with chronic alcohol use.[11]

The cross-sensitization process of stress and alcohol effects suggests that sex-specific adaptations occur with alcohol misuse and chronic use, which may contribute to alcohol craving, continued use, and relapse. The progression from alcohol misuse to AUD often includes overpowering cravings seen as a physiological need rather than a hedonic desire.[10] This craving is associated with compulsive seeking of alcohol, which becomes stronger in the context of alcohol cues or stress exposure, increasing the chances of relapse. Sex differences in stress assessment and cue reactivity in social drinkers and in patients with AUD have been reported. For example, findings in social drinkers indicate that the incentive value of alcohol may be less sensitized by negative mood and stress in female social drinkers compared with male social drinkers.[55,56] However, findings show that, compared to men with AUD, women with AUD demonstrate greater alcohol cue reactivity following negative mood induction.[57] Furthermore, HPA-axis hyporeactivity to social stress, alcohol cue exposure, and alcohol intake, as well as a blunted cortisol response to stress in women with AUD have been reported concurrently with enhanced emotional distress and greater craving, which, in turn, have been shown to increase the risk of relapse and return to alcohol use in early treatment.[11] Although conducted using separate stress- and cue-reactivity paradigms, this research consistently reflects robust sex-specific dissociations between participants with and without AUD in relation to stress system function and alcohol cue reactivity, supporting the notion that there are sex differences in the mechanisms that drive the transition to AUD, its maintenance, and the relapse to alcohol use. However, the specific link between the robust sex-specific stress and cue reactivity responses and actual binge and heavy alcohol intake in women are not clear and needs greater study in future research.

IMPLICATIONS FOR ONSET AND MAINTENANCE OF AUD IN WOMEN AND FUTURE DIRECTIONS

Sex differences in the onset of alcohol misuse and the development of AUD have been reported. The effects of greater exposure to and experience of stress, trauma, victimization, negative affect, and mood and anxiety disorders in women represent a specific risk pathway for the onset and development of AUD in women. However, estimation bias in occurrence of mood and anxiety disorders needs specific consideration in assessing these associations to alcohol misuse and AUD. Also, although this paper has not focused on genetic mechanisms and epidemiological and sociocultural factors that may explain sex differences, these areas also need further attention. Nonetheless, sex differences in the psychological and biological response to both stress and alcohol intake are well known. Animal studies have revealed that sex steroid hormones interact with

the HPA axis to influence stress regulation, and these sex hormones also modulate brain limbic, striatal, and frontal circuits to influence alcohol seeking in sex-specific ways.[11] However, research in humans assessing interactions between stress, reward, and sex steroid hormones has lagged behind. For example, fluctuations in sex hormones across the menstrual cycle may impact neuroadaptations in stress response and alcohol craving[11] as described below, and, in doing so, may point to specific prevention and treatment efforts.

Although not specifically examined in risk of AUD or in women with AUD, some evidence in other substance use disorders indicates that during the follicular phase of the menstrual cycle, positive rewarding drug effects may be potentiated in women to the same levels as men.[11] Similarly, increased levels of progesterone and decreased estrogen/progesterone ratio have been shown in women who misuse substances relative to healthy controls.[11] Such changes across the menstrual cycle may then alter brain responses to stress and cues as well as affect intensity of emotional responses and craving states in women with AUD relative to men with AUD.[11] As the hypothalamic-pituitary gonadal (HPG) axis modulates sex steroid levels during the menstrual cycle and influences stress responses in women, adaptations in the HPG and HPA axes with the transition to AUD may lead to altered levels of estrogen, progesterone, and their related neuroactive steroids. This could further predispose women to increased anxiety, negative emotion, and lowered tolerance to stress, which in turn may increase vulnerability to craving and compulsive alcohol use in women.

At a time when alcohol misuse is on the rise among girls, and binge drinking and AUD rates have substantially increased in women, there is a major gap in understanding the mechanisms and processes that specifically increase risks for the onset and development of AUD in girls and women and for the maintenance of AUD in women. Greater specific, targeted future research on risk pathways for girls and women can address the need for focused development of targeted prevention and early treatment efforts in females. Prevention and early treatment may reduce the prevalence rates of AUD—as well as the much higher rates of alcohol-related health problems and morbidity in women compared to men—and such efforts may increase alcohol recovery rates among women.

Acknowledgments

This work was supported in part by the National Institutes of Health/National Institute on Alcohol Abuse and Alcoholism grants R01-AA013892 and R01-AA026514.

Financial Disclosure

The authors declare that they have no competing financial interests.

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References

1. Vos T, Abajobir AA, Abbafati C, et al., for GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2017;390(10100):1211-1259. https://doi.org/10.1016/S0140-6736(17)32154-2.
2. Grant BF, Chou SP, Saha TD, et al. Prevalence of 12-Month Alcohol Use, High-Risk Drinking, and DSM-IV Alcohol Use Disorder in the United States, 2001-2002 to 2012-2013: Results From the National Epidemiologic Survey on Alcohol and Related Conditions. *JAMA Psychiatry.* 2017;74(9):911-923. https://doi.org/10.1001/jamapsychiatry.2017.2161.
3. Hingson RW, Zha W, White AM. Drinking beyond the binge threshold: Predictors, Consequences, and Changes in the U.S. *Am J Prev Med.* 2017;52(6):717-727. https://doi.org/10.1016/j.amepre.2017.02.014.
4. Keyes KM, Jager J, Mal-Sarkar T, et al. Is there a recent epidemic of women's drinking? A critical review of national studies. *Alcohol Clin Exp Res.* 2019;43(7):1344-1359. https://doi.org/10.1111/acer.14082.
5. Agabio R, Campesi I, Pisanu C, et al. Sex differences in substance use disorders: Focus on side effects. *Addict Biol.* 2016;21(5):1030-1042. https://doi.org/10.1111/adb.12395.
6. Blanchard RJ, Hebert M, Sakai RR, et al. Chronic social stress: Changes in behavioral and physiological indices of emotion. *Aggress Behav.* 1998;24(4):307-321. https://doi.org/10.1002/(SICI)1098-2337(1998)24:4<307::AID-AB6>3.0.CO;2-F.
7. Sinha R. How does stress increase risk of drug abuse and relapse? *Psychopharmacology (Berl).* 2001;158(4):343-359. https://doi.org/10.1007/s002130100917.
8. Sharrett-Field L, Butler TR, Reynolds AR, et al. Sex differences in neuroadaptation to alcohol and withdrawal neurotoxicity. *Pflugers Arch.* 2013;465(5):643-654. https://doi.org/10.1007/s00424-013-1266-4.
9. Mayor E. Gender roles and traits in stress and health. *Front Psychol.* 2015;6:779. https://doi.org/10.3389/fpsyg.2015.00779.

10. Sinha R. Chronic stress, drug use, and vulnerability to addiction. *Ann N Y Acad Sci.* 2008;1141:105-130. https://doi.org/10.1196/annals.1441.030.
11. Fox HC, Sinha R. Sex differences in drug-related stress-system changes: Implications for treatment in substance-abusing women. *Harv Rev Psychiatry.* 2009;17(2):103-119. https://doi.org/10.1080/10673220902899680.
12. Rothman EF, Edwards EM, Heeren T, et al. Adverse childhood experiences predict earlier age of drinking onset: Results from a representative US sample of current or former drinkers. *Pediatrics.* 2008;122(2):e298-e304. https://doi.org/10.1542/peds.2007-3412.
13. Oram S, Khalifeh H, Howard LM. Violence against women and mental health. *Lancet Psychiatry.* 2017;4(2):159-170. https://doi.org/10.1016/S2215-0366(16)30261-9.
14. Evans BE, Greaves-Lord K, Euser AS, et al. Stress reactivity as a prospective predictor of risky substance use during adolescence. *J Stud Alcohol Drugs.* 2016;77(2):208-219. https://doi.org/10.15288/jsad.2016.77.208.
15. Cheng HG, Anthony JC. Female-male differences in alcohol dependence levels: Evidence on newly incident adolescent and young-adult drinkers in the United States, 2002-2014. *Int J Methods Psychiatr Res.* 2018;27(3):e1717. https://doi.org/10.1002/mpr.1717.
16. Olff M. Sex and gender differences in post-traumatic stress disorder: An update. *Eur J Psychotraumatol.* 2017;8(sup4). 10.1080/20008198.2017.1351204.
17. Finkelhor D, Shattuck A, Turner HA, et al. The lifetime prevalence of child sexual abuse and sexual assault assessed in late adolescence. *J Adolesc Health.* 2014;55(3):329-333. https://doi.org/10.1016/j.jadohealth.2013.12.026.
18. Theurel A, Gentaz E. The regulation of emotions in adolescents: Age differences and emotion-specific patterns. *PLoS One.* 2018;13(6):e0195501. https://doi.org/10.1371/journal.pone.0195501.
19. Chaplin TM, Niehaus C, Gonçalves SF. Stress reactivity and the developmental psychopathology of adolescent substance use. *Neurobiol Stress.* 2018;9:133-139. https://doi.org/10.1016/j.ynstr.2018.09.002.
20. Fujita F, Diener E, Sandvik E. Gender differences in negative affect and well-being: The case for emotional intensity. *J Pers Soc Psychol.* 1991;61(3):427-434. https://doi.org/10.1037/0022-3514.61.3.427.
21. Brady KT, Sinha R. Co-occurring mental and substance use disorders: The neurobiological effects of chronic stress. *Am J Psychiatry.* 2005;162(8):1483-1493. https://doi.org/10.1176/appi.ajp.162.8.1483.
22. Chaplin TM, Hong K, Bergquist K, et al. Gender differences in response to emotional stress: An assessment across subjective, behavioral, and physiological domains and relations to alcohol craving. *Alcohol Clin Exp Res.* 2008;32(7):1242-1250. https://doi.org/10.1111/j.1530-0277.2008.00679.x.
23. Stasiewicz PR, Maisto SA. Two-factor avoidance theory: The role of negative affect in the maintenance of substance use and substance use disorder. *Behav Ther.* 1993;24(3):337-356. https://doi.org/10.1016/S0005-7894(05)80210-2.
24. Becker JB, Perry AN, Westenbroek C. Sex differences in the neural mechanisms mediating addiction: A new synthesis and hypothesis. *Biol Sex Differ.* 2012;3(1):14. https://doi.org/10.1186/2042-6410-3-14.
25. McCaul ME, Roach D, Hasin DS, et al. Alcohol and women: A brief overview. *Alcohol Clin Exp Res.* 2019;43(5):774-779. https://doi.org/10.1111/acer.13985.
26. Albert PR. Why is depression more prevalent in women? *J Psychiatry Neurosci.* 2015;40(4):219-221. https://doi.org/10.1503/jpn.150205.
27. Menary KR, Kushner MG, Maurer E, Thuras P. The prevalence and clinical implications of self-medication among individuals with anxiety disorders. *J Anxiety Disord.* 2011;25(3):335-339. https://doi.org/10.1016/j.janxdis.2010.10.006.
28. Brady KT, Randall CL. Gender differences in substance use disorders. *Am J Psychiatry.* 1993;150(11):1707-1711. https://doi.org/10.1176/ajp.150.11.1707.
29. Sonne SC, Back SE, Zuniga CD, et al. Gender differences in individuals with comorbid alcohol dependence and post-traumatic stress disorder. *Am J Addict.* 2003;12(5):412-423. https://doi.org/10.1111/j.1521-0391.2003.tb00484.x.
30. Ralevski E, Southwick S, Jackson E, et al. Trauma- and stress-induced response in veterans with alcohol dependence and comorbid post-traumatic stress disorder. *Alcohol Clin Exp Res.* 2016;40(8):1752-1760. https://doi.org/10.1111/acer.13120.
31. Back SE, Sonne SC, Killeen T, et al. Comparative profiles of women with PTSD and comorbid cocaine or alcohol dependence. *Am J Drug Alcohol Abuse.* 2003;29(1):169-189. https://doi.org/10.1081/ADA-120018845.
32. Falk DE, Yi HY, Hilton ME. Age of onset and temporal sequencing of lifetime DSM-IV alcohol use disorders relative to comorbid mood and anxiety disorders. *Drug Alcohol Depend.* 2008;94(1-3):234-245. https://doi.org/10.1016/j.drugalcdep.2007.11.022.
33. Farris SG, Epstein EE, McCrady BS, et al. Do co-morbid anxiety disorders predict drinking outcomes in women with alcohol use disorders? *Alcohol Alcohol.* 2012;47(2):143-148. https://doi.org/10.1093/alcalc/agr155.
34. Baldwin JR, Arseneault L, Caspi A, et al. Childhood victimization and inflammation in young adulthood: A genetically sensitive cohort study. *Brain Behav Immun.* 2018;67:211-217. https://doi.org/10.1016/j.bbi.2017.08.025.
35. Kuhlman KR, Vargas I, Geiss EG, et al. Age of trauma onset and HPA axis dysregulation among trauma-exposed youth. *J Trauma Stress.* 2015;28(6):572-579. https://doi.org/10.1002/jts.22054.
36. Blaine SK, Sinha R. Alcohol, stress, and glucocorticoids: From risk to dependence and relapse in alcohol use disorders. *Neuropharmacology.* 2017;122:136-147. https://doi.org/10.1016/j.neuropharm.2017.01.037.
37. Koob GF. Addiction is a reward deficit and stress surfeit disorder. *Front Psychiatry.* 2013;4:72. https://doi.org/10.3389/fpsyt.2013.00072.
38. Thomasson HR. Gender differences in alcohol metabolism. In: Galanter M, Begleiter H, Deitrich R, et al., eds. *Recent Developments in Alcoholism. Volume 12: Alcoholism and Women.* Boston, MA: Springer; 2002:163-179. https://link.springer.com/chapter/10.1007/0-306-47138-8_9.
39. Hashimoto JG, Wiren KM. Neurotoxic consequences of chronic alcohol withdrawal: Expression profiling reveals importance of gender over withdrawal severity. *Neuropsychopharmacology.* 2008;33(5):1084-1096. https://doi.org/10.1038/sj.npp.1301494.
40. Rao U, Morris MC. Cortisol responses to psychosocial stress: The role of childhood maltreatment and depression. *Int J Public Ment Health Neurosci.* 2015;2(1):0018.
41. Moss HB, Vanyukov M, Yao JK, et al. Salivary cortisol responses in prepubertal boys: The effects of parental substance abuse and association with drug use behavior during adolescence. *Biol Psychiatry.* 1999;45(10):1293-1299. https://doi.org/10.1016/S0006-3223(98)00216-9.

42. Hinnant JB, Erath SA, El-Sheikh M. Harsh parenting, parasympathetic activity, and development of delinquency and substance use. *J Abnorm Psychol.* 2015;124(1):137-151. https://doi.org/10.1037/abn0000026.
43. Chaplin TM, Freiburger MB, Mayes LC, et al. Prenatal cocaine exposure, gender, and adolescent stress response: A prospective longitudinal study. *Neurotoxicol Teratol.* 2010;32(6):595-604. https://doi.org/10.1016/j.ntt.2010.08.007.
44. Chaplin TM, Visconti KJ, Molfese PJ, et al. Prenatal cocaine exposure differentially affects stress responses in girls and boys: Associations with future substance use. *Dev Psychopathol.* 2015;27(1):163-180. https://doi.org/10.1017/S0954579414000716.
45. King AC, Hasin D, O'Connor SJ, et al. A prospective 5-year re-examination of alcohol response in heavy drinkers progressing in alcohol use disorder. *Biol Psychiatry.* 2016;79(6):489-498. https://doi.org/10.1016/j.biopsych.2015.05.007.
46. Evans BE, Greaves-Lord K, Euser AS, et al. The relation between hypothalamic-pituitary-adrenal (HPA) axis activity and age of onset of alcohol use. *Addiction.* 2012;107(2):312-322. https://doi.org/10.1111/j.1360-0443.2011.03568.x.
47. Munro CA, McCaul ME, Wong DF, et al. Sex differences in striatal dopamine release in healthy adults. *Biol Psychiatry.* 2006;59(10):966-974. https://doi.org/10.1016/j.biopsych.2006.01.008.
48. Seo D, Ahluwalia A, Potenza MN, et al. Gender differences in neural correlates of stress-induced anxiety. *J Neurosci Res.* 2017;95(1-2):115-125. https://doi.org/10.1002/jnr.23926.
49. Seo D, Jia Z, Lacadie CM, et al. Sex differences in neural responses to stress and alcohol context cues. *Hum Brain Mapp.* 2011;32(11):1998-2013.
50. Ansell EB, Rando K, Tuit K, et al. Cumulative adversity and smaller gray matter volume in medial prefrontal, anterior cingulate, and insula regions. *Biol Psychiatry.* 2012;72(1):57-64. https://doi.org/10.1016/j.biopsych.2011.11.022.
51. Van Dam NT, Rando K, Potenza MN, et al. Childhood maltreatment, altered limbic neurobiology, and substance use relapse severity via trauma-specific reductions in limbic gray matter volume. *JAMA Psychiatry.* 2014;71(8):917-925. https://doi.org/10.1001/jamapsychiatry.2014.680.
52. Sinha R, Lacadie CM, Constable RT, et al. Dynamic neural activity during stress signals resilient coping. *Proc Natl Acad Sci U S A.* 2016;113(31):8837-8842. https://doi.org/10.1073/pnas.1600965113.
53. Rando K, Tuit K, Hannestad J, et al. Sex differences in decreased limbic and cortical grey matter volume in cocaine dependence: A voxel-based morphometric study. *Addict Biol.* 2013;18(1):147-160. https://doi.org/10.1111/adb.12008.
54. Rando K, Chaplin TM, Potenza MN, et al. Prenatal cocaine exposure and gray matter volume in adolescent boys and girls: relationship to substance use initiation. *Biol Psychiatry.* 2013;74(7):482-489. https://doi.org/10.1016/j.biopsych.2013.04.030.
55. Willner P, Field M, Pitts K, et al. Mood, cue and gender influences on motivation, craving and liking for alcohol in recreational drinkers. *Behav Pharmacol.* 1998;9(7):631-642. https://doi.org/10.1097/00008877-199811000-00018.
56. Nesic J, Duka T. Gender specific effects of a mild stressor on alcohol cue reactivity in heavy social drinkers. *Pharmacol Biochem Behav.* 2006;83(2):239-248. https://doi.org/10.1016/j.pbb.2006.02.006.
57. Rubonis AV, Colby SM, Monti PM, et al. Alcohol cue reactivity and mood induction in male and female alcoholics. *J Stud Alcohol.* 1994;55(4):487-494. https://doi.org/10.15288/jsa.1994.55.487.

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Current Reviews

Alcohol Res. 2020;40(2):06 • https://doi.org/10.35946/arcr.v40.2.06

Published: 25 June 2020.

Maternal Substance Use: Consequences, Identification, and Interventions

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Alcohol, tobacco, and cannabis are the substances most frequently used during pregnancy, and opioid-exposed pregnancies have increased fourfold. The purpose of this review is to describe the prevalence and consequences of prenatal exposure to alcohol, tobacco, cannabis, and opioids. Currently available screening questionnaires for prenatal substance use are summarized and contrasted with the measures available for prenatal alcohol use. Because screening for prenatal alcohol and substance use is but the prelude to efforts to mitigate the potential adverse consequences, attempts for the modification of these consequences are briefly reviewed. In addition, areas of future research related to the criminalization of prenatal substance use, which may inhibit both inquiry and disclosure, are discussed. Indeed, the full potential of effective interventions has yet to be realized.

KEY WORDS: prenatal alcohol substance use; screening and intervention

INTRODUCTION

Prenatal exposure to alcohol and other substances has become increasingly common. The substances used most frequently during pregnancy are alcohol, tobacco, and cannabis. Moreover, between 1999 and 2014, the number of women with opioid use disorder during labor and delivery quadrupled.[1] The purpose of this review is to describe the prevalence and consequences of prenatal exposure to alcohol, tobacco, cannabis, and opioids. Currently available screening questionnaires for prenatal substance use are summarized and contrasted with the measures available for prenatal alcohol use. Because screening for prenatal alcohol and substance use is but the prelude to efforts to mitigate the potential adverse consequences, attempts for the modification of these consequences are also briefly reviewed.

It should be noted that this review article is not intended to be a systematic review of the world literature on either prenatal substance use or its prevention. Rather, it is a narrative literature review

that is meant to be illustrative and to stimulate areas of future research because the full potential of effective interventions has yet to be realized.

THE CONSEQUENCES OF PRENATAL SUBSTANCE USE

The consequences of prenatal substance use differ depending on the specific substances used. The most commonly used substances include alcohol, tobacco, cannabis, and opioids.

Prenatal Alcohol Use and Its Consequences

The estimated percentage of prenatal alcohol use is approximately 15%, with past month use being approximately 13%.[2,3] A Centers for Disease Control and Prevention survey conducted from 2015 to 2017 found that nearly 4% of pregnant women had engaged in binge drinking in the prior 30 days.[4] Alcohol use during pregnancy is a highly preventable cause of birth defects and developmental disabilities.[5] Despite the recognition of the teratogenic properties of alcohol, many women continue to disregard advisories on avoiding alcohol during pregnancy.[6]

There is no known safe level of alcohol use while pregnant because there is no exact dose-response relationship between the amount of alcohol consumed during the prenatal period and the extent of damage caused by alcohol in the fetus.[7] Thus, an infant born to a mother who drank alcohol while pregnant may be normal or may manifest alcohol-related birth defects (e.g., problems with the heart, kidneys, bones, or hearing), alcohol-related neurodevelopmental disorders (e.g., intellectual disabilities or problems with behavior and learning), or fetal alcohol spectrum disorders (FASD), which includes a wide range of effects, from mild to severe. An individual with FASD might have abnormal facial features; small head size; shorter than average height; low body weight; poor coordination; hyperactive behavior; difficulty with attention; poor memory; difficulties in school, especially with mathematics; learning disabilities; speech and language delays; intellectual disability or low IQ; poor reasoning and judgment skills; sleep and sucking problems as a baby; vision or hearing problems; and problems with the heart, kidneys, or bones.[8]

A recent multisite study using active case ascertainment methods estimated that the prevalence of FASD among first graders ranged from 1% to 5%.[9] This is concerning because these disorders are associated with life-long disabilities. However, early intervention treatment services can improve a child's development and function.[8]

There is continuing uncertainty about the effects of low and low-to-moderate levels of alcohol intake during pregnancy.[10] For example, a recent cohort study reported craniofacial changes with almost any level of prenatal alcohol intake, but the clinical significance of these changes is not known.[11] Factors that may influence the effects of prenatal alcohol use include patterns of maternal drinking, maternal and fetal genetics, as well as socioeconomic and ethnic factors. Because there is no proven "safe" level of alcohol exposure during pregnancy, the most prudent advice for pregnant women is to abstain from drinking.[12]

Prenatal Tobacco Use and Its Consequences

Cigarette smoking in the antepartum period is common. Past month use of tobacco products among pregnant women was approximately 15% according to the 2017 National Survey on Drug Use and Health report.[13] Tobacco products include the use of alternative forms of nicotine, such as e-cigarettes and vaping, which until recently, have been perceived to be less harmful. For example, in 2015, as many as 7% of women with a recent live birth in Oklahoma and Texas reported using an electronic vapor product shortly before, during, or after pregnancy.[14] Data specific to the effects of prenatal use of electronic vapor products are sparse. However, the Centers for Disease Control and Prevention has issued interim guidance that electronic cigarette products should never be used by pregnant women or adults who do not currently use tobacco products as it investigates

the more than 200 cases of severe pulmonary disease associated with their use.[15]

The use of any tobacco product during pregnancy is associated with adverse maternal, fetal, and neonatal outcomes. Examples of the adverse consequences of tobacco use may begin with subfertility and delay in conception among women who smoke and extend to pregnancy outcomes, which include increased risk of spontaneous pregnancy loss, placental abruption, preterm premature rupture of membranes, placenta previa, preterm labor and delivery, low birth weight, and ectopic pregnancy. Prenatal cigarette smoking may exert effects beyond pregnancy as well and is associated with increased risks of asthma, infantile colic, and childhood obesity.[16]

Prenatal Cannabis Use and Its Consequences

Past month cannabis use among pregnant women ages 18 to 44 increased between 2002 and 2017 from approximately 3% to 7%.[17] Among pregnant adolescents, past month use (15%) was even higher.[18] A recent cross-sectional study using data from 367,403 pregnancies among 276,991 women in Northern California found that self-reported daily, weekly, and monthly cannabis use before and during pregnancy increased between 2009 and 2017. The greatest increases were for daily use, reaching 25% among those who used in the year before pregnancy and 21% among those who used during pregnancy.[19] Explanations for the increases in prenatal use include increasing acceptance of cannabis use and decreasing perceptions of cannabis-related harms.[20]

The association between prenatal cannabis use and maternal, perinatal, and neonatal outcomes is unclear.[21] A 2016 systematic review and meta-analysis concluded that maternal marijuana use during pregnancy was not an independent risk factor for adverse neonatal outcomes, such as low birth weight or preterm delivery, after adjusting for confounding factors like tobacco use.[22] However, limitations to the generalizability of this meta-analysis include the relatively few women in the risk-adjusted group, indicating that the meta-analysis was underpowered to stratify for all secondary outcomes of interest. Another systematic review and meta-analysis from the same time frame found that pregnant women who used marijuana had increased odds of being anemic and that infants exposed to cannabis in utero had decreased birth weight and were more likely to require neonatal intensive care.[23] The researchers from this review acknowledged that because many cannabis users often use tobacco and alcohol as well, discerning a cannabis-only effect was not possible. A population-based cohort study of 661,617 women in Ontario, Canada, showed that the percentage of preterm births among self-reported cannabis users was 12% compared to 6% among nonusers, with this increase persisting even after adjusting for confounding factors.[24] Until there is definitive evidence demonstrating the safety of prenatal marijuana use, concerns that marijuana may interfere with neurodevelopment as well as have other effects have resulted in the American College of Obstetricians and Gynecologists (ACOG) advising women who are pregnant or thinking about pregnancy to avoid using marijuana and other cannabinoids.[25]

Prenatal Opioid Use and Its Consequences

Opioid use among pregnant women increased fourfold between 1999 and 2014 and is present in approximately 3% of pregnancies.[26] Women who use opioids during pregnancy are a diverse group because opioid use may occur in the context of medical care, opioid misuse, or untreated opioid use disorder.[27]

Prenatal opioid use can have a far-reaching clinical impact on infant outcomes. Infants with prenatal opioid exposure are typically born smaller and may have neonatal opioid withdrawal syndrome (NOWS). Infants with NOWS experience withdrawal from opioids and require additional medical care.[28] Characteristics of NOWS, also known as neonatal abstinence syndrome (NAS), include disturbances in gastrointestinal, autonomic, and central nervous systems, leading to irritability,

high-pitched crying, poor sleep, and uncoordinated sucking reflexes that lead to poor feeding. In 2014, a baby was born with NOWS in the United States every 15 minutes.[29,30]

The full impact of opioid exposure during pregnancy on fetal, infant, and childhood outcomes, however, is still unknown. Explanations include the possibility of exposure to other substances as well as concomitant maternal, medical, psychological, and socioeconomic issues. There is a growing body of evidence about the association of opioids with specific birth defects, such as congenital heart defects, neural tube defects, and clubfoot.[31]

For pregnant women with opioid use disorder, substitution treatment with opioid agonists, such as methadone and buprenorphine, imparts important benefits particularly when compared to continued illicit drug use. Advantages include more stable maternal drug levels, reduced withdrawal and drug-seeking behavior, and improved self-care, which should lead to a better pregnancy outcome because of reduced risk for fetal distress, miscarriage, growth restriction, and preterm birth.[32]

Compared to data on buprenorphine-maintained pregnancies, more longitudinal data on methadone-exposed pregnancies are available. In a prospective longitudinal study, 68 methadone-exposed children and 88 nonmethadone-exposed children were evaluated at 2.0 and 4.5 years for executive functioning and later emotional behavioral and emotional adjustment.[33] The methadone-exposed children had worse inhibitory control than the nonexposed children, when taking maternal education and prenatal benzodiazepine use into account. Another study used a school readiness framework to assess the health and neurodevelopmental outcomes of a regional cohort of 100 methadone-exposed children and 110 randomly identified nonmethadone-exposed children who were studied from birth to 4.5 years. Children born to opioid-dependent mothers had higher rates of delay and impairment across all outcome domains, with multiple domain problems being common. Impaired school readiness was associated with greater maternal substance use, higher social risk, male sex, and lower quality caregiving environments.[34]

A systematic review and meta-analysis synthesized data from 41 studies on the neurodevelopment of prenatal methadone-exposed children. The analysis included 1,441 children whose mothers were prescribed methadone during pregnancy and 842 children whose mothers did not receive methadone.[25] Methadone-exposed children appeared to be at increased risk for neurodevelopmental impairment, with lower scores on the Mental Development Index and Psychomotor Development Index, as well as atypical visual evoked potentials, strabismus, and nystagmus. However, these findings about impairment may be biased, with the studies not accounting for factors other than methadone. Indeed, results from this meta-analysis confirm the need for more research and the many factors that can impact pregnancy outcome.

SCREENING FOR PRENATAL SUBSTANCE USE

Early universal screening of pregnant women for alcohol use, substance use, or both is recommended by ACOG because alcohol and substance use is not typically disclosed spontaneously by patients. ACOG recommends clinicians use validated questionnaires or have a conversation with patients but does not endorse using routine urine toxicology tests.[35,36] Moreover, a positive screening questionnaire does not result in a diagnosis. Rather, such a result is an opportunity for a patient and her clinician to review health practices and make changes, if appropriate.[37]

Screening for Prenatal Alcohol Use

There is no known safe level of alcohol consumption during pregnancy.[38] Alcohol is a teratogen; in other words, it is capable of interfering with fetal development, resulting in birth defects. Although the consequences of light alcohol use among women, defined as consuming up to 32 g of alcohol per week, on pregnancy outcomes remain unsettled in the absence of

sufficient evidence, the potential for harm cannot be ruled out.[12] Hence, ACOG has recommended that all women seeking obstetric–gynecologic care be screened for alcohol use annually and within the first trimester of pregnancy.

Screening questionnaires for prenatal alcohol use have been well studied. For example, a systematic review of brief screening questionnaires to identify problem drinking during pregnancy evaluated seven instruments given to 6,724 participants.[39] The measures included the TWEAK (Tolerance, Worried, Eye-Opener, Amnesia, K/Cut Down); the T-ACE (Tolerance [number of drinks], Annoyance, Cut Down, Eye-Opener); CAGE (Cut Down, Annoyed, Guilty, Eye-Opener), NET (Normal Drinker, Eye-Opener, Tolerance); AUDIT (Alcohol Use Disorder Identification Test); AUDIT-C (AUDIT Alcohol Consumption Questions), and SMAST (Short Michigan Alcoholism Screening Test). The screening questionnaires were compared with a structured interview to ascertain drinking status as a reference standard. The T-ACE, AUDIT-C, and TWEAK were the three questionnaires identified to be the most promising screening tools for identifying risk drinking in pregnant women. However, the sensitivity and specificity of these three questionnaires outside the United States is unknown.

Screening for Prenatal Substance Use

Screening instruments for prenatal alcohol use have been well studied, whereas screening instruments for substances other than alcohol have been less well developed.[26,40] The World Health Organization (WHO) guidelines for the identification and management of substance use and substance use disorder during pregnancy list the Substance Use Risk Profile-Pregnancy (SURP-P) scale,[41] the proprietary 4P's Plus©,[42] and the National Institute on Drug Abuse (NIDA) Quick Screen–Modified Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST)[43] as potential screening measures for pregnant women, even though not all of these instruments had been evaluated among that population at the time of its recommendation.[44]

Several recent studies have evaluated the accuracy of various screening tools for prenatal substance use. In one prospective cross-sectional study conducted in Baltimore, MD, with 500 pregnant women, stratified by trimester and use of prenatal care, researchers administered three index tests and compared them to reference tests.[45] The three index tests were the proprietary 4P's Plus©, NIDA Quick Screen–ASSIST), and the SURP-P. The reference tests were urine and hair testing, which captured substance use up to the past 90 days. Alcohol use was not evaluated. The researchers found that there were differences in validity indices (i.e., sensitivity, specificity, positive predictive value, and negative predictive value) by age and race, but not by trimester, for all screening tools. The SURP-P and 4P's Plus© were highly sensitive across all trimesters, races, and age groups.

Another prospective cross-sectional screening accuracy study compared five screening instruments on their ability to identify illicit drug, opioid, and alcohol use under privacy expectations consistent with current practice. The participants included 1,220 pregnant women who were receiving care in Boston, MA; Detroit, MI; or New Haven, CT. The women were socioeconomically diverse and had a mean age of 29 years. The study used a reference standard of substance use in three classes (i.e., illicit drugs, opioids, and alcohol); results were considered positive if use was evident via a 30-day calendar recall or urine toxicology analysis.[46] The illicit drug use reference standard included marijuana, cocaine, heroin, amphetamines, barbiturates, and hallucinogens. The five screening instruments for substance use in pregnancy were the SURP-P; CRAFFT, a five-item screener with items related to car, relax, alone, forget, friends, and trouble; 5Ps, with items on parents, peers, partner, pregnancy, past (i.e., an adaptation of the 4P's Plus©); Wayne Indirect Drug Use Screener (WIDUS); and NIDA Quick Screen–ASSIST. None of the five measures showed both high sensitivity and high specificity, and the area under the curve was low for nearly all measures,

indicating that none could be recommended for applied practice with pregnant women.

A companion study compared the same five measures in the identification of substance use disorder, including alcohol, cannabis, opioids, and stimulants, among the 1,220 pregnant women.[47] Participants completed the Mini International Neuropsychiatric Interview 7.0.2, a short, structured diagnostic interview to identify substance use disorder, including alcohol; cannabis; stimulants, such as cocaine or amphetamines; and opioids, such as heroin and the nonmedical use of prescription drugs.[48] Substance use disorder is distinct from substance use and represents a more significant and persistent pattern of consumption that may increase the risk of adverse infant outcomes as well as indicate that the pregnant woman may need evaluation and referral for specialty treatment.[49] Of the 1,220 women in this study, more than 15% satisfied diagnostic criteria for substance use disorder and more than 30% reported having used alcohol or other substances in the past month. There was little overlap between the women who had substance use disorder and the women who had used alcohol or other substances within the past month. Nearly 10% of the women satisfied criteria for alcohol use disorder, as defined in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders*, and 9.0% satisfied criteria for substance use disorder. Specifically, cannabis use disorder was the most common substance disorder diagnosed (8%). Approximately 3% satisfied criteria for more than one disorder.

There were considerable variations by site. For example, alcohol use disorder was the most common in Boston (15%) but infrequent in New Haven (5%). In contrast, substance use disorder was the most common in Detroit (17%) but less frequent in Boston (3%). Measures of merit (i.e., sensitivity, specificity, accuracy, and area under the receiver operating curve [AUROC]) were calculated with 95% confidence intervals [CI] for the NIDA Quick Screen, CRAFFT, SURP-P, WIDUS, and 5Ps, using substance use disorder as the criterion standard. The CRAFFT (AUROC=0.75, 95% CI [0.72, 0.79]) and SURP-P (AUROC=0.74, 95% CI [0.71, 0.78]) had the highest AUROCs for identifying substance use disorder, including alcohol. In contrast, the NIDA Quick Screen had the lowest AUROC (AUROC=0.62, 95% CI [0.59, 0.65]) for identifying substance use disorder, including alcohol. Overall, the tested measures were more accurate in identifying alcohol use disorder than substance use disorder (e.g., for identifying alcohol use disorder, the AUROCs for the CRAFFT and SURP-P were 0.78 and 0.77, respectively).

Barriers to Early Identification by Screening

Pregnant women with substance use disorder are at increased risk for adverse health and social outcomes, making early identification crucial.[50] Because substance use is substantially underreported, even among women who participate regularly in urine drug screens, use of validated questionnaires to identify prenatal alcohol and substance use has been recommended.[26,51]

There are, however, at least two barriers to these recommendations. First, as discussed in the preceding section, current screening questionnaires have been found to be inadequate measures. According to a 2010 survey of obstetrician-gynecologists, 58% did not use a validated screening tool to assess alcohol risk despite there being several validated tools available.[52] It is likely that even fewer will use a screening tool for prenatal substance use, particularly as such tools are less well developed. A second barrier includes the punitive consequences stemming from state laws regarding prenatal substance use, which can result in patients not wanting to disclose and physicians not wanting to learn about their patients' behaviors.[53-55] Hence, in addition to patients' previous fears about stigmatization because of use, disclosure could now pose a legal risk.[56] An example of a punitive policy includes treating substance use during pregnancy as child abuse or neglect. This policy may arise from a desire to discourage women from using substances while pregnant, to encourage

women to seek treatment, and to ensure the safety of the neonate.[57]

The association between states with punitive or reporting policies related to substance use in pregnancy and rates of NAS was recently evaluated in a study of 4,567,963 births from 8 U.S. states in varying years between 2003 and 2014.[57] States without punitive or reporting policies were compared with states that had such policies, before and after policy enactment. The main outcome measure was the rate of NAS. States that criminalized substance use during pregnancy (e.g., grounds for civil commitment, child abuse, or neglect) had significantly higher rates of NAS in the 1st full year after enactment and more than 1 full year after enactment. In contrast, there was no association with neonatal abstinence rates in states with policies requiring reporting of suspected prenatal substance use. A possible explanation for this difference includes the extent to which pregnant women disengage from health care services when punitive measures are enforced, whereas reporting policies may not dissuade pregnant women from engaging with health care services, resulting in greater conversations between physicians and their patients. However, neither the punitive nor the reporting approach resulted in reduced rates of NAS, which was the presumed, desired outcome of these policies.

AFTER SCREENING: INTERVENTION

Because screening for prenatal alcohol and substance use is but the prelude to efforts to mitigate the potential adverse consequences, brief intervention and referral to treatment, if indicated, have also been recommended.[56] Brief interventions and psychosocial interventions have been examined by investigators and organizations such as the WHO, which sought to develop evidence-based global guidelines for identifying and managing substance use and substance use disorder in pregnancy.[42] Global guidelines were desired because although several high-income countries had developed national guidelines, low- and middle-income countries had not. However, the WHO noted that much of the evidence underlying the effectiveness of screening and brief interventions during pregnancy originated from a time when reporting standards and measures of bias were not in consistent use. Nonetheless, the evidence indicated that asking women about alcohol and other substance use in a detailed and comprehensive way may increase their awareness of the risks associated with these practices and prompt them to modify their behavior.

Psychosocial Interventions for Prenatal Alcohol Use

In late 2018, the U.S. Preventive Services Task Force (USPSTF) renewed its recommendation for screening adults ages 18 year or older, including pregnant women, for unhealthy alcohol use and providing persons engaged in risky or hazardous drinking with brief behavioral counseling interventions to reduce unhealthy alcohol use (i.e., a grade B recommendation meaning that there is high certainty that the net benefit is moderate, or moderate certainty that the net benefit is moderate to substantial).[56] The USPSTF bounds the harms of screening and brief behavioral counseling interventions for unhealthy alcohol use in adults as small to none, based on the likely minimal risks of completing screening questionnaires, the noninvasive nature of the interventions, and the absence of reported harms in the evidence of the behavioral interventions.

The USPSTF makes three special comments with regards to pregnant women. First, any alcohol use by pregnant women is unhealthy. Second, validated alcohol screening tools for pregnant women are available, including the T-ACE and TWEAK. Third, brief counseling interventions among pregnant women have increased the likelihood that women remain abstinent from alcohol use during pregnancy.

Most interventions for FASD have been reported in North America, which has lower FASD prevalence compared to Europe and other sites around the world.[57] Context-related differences may impact on the effectiveness of

the interventions. For example, in a systematic review of prevention interventions to reduce prenatal alcohol exposure and FASD in indigenous communities, reviewers evaluated studies conducted from 1989 to 2017. A total of 10 studies from an initial sample of 712 articles were included if inclusion criteria were met. Comparisons of study effects were made difficult by heterogenous study designs, target populations, and interventions. The reviewers concluded that there was minimal evidence to support the belief that interventions intended to reduce the risk of prenatal alcohol exposure or FASD in indigenous populations have been effective.[58]

Psychosocial Interventions for Prenatal Cigarette Smoking

Psychosocial interventions for supporting women to stop smoking during pregnancy were assessed by the Cochrane Pregnancy and Childbirth Group.[59] This review included 102 randomized controlled trials, with 120 intervention arms. Data from 88 randomized controlled trials, involving more than 28,000 women, were analyzed. Intervention strategies included counseling, health education, feedback, incentives, social support, and exercise. Nearly all studies were conducted in high-income countries. Results from the review yielded moderate- to high-quality evidence that psychosocial interventions increased the proportion of pregnant women who had stopped smoking by late pregnancy (35%), with a 17% reduction in infants born with low birth weight, and a 22% reduction in neonatal intensive care admissions. There did not appear to be any adverse psychological effects from the interventions.

Psychosocial Interventions to Reduce Other Prenatal Substance Use

Screening, brief intervention, and referral to treatment in the perinatal period have been recommended for prenatal substance use.[60] Subsequent to this recommendation, at least two systematic reviews of the evidence for psychosocial interventions have been completed.

The first systematic review included four articles published between 2002 and 2013. It began with 3,792 unique potential publications, but the vast majority did not meet a priori quality criteria. Limited, but promising, evidence of brief interventions reducing illicit drug use among postpartum women was found.[61]

The second systematic review was completed by researchers from the Cochrane Collaboration. They sought to evaluate the evidence on the effect of psychosocial interventions, such as contingency management (CM) and motivational interviewing-based (MIB) techniques compared to that of usual care for pregnant women in outpatient illicit drug treatment programs.[62] This group reviewed 14 studies, with 1,298 pregnant women who received either CM or MIB techniques in addition to other comprehensive care. The women in the control group received usual care that included pharmacological management, counseling, prenatal care, transportation, and/or childcare. There were no differences in retention or abstinence behavior between CM/MIB techniques and usual comprehensive care. The quality of evidence from these studies was assessed to be low to moderate.

SUMMARY

Prenatal exposure to alcohol, tobacco, and marijuana has become increasingly common. In addition, there has been a fourfold increase in the number of opioid-exposed pregnancies. Prenatal exposure to alcohol and other substances may have an adverse impact on a developing fetus. Since pregnant women may be reluctant to disclose their use or may not appreciate the potential for harm, early identification is desirable. However, identification is currently limited by the lack of adequate screening tools and the fear of legal and other sanctions, which may limit both inquiry and disclosure. Although effective interventions for prenatal alcohol, cigarette, and other substances are available, these interventions rely on identification and behavioral counseling. It is likely that the full potential of effective interventions cannot yet be realized in the current setting.

Financial disclosure

The author receives royalty payments from UpToDate.

Publisher's note

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References

1. Haight SC, Ko JY, Tong VT, et al. Opioid use disorder documented at delivery hospitalization—United States, 1999-2014. *MMWR Morb Mortal Wkly Rep*. 2018;67(31):845-849. http://doi.org/10.15585/mmwr.mm6731a1.
2. Denny CH, Acero CS, Naimi TS, et al. Consumption of alcohol beverages and binge drinking among pregnant women aged 18-44 years—United States, 2015-2017. *MMWR Morb Mortal Wkly Rep*. 2019;68 (16):365-368. http://doi.org/10.15585/mmwr.mm6816a1.
3. Terplan M, Cheng D, Chisholm MS. The relationship between pregnancy intention and alcohol use behavior: An analysis of PRAMS data. *J Subst Abuse Treat*. 2014;46(4):506-510. http://doi.org/10.1016/j.jsat.2013.11.001.
4. Warren KR. A review of the history of attitudes toward drinking in pregnancy. *Alcohol Clin Exp Res*. 2015;39(7):1110-1117. http://doi.org/10.1111/acer.12757.
5. Feldman HS, Jones KL, Lindsay S, et al. Prenatal alcohol exposure patterns and alcohol-related birth defects and growth deficiencies: A prospective study. *Alcohol Clin Exp Res*. 2012;36(4):670-676. http://doi.org/10.1111/j.1530-0277.2011.01664.x.
6. Centers for Disease Control and Prevention. *Fetal Alcohol Spectrum Disorders (FASDs). Basics About FASDs*. https://www.cdc.gov/ncbddd/fasd/facts.html. Accessed January 30, 2020.
7. May PA, Chambers CD, Kalberg WO, et al. Prevalence of fetal alcohol spectrum disorders in 4 US communities. *JAMA*. 2018;319(5):474-482. http://doi.org/10.1001/jama.2017.21896.
8. Chang G. *Alcohol Intake and Pregnancy*. May 2019. https://www.uptodate.com/contents/alcohol-intake-and-pregnancy. Accessed January 30, 2020.
9. Muggli E, Matthews H, Penington A, et al. Association between prenatal alcohol exposure and craniofacial shape of children at 12 months of age. *JAMA Pediatr*. 2017;171(8):771-780. http://doi.org/10.1001/jamapediatrics.2017.0778.
10. Mamluk L, Edwards HB, Savovic J, et al. Low alcohol consumption and pregnancy and childhood outcomes: Time to change guidelines indicating apparently "safe" levels of alcohol during pregnancy? A systematic review and meta-analysis. *BMJ Open*. 2017;7(7):e015410. http://doi.org/10.1136/bmjopen-2016-015410.
11. McCance-Katz EF. *National Survey on Drug Use and Health: 2018*. Rockville, MD: Substance Abuse and Mental Health Services Administration; August 2019. https://www.samhsa.gov/data/report/dr-elinore-f-mccance-katz-webcast-slides-national-survey-drug-use-and-health-2018. Accessed January 30, 2020.
12. Kapaya M, D'Angelo DV, Tong VT, et al. Use of electronic vapor products before, during, and after pregnancy among women with a recent live birth—Oklahoma and Texas, 2015. *MMWR Morbid Mortal Wkly Rep.* 2019;68(8):189-194. http://doi.org/10.15585/mmwr.mm6808a1.
13. Schier JG, Meiman JG, Layden J, et al. Severe pulmonary disease associated with electronic-cigarette–product use—Interim guidance. *MMWR Morb Mortal Wkly Rep*. 2019;68(36):787-790. http://doi.org/10.15585/mmwr.mm6836e2.
14. Committee on Underserved Women, Committee on Obstetric Practice. Committee Opinion Number 721: Smoking cessation during pregnancy. *Obstet Gynecol*. 2017;130(4):e200-e204. http://doi.org/10.1097/AOG.0000000000002353.
15. Volkow ND, Han B, Compton WM, et al. Self-reported medical and non-medical cannabis use among pregnant women in the United States. *JAMA*. 2019;322(2):167-169. http://doi.org/10.1001/jama.2019.7982.
16. Salas-Wright CP, Vaughn MG, Ugalde J, et al. Substance use and teen pregnancy in the United States: Evidence from NSDUH 2002-2012. *Addict Behav*. 2015;45:218-225. http://doi.org/10.1016/j.addbeh.2015.01.039.
17. Young-Wolff KC, Sarovar V, Tucker LY, et al. Self-reported daily, weekly, and monthly cannabis use among women before and during pregnancy. *JAMA Netw Open*. 2019;2(7):e196471. http://doi.org/10.1001/jamanetworkopen.2019.6471.
18. Hill KP. Medical use of cannabis in 2019. *JAMA*. August 2019. http://doi.org/10.1001/jama.2019.11868.
19. Silverstein M, Howell EA, Zuckerman B. Cannabis use in pregnancy: A tale of 2 concerns. *JAMA*. 2019;322(2):121-122. http://doi.org/10.1001/jama.2019.8860.
20. Conner SN, Bedell V, Lipsey K, et al. Maternal marijuana use and adverse neonatal outcomes. *Obstet Gynecol*. 2016;128(4):713-723. http://doi.org/10.1097/AOG.0000000000001649.
21. Gunn JKL, Rosales CB, Center KE, et al. Prenatal exposure to cannabis and maternal and child health outcomes: A systematic review and meta-analysis. *BMJ Open*. 2016;6(4):e009986. http://doi.org/10.1136/bmjopen-2015-009986.
22. Corsi DJ, Walsh L, Weiss D, et al. Association between self-reported prenatal cannabis use and maternal, perinatal, and neonatal outcomes. *JAMA*. 2019;322(2):145-152. http://doi.org/10.1001/jama.2019.8734.
23. Volkow ND, Compton WE, Wargo EM. The risks of marijuana use during pregnancy. *JAMA*. 2017;317(2):129-130. http://doi.org/10.1001/jama.2016.18612.
24. Haight SC, Ko JY, Tong VT, et al. Opioid use disorder documented at delivery hospitalization—United States, 1999-2014. *MMWR Morb Mortal Wkly Rep*. 2018;67(31):845-849. http://doi.org/10.15585/mmwr.mm6731a1.
25. Committee on Obstetric Practice. Committee Opinion No. 711: Opioid use and opioid use disorder in pregnancy. *Obstet Gynecol*. 2017;130(2):e81-e94. http://doi.org/10.15585/mmwr.mm6731a1.
26. Ecker J, Abuhamad A, Hill W, et al. Substance use disorders in pregnancy: Clinical, ethical, and research imperatives of the opioid epidemic: A report of a joint workshop of the Society for Maternal-Fetal Medicine, American College of Obstetricians and Gynecologists, and American Society of Addiction Medicine. *Am J Obstet Gynecol*. 2019;221(1):B5-B28. http://doi.org/10.1016/j.ajog.2019.03.022.
27. Honein MA, Boyle C, Redfield RR. Public health surveillance of prenatal opioid exposure in mothers and infants. *Pediatrics*. 2019;143(3):e20183801. http://doi.org/10.1542/peds.2018-3801.
28. Sanlorenzo LA, Stark AR, Patrick SW. Neonatal abstinence syndrome: An update. *Curr Opin Pediatr*. 2018;30(2):182-186. http://doi.org/10.1097/MOP.0000000000000589.
29. Yazdy MM, Desai RJ, Brogly SB. Prescription opioids in pregnancy and birth outcomes: A review of the literature. *J Pediatr Genet*. 2015;4(2):56-70. http://doi.org/10.1055/s-0035-1556740.
30. Konijnenberg C, Melinder A. Prenatal exposure to methadone and buprenorphine: A review of the potential effects on cognitive development. *Child Neuropsychol*. 2011;17(5):495-519. http://doi.org/10.1080/09297049.2011.553591.

31. Levine TA, Woodward LJ. Early inhibitory control and working memory abilities of children prenatally exposed to methadone. *Early Hum Dev*. 2018; 116:68-75. http://doi.org/10.1016/j.earlhumdev.2017.11.010.
32. Lee SJ, Pritchard VE, Austin NC, et al. Health and neurodevelopment of children born to opioid-dependent mothers at school entry. *J Dev Behav Pediatr*. 2020;41(1):48-57. http://doi.org/10.1097/DBP.0000000000000711.
33. Monnelly VJ, Hamilton R, Chappell FM, et al. Childhood neurodevelopment after prescription of maintenance methadone for opioid dependency in pregnancy: A systematic review and meta-analysis. *Dev Med Child Neurol*. 2019;61(7):750-760. http://doi.org/10.1111/dmcn.14117.
34. American College of Obstetricians and Gynecologists, Committee on Ethics. *Committee Opinion No. 633: Alcohol Abuse and Other Substance Use Disorders: Ethical Issues in Obstetric and Gynecologic Practice*. June 2015. https://www.acog.org/-/media/project/acog/acogorg/clinical/files/committee-opinion/articles/2015/06/alcohol-abuse-and-other-substance-use-disorders-ethical-issues-in-obstetric-and-gynecologic-practice.pdf. Accessed January 9, 2019.
35. Chang G. Screening for alcohol and drug use during pregnancy. *Obstet Gynecol Clin N Am*. 2014;41(2):205-212. http://doi.org/10.1016/j.ogc.2014.02.002.
36. National Institute on Alcohol Abuse and Alcoholism. *Fetal Alcohol Exposure*. December 2019. https://www.niaaa.nih.gov/sites/default/files/FASD.pdf. Accessed December 11, 2019.
37. Burns E, Gray R, Smith LA. Brief screening questionnaires to identify problem drinking during pregnancy: A systematic review. *Addiction*. 2010;105(4):601-614. http://doi.org/10.1111/j.1360-0443.2009.02842.x.
38. DeVido J, Bogunovic O, Weiss RD. Alcohol use disorders in pregnancy. *Harv Rev Psychiatry*. 2015;23(2):112-121. http://doi.org/10.1097/HRP.0000000000000070.
39. Yonkers KA, Gotman N, Kershaw T, et al. Screening for prenatal substance use: Development of the substance use risk profile-pregnancy scale. *Obstet Gynecol.* 2010;116(4):827-833. http://doi.org/10.1097/AOG.0b013e3181ed8290.
40. Chasnoff I, Wells A, McGourty R, et al. Validation of the 4 P's Plus screen in pregnancy. *J Perinatol*. 2007;27(12):744-748. http://doi.org/10.1038/sj.jp.7211823.
41. National Institute on Drug Abuse. *Resource Guide: Screening for Drug Use in General Medical Settings*. 2012. https://www.drugabuse.gov/publications/resource-guide/preface. Accessed September 14, 2019.
42. World Health Organization. *Guidelines for the Identification and Management of Substance Use and Substance Use Disorders in Pregnancy*. 2014. https://www.who.int/substance_abuse/publications/pregnancy_guidelines/en. Accessed January 30, 2020.
43. Coleman-Cowger VH, Oga EA, Peters EN, et al. Accuracy of three screening tools for prenatal substance use. *Obstet Gynecol*. 2019;133(5):952-961. http://doi.org/10.1097/AOG.0000000000003230.
44. Ondersma SJ, Chang G, Blake-Lamb T, et al. Accuracy of five self-report screening instruments for substance use in pregnancy. *Addiction*. 2019;114(9):1683-1693. http://doi.org/10.1111/add.14651.
45. Chang G, Ondersma SJ, Blake-Lamb T, et al. Identification of substance use disorders among pregnant women: A comparison of screeners. *Drug Alcohol Depend*. 2019;205: 107651. http://doi.org/10.1016/j.drugalcdep.2019.107651.
46. Sheehan DW, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*. 1998;59(supp 20):22-33. PMID: 9881538.
47. Edwards AC, Ohlsson H, Svikis DS, et al. Protective effects of pregnancy on risk of alcohol use disorder. *Am. J. Psychiatry*. 2019;176(2):138-145. http://doi.org/10.1176/appi.ajp.2018.18050632.
48. Kozhimannil KB, Dowd WN, Ali MM, et al. Substance use disorder treatment admissions and state-level prenatal substance use policies: Evidence from a national treatment database. *Addict Behav*. 2019;90:272-277. http://doi.org/10.1016/j.addbeh.2018.11.019.
49. Garg M, Garrison L, Leeman L, et al. Validity of self-reported drug use information among pregnant women. *Matern Child Health J*. 2016;20(1):41-47. http://doi.org/10.1007/s10995-015-1799-6.
50. Anderson BL, Dan EP, Floyd RL, et al. Knowledge, opinions, and practice patterns of obstetrician-gynecologists regarding their patients' use of alcohol. *J Addict Med*. 2010;4(2):114-121. http://doi.org/10.1097/ADM.0b013e3181b95015.
51. Flavin J, Paltrow LM. Punishing pregnant drug-using women: Defying law, medicine, and common sense. *J Addict Dis*. 2010;29(2):231-244. https://doi.org/10.1080/10550881003684830.
52. Guttmacher Institute. *Substance Use During Pregnancy*. 2020. https://www.guttmacher.org/state-policy/explore/substance-use-during-pregnancy. Accessed February 3, 2020.
53. Angelotta C, Applebaum PS. Criminal charges for child harm from substance use in pregnancy. *J Am Acad Psychiatry Law*. 2017;45(2):193-203.
54. Stone R. Pregnant women and substance use: Fear, stigma, and barriers to care. *Health Justice*. 2015;3(2). http://doi.org/10.1186/s40352-015-0015-5.
55. Faherty LJ, Kranz Am, Russell-Fritch J, et al. Association of punitive and reporting state policies related to substance use in pregnancy with rates of neonatal abstinence syndrome. *JAMA Netw Open*. 2019;2(1):e1914078. http://doi.org/10.1001/jamanetworkopen.2019.14078.
56. U.S. Preventive Services Task Force. Screening and behavioral counseling interventions to reduce unhealthy alcohol use in adolescents and adults. *JAMA*. 2018;320(18):1899-1909. http://doi.org/10.1001/jama.2018.16789.
57. Adebiyi BO, Mukumbang FC, Erasmus C. The distribution of available prevention and management interventions for fetal alcohol spectrum disorder (2007 to 2017): Implications for collaborative actions. *Int J Environ Res Public Health*. 2019;16(12):E2244. http://doi.org/10.3390/ijerph16122244.
58. Symons M, Pedruzzi RA, Bruce K, et al. A systematic review of prevention interventions to reduce prenatal alcohol exposure and fetal alcohol spectrum disorder in indigenous communities. *BMC Public Health*. 2018;18(1):1227. http://doi.org/10.1186/s12889-018-6139-5.
59. Chamberlain C, O'Mara-Eves A, Porter J, et al. Psychosocial interventions for supporting pregnant women to stop smoking. *Cochrane Database Syst Rev*. 2017;10:CD001055. http://doi.org/10.1002/14651858.CD001055.pub4.
60. Wright TE, Terplan M, Ondersma SJ, et al. The role of screening, brief intervention, and referral to treatment in the perinatal period. *Am J Obstet Gynecol*. 2016;215(5):539-547. http://doi.org/10.1016/j.ajog.2016.06.038.
61. Farr SL, Hutchings YL, Ondersma SJ, et al. Brief interventions for illicit drug use among peripartum women. *Am J Obstet Gynecol*. 2014;211(4):336-343. http://doi.org/10.1016/j.ajog.2014.04.005.
62. Terplan M, Ramanadhan S, Locke A, et al. Psychosocial interventions for pregnant women in outpatient illicit drug treatment programs compared to other interventions. *Cochrane Database Syst Rev*. 2015;2(4):CD006037. http://doi.org/10.1002/14651858.CD006037.pub3.

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Current Reviews

Alcohol Res. 2020;40(2):07 • https://doi.org/10.35946/arcr.v40.2.07

Published: 13 August 2020

Alcohol Screening, Brief Intervention, and Referral to Treatment (SBIRT) for Girls and Women

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Females ages 12 and older are the fastest growing segment of alcohol consumers in the United States, with the past decade showing a 16% increase in alcohol use per 12-month period and a 58% increase in high-risk drinking (i.e., > 3 drinks in a day and/or > 7 drinks in a week) per 12-month period. The increase in alcohol use and risk drinking poses unique and serious consequences for women. Women have a more rapid progression to alcohol-related problems and alcohol use disorders (AUD) than men, and if pregnant, women can potentially expose the fetus to alcohol. Screening, brief intervention, and referral to treatment (SBIRT) is an evidence-based, integrated public health approach used to identify and address risky alcohol use among women in a variety of health and social service settings. This article presents the current status of SBIRT among girls ages 12 and older, women of childbearing age, and older women. Screening instruments, brief interventions, and implementation issues specific to women of all ages are described. Through this review of the current literature, care providers can determine best practices for the prevention and treatment of risk drinking in women of all ages presenting in health care settings.

KEY WORDS: brief intervention; risk; alcohol; SBIRT; screening; women; female adolescents

INTRODUCTION

Alcohol is the most commonly consumed substance among Americans ages 12 and older, and women are the fastest growing segment of alcohol consumers in the United States.[1,2] Female alcohol consumption that meets criteria for risk drinking, defined as more than three drinks in a single day or more than seven drinks per week, has the potential to negatively affect the health and well-being of women across their life spans.[3] Evidence indicates converging patterns of alcohol consumption between men and women resulting from recent increases in female alcohol

use behaviors.[2,4,5] For instance, data collected in the past decade reveal that among U.S. women, alcohol use increased by 16% per 12-month period, high-risk drinking increased by 58% per 12-month period, and diagnoses of alcohol use disorder (AUD)—as defined in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders*—increased by 84% per 12-month period.[2] These increases have unique and serious consequences for women given that they experience a more rapid progression—at lower consumption levels—to alcohol-related problems and AUD than men.[6,7]

This recent increase in female alcohol consumption underlines a need for additional research and clinical efforts to address alcohol use among girls and women.[2,4] Because risky drinking poses unique and detrimental consequences to all women, age and life circumstances should not preclude any subset of girls or women from research or clinical efforts to address this growing public health concern. Indeed, risky alcohol use is prevalent among young girls;[8,9] pregnant and postpartum women;[10,11] victims of child abuse,[12] sexual trauma,[13] and intimate partner violence;[14] female veterans;[15] incarcerated girls and women;[16] sexual-minority women;[17] and older women.[5] Due to alcohol's nondiscriminatory nature towards varying groups of women, universal screening, brief intervention, and referral to treatment (SBIRT) appears to be an appropriate, evidence-based public health approach capable of identifying and addressing risky alcohol use among females in a variety of health and social service settings.[18] This article presents a review of the literature regarding the role of SBIRT in addressing risky alcohol consumption among girls (ages 12 to 18), women of childbearing age (i.e., ages 18 to 44), and older women (i.e., ages 65 and older). There is a general lack of currently available research data specific to women ages 45 to 64, but other than risk of pregnancy associated with women ages 18 to 44, the role of SBIRT is similar for women ages 45 to 64 to that for younger women. Databases used for this review include PubMed, Cochrane Library, Google Scholar, and Academic Search Complete. The reference lists of selected articles and texts were also explored.

SBIRT

The current SBIRT model is based on a recommendation from the National Academy of Medicine (previously called the Institute of Medicine) to develop integrated service systems that bridge the gap between primary prevention and treatment services for individuals with problematic alcohol and/or illicit drug use.[19] In 2003, the Substance Abuse and Mental Health Services Administration (SAMHSA) established an initial SBIRT grant program, with the intent of integrating behavioral health services into settings where individuals who engaged in risky substance use behaviors could be identified and offered an appropriate level of intervention and care.[20] Findings from this initiative suggest that SBIRT is associated with improvements in alcohol use outcomes.[20,21]

The U.S. Preventive Services Task Force (USPSTF), an independent entity consisting of experts in preventive medicine, recently updated its recommendation for care providers. This update recommends that care providers screen all adults ages 18 and older, including pregnant women, for risky alcohol use and provide brief behavioral counseling interventions, when appropriate, to reduce unhealthy alcohol use.[22] Screening adolescents younger than age 18 was not included in the updated recommendation; the USPSTF concluded that there is insufficient evidence to properly assess the benefits versus risks for alcohol screening and brief interventions (BI).[22] The American Academy of Pediatrics (AAP), however, has recommended the practice of screening and providing BI to adolescent alcohol users, citing low cost, minimal potential for harm, and emerging evidence of the benefit that SBIRT may have among adolescent alcohol users.[23]

SBIRT is intended to identify, reduce, and prevent problematic alcohol use behaviors and is made up of three key components: screening, brief intervention, and referral to treatment. Ideally, the first step of the SBIRT process is to administer a validated prescreen

instrument to all presenting individuals in a practice setting, as part of the routine intake procedure, to identify those who are drinking at or above risky levels.[24,25,26] When prescreen instruments detect consumption at risk levels, measured by standard drinks (14 grams or 0.6 fluid ounces of pure alcohol) consumed, a more comprehensive assessment can be conducted to gauge the severity of alcohol use and inform BI and/or treatment options.[3] For example, the National Council for Behavioral Health recommends that a symptom checklist or other validated assessment be used to obtain alcohol-related symptoms from individuals whose prescreen indicates risky consumption.[26] If it is determined that an individual is consuming alcohol at moderate risk levels (i.e., above NIAAA threshold for low-risk consumption but not at a level indicative of AUD), then the second step in the SBIRT process is to complete a BI protocol. BIs are often based on principles of motivational interviewing (MI) and aim to increase awareness of alcohol-related risks and consequences and to encourage motivation for change. If an individual is identified to be drinking at levels that are suggestive of AUD, then referral to specialized treatment for further assessment and care is recommended.[27]

SCREENING

SBIRT begins with universal screening, the goal of which is to identify individuals who have, or are at risk of developing, alcohol-related problems.[27] Universal screening that is adherent to SBIRT standards, and described in multiple SBIRT practice guides, involves the administration of a validated prescreen instrument that has been limited to a few questions needing only simple responses.[24,26,28,29] Ideal screening instruments have high sensitivity and specificity ratings, with cutoff scores designed to maximize both ratings in order to minimize false positives and false negatives.[30] However, for prescreen instruments that are intended to be universally administered, priority is often given to sensitivity over specificity so that individuals in large clinical populations (e.g., women in primary or reproductive care settings who consume alcohol while pregnant) are appropriately identified for further assessment.[30,31]

This article classifies screening instruments into prescreen and screen categories. The purpose of prescreening is to assess an individual's frequency and quantity of alcohol use to determine whether the person is drinking at age-specific risk levels, whereas the purpose of screening is to elicit alcohol-related symptoms from those that have been identified as drinking at risk levels. Prescreens and screens should work in succession, and because many instruments are capable of serving both screening purposes, this dual process is sometimes consolidated into a single step within clinical practice settings.

Universal prescreening and screening efforts must be conducted using valid, age-appropriate instruments with cutoff scores that are tailored to a population's sex and age (see Table 1).[32] Following is an overview of screening practices and instruments that have been validated for use within specified age groups of girls and women.

Adolescents

NIAAA, SAMHSA, and AAP recommend that care providers screen all adolescents and young adults ages 12 to 21 for alcohol and substance use behaviors using validated screening instruments on a yearly basis and, as needed, during acute care visits.[33] There are currently three prescreen options that are applicable to adolescents: the two age-specific questions found in NIAAA's *Alcohol Screening and Brief Intervention for Youth: A Practitioner's Guide*;[29] the first three questions of the Screening to Brief Intervention (S2BI); and the three-item Alcohol Use Disorders Identification Test–Concise (AUDIT-C).[33] The two age-specific questions found within NIAAA's guide ask about an adolescent's personal alcohol use as well as that of their friends and is appropriate for children and adolescents between the ages of 9 and 18. This AAP-endorsed guide includes elementary, middle, and high school age-appropriate variations of these two questions, which allow for accurate correlation of patient responses to current or potential risky alcohol consumption.[29] The S2BI instrument screens

for alcohol, tobacco, marijuana, and illicit drug use by asking a single frequency-of-use question per substance. This screener is highly sensitive and specific at discerning among various risk categories, from no use to severe substance use disorder (SUD). Although not a formal diagnostic instrument, the S2BI has been shown to closely correspond with the likelihood of current SUD.[34] The AUDIT-C, validated for use with young people ages 12 to 19, has three questions to identify the quantity and frequency of alcohol consumption.[32,35,36]

When adolescents score positive on a prescreen instrument, indicating some level of risky alcohol consumption, they are asked to respond to additional, more specific screening questions to determine whether a BI or referral to treatment is appropriate. Screening instruments that have been validated for use with adolescents and can be used to inform next steps include the 10-item Alcohol Use Disorders Identification Test (AUDIT); the Brief Screener for Tobacco, Alcohol, and Other Drugs (BSTAD); and the Car, Relax, Alone, Forget, Friends, Trouble (CRAFFT) screening instrument.[23,32,37] The AUDIT is the most widely tested alcohol screening instrument and is commonly used to assist in the early identification of individuals engaging in risky drinking behaviors.[22] Furthermore, the AUDIT has been validated for use among young people,and evidence suggests a lack of gender bias between female and male adolescents.[32,35] The BSTAD, an adaptation of the questions found within NIAAA's guide includes questions on alcohol, tobacco, and drugs, and has been shown to be highly sensitive and specific at identifying risky past-year alcohol use among adolescents ages 12 to 17.[38] Recommended by both NIAAA and AAP, the CRAFFT has been validated across pediatric settings to identify risky substance use behaviors among adolescents.[18,39] Interestingly, the CRAFFT was able to detect preconception substance use in a small cohort of pregnant adolescents and young women between ages 17 and 25.[33,40] The CRAFFT has many advantages, including a short administration time and high sensitivity and specificity.[33] It also shows no evidence of gender bias.[36]

Screening adolescents for risky alcohol use can be incorporated into psychosocial approaches. For example, the home environment, education and employment, eating, peer-related activities, drugs, sexuality, suicide/depression, and safety from injury and violence (HEEADSSS) and the strengths, school, home, activities, drugs/substance use, emotions/depression, sexuality, safety (SSHADESS) tools are interview frameworks specifically designed for use with adolescents in health care settings.[23,33] The HEEADSSS interview is a practical, complementary strategy that establishes rapport by asking less threatening questions at the beginning of the encounter before transitioning to more personal or potentially intrusive topics such as substance use.[33] The SSHADESS interview covers the same life areas as the HEEADSSS, but it also underscores adolescents' resiliency by identifying their perceived and realized strengths before asking questions related to environmental context or risky behaviors.[23]

A caveat is that an assurance of confidentiality is needed to improve the accuracy of adolescent screening responses. Because most adolescents are not comfortable discussing topics like alcohol use and sexual activity in the presence of a parent or guardian, clinicians are encouraged to create scripts or other procedures to excuse the accompanying adult from a portion of the health exam.[33] For example, asking the adult to leave the room during the physical exam portion validates the adolescent's developmental need for privacy and creates space for a confidential discussion concerning alcohol and other potentially risky behaviors.[33] Federal and state privacy laws entitle adolescents to privacy regarding substance use treatment, so adolescents may further benefit from a script ensuring that what is disclosed to the provider will not be shared with their caregiver unless an immediate risk of injury to oneself or another is divulged.[33]

Women of Childbearing Age

For women of childbearing age, the USPSTF supports the use of brief prescreening instruments for alcohol with 1 to 3 items—such as the

AUDIT-C or the NIAAA-recommended Single Alcohol Screening Question (SASQ), also referred to as the "single binge drinking question"—to quickly identify women who may be at risk.[22,41,42] The use of a single binge drinking question has also been recommended as a first step to effectively and efficiently identify women who are likely to be at risk of an alcohol-exposed pregnancy (AEP).[43] For example, a single binge drinking question was found to correctly identify 99% of women, from two countries and cultures, who had been identified as at risk of an AEP.[43] The Quick Drinking Screen (QDS) is another brief instrument that is efficacious at initially identifying women at risk of an AEP.[44] Items from the QDS were measured against data collected from a 90-day timeline followback (TLFB) assessment among a sample of women already determined to be at risk of an AEP. The results found that the women's answers to QDS items were highly similar to their 90-day TLFB responses.[43]

Once a brief prescreening measure identifies a woman who is likely to be at risk for alcohol misuse and/or an AEP, it is recommended that a more comprehensive instrument be administered.[22,43] For example, the 10-item AUDIT is an efficacious measure that has been validated for use with this population.[45] There are also several assessments designed specifically for women of childbearing age, including pregnant women and women at risk of an AEP. It is recommended that universal prescreening among women of childbearing age be used to identify and assess women at risk of an AEP.[45,46] Screening this population provides the opportunity for early intervention among women who may have consumed alcohol prior to becoming aware of their pregnancy. Screening also alerts care providers of consumption levels indicative of AUD so that they can refer these women for specialized treatment.

The Tolerance, Annoyed, Cut Down, Eye-Opener (T-ACE) questionnaire was the first validated screening instrument developed to identify drinking among pregnant women. It is often used in reproductive settings, including maternity care and gynecological clinics.[25,31] In comparison to the AUDIT, the four-item T-ACE has shown slightly higher sensitivity at detecting current alcohol consumption among pregnant women.[31] In addition, the T-ACE accurately identifies varying levels of alcohol consumption and is acceptable for use among culturally diverse obstetric populations.[31] The five-item Tolerance, Worried, Eye-Opener, Amnesia, K/Cut Down (TWEAK) screening instrument is another validated questionnaire for identifying drinking among women, including those who are pregnant and those at risk of an AEP.[25,31,45] Although the TWEAK questionnaire appears to be highly sensitive at identifying heavy patterns of alcohol consumption, primarily among white women, it is less sensitive at detecting lower levels of drinking that could still be considered at risk.[25,47]

In addition to the T-ACE and TWEAK, the USPSTF also recommends the Normal Drinker, Eye-Opener, Tolerance (NET), and the Parents, Partner, Past, Present Pregnancy (4P's Plus) as screening measures capable of assessing alcohol use among pregnant women.[22,47,48] Nonetheless, the T-ACE and TWEAK reportedly perform best among pregnant women and do not appear to have a significant advantage over one another, because both are well-validated screening measures that can be quickly administered in a variety of women's health settings.[18]

Older Women

Older women are often missed by screening efforts because their alcohol-related symptoms are often mistaken for signs of aging.[49] For this reason, systems must be put into place to ensure universal screening on a recurring basis in settings that care for older women.[50] Alcohol screening should take place any time new mental or physical health symptoms arise, before prescribing a new medication, in response to major life changes (e.g., retirement, death of a spouse), and on a yearly basis as part of routine physical and mental health services.[50,51] Providers should be aware that a history of risky alcohol use among older adults often predicts future increases in drinking.[50] Prescreening questions like "During your lifetime,

have you ever used alcohol?" followed by "During the past year, have you had four or more drinks on a single occasion?" help to determine whether more comprehensive assessments are warranted.[51,52] The AUDIT-C and the two-item Substance Use Brief Screen (SUBS) are also prescreen options available for use with this population.[53-55]

Several screening instruments have been validated for use with older adults. Measures like the AUDIT include screening questions on lifetime problems to assess current alcohol-related risk.[54,56] Other screening tools include the Cut Down, Annoyed, Guilty, Eye-Opener (CAGE), the Michigan Alcoholism Screening Test—Geriatric Version (MAST-G), the Short MAST-G, and the Comorbidity Alcohol Risk Evaluation Tool (CARET).[54,57] All of these instruments gather information about the level of consumption and offer decision support for care providers.[50,54] In general, alcohol screening and assessment instruments among older women should contain questions about the frequency and quantity of alcohol use, experiences with drinking-related consequences, medication use, and feelings of depression.[50]

SCREENING RECOMMENDATIONS

There are very few studies on alcohol screening specific to adolescent females and older adult females beyond childbearing age, with a majority of information coming from mixed-gender studies. The largest body of evidence on screening women is for those of childbearing age, likely due to the added risks and harms associated with prenatal alcohol exposure. Nonetheless, universal screening should begin in early adolescence and be repeated at regular intervals across settings that provide health care and social services to girls and women. However, although alcohol screening instruments elicit important information about an individual's level of risk and alcohol-related symptoms, these tools are not a replacement for a complete substance use assessment. Because these instruments are brief and, in many cases, can be self-administered, it is often recommended that care providers use them as decision support aids to guide additional steps based on the preliminary level of risk indicated by these alcohol screening instruments.

The successful implementation of a screening protocol depends on the setting in which it is delivered. For example, settings with access to interdisciplinary professionals may find that longer, more thorough assessment instruments are practical, whereas settings with fewer resources are likely to benefit from utilizing brief instruments like the AUDIT, which has been validated for use across age groups.[32,35,56] Additionally, questions or measures may be added to assessment protocols to identify other factors known to be associated with female alcohol use behaviors (e.g., age of onset, depression and anxiety, childhood and/or intimate partner abuse, co-occurring substance use behaviors) to better inform BI and referral to treatment practices.[13,16,58,59] Moreover, care providers need to remain mindful regarding the language they use to describe alcohol-related concerns so as not to further stigmatize female populations.[60] For example, some women may be sensitive to language such as "alcoholic," "addict," or "abuser"; the use of such language may dissuade women from providing relevant information pertaining to their alcohol use behaviors. Therefore, care providers are advised to use medically accurate terms throughout their discussions regarding alcohol and substance use behaviors.[55,60]

BRIEF INTERVENTIONS

BIs are evidence-based practices that are short, targeted conversations between women and clinicians that follow screening results indicative of risky alcohol consumption. The overall goal of BIs is to help adolescent girls and women who are at risk of alcohol-related consequences by increasing their awareness about the ways alcohol use may put them at risk and encouraging their self-motivation for change.[27,61] Common components of BIs include conversations on standard drink sizes, low- versus high-risk drinking limits, and potential health effects and

social consequences of drinking.[3,62] Another common element of BIs is providing personalized normative feedback, with evidence supporting the use of gender-specific feedback for women.[63,64,65] BIs can be delivered by professionals with different backgrounds and expertise, and they can take place in face-to-face settings, over the phone, or through electronic means.[61,66] How effective BIs are can depend on the number of sessions and length of time allotted for each session. For example, systematic reviews and meta-analyses have found that very brief (i.e., ≤ 5 min) and brief single-contact interventions (i.e., 6 to 15 min) tend to be less effective than brief multicontact interventions (i.e., each contact ≤ 15 min), which evidence shows is the most effective across populations and outcomes.[18,63,67] Additionally, one meta-analysis found that extended BIs (defined by the author as BIs that required several visits, or multicontact interventions) resulted in significant change in alcohol consumption for women but not men.[68]

BIs for risky alcohol use are often based on the principles of MI. Using this collaborative, client-centered approach, providers help females explore and resolve their ambivalence toward changing unhealthy behaviors (e.g., alcohol consumption at risk levels).[69] A core tenet of MI is the use of nonconfrontational techniques to allow individuals to guide themselves toward change without feeling the need to defend their choices.[69]

Adolescents

AAP recommends basing the degree of intervention delivery for youth on the level of risk identified at the time of screening. When no alcohol use is reported, clinicians are encouraged to provide positive verbal reinforcements to motivate continued abstinence. Evidence suggests that even a few positive words from a health care provider may delay alcohol use initiation, and thus extend time for adolescent brain maturation.[23] These positive reinforcements may be critical for female adolescents to receive, especially girls at risk of early alcohol initiation,[7,58] because of the detrimental effects of alcohol on the female developing brain.[70] When infrequent alcohol use is endorsed by female adolescents, such as when an S2BI result indicates alcohol use of one to two times the previous year, it is recommended that care providers advise adolescents to abstain. This advice may combine information on negative health consequences with recognition of personal strengths and positive attributes.[23]

BIs are recommended when an adolescent screens positive for drinking at risky levels. Evidence from a recent meta-analysis of 185 studies examining the effects of alcohol-related BIs for adolescents and young adults found that the interventions effectively reduced drinking and alcohol-related consequences, with effects lasting up to 1 year and showing no demographic variance.[65]

BIs that utilize MI have been found to be effective with substance-using adolescent populations. Much of the research supporting this view falls into the harm-reduction continuum: that is, adolescents do not move directly into abstinence but rather gradually decrease their risky behavior.[71,72] In addition to the effectiveness of MI techniques within this population, a systematic review and meta-analysis conducted by Carney and Myers also found that adolescents showed a preference for individualized interventions (i.e., compared with a group format) conducted over multiple sessions (i.e., compared with a single event).[67]

In alignment with the USPSTF finding of there being insufficient evidence to evaluate the utility of BIs among alcohol-using adolescent populations, evidence specific to adolescent females who receive brief alcohol interventions is also lacking and warrants future investigation. In a recent systematic review and meta-analysis of the literature on brief alcohol interventions for adolescents and young adults, Tanner-Smith and Lipsey found a limited number of studies with boy-only or girl-only samples that reported little to no evidence of differential effectiveness based on gender.[65] There is some evidence, however, suggesting that BIs for alcohol use may be particularly effective for adolescent girls, especially when the provider is also female and the information is delivered in the context of an ongoing provider–patient relationship.[73]

Women of Childbearing Age

There is strong evidence supporting the use of BIs among pregnant and nonpregnant women of childbearing age as a means of reducing levels of alcohol consumption and risks associated with AEPs.[18,62,74] For example, in one large multisite trial, approximately 69% of women who, at intake, were drinking at risky levels and not using effective contraceptive methods reduced their risk of an AEP at the 9-month follow-up after receiving an intervention incorporating MI. The women in this study achieved risk reduction by abstaining from alcohol or drinking below risky levels, by using effective contraceptive methods every time they had vaginal intercourse with a fertile male, or both.[75] A number of randomized controlled trials with pregnant women have also reported significant reductions in alcohol use and improved newborn outcomes following the facilitation of BIs.[62]

In addition to previously mentioned common components of BIs (e.g., personalized normative feedback), interventions with women of childbearing age often also include feedback on the potential effects of alcohol on fetal and child development.[25,64] It is recommended that postpartum women receive information on infant exposure to alcohol through breastmilk and that contraceptive use should be incorporated into BIs with nonpregnant women who are at risk of an AEP.[25,64]

Efficacious prevention and intervention programs have been developed for use with women of childbearing age. One example is the CHOICES program and its adaptations: BALANCE, EARLY, and CHOICES Plus.[76,77,78] CHOICES is an established AEP prevention program based on the principles of MI and designed to provide nonpregnant women of childbearing age with information to help them make informed choices on ways to avoid an AEP.[43] The CHOICES protocol has been widely disseminated across health and social service settings (e.g., primary care facilities, jails, sexually transmitted disease clinics).[75,78,79] Also, as a result of meeting rigorous peer-review criteria, the CHOICES program was included in SAMHSA's Evidence-Based Practices Resource Center (https://www.cdc.gov/ncbddd/fasd/choices-importance-preventing-alcohol-exposed-pregnancies.html).

Older Women

Although limited, studies on BIs with older adults suggest that BIs are effective at reducing risky alcohol consumption, with sustained reductions ranging from 2 to 18 months.[80,81,82] The content and format of most BIs are similar, as are the recommendations, whether delivered to younger or older cohorts. For example, providers are advised to use nonstigmatizing and nonjudgmental language when discussing screening results and any potential alcohol-related health consequences with women.[55] Regarding older women, some experts suggest that providers may find that incorporating the women's family and friends into various parts of the BI process may prove successful.[51]

Other BIs

Multiple BI models have been created to aid in the facilitation of BI conversations.[25,27] A systematic review of BIs for risky drinking in primary care settings reported that a majority are arranged according to the SAMHSA-endorsed Feedback, Responsibility, Advice, Menu of strategies, Empathy, Self-efficacy (FRAMES) model.[33,64] Other BI models that are endorsed by SAMHSA include the Feedback, Listen, Options (FLO) model, the Brief Negotiated Interview (BNI) Steps, and the BNI and Active Referral to Treatment: Provider Training Algorithms.[27] All of these models serve as useful guides for delivering BIs and are presumed to be equally efficacious regardless of age or gender. Practitioners should choose the model that best suits their work setting.

In summary, BIs are valuable tools for reducing alcohol consumption and its associated risks (e.g., AEPs). It is vital to consider that despite a number of randomized controlled trials suggesting similar efficacy for brief alcohol interventions among women and men,[83,84] women have been less likely to receive BIs in practice. As such, lending attention to this issue is critical considering that the prevalence rates for alcohol use among women are rising.[85]

REFERRAL TO TREATMENT

Referral to treatment is a process designed to assist women with accessing specialized treatment, selecting facilities, and navigating barriers that may prevent treatment engagement.[27] Treatment options for women with AUD may include residential treatment, outpatient psychological therapy (e.g., family, group, conjoint, individual), medication-assisted treatment, self-help or support group programs (e.g., 12-step programs such as Alcoholics Anonymous), harm reduction approaches, use of a recovery coach, or any combination of these. There are also treatment options that cater exclusively to women, such as the Women for Sobriety program and women-only Alcoholics Anonymous groups. Specialized alcohol treatment should be personalized to the woman, taking into account her medical, social, and cultural needs. Providers should be aware of local treatment options in order to conduct warm handoffs—referrals facilitated in the presence of the patient to encourage communication and partnership between the patient and treatment team—when needed. Providers should also pay special attention to the treatment selection for pregnant and postpartum women to ensure that appropriate medical care and social support options are available.[25] Providers may also choose to access SAMHSA's online resource guide, which includes samples of scripts, procedures, and links to treatment locator websites.[27] Other referral resources include NIAAA's online Alcohol Treatment Navigator tool (https://alcoholtreatment.niaaa.nih.gov) and NIAAA's publicly available resource guides, with information specific to referrals: *Alcohol Screening and Brief Intervention for Youth: A Practitioner's Guide*[29] and *Helping Patients Who Drink Too Much: A Clinician's Guide*.[28]

Referral to treatment is a critical, yet often overlooked, component of SBIRT. Although some studies have found it effective to link individuals to specialty treatments,[86,87] evidence from many others suggests that it is often difficult to link individuals in need of alcohol-related specialized care to substance use treatment services. For example, a meta-analysis of nine studies found no evidence that brief alcohol interventions were efficacious for increasing the use of alcohol-related services.[88] Referral to treatment is further compounded by gender-specific barriers to treatment that impact women's ability to engage in services. In general, women are less likely than men to initiate alcohol treatment services, and when they do, research suggests that women often contend with stigma, negative staff attitudes, lack of affordable or safe childcare options, and concerns over child custody.[89] When they do access treatment services, more women than men present with histories of trauma and abuse, psychological distress and mental health concerns, interpersonal and family-related issues, and financial constraints.[90] Barriers on a systemic level include lack of treatment options because of geographic isolation and lack of awareness among care providers regarding local treatment options that are capable of addressing the unique needs of adolescent girls and women in treatment settings.[89]

BARRIERS AND FACILITATORS TO SBIRT IMPLEMENTATION

A number of health and social service providers (e.g., physicians, nurses, social workers, psychologists, midwives) are qualified to effectively implement SBIRT across a variety of patient and client settings. However, studies of SBIRT implementation reveal that few providers feel comfortable doing so, with the lowest screening and counseling rates seen among young adult and women's reproductive care providers.[18] For example, one study found that one-third of women who endorsed alcohol consumption in women's health clinics were not asked how much they drank and that a majority of women drinking at risk levels did not receive advice on low-risk limits.[91] Another study concluded that approximately half of women at risk of an AEP did not receive information pertaining to this risk from their health care providers.[91] These findings corroborate national survey data of family planning clinicians, which found that of these clinicians,

approximately one-third used a validated screening measure and one-fifth provided a referral that consisted of more than a list of treatment options.[92]

Qualitative analyses conducted among health care providers have revealed several common barriers to implementing SBIRT, including time constraints, competing priorities, cost, and privacy and confidentiality concerns.[93-96] Barriers that pediatric providers cited include concerns regarding the willingness of adolescents to return for follow-up, limited access to and knowledge of adolescent treatment programs or local expertise, and confidentiality concerns.[94] Additional SBIRT barriers that prenatal care providers identified included lack of rapport between providers and women presenting for an initial prenatal consultation; providers' misperception that there is a low prevalence of alcohol use by pregnant women; providers' lack of skills, training, and follow-up protocol; women's underreporting or false disclosure of alcohol consumption; and providers' concerns over creating guilt and anxiety among pregnant women.[95,96]

Many of these provider-identified barriers should be considered in combination with, and resulting from, U.S. state policies mandating that health care providers report perinatal substance use to child welfare agencies.[97,98] For instance, in 2017, Jarlenski and colleagues conducted a systematic content analysis that identified 24 states with statutes around reporting perinatal substance use by health care providers. Twenty of the states identified had mandatory reporting statutes, while 11 states specified a penalty capable of resulting in a misdemeanor charge for health care providers who failed to report known perinatal substance use.[98] Furthermore, some state statutes allow for involuntary commitment and custody loss solely as a result of prenatal substance use, thus creating an ethical and moral dilemma for prenatal care providers because this violates the principles of patient autonomy and beneficence.[99] This issue was further complicated for prenatal care providers by updated recommendations from the American College of Obstetricians and Gynecologists and the Centers for Disease Control and Prevention, which advise providers to conduct universal screening at initial prenatal appointments.[46,98]

In addition to the barriers faced by prenatal care providers, pregnant women engaged in substance use behaviors often face their own barriers to receiving care, such as fear of stigmatization and legal consequences. This may result in a lack of engagement in prenatal care altogether, thus eliminating the potential for SBIRT implementation and posing significant risks to the health of both mother and child.[60]

Older women also face unique barriers to alcohol intervention and treatment efforts. These include financial limitations and lack of mobility and transportation. Older women also report higher rates of stigma, shame, and guilt than younger women, which may lead to an increased prevalence of isolation, anxiety, and depression.[51]

Approaches to Facilitating SBIRT Implementation

In response to the many recognized barriers, research has begun to identify approaches that facilitate successful SBIRT implementation. So far, evidence suggests that having a practice champion, utilizing an interprofessional team, communicating the details of each SBIRT step, developing relationships with referral partners, instituting ongoing SBIRT training for sustainability, aligning SBIRT practices with the organization's flow, and integrating SBIRT into electronic health records are all ways to facilitate ongoing SBIRT efforts.[24] Additionally, a study of ongoing SBIRT facilitation compared usual care and two adolescent SBIRT delivery modalities (pediatrician-only and pediatrician with an embedded behavioral clinician) and found that although substance use outcomes did not differ between pediatrician-only and embedded behavioral clinician groups, adolescents in the embedded group reported fewer depression symptoms at follow-up.[100] The inclusion of a

behavioral clinician in pediatric settings may be especially beneficial to adolescent girls in light of recent evidence that higher levels of depression severity among girls ages 13 to 16 predicted alcohol use in the following year.[59]

Technology

The use of technology is an additional option for overcoming SBIRT barriers in clinical settings that lack available staff and time resources for ongoing face-to-face implementation.[101] Technology is increasingly being used to facilitate various SBIRT components, with preliminary evidence observed among adolescent girls and women looking promising.[74,102,103] A recent systematic review of women's experiences with technology-based screening found that the perception of anonymity made it easier to divulge potentially stigmatizing information compared to in-person, face-to-face screening methods. Therefore, technology-based screening has the potential to increase disclosure rates and intervention receipt.[104] Studies also suggest that women feel less embarrassed and less afraid of judgment when they participate in technology-based interventions, and the flexibility offered by some technology-based treatments may also be appealing to women who are not willing or able to participate in more formal treatment programs because of family and societal roles.[104]

Nevertheless, whether electronic SBIRT can be effective as a stand-alone entity has yet to be established. One recent study demonstrated successful implementation of a technology-based alcohol intervention (i.e., sans personnel) among women of childbearing age;[66] however, interaction findings from other studies suggest that various female groups may have other intervention needs.[105] For example, Choo and colleagues reported that although female victims of intimate partner violence were receptive to electronic screening and advice, they also desired empathy and compassion from human interaction provided during intervention delivery.[105] Still, evidence has suggested that electronically delivered SBIRT components are mutually beneficial to both women and providers.[103,106] In the future, the use of electronic approaches could also assist in the translation of research findings into routine care settings by standardizing intervention delivery methods while maintaining wide applicability across health and social service settings.[107]

FUTURE DIRECTIONS

More research is needed to evaluate the effectiveness, efficacy, and feasibility of SBIRT practices among females, primarily those in younger and older cohorts, and those at risk of AEPs.[4,10,59,64] Recent reports showed increases in alcohol use among adolescent girls, with evidence suggesting a reversal from traditional male excess to slight female excess in 8th grade, and by 12th grade, 35% of girls reported past-month alcohol use, corresponding to a 250% increase from 8th grade.[9,102] Age of alcohol use initiation is particularly worrisome among adolescent females, given that early initiating females drink more than all male adolescents from ages 12 to 17.[8] Additionally, the association between depression severity and alcohol use appears to be more salient for early adolescent girls than for boys of the same age, with observations suggesting that alcohol use both predicts and is a consequence of depression.[59] Research is also needed to address alcohol use among older women due to population increases. Given the aging of the baby-boom generation, population projections estimate that by 2040, the proportion of women to men ages 65 or older will be 127 to 100.[51,108]

SBIRT is essential for the ongoing identification and intervention of risky alcohol use behaviors among adolescent girls and women. As the prevalence rate of female alcohol use increases, so too should the implementation of SBIRT. These prevention and intervention efforts can help promote lifelong health and well-being among women, with special attention paid to younger and older cohorts, and those at risk of an AEP.

Table 1 Alcohol Screening Instruments

Instrument	No. of Items in Instrument	Approx. Time to Administer (min)	Applicable Population	Scoring That Indicates Risk and Statistical Performance (Sensitivity; Specificity)	Copyright, Source(s), and Cost‡‡	Link(s)
NIAAA *Alcohol Screening and Brief Intervention for Youth: A Practitioner's Guide*[29]	2 to 3 depending on severity	~2	Adolescents ages 9 to 18	Elementary or middle school adolescents (≤ 15 years old) reporting any alcohol use (0.89; 0.91)[33] High school adolescents (≥ 16 years old) reporting ≥ 6 days of past-year alcohol use (0.88; 0.81)[33]	Copyright: N/A Source: N/A Cost: Free online	Publicly available NIAAA guide containing screening questions (page 8): https://www.niaaa.nih.gov/sites/default/files/publications/YouthGuide.pdf
Screening to Brief Intervention (S2BI)[34*]	3 (additional 4 if past-year use indicated)	~2	Adolescents ages 12 to 17	Adolescents reporting alcohol use *once or twice* in the past year (0.96; 0.92) Adolescents reporting alcohol use *monthly* in the past year (0.79; 0.96) Adolescents reporting alcohol use *weekly or more* in the past year (1.00; 0.88)	Copyright: N/A Source: N/A Cost: Free online	Publicly available NIDA link to online version with options for patient or clinician administration: https://www.drugabuse.gov/ast/s2bi/#/
Brief Screener for Tobacco, Alcohol, and Other Drugs (BSTAD)[38*]	6 (additional 3 to 11 if past-year use indicated)	~2	Adolescents ages 12 to 17	≥ 2 days of past-year alcohol use (0.96; 0.85)	Copyright: N/A Source: N/A Cost: Free online	Publicly available NIDA link to web-based instrument with options for patient or clinician administration: https://www.drugabuse.gov/ast/bstad/#/
Alcohol Use Disorders Identification Test (AUDIT)	10	~2 to 3	Adolescent girls ages 12 to 19, adults,§ pregnant women, older adults	Positive score indicating risk: Adolescent girls: ≥ 5 (0.95; 0.77)[32] Adults: ≥ 8 (0.38–0.73; 0.89–0.97)[18]** Pregnant women: > 0[18] Older adults: ≥ 5 (0.86; 0.87)[54]	Copyright: 1989, Thomas Babor and the World Health Organization Sources: World Health Organization, Division of Mental Health & Prevention of Substance Abuse, 1211 Geneva 27, Switzerland Email: Publications@who.int Thomas F. Babor, Alcohol Research Center, University of Connecticut, Farmington, CT Cost: Core questionnaire can be reproduced without permission; test and manual are free; training module costs $75	Publicly available link to self-report instrument: https://cde.drugabuse.gov/sites/nida_cde/files/AUDIT-SelfReport_v1.0_2014May20.pdf

Instrument	No. of Items in Instrument	Approx. Time to Administer (min)	Applicable Population	Scoring That Indicates Risk and Statistical Performance (Sensitivity; Specificity)	Copyright, Source(s), and Cost‡‡	Link(s)
Alcohol Use Disorders Identification Test-Concise (AUDIT-C)	3	~1	Adolescent girls ages 12 to 19, adult women,† pregnant women, older adults	Adolescent girls: ≥ 3 (0.96; 0.65)[32] Adult women: ≥ 3 (0.73–0.97; 0.34–0.89)[18] Pregnant women: > 0 (NR‡)[18] Older adults: ≥ 4 (0.94; 0.80)[54]	Copyright: N/A Source: N/A Cost: Free online	Publicly available SAMHSA link: https://www.integration.samhsa.gov/images/res/tool_auditc.pdf
Car, Relax, Alone, Forget, Friends, Trouble (CRAFFT)[37]*	4 (additional 5 if past-year use indicated)	~2 to 3	Adolescents ages 12 to 21	≥ 1 (0.94; 0.74)[30,39] Optimal cutoff score indicating heightened risk for SUD: ≥ 2 (0.79; 0.97)[39]	Copyright: 2001, Boston Children's Hospital Source: The Center for Adolescent Substance Abuse Research, Children's Hospital, 300 Longwood Ave., Boston, MA 02115 Phone: 617-355-5433 Email: crafft@childrens.harvard.edu Cost: N/A	Publicly available SAMHSA link which states that the CRAFFT may be reproduced in [this] exact form for use in clinical settings courtesy of the Center for Adolescent Substance Abuse Research at the Boston Children's Hospital: https://www.integration.samhsa.gov/clinical-practice/sbirt/CRAFFT_Screening_interview.pdf Link from Boston Children's Hospital with additional information: http://crafft.org/
NIAAA Single Item Alcohol Screening Questionnaire (SASQ)[52]	1	~1	Adults	≥ 1 (0.82; 0.79)[18]	Copyright: N/A Source: N/A Cost: N/A	Publicly available SAMHSA link to NIAAA's *Helping Patients Who Drink Too Much: A Clinician's Guide,* which includes NIAAA SASQ (page 4): https://www.integration.samhsa.gov/clinical-practice/Helping_Patients_Who_Drink_Too_Much.pdf Publicly available USPSTF Final Recommendation Statement: *Unhealthy Alcohol Use in Adolescents and Adults: Screening and Behavioral Counseling Interventions,* includes NIAAA SASQ question: https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/unhealthy-alcohol-use-in-adolescents-and-adults-screening-and-behavioral-counseling-interventions

Instrument	No. of Items in Instrument	Approx. Time to Administer (min)	Applicable Population	Scoring That Indicates Risk and Statistical Performance (Sensitivity; Specificity)	Copyright, Source(s), and Cost‡‡	Link(s)
Quick Drinking Screen (QDS)[44,109]	3	~1	Adults	Scoring based on presence of NIAAA defined at-risk drinking (i.e., more than 3 drinks on any day or 7 drinks per week for adult women) in past 90 days[43††]	Copyright: 2003, Sobell & Sobell Source: Linda C. Sobell, PhD, ABPP, Center for Psychological Studies, Nova Southeastern University, 3301 College Ave., Fort Lauderdale, FL 33314 Email: sobelll@nova.edu Cost: Free	Publicly available link that states that this screener can be freely used as it is in the public domain: https://www.nova.edu/gsc/forms/quick_drinking_screen.pdf
Tolerance, Annoyed, Cut Down, Eye Opener (T-ACE)[31]	4	~1	Women of childbearing age	≥ 2 (0.69–0.88; 0.71–0.89)[25]	Copyright: 1989, Harcourt Health Sciences; permission needed to publish Sources: S. Martier, Ob/Gyn, 4707 Saint Antoine, Detroit, MI 48201 Permissions Department, Mosby, Inc. (a division of Elsevier), 6277 Sea Harbor Dr., Orlando, FL Phone: 407-345-3994 http://www.us.elsevierhealth.com/ Cost: N/A	Publicly available NIAAA link containing copyright information: https://pubs.niaaa.nih.gov/publications/t_ace.htm Publicly available NIAAA link containing T-ACE questions: https://pubs.niaaa.nih.gov/publications/arh28-2/78-79.htm
Tolerance, Worried, Eye Opener, Amnesia, K-Cut Down (TWEAK)[31]	5	~2	Pregnant women	≥ 2 (0.71–0.91; 0.73–0.83)[25]	Copyright: None Source: Marcia Russell Prevention Research Center, 1995 University Avenue, Suite 450, Berkeley, CA 94704 Phone: 510-883-5703 Email: russell@prev.org Cost: Free	Publicly available NIAAA link with more information: https://pubs.niaaa.nih.gov/publications/assessingalcohol/instrumentpdfs/74_tweak.pdf
Normal Drinker, Eye-Opener, Tolerance (NET)[47]	3	~1	Pregnant women	≥ 2 (0.61; 0.87)[47]	Copyright: 1989, Lippincott Williams & Wilkins Source: Lippincott Williams & Wilkins Permissions Department, 351 West Camden St., Baltimore, MD 21201 Phone: 410-528-4050 Email: permissions@lww.com http://www.lww.com/permissions/index.htm Cost: N/A	Not publicly available
Parents, Partner, Past, Present Pregnancy (4P's Plus)[48]*	5	~1	Pregnant women	≥ 1 (0.87; 0.76)[48]	Copyright: The National Training Institute/NTI Upstream Source: NTI Upstream, 180 N. Michigan Ave., Suite 700, Chicago, IL 60601 Cost: Licensing fees may apply	Publicly available link with more information: https://www.ntiupstream.com/4psabout

Instrument	No. of Items in Instrument	Approx. Time to Administer (min)	Applicable Population	Scoring That Indicates Risk and Statistical Performance (Sensitivity; Specificity)	Copyright, Source(s), and Cost‡‡	Link(s)
Substance Use Brief Screen (SUBS)[53*]	4	~1	Adults	Any response other than "never" on alcohol binge question: (0.85; 0.77)	Copyright: N/A Source: N/A Cost: N/A	Publicly available NIH publication with more information: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4475501/
Cut Down, Annoyed, Guilty, Eye-Opener (CAGE)[57]	4	~1	Adults	≥ 2 (0.14–0.39; 0.97)	Copyright: None Source: N/A Cost: Freely available as it is in the public domain and no permission is necessary unless used in a profit-making endeavor	Publicly available SAMHSA link: https://www.integration.samhsa.gov/clinical-practice/sbirt/CAGE_questionaire.pdf
Michigan Alcohol Screening Test–Geriatric Version (MAST-G)[57]	24	~5 to 10	Older adults	≥ 5 (0.70–0.91; 0.81–0.85)	Copyright: 1991, The Regents of the University of Michigan Source: Frederick C. Blow, PhD, University of Michigan Alcohol Research Center, 400 E. Eisenhower Parkway, Suite A, Ann Arbor, MI 48104 Phone: 313-998-7952 Cost: Free online	Publicly available NIH link to SAMHSA's *Substance Abuse Among Older Adults: Treatment Improvement Protocol No. 26* (page 55): https://www.ncbi.nlm.nih.gov/books/NBK64419/pdf/Bookshelf_NBK64419.pdf
Short Michigan Alcohol Screening Test–Geriatric Version (SMAST-G)[57]	10	Not reported	Older adults	≥ 2 (0.52; 0.96)	Copyright: 1991, The Regents of the University of Michigan Source: N/A Cost: N/A	Publicly available link provided by The Hartford Institute for Geriatric Nursing, New York University, Rory Meyers College of Nursing: https://consultgeri.org/try-this/general-assessment/issue-17.pdf
Comorbidity Alcohol Risk Evaluation Tool (CARET)	10	~2 to 5	Older adults	A positive response in any of the seven risk categories (0.92; 0.51)[54]	Copyright: N/A Source: N/A Cost: N/A	Not publicly available

NIAAA = National Institute on Alcohol Abuse and Alcoholism; NIDA = National Institute on Drug Abuse; NIH = National Institutes of Health; SAMHSA = Substance Abuse and Mental Health Services Administration.

* Instrument screens for alcohol and other substances.

† Recommended AUDIT-C cutoff score is different for adult women (≥ 3) and men (≥ 4).[18]

‡ Not reported.

§ Recommended AUDIT cutoff score is the same for adult women and men (≥ 8).[18]

** Several U.S.-based studies show more optimal balances of sensitivity and specificity at lower AUDIT cutoffs (e.g., 3, 4, 5); preliminary findings from the USPSTF 2018 updated evidence report and systematic review indicates that lower cutoffs may be preferred.[18]

†† Sensitivity and specificity are not reported for this instrument.

‡‡ N/A, information was not available or retrievable. None, the instrument explicitly states that no copyright is held. Cost: N/A, no information was found regarding cost. Free/free online, the information pertaining to the instrument explicitly states that it is available to the public.

Financial disclosure

The authors declare that they have no competing financial interests.

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References

1. Substance Abuse and Mental Health Services Administration (SAMHSA). *Key Substance Use and Mental Health Indicators in the United States: Results from the 2018 National Survey on Drug Use and Health.* Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration; 2019.
2. Grant BF, Chou SP, Saha TD, et al. Prevalence of 12-month alcohol use, high-risk drinking, and DSM-IV alcohol use disorder in the United States, 2001-2002 to 2012-2013: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *JAMA Psychiatry.* 2017;74(9):911-923. http://doi.org/10.1001/jamapsychiatry.2017.2161.
3. Dawson DA, Li T-K, Grant BF. A prospective study of risk drinking: at risk for what? *Drug and Alcohol Depend.* 2008; 95(1-2): 62-67. https://doi.org/10.1016/j.drugalcdep.2007.12.007.
4. Slade T, Chapman C, Swift W, et al. Birth cohort trends in the global epidemiology of alcohol use and alcohol-related harms in men and women: Systematic review and metaregression. *BMJ Open.* 2016;6(10):e011827. http://doi.org/10.1136/bmjopen-2016-011827.
5. Han BH, Moore AA, Sherman S, et al. Demographic trends of binge alcohol use and alcohol use disorders among older adults in the United States, 2005-2014. *Drug Alcohol Depend.* 2017;170:198-207. http://doi.org/10.1016/j.drugalcdep.2016.11.003.
6. Ceylan-Isik AF, McBride SM, Ren J. Sex difference in alcoholism: Who is at a greater risk for development of alcoholic complication? *Life Sci.* 2010;87(5-6):133-138. http://doi.org/10.1016/j.lfs.2010.06.002.
7. Foster KT, Hicks BM, Iacono WG, et al. Gender differences in the structure of risk for alcohol use disorder in adolescence and young adulthood. *Psychol Med.* 2015;45(14):3047-3058. http://doi.org/10.1017/S0033291715001014.
8. Bolland KA, Bolland JM, Tomek S, et al. Trajectories of adolescent alcohol use by gender and early initiation status. *Youth Soc.* 2016;48(1):3-32. http://doi.org/10.1177/0044118X13475639.
9. Johnston LD, Malley PMO, Miech RA, et al. *Monitoring the Future National Survey Results on Drug Use, 1975-2015: Overview, Key Findings on Adolescent Drug Use.* Ann Arbor, MI: Institute for Social Research, The University of Michigan; 2016.
10. Denny CH, Acero CS, Naimi TS, et al. Consumption of alcohol beverages and binge drinking among pregnant women aged 18-44 years – United States, 2015-2017. *MMWR Morb Mortal Wkly Rep.* 2019;68(16):365-368. http://doi.org/10.15585/mmwr.mm6816a1.
11. May PA, Hasken JM, Blankenship J, et al. Breastfeeding and maternal alcohol use: Prevalence and effects on child outcomes and fetal alcohol spectrum disorders. *Reprod Toxicol.* 2016;63:13-21. http://doi.org/10.1016/j.reprotox.2016.05.002.
12. Salter M, Breckenridge J. Women, trauma and substance abuse: Understanding the experiences of female survivors of childhood abuse in alcohol and drug treatment. *Int J Soc Welf.* 2014;23(2):165-173. http://doi.org/10.1111/ijsw.12045.
13. Hannan SM, Orcutt HK, Miron LR, et al. Childhood sexual abuse and later alcohol-related problems: Investigating the roles of revictimization, PTSD, and drinking motivations among college women. *J Interpers Violence.* 2017;32(14):2118-2138. http://doi.org/10.1177/0886260515591276.
14. Devries KM, Child JC, Bacchus LJ, et al. Intimate partner violence victimization and alcohol consumption in women: A systematic review and meta-analysis. *Addiction.* 2014;109(3):379-391. http://doi.org/10.1111/add.12393.
15. Hoggatt KJ, Jamison AL, Lehavot K, et al. Alcohol and drug misuse, abuse, and dependence in women veterans. *Epidemiol Rev.* 2015;37(1):23-37. http://doi.org/10.1093/epirev/mxu010.
16. McKee SA, Hilton NZ. Co-occurring substance use, PTSD, and IPV victimization: Implications for female offender services. *Trauma Violence Abuse.* 2019;20(3):303-314. http://doi.org/10.1177/1524838017708782.
17. McCabe SE, Hughes TL, Bostwick WB, et al. Sexual orientation, substance use behaviors and substance dependence in the United States. *Addiction.* 2009;104(8):1333-1345. http://doi.org/10.1111/j.1360-0443.2009.02596.x.
18. O'Connor EA, Perdue LA, Senger CA, et al. *Screening and Behavioral Counseling Interventions to Reduce Unhealthy Alcohol Use in Adolescents and Adults: An Updated Systematic Review for the U.S. Preventive Services Task Force.* Rockville, MD: Agency for Healthcare Research and Quality; 2018. http://doi.org/10.1001/jama.2018.12086.
19. Institute of Medicine, Committee on Treatment of Alcohol Problems. *Broadening the Base of Treatment for Alcohol Problems.* Washington, DC: National Academy of Sciences; 1990.
20. Aldridge A, Linford R, Bray J. Substance use outcomes of patients served by a large US implementation of Screening, Brief Intervention and Referral to Treatment (SBIRT). *Addiction.* 2017;112(suppl 2):43-53. http://doi.org/10.1111/add.13651.
21. The InSight Project Research Group. SBIRT outcomes in Houston: Final report on InSight, a hospital district-based program for patients at risk for alcohol or drug use problems. *Alcohol Clin Exp Res.* 2009;33(8):1374-1381. http://doi.org/10.1111/j.1530-0277.2009.00967.x.
22. US Preventive Services Task Force. Screening and behavioral counseling interventions to reduce unhealthy alcohol use in adolescents and adults: US Preventive Services Task Force Recommendation Statement. *JAMA.* 2018;320(18):1899-1909. http://doi.org/10.1001/jama.2018.16789.
23. Committee on Substance Use and Prevention. Substance use Screening, Brief Intervention, and Referral to Treatment. *Pediatrics.* 2016;138(1):e1-e15. https://doi.org/10.1542/peds.2016-1211.
24. Hargraves D, White C, Frederick R, et al. Implementing SBIRT (Screening, Brief Intervention and Referral to Treatment) in primary care: Lessons learned from a multi-practice evaluation portfolio. *Public Health Rev.* 2017;38:31. http://doi.org/10.1186/s40985-017-0077-0.
25. Shogren MD, Harsell C, Heitkamp T. Screening women for at-risk alcohol use: An introduction to Screening, Brief Intervention, and Referral to Treatment (SBIRT) in women's health. *J Midwifery Womens Health.* 2017;62(6):746-754. http://doi.org/10.1111/jmwh.12659.

26. National Council for Behavioral Health. *Implementing Care for Alcohol & Other Drug Use in Medical Settings. An Extension of SBIRT.* 2018. https://www.thenationalcouncil.org/wp-content/uploads/2018/03/021518_NCBH_ASPTReport-FINAL.pdf?daf=375ateTbd56. Accessed January 29, 2020.
27. SAMHSA, HRSA Center for Integrated Health Services. *SBIRT: Screening, Brief Intervention, and Referral to Treatment.* https://www.integration.samhsa.gov/clinical-practice/sbirt#why? Accessed August 11, 2019.
28. NIAAA. *Helping Patients Who Drink Too Much: A Clinician's Guide.* 2016. https://www.issup.net/knowledge-share/publications/2017-07/helping-patients-who-drink-too-much-clinicians-guide. Accessed January 29, 2020.
29. NIAAA. *Alcohol Screening and Brief Intervention for Youth: A Practitioner's Guide.* 2015. https://www.niaaa.nih.gov/sites/default/files/publications/YouthGuide.pdf. Accessed January 29, 2020.
30. Pilowsky DJ, Wu L-T. Screening instruments for substance use and brief interventions targeting adolescents in primary care: A literature review. *Addict Behav.* 2013;38(5):2146-2153. http://doi.org/10.1016/j.addbeh.2013.01.015.
31. Chang G. Alcohol-screening instruments for pregnant women. *Alcohol Res Health.* 2001;25(3):204-209.
32. Liskola J, Haravuori H, Lindberg N, et al. AUDIT and AUDIT-C as screening instruments for alcohol problem use in adolescents. *Drug Alcohol Depend*. 2018;188:266-273. http://doi.org/10.1016/j.drugalcdep.2018.04.015.
33. Kowalchuk A, Mejia de Grubb M, Gonzalez S, et al. Addressing substance use with the adolescent in primary care: The SBIRT Model. In: Morelli V, ed. *Adolescent Health Screening: An Update in the Age of Big Data.* St. Louis, MO: Elsevier Inc.; 2019:165-177. https://doi.org/10.1016/B978-0-323-66130-0.00013-2.
34. Levy S, Weiss R, Sherritt L, et al. An electronic screen for triaging adolescent substance use by risk levels. *JAMA Pediatr.* 2014;168(9):822–828. http://doi.org/10.1001/jamapediatrics.2014.774.
35. Toner P, Böhnke JR, Andersen P, et al. Alcohol screening and assessment measures for young people: A systematic review and meta-analysis of validation studies. *Drug Alcohol Depend.* 2019;202:39-49. http://doi.org/10.1016/j.drugalcdep.2019.01.030.
36. Cook RL, Chung T, Kelly TM, et al. Alcohol screening in young persons attending a sexually transmitted disease clinic. Comparison of AUDIT, CRAFFT, and CAGE instruments. *J Gen Intern Med.* 2005;20(1):1-6. http://doi.org/10.1111/j.1525-1497.2005.40052.x.
37. Knight JR, Sherritt L, Harris SK, et al. Validity of brief alcohol screening tests among adolescents: A comparison of the AUDIT, POSIT, CAGE, and CRAFFT. *Alcohol Clin Exp Res.* 2003;27(1):67-73. http://doi.org/10.1097/01.ALC.0000046598.59317.3A.
38. Kelly SM, Gryczynski J, Mitchell SG, et al. Validity of brief screening instrument for adolescent tobacco, alcohol, and drug use. *Pediatrics.* 2014;133(5):819-826. http://doi.org/10.1542/peds.2013-2346.
39. Mitchell SG, Kelly SM, Gryczynski J, et al. The CRAFFT cut-points and DSM-5 criteria for alcohol and other drugs: A re-evaluation and re-examination. *Subst Abus.* 2015;35(4):376-380. http://doi.org/10.1080/08897077.2014.936992.
40. Chang G, Orav EJ, Jones JA, et al. Self-reported alcohol and drug use in pregnant young women: A pilot study of associated factors and identification. *J Addict Med.* 2011;5(3):221-226. http://doi.org/10.1097/ADM.0b013e318214360b.
41. Johnson KE, Sobell MB, Sobell LC. Using one question to identify women at risk for an alcohol-exposed pregnancy. *J Am Osteopath Assoc.* 2010;110(7):381-384. http://doi.org/10.1037/e601142009-001.
42. Bradley KA, DeBenedetti AF, Volk RJ, et al. AUDIT-C as a brief screen for alcohol misuse in primary care. *Alcohol Clin Exp Res*. 2007;31(7):1208-1217. http://doi.org/10.1111/j.1530-0277.2007.00403.x.
43. Velasquez MM, Sobell LC, Sobell MB, et al. *Women and Drinking: Preventing Alcohol-Exposed Pregnancies.* Boston, MA: Hogrefe Publishing; 2016.
44. Dum M, Sobell LC, Sobell MB, et al. A Quick Drinking Screen for identifying women at risk for an alcohol-exposed pregnancy. *Addict Behav.* 2009;34(9):714-716. http://doi.org/10.1016/j.addbeh.2009.04.001.
45. Sarkar M, Burnett M, Carrière S, et al. Screening and recording of alcohol use among women of child-bearing age and pregnant women. *Can J Clin Pharmacol.* 2009;16(1):e242-e263.
46. Wright TE, Terplan M, Ondersma SJ, et al. The role of Screening, Brief Intervention, and Referral to Treatment in the perinatal period. *Am J Obstet Gynecol.* 2016;215(5):539-547. http://doi.org/10.1016/j.ajog.2016.06.038.
47. Bradley KA, Boyd-Wickizer J, Powell SH, et al. Alcohol screening questionnaires in women: A critical review. *JAMA.* 1998;280(2):166-171. http://doi.org/10.1001/jama.280.2.166.
48. Chasnoff IJ, Wells AM, Mcgourty RF, et al. Validation of the 4P's Plus screen for substance use in pregnancy validation of the 4P's Plus. *J Perinatol.* 2007;27:744-748. http://doi.org/10.1038/sj.jp.7211823.
49. Kuerbis A, Sacco P, Blazer DG, et al. Substance abuse among older adults. *Clin Geriatr Med.* 2014;30(3):629-654. http://doi.org/10.1016/j.cger.2014.04.008.
50. Blow FC, Barry KL. Use and misuse of alcohol among older women. *Alcohol Res Health.* 2002;26(4):308-315.
51. Goldstein NS, Hodgson N, Savage C, et al. Alcohol use and the older adult woman. *J Nurse Pract.* 2015;11(4):436-442. http://doi.org/10.1016/j.nurpra.2015.01.016.
52. Smith PC, Schmidt SM, Allensworth-Davies D, et al. Primary care validation of a single-question alcohol screening test. *J Gen Intern Med.* 2009;24(7):783-788. http://doi.org/10.1007/s11606-009-0928-6.
53. McNeely J, Strauss SM, Saitz R, et al. A brief patient self-administered substance use screening tool for primary care: Two-site validation study of the Substance Use Brief Screen (SUBS). *Am J Med.* 2015;128(7):784.e9-784.e19. http://doi.org/10.1016/j.amjmed.2015.02.007.
54. Schonfeld L. Adapting SBIRT for older adults. In: Kuerbis A, Moore AA, Sacco P, et al., eds. *Alcohol and Aging: Clinical and Public Health Perspectives.* New York, NY: Springer International Publishing; 2016:215-232. http://doi.org/10.1007/978-3-319-47233-1_14.
55. Han BH, Moore AA. Prevention and screening of unhealthy substance use by older adults. *Clin Geriatr Med.* 2018;34(1):117-129. http://doi.org/10.1016/j.cger.2017.08.005.
56. Moore AA, Kuerbis A, Sacco P, et al. Screening and assessment of unhealthy alcohol use in older adults. In: Kuerbis A, Moore AA, Sacco P, et al., eds. *Alcohol and Aging: Clinical and Public Health Perspectives.* New York, NY: Springer International Publishing; 2016:169-180. http://doi.org/10.1007/978-3-319-47233-1_11.
57. Berks J, McCormick R. Screening for alcohol misuse in elderly primary care patients: A systematic literature review. *Int Psychogeriatr.* 2008;20(6):1090-1103. http://doi.org/10.1017/S1041610208007497.

58. Schinke SP, Fang L, Cole KCA. Substance use among early adolescent girls: Risk and protective factors. *J Adolesc Health.* 2008;43(2):191-194. http://doi.org/10.1016/j.jadohealth.2007.12.014.
59. Schleider JL, Ye F, Wang F, et al. Longitudinal reciprocal associations between anxiety, depression, and alcohol use in adolescent girls. *Alcohol Clin Exp Res.* 2019;43(1):98-107. http://doi.org/10.1111/acer.13913.
60. Stone R. Pregnant women and substance use: Fear, stigma, and barriers to care. *Health Justice.* 2015;3(1):1-15. http://doi.org/10.1186/s40352-015-0015-5.
61. Thibaut F, Chagraoui A, Buckley L, et al. WFSBP and IAWMH Guidelines for the treatment of alcohol use disorders in pregnant women. *World J Biol Psychiatry.* 2019;20(1):17-50. http://doi.org/10.1080/15622975.2018.1510185.
62. Gebara CF, Bhona FM, Ronzani TM, et al. Brief intervention and decrease of alcohol consumption among women: A systematic review. *Subst Abuse Treat Prev Policy.* 2013;8(1):4-8. http://doi.org/10.1186/1747-597X-8-31.
63. Jonas DE, Garbutt JC, Amick HR, et al. Behavioral counseling after screening for alcohol misuse in primary care: A systematic review and meta-analysis for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2012;157(9):645-654. http://doi.org/10.7326/0003-4819-157-9-201211060-00544.
64. Kaner EF, Beyer FR, Muirhead C, et al. Effectiveness of brief alcohol interventions in primary care populations. *Cochrane Database Syst Rev.* 2018;(2):1-248. http://doi.org/10.1002/14651858.CD004148.pub4.
65. Tanner-Smith EE, Lipsey MW. Brief alcohol interventions for adolescents and young adults: A systematic review and meta-analysis. *J Subst Abuse Treat.* 2015;51:1-18. http://doi.org/10.1016/j.jsat.2014.09.001.
66. Nayak MB, Kaskutas LA, Mericle AA. Randomized trial of an innovative electronic screening and brief intervention for reducing drinking among women of childbearing age. *J Addict Med.* 2019;13(6):450-459. http://doi.org/10.1097/ADM.0000000000000518.
67. Carney T, Myers B. Effectiveness of early interventions for substance-using adolescents: Findings from a systematic review and meta-analysis. *Subst Abuse Treat Prev Policy.* 2012;7(25):1-15. http://doi.org/10.1186/1747-597X-7-25.
68. Poikolainen K. Effectiveness of brief interventions to reduce alcohol intake in primary health care populations: A meta-analysis. *Prev Med.* 1999;28(5):503-509. http://doi.org/10.1006/pmed.1999.0467.
69. William R, Miller SR. *Motivational Interviewing: Helping People Change.* New York, NY: Guilford Press; 2012.
70. Seo S, Beck A, Matthis C, et al. Risk profiles for heavy drinking in adolescence: Differential effects of gender. *Addict Biol.* 2019;24(4):787-801. http://doi.org/10.1111/adb.12636.
71. Jensen CD, Cushing CC, Aylward BS, et al. Effectiveness of motivational interviewing interventions for adolescent substance use behavior change: A meta-analytic review. *J Consult Clin Psychol.* 2011;79(4):433-440. http://doi.org/10.1037/a0023992.
72. D'Amico EJ, Parast L, Shadel WG, et al. Brief motivational interviewing intervention to reduce alcohol and marijuana use for at-risk adolescents in primary care. *J Consult Clin Psychol.* 2015;344(6188):1173-1178. http://doi.org/10.1037/ccp0000332
73. D'Souza-Li L, Knight JR, Sherritt L, et al. Does patient or clinician gender modify the efficacy of a primary care brief intervention for adolescent alcohol use? *Addict Sci Clin Pract.* 2015;10(suppl 2):O16. http://doi.org/10.1186/1940-0640-10-S2-O16.
74. Hai AH, Hammock K, Velasquez MM. The efficacy of technology-based interventions for alcohol and illicit drug use among women of childbearing age: A systematic review and meta-analysis. *Alcohol Clin Exp Res*. 2019;43(12):2464-2479. http://doi.org/10.1111/acer.14203.
75. Floyd RL, Sobell M, Velasquez MM, et al. Preventing alcohol-exposed pregnancies: A randomized controlled trial. *Am J Prev Med.* 2007;32(1):1-10. http://doi.org/10.1016/j.amepre.2006.08.028.
76. Ceperich SD, Ingersoll KS. Motivational interviewing + feedback intervention to reduce alcohol-exposed pregnancy risk among college binge drinkers: Determinants and patterns of response. *J Behav Med.* 2011;34(5):381-395. http://doi.org/10.1007/s10865-010-9308-2.
77. Ingersoll KS, Ceperich SD, Hettema JE, et al. Preconceptional motivational interviewing interventions to reduce alcohol-exposed pregnancy risk. *J Subst Abuse Treat.* 2013;44(4):407-416. http://doi.org/10.1016/j.jsat.2012.10.001.
78. Velasquez MM, von Sternberg KL, Floyd RL, et al. Preventing alcohol and tobacco exposed pregnancies: CHOICES Plus in primary care. *Am J Prev Med.* 2017;53(1):85-95. http://doi.org/10.1016/j.amepre.2017.02.012.
79. Hutton HE, Chander G, Green PP, et al. A novel integration effort to reduce the risk for alcohol-exposed pregnancy among women attending urban STD clinics. *Public Health Rep.* 2014;129:56-62. http://doi.org/10.1177/00333549141291S109.
80. Kuerbis A, Sacco P. A review of existing treatments for substance abuse among the elderly and recommendations for future directions. *Subst Abuse.* 2013;7:13-37. http://doi.org/10.4137/SART.S7865.
81. Fleming MF, Barry KL, Manwell LB, et al. Brief physician advice for problem alcohol drinkers. A randomized controlled trial in community-based primary care practices. *JAMA.* 1997;277(13):1039-1045. http://doi.org/10.1001/jama.1997.03540370029032.
82. Schonfeld L, King-Kallimanis BL, Duchene DM, et al. Screening and brief intervention for substance misuse among older adults: The Florida BRITE Project. *Am J Public Health.* 2010;100(1):108-114. http://doi.org/10.2105/AJPH.2008.
83. Ballesteros J, González-Pinto A, Querejeta I, et al. Brief interventions for hazardous drinkers delivered in primary care are equally effective in men and women. *Addiction.* 2004;99(1):103-108. http://doi.org/10.1111/j.1360-0443.2004.00499.x.
84. Kaner E, Bland M, Cassidy P, et al. Effectiveness of screening and brief alcohol intervention in primary care (SIPS trial): Pragmatic cluster randomised controlled trial. *BMJ*. 2013;346:1-14. http://doi.org/10.1136/bmj.e8501.
85. Álvarez-Bueno C, Rodríguez-Martín B, García-Ortiz L, et al. Effectiveness of brief interventions in primary health care settings to decrease alcohol consumption by adult non-dependent drinkers: A systematic review of systematic reviews. *Prev Med.* 2015;76:S33-S38. http://doi.org/10.1016/j.ypmed.2014.12.010.
86. Tait RJ, Hulse GK, Robertson SI. Effectiveness of a brief-intervention and continuity of care in enhancing attendance for treatment by adolescent substance users. *Drug Alcohol Depend.* 2004;74(3):289-296. http://doi.org/10.1016/j.drugalcdep.2004.01.003.
87. Sterling S, Kline-Simon AH, Jones A, et al. Specialty addiction and psychiatry treatment initiation and engagement: Results from an SBIRT randomized trial in pediatrics. *J Subst Abuse Treat.* 2017;82:48-54. http://doi.org/10.1016/j.jsat.2017.09.005.

88. Glass JE, Hamilton AM, Powell BJ, et al. Specialty substance use disorder services following brief alcohol intervention: A meta-analysis of randomized controlled trials. *Addiction.* 2015;110(9):1404-1415. http://doi.org/10.1111/add.12950.
89. Greenfield SF, Brooks AJ, Gordon SM, et al. Substance abuse treatment entry, retention, and outcome in women: A review of the literature. *Drug Alcohol Depend.* 2007;86(1):1-21. http://doi.org/10.1016/j.drugalcdep.2006.05.012.
90. Center for Substance Abuse Treatment. *Substance Abuse Treatment: Addressing the Specific Needs of Women.* Rockville, MD: Substance Abuse and Mental Health Services Administration; 2009.
91. Hettema J, Cockrell S, Russo J, et al. Missed opportunities: Screening and brief intervention for risky alcohol use in women's health settings. *J Womens Health.* 2015;24(8):648-654. http://doi.org/10.1089/jwh.2014.4961.
92. Hall KS, Harris LH, Dalton VK. Women's preferred sources for primary and mental health care: Implications for reproductive health providers. *Womens Health Issues.* 2017;27(2):196-205. http://doi.org/10.1016/j.whi.2016.09.014.
93. Sterling S, Kline-Simon AH, Weisner C, et al. Pediatrician and behavioral clinician-delivered screening, brief intervention and referral to treatment: Substance use and depression outcomes. *J Adolesc Health.* 2018;62(4):390-396. http://doi.org/10.1016/j.jadohealth.2017.10.016.
94. Levy S, Wiseblatt A, Straus JH, et al. Adolescent SBIRT practices among pediatricians in Massachusetts. *J Addict Med.* June 2019:1. http://doi.org/10.1097/ADM.0000000000000551.
95. Gotham HJ, Wilson K, Carlson K, et al. Implementing substance use screening in family planning. *J Nurse Pract.* 2019;15(4):306-310. http://doi.org/10.1016/j.nurpra.2019.01.009.
96. Oni HT, Buultjens M, Abdel-Latif ME, et al. Barriers to screening pregnant women for alcohol or other drugs: A narrative synthesis. *Women Birth.* 2019;32(6):479-486. http://doi/org/10.1016/j.wombi.2018.11.009.
97. Subbaraman MS, Thomas S, Treffers R, et al. Associations between state-level policies regarding alcohol use among pregnant women, adverse birth outcomes, and prenatal care utilization: Results from 1972 to 2013 vital statistics. *Alcohol Clin Exp Res.* 2018;42(8):1511-1517. http://doi.org/10.1111/acer.13804.
98. Jarlenski M, Hogan C, Bogen DL, et al. Characterization of U.S. state laws requiring health care provider reporting of perinatal substance use. *Womens Health Issues.* 2017;27(3):264-270. http://doi.org/10.1016/j.whi.2016.12.008.
99. Committee Opinion No. 633: Alcohol abuse and other substance use disorders: Ethical issues in obstetric and gynecologic practice. *Obstet Gynecol.* 2015;125(6):1529-1537. http://doi.org/10.1097/01.AOG.0000466371.86393.9b.
100. Sterling S, Kline-Simon AH, Satre DD, et al. Implementation of Screening, Brief Intervention, and Referral to Treatment for adolescents in pediatric primary care: A cluster randomized trial. *JAMA Pediatr.* 2015;169(11):1-17. http://doi.org/10.1001/jamapediatrics.2015.3145.
101. Hingson RW, Heeren T, Edwards EM, et al. Young adults at risk for excess alcohol consumption are often not asked or counseled about drinking alcohol. *J Gen Intern Med.* 2012;27(2):179-184. http://doi.org/10.1007/s11606-011-1851-1.
102. Schwinn TM, Schinke SP, Hopkins J, et al. An online drug abuse prevention program for adolescent girls: Posttest and 1-year outcomes. *J Youth Adolesc.* 2018;47(3):490-500. http://doi.org/10.1007/s10964-017-0714-4.
103. Gance-Cleveland B, Leiferman J, Aldrich H, et al. Using the Technology Acceptance Model to develop StartSmart: mHealth for screening, brief intervention, and referral for risk and protective factors in pregnancy. *J Midwifery Womens Health.* 2019;64(5):630-640. http://doi.org/10.1111/jmwh.13009.
104. Verhoeks C, Teunissen D, van der Stelt-Steenbergen A, et al. Women's expectations and experiences regarding e-health treatment: A systematic review. *Health Informatics J.* 2019;25(3):771-787. http://doi.org/10.1177/1460458217720394.
105. Choo EK, Zlotnick C, Strong DR, et al. BSAFER: A Web-based intervention for drug use and intimate partner violence demonstrates feasibility and acceptability among women in the emergency department. *Subst Abuse.* 2016;37(3):441-449. http://doi.org/10.1080/08897077.2015.113475.
106. Olmstead TA, Yonkers KA, Ondersma SJ, et al. Cost-effectiveness of electronic- and clinician-delivered Screening, Brief Intervention and Referral to Treatment for women in reproductive health centers. *Addiction.* 2019;114(9):1659-1669. http://doi.org/10.1111/add.14668.
107. Walton MA, Chermack ST, Shope JT, et al. Effects of a brief intervention for reducing violence and alcohol misuse among adolescents: A randomized controlled trial. *JAMA.* 2010;304(5):527-535. http://doi.org/10.1001/jama.2010.1066.
108. Breslow RA, Castle IP, Chen CM, et al. Trends in alcohol consumption among older Americans: National Health Interview surveys, 1997 to 2014. *Alcohol Clin Exp Res.* 2017;41(5):976-986. http://doi.org/10.1111/acer.13365.
109. Letourneau B, Sobell LC, Sobell MB, et al. Two brief measures of alcohol use produce different results: AUDIT-C and Quick Drinking Screen. *Alcohol Clin Exp Res.* 2017;41(5):1035-1043. http://doi.org/10.1111/acer.13364.

ALCOHOL RESEARCH
Current Reviews

Alcohol Res. 2020;40(2):08 • https://doi.org/10.35946/arcr.v40.2.08

Published: 30 July 2020

Treatment Interventions for Women With Alcohol Use Disorder

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Women with alcohol use disorder (AUD) experience more barriers to AUD treatment and are less likely to access treatment than men with AUD. A literature review identified several barriers to women seeking help: low perception of a need for treatment; guilt and shame; co-occurring disorders; employment, economic, and health insurance disparities; childcare responsibilities; and fear of child protective services. Women entering treatment present with more severe AUD and more complex psychological, social, and service needs than men. Treatment program elements that may reduce barriers to AUD treatment include provision of childcare, prenatal care, treatment for co-occurring psychological problems, and supplemental social services. Research has suggested that outcomes for women are best when treatment is provided in women-only programs that include female-specific content. To date, research on treatments tailored to the individual needs of women is limited, but research on mechanisms of change has suggested the importance of targeting anxiety and depression, affiliative statements in treatment, abstinence self-efficacy, coping skills, autonomy, and social support for abstinence. Future research should focus on early interventions, linkages between primary care or mental health clinics and AUD treatment settings, and integrated treatments for co-occurring AUD and other disorders. Further research should also explore novel treatment delivery approaches such as digital platforms and peer support groups.

KEY WORDS: alcohol use disorder; barriers; mechanisms of change; outcomes; treatment; women

INTRODUCTION

Historically, women with alcohol use disorder (AUD) have been an underserved population. In the United States, more than 5 million adult women, or 4.2% of the adult female population, meet criteria for current AUD.[1] Although this percentage is half that of adult men (8.4%), among adolescents, more females than males meet criteria for current AUD (2.7% vs. 2.3%),[1] and recent research has suggested that the gender gap in alcohol use and alcohol-related harm is narrowing.[2] Heterogeneity in rates of AUD is found among different racial/ethnic groups, with higher rates among Black and Hispanic women than among White women,[3] and rates of AUD among gender minority women also are higher than among heterosexual women.[4]

A smaller proportion of women than men received AUD treatment both in the past year[1] (7.9% of adult women vs. 9.2% of adult men; 4.6% of adolescent females vs. 7.4% of adolescent males) and in their lifetime[5] (15.0% of women and 22.0% of men with AUD who are younger than age 45). Utilization rates for treatment services by women and men do not differ across different racial/ethnic groups.[5] Given the increasing rates of AUD among women and the lower rates of treatment utilization among women, a rethinking of AUD treatment for women is in order. The purpose of this article is to describe the barriers to treatment entry experienced by women with AUD, the unique characteristics and presenting concerns of women with AUD who do seek treatment, and the current knowledge about effective treatments. Sources of information for this review included a comprehensive review published in 2013,[6] articles identified in a search in PsycINFO® using the search terms "women," "alcohol," and "treatment," and articles identified through selective reviews to identify key publications on trauma-informed treatment and substance use disorder (SUD) in female veterans.

WOMEN SEEKING AUD TREATMENT

Women seeking AUD treatment differ from men in their sociodemographic characteristics and psychological profiles. They experience some unique barriers to accessing treatment and present to treatment with some needs that differ from men in AUD treatment.

Characteristics of Women With AUD at Treatment Entry

Women seeking AUD treatment vary along a number of dimensions that may impact their access to treatment, treatment needs, and treatment response.

Sociodemographic characteristics and substance use

Women who present to AUD treatment often have markedly different characteristics and backgrounds than men in these treatment settings. Such distinctions among women include younger age, more severe alcohol and drug use histories, less education, lower income, higher unemployment, more housing needs, more children living at home, and higher parental stress.[6] In terms of substance misuse, rates differ among subgroups. For example, non-Hispanic White and American Indian/Alaska Native women are more likely than women of other racial/ethnic groups to identify alcohol as their primary substance of use when entering treatment for SUD.[7] Among pregnant women entering treatment for SUD, approximately 18% identified alcohol as their primary substance of use.[7] In a study of women veterans with SUD, researchers found that entry into and engagement with treatment were associated with having a co-occurring psychological disorder and receiving services at facilities offering women's treatment.[8]

Psychological co-occurrences

Compared to men, women who enter AUD/SUD treatment generally report higher levels of physical and mental health concerns. Rates of co-occurring disorders vary with the treatment setting and population. Epidemiologic data suggest that compared with men with AUD, women with AUD have a higher prevalence of co-occurring DSM-IV Axis I disorders (84.2% vs. 75.5%),

a similar prevalence of other drug dependence (15.2% vs. 14.3%), a higher prevalence of mood and anxiety disorders (53.1% vs. 29.1% and 44.3% vs. 26.2%, respectively), and a similar prevalence of personality disorders (36.5% vs. 33.3%).[9] A recent nationwide study of veterans with AUD found that women veterans had more psychological and substance use comorbidities than men.[10] In addition, women in SUD treatment have a much higher prevalence (up to 80.0%) of lifetime physical, sexual, and/or emotional abuse and trauma, and concerns about current domestic violence are common.[11] Rates of current post-traumatic stress disorder (PTSD) among women in SUD treatment range from 25.0% to 55.0%.[12]

Barriers to Treatment

Women who do not receive AUD treatment have some sociodemographic difference from women in AUD treatment. For example, a sample of women with AUD who were not in treatment but perceived a need for treatment were less educated, had a family income less than $75,000, and were more likely to use psychotropic medications compared to those who did not perceive a need for treatment.[13] Women experience both internal and external barriers to AUD treatment. These barriers may partially explain the gender discrepancy in treatment initiation rates and include low perception of need for treatment; guilt and shame stemming from the discrepancy between traditional gender expectations and societal views of women with AUD; depression and other co-occurring disorders; greater employment, economic, and health insurance disparities relative to men; childcare responsibilities; and fear of child protective services.[6]

Recent research has suggested that traditional gender expectations and lay beliefs about AUD may contribute to lower AUD treatment utilization among women. Lale and colleagues found that compared to men, women were more likely to attribute AUD to "bad character" and less likely to attribute AUD to genetics.[14] Women also worry that they will be perceived as "bad mothers" and potentially lose custody of their children if they disclose having an alcohol problem.[7] Relatedly, women are more likely than men to experience feelings of embarrassment, to experience fear, to have the belief that no one can help, and to have the belief that their problem is not serious enough to require AUD treatment.[15] In addition to these intrapersonal barriers, women may experience less social support to enter AUD treatment than men do. Women with AUD are more likely than men to be in an intimate relationship with a partner who also has AUD,[16] and women tend to have less spousal and family support for recovery.[17] Further, women generally report more logistical barriers to treatment utilization, including greater difficulties with transportation, lack of available childcare, and inadequate insurance coverage.[17]

Compared to men, women are more likely to seek AUD treatment through a general versus substance use-specific health care sector[18] or in the context of treatment at a general mental health clinical setting,[19,20] and less likely to be court mandated to treatment.[21] Women with AUD also generally report stressful life events and nonsubstance-related mental health concerns as their primary reasons for seeking treatment.[22] Welfare, child welfare, and legal systems provide additional portals through which some women enter AUD treatment.[21] Primary care physicians, gynecologists, and psychiatrists may benefit from focused training in identification and referral of women with AUD to offset the gender discrepancy observed in women's entry into AUD treatment. Relatedly, women have shown a preference for AUD treatment settings that offer childcare.[23] Thus, more easily accessible, children-friendly treatment centers with wide availability are also likely to improve treatment utilization among women with AUD.

AUD TREATMENT SERVICES FOR WOMEN

Treatment Retention

In general, the literature is mixed regarding AUD treatment attrition and gender differences.[6] Previous studies have found that women tend to have longer inpatient stays and that longer inpatient

stays are associated with an increase in sustained abstinence for women but not for men.[22,24] Bravo and colleagues reported that women engaged in outpatient AUD treatment longer and discontinued treatment at a lower rate than men.[25] In a comprehensive review, Greenfield and colleagues concluded that although there are no gender differences in attrition, predictors and mediators of treatment retention differ by gender.[23] Predictors of better treatment retention among women include demographic variables, such as lower psychiatric impairment, higher socioeconomic status, and greater social support and stability,[23] and program variables, such as female-specific treatment and facilities that allow children to stay with their mothers.[6] A recent investigation of 1.8 million individuals who received SUD treatment at federally funded facilities found that, across treatment settings, women and men did not differ in rates of early discharge.[26] However, when treatment settings were stratified by type (detoxification, residential, and ambulatory), women were more likely than men to leave detoxification treatment prematurely. The authors suggested that lower rates of female-specific services and higher rates of psychiatric co-occurring disorders within detoxification settings might have accounted for this gender difference.

Treatment Outcome

In general, studies of mixed-gender treatment programs have found few gender differences in short-term outcomes for AUD across a range of interventions, samples, and sites, despite women at baseline generally presenting with more severe clinical issues.[6] For example, in their analysis of five randomized clinical trials (RCTs) of intensive outpatient contingency management for AUD and SUD, Rash and Petry found no differences between men and women's abstinence rates during the 3-month treatment period, although women initially presented with more financial, family/social, and psychiatric problems.[27] Likewise, a study of a large outpatient AUD treatment cohort in Spain found no differences between men and women in alcohol consumption 1 year posttreatment, despite women presenting with more symptoms of dependence at baseline.[25]

Results have been more mixed regarding women's long-term outcomes compared to men.[6] In the same study from Spain described above, women had superior drinking outcomes compared to men at 5, 10, and 20 years posttreatment.[25] Conversely, Litt and colleagues found that women had worse drinking outcomes than men in the 2 years following outpatient AUD treatment.[28] These poorer outcomes may have been due to the nature of the active treatment, which focused on altering the participant's social network to gain more support for abstinence; women in the study had less abstinence-supportive social networks and more difficulty altering these networks.

Historically, gender has typically not been taken into consideration in psychopharmacologic treatment for AUD, and women have been underrepresented in AUD medication trials.[29] However, research has begun to improve in this area. A review by Agabio and colleagues found that too few studies of disulfiram had included women to test potential gender differences in response to this medication.[30] There were a sufficient number of studies on acamprosate and naltrexone, which showed that both medications were generally efficacious for women; however, results of gender comparisons were too variable to draw firm conclusions. Canidate and colleagues conducted a systematic review of seven studies on naltrexone for the treatment of AUD among women.[31] Among this limited number of studies, naltrexone was found to have a modest effect on drinking quantity and time of relapse but not on the overall frequency of drinking among women. The authors concluded that the effect of naltrexone on women is currently understudied. This Canidate article highlights the need to continue to use rigorous research designs to study differences in the efficacy of naltrexone on women versus men.

Reducing Barriers to Treatment for Women

A comprehensive review identified six major elements of SUD treatment programs for women

that reduce barriers to treatment and/or address women's unique needs.[32] These include the provision of childcare, prenatal care, women-only treatment, treatment for co-occurring mental health problems, a comprehensive approach to treatment, and supplemental services that address women-focused topics. Each of these elements was linked to favorable treatment outcomes. In a qualitative meta-synthesis of programs that included women and their children, several treatment processes were identified by different stakeholders (clients, clinicians, and program administrators) as instrumental to positive outcomes: developing a sense of agency, giving and receiving social support, engaging with program staff, fostering self-disclosure, recognizing self-destructive patterns of behavior, setting goals, and feeling motivated by the presence of children.[33] Although some of these processes are common to any AUD treatment, it is necessary to recognize the unique blend of common and specific treatment processes that are effective for women in treatment with their children. Although studies have repeatedly identified the importance of including children-supportive services in women's SUD treatment programs, a 2018 Substance Abuse and Mental Health Services Administration (SAMHSA) survey found that only 5.8% of SUD treatment facilities provided childcare and only 2.6% of residential programs provided beds for clients' children.[34]

Guiding Principles for Women's AUD Treatment

Recognizing the unique treatment needs of women with AUD and SUD, SAMHSA published a set of evidence-based principles to guide gender-responsive treatment for women.[7] These guidelines include several recommendations. For example, they recommend developing cultural competence to frame women's AUD symptoms and treatment in their socioeconomics contexts (e.g., employment, income, housing). They suggest that providers acknowledge the unique significance of women's relationships and attend to the "caregiver roles that women often assume throughout the course of their lives." Relatedly, the guidelines address stigma by noting the importance of "recognizing that ascribed roles and gender expectations across cultures affect societal attitudes toward women who abuse substances." Other recommendations state that SUD treatments for women adopt a trauma-informed approach, which often emphasizes women's strengths, and address "women's unique health concerns" through "an integrated and multidisciplinary approach." The SAMHSA guidelines conclude that clinical treatment services (e.g., screening, mental health services), clinical support services (e.g., parenting education, job training), and community support services (e.g., childcare, transportation) would work collaboratively to facilitate comprehensive AUD treatment for women of diverse backgrounds.[7]

Advances and Gaps in Treatment Development for Women

With increasing recognition of the unique clinical profiles of women with AUD has come increasing attention to whether AUD treatment programs are serving the needs of women. The 2018 SAMHSA annual survey of substance use treatment programs found that 49% of programs surveyed provided special programs or groups for women and 23% provided services for pregnant or postpartum women.[34] In contrast, data from the Veterans Health Administration (VHA) revealed that most VHA facilities offered SUD services to women but that most of these services were generic rather than female-specific (85% vs. 30%).[35]

The need for specialized services for women has both an empirical and a clinical rationale. As reviewed earlier in this article, compared to men, women are less likely to seek AUD treatment, have different social contexts, present with different profiles of co-occurring disorders, and have a unique and complex set of service needs that may not be addressed in a standard, mixed-gender AUD treatment program.[9,36] Thus, treatment programs and researchers have been seeking to create and evaluate services intended to attract women to AUD treatment and improve

outcomes. AUD services for women vary along two dimensions—whether they are provided in a mixed-gender or women-only treatment setting and whether the content of the treatment is generic or tailored specifically to women's clinical and other service needs.[37] Thus, delivery of AUD treatment to women may occur in (a) mixed-gender programs with no female-specific programming, (b) mixed-gender programs with female-specific programming, (c) single-gender (women-only) programs with no female-specific programming, or (d) single-gender (women-only) programs with female-specific programming.

Mixed-gender versus single-gender treatment

Single-gender treatment services seem appealing because they have the potential to provide an environment in which women may feel more comfortable sharing emotional and personal information. For instance, it is possible that among women who have a history of trauma or abuse from men, single-gender treatment might be preferable because of the possibility that participation in a mixed-gender program could trigger trauma-related symptoms. In addition, given the broader literature on the relative interactional dominance of men in mixed-gender groups, women may have more opportunities to participate when in women-only groups.[38] However, research on women's treatment preferences yields a more nuanced picture. Although some research suggests that women prefer women-only groups,[23] a narrative analysis of interviews with women with a range of SUD treatment experiences found that the women reported concerns and anxiety about being in women-only treatment because of their own history of dysfunctional relationships with women and their greater comfort in being with men.[39] However, women in the study reported positive experiences once they entered women-only services.

Few studies have compared women's outcomes from mixed-gender versus women-only programs that were not adapted with female-specific content. In one early study, Bride compared the outcomes for women who were in a mixed-gender program to the outcomes for women who later participated in the same program that had become a women-only program with no female-specific content.[40] Outcomes were similar between the two samples.

More extensive research has compared mixed-gender to single-gender programs that incorporate female-specific themes, services, or content. For example, interviewed providers of services for female veterans with SUD identified five female-specific themes and services that they viewed as key to treatment: a focus on safety; scheduling that accommodates women's work and family responsibilities; flexibility in the resources provided; staff trained in serving women's clinical needs; provision of on-site childcare; and a positive, supportive, nonconfrontational treatment environment.[41] Although some of these treatment elements may be relevant to treatment for any patient with SUD, the combination of these elements was seen as key to successful treatment for the female veteran population. In addition to treatment elements, female-specific content has focused on clinical issues of particular significance to women, such as trauma, physical abuse, relationships, parenting, assertiveness, and treatment of co-occurring disorders.

One of the earliest studies of women-only treatment with female-specific content was the Early Treatment of Women with Alcohol Addiction (EWA) study.[42] A 2-year follow-up of women found better clinical outcomes in the EWA than mixed-gender treatment, and a long-term study of mortality revealed lower mortality rates for younger women who participated in the EWA program than the mixed-gender treatment.[43] A later study of a large sample of women in women-only versus mixed-gender residential SUD treatment found that women were twice as likely to complete the women-only treatment and that higher retention was associated with higher rates of abstinence posttreatment.[44,45] More recent studies have found that (a) treatment retention and entry to aftercare were enhanced by gender-specific services in an intensive treatment program that also provided transitional housing, particularly for women who completed residential treatment;[46] (b) women-only treatment predicted

better legal and drug outcomes but no differences in alcohol use outcomes;[47] and (c) women in the single-gender treatment had significantly less substance use (participants were primary stimulant users) and less criminal activity than those in the mixed-gender treatment.[48] In contrast, Kaskutas and colleagues found that a mixed-gender, comprehensive, hospital-based treatment resulted in better alcohol abstinence outcomes than women-only treatment and was superior to generic, community-based, mixed-gender treatment.[49]

Single-gender treatment with no female-specific programming

Some empirically supported treatments have been tested in female samples with any adaptation of the treatment to women's treatment needs. Two studies compared behavioral couple therapy to individual treatment for women with AUD and their male partners.[50,51] O'Farrell and colleagues compared behavioral couple therapy to individual treatment for women with SUD and their male partners.[52] All three studies found that the behavioral couple therapy led to positive changes in alcohol or drug use, with better alcohol or drug use outcomes for the women receiving couple therapy. In their study, McCrady and colleagues found that women presenting with higher levels of relationship distress and women with co-occurring Axis I or II disorders had greater improvements in drinking.[50] Note, however, that couple therapy is a modality available to only a small proportion of the population of women with AUD. Notably, when given the choice, even women with male partners indicated a preference for individual rather than couple therapy, stating that they wanted to work on their own problems, did not see their partners as supportive, or thought the logistics of scheduling couple sessions was too difficult.[53]

Chronic care models for persons with serious mental illness and SUD are another empirically supported approach that has been tested in female samples without female-specific programming. These models have been developed and tested with homeless women who have AUD. The chronic care model emphasizes availability of a primary care provider, care management, education about alcohol, and referral to addiction services. Compared to women who received treatment as usual in a health care clinic for homeless women, women who participated in the chronic care program engaged with more SUD treatment services in the 3 months after starting the program.[54]

Single-gender treatment with female-specific programming

There has been substantial research on women-only treatment with female-specific content. For example, Polcin and colleagues compared intensive, nine-session motivational interviewing (MI) for women with standard one-session MI.[55] For the intensive treatment, therapists were trained to use MI to focus on alcohol use as well as female-specific themes—such as personal relationships, issues related to parenting, abuse, and barriers to treatment—and other psychological concerns, such as low self-esteem or co-occurring disorders. Compliance with the treatment was high (80% of heavy drinkers completed at least seven sessions), and women receiving intensive MI reduced their drinking more than women receiving standard MI. Connors and Walitzer developed and tested an intervention to help heavy-drinking, nonalcohol-dependent women reduce their drinking.[56,57] The intervention focused on skills to reduce drinking and other life skills believed to be relevant to women, such as problem-solving, communication and assertiveness, and strategies to enhance their social support system. Compared to treatment focused only on drinking, women who also received the life skills interventions and booster sessions had outcomes that were more positive.

Another single-gender treatment with women-specific programming was developed by Epstein and colleagues. The outpatient, female-specific cognitive behavioral treatment (FS-CBT) was an adaptation of a the gender-neutral cognitive behavior therapy manual-guided treatment for AUD.[58] The FS-CBT manual (a) highlighted two clinical themes meaningful to women, self-care and autonomy; (b) included female-specific

interventions focused on coping with negative emotions and developing/enhancing women's social network supportive of abstinence; and (c) provided women-specific examples throughout to personalize the material to each woman's issues, such as dealing with heavy drinkers in the social network, parenting, life-stage transitions, trauma, self-esteem, and relationships.[59] In an RCT comparing FS-CBT to an evidence-based, gender-neutral CBT for AUD, Epstein and McCrady found that women in both treatment conditions were highly engaged, reported a high level of satisfaction with the treatment, significantly reduced their drinking, and improved in other areas of life functioning such as depression, anxiety, autonomy, and sociotropy.[58] There were no treatment condition effects, and the FS-CBT treatment was equally effective as the gender-neutral one. In a subsequent RCT, Epstein and colleagues tested the individual modality FS-CBT treatment versus a new group therapy format of the same contents in a "pure comparison" design.[60] Both FS-CBT treatment modalities (individual and group therapy) resulted in significant positive changes in drinking, depression, anxiety, coping skills, self-confidence, interpersonal functioning, and self-care even though treatment attendance and therapeutic alliance were greater in the individual FS-CBT condition. Cost-effectiveness analyses favored the group format.[61]

In a pilot study, Greenfield and colleagues tested a women-only Women's Recovery Group (WRG, $n = 16$) for SUD against mixed-gender Group Drug Counseling (GDC, $n = 7$ women, 10 men).[62] WRG included cognitive behavioral and relapse prevention elements, as well as "repair work" relevant for women (repairing SUD-related damage to relationships and self, and learning to enjoy life without substances).[63] GDC was a traditional mixed-gender treatment program focused on substance-related topics with no gender-specific content. During treatment, the groups did not differ in substance[62] or psychiatric improvement;[64] however, women in WRG continued to reduce substance use in the 6 months posttreatment, and also reported higher satisfaction with the treatment they received.

In a subsequent, larger RCT,[65] with a similar design except that the WRG groups offered rolling admission, outcomes of 52 women in WRG were compared with those of 48 women in GDC (with 58 men in GDC). All participants had SUD or AUD. Women in both treatments reduced drinking, and there were no treatment condition differences in within- or posttreatment drinking outcomes. Because WRG had both a women-only group composition and female-specific content compared to GDC, which had both a mixed-gender format and no female-specific content, it is unclear whether study results were linked to group composition, female-specific content, or both, but both the pilot and the larger RCT demonstrated that WRG is at least comparable to a typical "treatment-as-usual" such as a mixed-gender GDC in community settings. The authors also noted that the WRG in the larger trial was delivered on a rolling admissions basis and suggested that the revised format may have diluted the impact of the WRG.

In a series of three studies on putative mechanisms of change in WRG, secondary analyses of the pilot and/or larger RCT data from studies just described here above, showed that more affiliative statements were made in WRG than GDC[66,67] and that more affiliative statements were associated positively with women's drinking outcomes during and 6 months after treatment, particularly in the WRG condition.[68] Sugarman and colleagues created and piloted (for feasibility, acceptability, and satisfaction) a web-based, gender-specific individual psychoeducation intervention based on WRG content.[69] The gender-specific modules might ultimately comprise a female-specific component of care to be delivered in a mixed-gender setting.

Najavits and colleagues reported an RCT comparing the A Woman's Path to Recovery (WPR) model to the gender-neutral 12-Step Facilitation (TSF) model for women veterans with SUD, the majority of whom (i.e., more than 74%) had current AUD.[70] The WPR model is based on cognitive behavioral, interpersonal, and emotive therapy methods, and theory on gender differences in addiction and recovery. The "exploration" phase of the treatment highlights five themes:

"body and sexuality, stress, relationships, trauma and violence, and thrill-seeking."[70(p211)] The "healing" section covers "recovery methods in four domains—relationships, beliefs, actions, and feelings."[70(p211)] Both WPR and TSF were single-gender groups, facilitated by women clinicians, and provided compensation to offset potential childcare costs or other financial barriers to participation. The treatments resulted in similar improvements in alcohol and drug use, coping skills, and psychiatric functioning. The authors noted that female-specific treatment content might be less relevant to veterans than to their civilian counterparts because male-dominated military culture may diminish traditional gender experiences for women.

In summary, several forms of empirically supported treatments have been tested and found to be efficacious with women, and several women-only treatments with female-specific content have been tested in rigorous RCTs. Overall, most of these studies have found limited evidence for superior alcohol use outcomes, but several of these studies have found greater satisfaction with the female-specific format and treatment content. Because these programs are appealing to women, they may increase women's utilization of AUD treatment, and enhance both engagement and retention in AUD treatment.

Treatment for Co-occurring Disorders

Treatment for co-occurring disorders may be indicated for the many women with AUD who present with additional mental health concerns. Interventions that address the co-occurrence of AUD with trauma and PTSD, mood disorders, and borderline personality disorder may be especially relevant for women.

Trauma

Given the highly elevated rates of trauma among women with AUD/SUD, SAMHSA has suggested that treatment for this population may benefit from adopting principles of trauma-informed care.[7] A trauma-informed approach recognizes the prevalence and impact of trauma in women with AUD and adjusts treatment accordingly, even if clients do not meet diagnostic criteria for PTSD. Trauma-informed AUD treatment does not need to target trauma explicitly, but rather may consider trauma in the assessment and planning phases of treatment. For example, SAMHSA recommends that AUD treatment providers should assess women at intake for trauma histories and PTSD symptomatology and refer clients with severe symptomatology to providers who have experience working with traumatized populations (i.e., if they lack such experience themselves). Another recommendation is to "avoid triggering trauma reactions or re-traumatizing women." For example, violating a client's trust or disregarding a client's emotions or experiences may trigger trauma reactions. SAMHSA also recommends that programs should "adjust staff behavior" and modify the treatment environment "to support clients' coping capacities and safety concerns." Specific strategies may include ensuring that urine specimens are collected in a private setting and establishing consistency in the treatment program's routines and enforcement of rules. In addition, AUD treatment providers should "allow survivors to manage their trauma symptoms" in a manner conducive to AUD treatment engagement and success. For example, allowing clients to express strong feelings without facing judgment and explicitly addressing trauma only when a client is ready are considered trauma-informed approaches. Finally, SAMHSA recommends that trauma-informed AUD treatment for women should "emphasize skills and strengths, interactive education, growth, and change beyond stabilization." Specific skills to incorporate into treatment may include assertiveness training and relaxation techniques.

Covington developed the Helping Women Recover program for the treatment of SUD.[71] Following the principles of trauma-informed care, this treatment aims to provide a "healing" (i.e., safe, empowering, relational) environment that emphasizes strengths and is sensitive to cultural and gender issues. Treatment modules include topics hypothesized to be essential to women's recovery: a focus on self and the integration of roles with feelings, thoughts, and attitudes;

healthy interpersonal relationships; sexuality; and spirituality. Covington also developed the Beyond Trauma: A Healing Journey for Women treatment program, which teaches women how to identify trauma and other forms of abuse, helps them understand typical reactions to trauma and abuse, and fosters the development of coping skills.[72] In an RCT with incarcerated women, 77% of whom were primary stimulant users, Messina and colleagues integrated the Helping Women Recover and Beyond Trauma protocols into a gender-responsive treatment (GRT) program.[73] GRT was compared to a standard prison-based therapeutic community (TC), which, like GRT, was single-gender and targeted SUD, but unlike GRT did not focus on gender-specific issues or trauma histories. Both conditions improved women's psychological well-being and alcohol use outcomes, but women in GRT also had more favorable outcomes for drug use, length of aftercare treatment engagement, and rate of reincarceration in the year following release from parole. A subsequent analysis showed that women with physical/sexual abuse histories had significantly better posttreatment depression and substance use outcomes following GRT than TC.[74]

An extension of trauma-informed care is treatment for co-occurring SUD and PTSD. In general, this co-occurrence is complex and difficult to treat because SUD and PTSD are reciprocally functional and often exacerbate each other.[75,76] Drinking or drug use often functions to self-medicate PTSD symptoms and enable avoidance of remembering traumatic events. Reducing substance use may initially intensify PTSD symptoms and thus predispose the client to relapse. An increasing focus has emerged on targeting PTSD and SUD concurrently.[75,76] This integrated focus is particularly relevant to women who present to SUD treatment and often have elevated rates of trauma history and PTSD.[12]

Recently, integrated models of treatment for PTSD and SUD have been developed and tested with mixed results. For instance, Najavits developed Seeking Safety (SS), a CBT-based treatment model that aims to reduce co-occurring PTSD and SUD by enhancing coping skills.[77] SS emphasizes themes of establishing safety, taking back power, being honest, setting boundaries, practicing compassion, healing from anger, grounding, creating meaning, and increasing self-care. Hien and colleagues tested the efficacy of SS and another active treatment condition Relapse Prevention against a treatment-as-usual control condition.[78] Women in SS and relapse prevention had comparable posttreatment reductions in both PTSD and SUD symptoms, and both treatments were superior to the control condition. Likewise, a study conducted through the National Institute on Drug Abuse Clinical Trials Network found no differences in PTSD or SUD outcomes between an abbreviated version of SS and a health education control condition, both delivered as adjuncts to standard SUD treatment.[79]

Morrissey and colleagues studied another integrated treatment approach for women with SUD.[80] The researchers used a quasi-experimental design to examine a large cohort treated across nine sites. Participants were mostly of low socioeconomic status and had serious mental and/or physical health problems as well as an interpersonal trauma history. The integrated treatment was associated with lower substance use and improved general mental health but not with reduced PTSD symptoms. Overall, it remains unclear whether integrated treatments for PTSD and AUD/SUD in women are superior to stand-alone SUD treatments. Widespread methodological limitations in the current literature warrant continued investigation of integrated treatments, including outcomes that may be specific to women with AUD.[75,76]

Mood disorders

Another promising area of treatment development for women is integrated behavioral therapy for SUD and depression. Treating depression and AUD concurrently may be important because negative affect is a particularly salient trigger for drinking among women. In turn, regular heavy drinking may inhibit recovery from mood disorders. Further, more women than men with AUD have a co-occurring mood disorder, and

there is an elevated suicide risk among women with AUD.[6] However, research on integrated AUD and mood disorder treatments for women is limited. For example, in a pilot study, researchers tested 8 sessions of interpersonal psychotherapy as an adjunct to outpatient AUD treatment for 14 women with co-occurring AUD and major depression.[81] The study found that women were highly engaged and satisfied with the adjunct treatment and reported follow-up reductions in drinking, depressive symptoms, and interpersonal problems. A study of men and women with depressive symptoms and hazardous drinking compared the effects of integrated alcohol-depression treatment, alcohol-only treatment, and depression-only treatment.[82] The integrated treatment generally produced the best alcohol and depression outcomes for both women and men. In the nonintegrated treatments, women's drinking and depressive symptoms improved more in the depression-only treatment, whereas men improved more in the alcohol-only treatment. These findings highlight the unique benefit of treating depression among women with co-occurring AUD and suggest the need for more RCTs targeting this co-occurrence in women.

Given that drinking and antidepressant use are generally contraindicated adds to the significance of concurrent treatment of AUD and depression to maximize the effectiveness of psychotropic medications.[6] One RCT tested the effect of citalopram plus naltrexone and clinical case management for men and women with AUD and depression.[83] Compared to placebo, citalopram did not produce greater improvements in drinking or mood with one exception: women (but not men) on citalopram had a higher percentage of abstinent days. These findings point to the potential for tailoring antidepressant treatment to maximize treatment benefits for women with co-occurring AUD and depression.

Borderline personality disorder

Research has demonstrated elevated rates (i.e., of approximately 18%) of borderline personality disorder (BPD) in women seeking treatment for AUD.[84] Dialectical behavior therapy (DBT) is an empirically supported treatment for BPD that has been successfully adapted for co-occurring SUD.[85] A systematic review found that DBT has shown positive potential for the treatment of women with co-occurring SUD and BPD,[86] leading to reductions in substance use, suicidal/self-injurious behaviors, treatment attrition, and social functioning problems. No studies that tested DBT specifically with women who have co-occurring AUD and BPD have been found.

Mechanisms of Change: How Change Occurs

The goal of understanding moderators and mechanisms of change in treatment is to identify how patient characteristics interact with treatments, identify variables key to successful change, and then develop or modify treatments to target those variables more efficiently in treatment. Currently, there are relatively limited data on moderators and mechanisms of change in alcohol use during and after AUD treatment for women. Moderators are defined as "specification variables" that impact the association between two other variables,[87] for instance, the effect of baseline major depressive disorder on treatment outcome of female-specific versus gender-neutral treatment for AUD. A mediator is an "intervening variable" that "transmits the effect of the independent variable on the dependent variable";[87] for instance, cognitive behavioral treatment of AUD has its effect on drinking outcome in part by increased use of effective coping skills among clients.

Research on moderators of outcome has elucidated the need for heterogeneity in samples and helped to refine female-specific treatments.[87] For example, findings that anxiety pretreatment and depression pre- and posttreatment predicted poorer drinking outcomes for women[88] suggest the value of including interventions to alleviate depression and anxiety in female-specific AUD treatment. Recent and more sophisticated research has studied the interaction of moderators and mediators of treatment response. For instance, Holzhauer and colleagues combined a moderator

analysis with testing the intensity and timing of reductions in drinking after specific outpatient treatment sessions that targeted depression and anxiety in female-specific AUD treatment.[89] Three moderators assessed at baseline—depression, anxiety, and self-efficacy to remain abstinent in negative affect situations—predicted sudden gains (i.e., a steep decrease in drinking) after Session 5 or 6, which included interventions to attenuate negative affect. The results suggest that women who enter treatment struggling with negative affect may respond well to very specific, targeted interventions for those problems.

Hallgren and colleagues examined three hypothesized mechanisms of change—abstinence self-efficacy, coping skills, and therapeutic alliance—in outpatient AUD treatment for women.[90] These authors used daily data from the individual versus group female-specific parent study[60] and sophisticated longitudinal statistical modeling to quantify rates of change around initiation of abstinence for each participant in outpatient FS-CBT. They also tested time-linked change in mediators before each of the 12 therapy sessions. Data on daily drinking and craving were available for the baseline, in-treatment, and 12-month follow-up periods. Results focused on two subgroups of women: those who had initiated abstinence before treatment and those who initiated abstinence during treatment. Those who initiated abstinence during treatment showed marked improvements in two key hypothesized mechanisms of change (abstinence self-efficacy and coping skills) during the week that they initiated abstinence. Women who were abstinent at the start of treatment maintained higher abstinence self-efficacy and coping skills throughout treatment. Previously, Hallgren and colleagues had found that daily-rated alcohol craving (a different mediator) decreased in relation to initiation of abstinence in men and women in outpatient CBT for AUD.[91]

Using Network Analysis, a novel statistical approach that uses multilevel vector autoregression estimation for multiple time series data to simultaneously examine change among several hypothesized mechanisms of change, Holzhauer and colleagues compared pathways to drinking reduction among women in gender-neutral versus FS-CBT.[59,92] Across treatments, women changed their drinking via increased coping skills, abstinence self-efficacy, and increased autonomy. For women in FS-CBT, change in drinking also occurred through decreases in sociotropy and increases in social support for abstinence. Surprisingly, change in depression was linked to better drinking outcomes for women in gender-neutral CBT.

Going forward, continuing moderated mediation studies that examine the response of gender-specific moderators of response to medications or behavioral interventions for AUD, and the mechanisms by which these treatments operate for specific subpopulations, will help guide the development of personalized medicine for addiction.[30] A moderated mediation approach can facilitate examination of individual differences and sample heterogeneity that are linked to drinking outcomes and help to identify gender differences in pathways to successful treatment outcomes.

CONCLUSIONS AND RECOMMENDATIONS

Since the National Institutes of Health mandate in 1994 that biomedical research include female participants in clinical research,[93] a substantive body of literature emerged describing the unique aspects of AUD among women, which led to an accelerated development of treatments targeting women's unique clinical presentation. In 2006, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) identified women as an understudied population in treatment research and prioritized research to better understand the mechanisms by which treatments for AUD effect change in drinking.[94,95] Findings that drinking outcomes of female-specific and gender-neutral treatments may be similar does not mean that the development of female-specific treatments should not be pursued. First, there is evidence that mechanisms of women's response to treatment

(i.e., pathways to change) may differ from that of men, and identification of these gender-specific pathways can guide the development of efficient, gender-differentiated active ingredients in treatment. Second, there may be greater benefits of women-specific (vs. gender-neutral) treatment for secondary outcomes, such as psychosocial well-being, psychiatric health, pregnancy outcomes, and HIV risk reduction. Third, further study is needed on whether the availability of women-specific and women-only treatments enhances treatment access and engagement for women with AUD.

Gaps in knowledge remain; however, increasingly sophisticated research approaches are available to continue to tackle the questions of how and which treatments work best for whom. The contemporary focus on personalized medicine[96,97] extends to women with AUD; the end goal is not only to provide an array of specialized treatment options specifically tailored to enhance women's treatment access and engagement but also to provide science-based treatment elements and options uniquely matched to various common clinical presentations among women with AUD.

A critical problem to resolve is treatment access and utilization. Only 15% of women with lifetime AUD ever seek treatment for it, and women experience multiple individual-based barriers to accessing treatment. In addition, systemic barriers to AUD treatment for women need attention, as a minority of substance use treatment services in the United States offer gender-segregated or female-specific programming. Extant literature suggests that women may prefer gender-segregated treatment for AUD but also suggests this treatment offers no added benefit in the absence of female-specific programming content. Thus, widespread availability of female-only treatment settings that include evidence-based female-specific interventions and content is likely to increase treatment utilization and enhance outcomes for women with AUD. In order to populate female-only treatment settings with female-specific programming, we need to develop an array of evidence-based options. A number of RCTs have yielded newly available, evidence-based female-specific treatment protocols for AUD and SUD treatment that are at least equivalent in positive outcomes to evidence-based control treatments.[59,60,62,70,74,79] Outcomes for secondary (non-AUD) patient problems, such as depression and anxiety,[59,60] trauma symptoms,[69] cardiovascular function,[98] health behaviors, drug use, and quality of life[99,100] from these female-specific treatments also have been positive. NIAAA's focus on implementation studies in conjunction with the study of mechanisms of change[101] should accelerate testing the incorporation of female-specific interventions into community settings—not just addiction specialty clinics but also primary care and general mental health settings. These interventions should ultimately lead to algorithms for optimal personalization of treatment components to individuals' clinical presentation. In the meantime, since most women currently receive treatment in gender-neutral settings, it is important to address women's specific needs even in the context of mixed-gender, gender-neutral[102] clinical programming. Research to address unresolved gaps in the knowledge base is needed. For example, does the availability of female-specific programming, whether in female-segregated or mixed-gender settings, increase AUD treatment utilization by women? In addition, there is a dearth of rigorous RCTs comparing female-only versus mixed-gender treatment formats that contain female-specific programming to test differential treatment engagement and positive outcomes.

Notable areas of additional needed research on women and AUD treatment follow.

Prevention

Women who enter treatment for AUD present with greater addiction and more severe psychosocial issues than men. Secondary prevention research has focused on engaging women in treatment as well as on providing alcohol psychoeducation earlier in women's problem drinking careers, which may help arrest the telescoped trajectory to AUD and SUD and the corresponding psychosocial decline.

Setting

Women are more likely to self-identify as having an alcohol problem and enter AUD treatment through a medical or mental health portal than a substance use specialty clinic. For instance, women may obtain AUD treatment in the course of seeking treatment for a co-occurring psychiatric disorder, such as PTSD or depression, in a general mental health setting.[19,20] Also, brief interventions in primary care settings have been found to be promising in reducing drinking among less complex cases of women with low co-occurrence,[103] but no studies have examined the co-location of more intensive outpatient female-specific AUD treatments in primary care or women's medical clinic settings.

Treatment Silos

Increasing rates of drug use among women point to a need for integrated AUD and SUD female-specific treatments. Although some evidence-based treatments are available,[103] the net can be cast even wider to include a range of health behaviors such as nutrition, sleep, exercise, smoking cessation, and use of benzodiazepines. Framing AUD treatment for women in the context of a general health and wellness approach that addresses other health behaviors may increase appeal, reduce stigma, and enhance utilization.

Digital Delivery Platforms

Testing telehealth platforms for individual and group AUD treatments may help reduce barriers to use among women. Likewise, testing ancillary smartphone applications that link women to in vivo coping skills training and social network support could enhance outcomes of existing in-person programs or serve as stand-alone aids for women who face insurmountable treatment entry barriers.

Female-Specific, Coping-Skills-Based, Peer Support Groups

Female-specific, coping-skills-based, peer support groups are not widely available. The evidence base for women's Alcoholics Anonymous meetings needs to be established. In addition, the recent positive development of a recovery coach industry may help with in vivo social support especially for women, but research is necessary to establish an evidence base.

Medications

Research on medications for women with AUD as one treatment element should continue. A precision medicine approach testing gender, genetic profiles, and specific medications is an important avenue to pursue.

Mechanisms of Change Research

Research on mechanisms of change is crucial to untangle whether similar drinking outcomes of women and men with AUD are achieved via gender-specific pathways to change and to identify active ingredients and mediators of treatment change best suited for women with only AUD and for women with specific types of co-occurring disorders. New methodologies in statistics, neuroscience, and research design are helping to clarify these questions; however, additional research is needed to streamline and personalize optimally efficient treatment components for every woman seeking care for AUD.

Acknowledgments

This article was supported in part by NIAAA grant T32 AA018180.

Financial Disclosure

The authors declare that they have no competing financial interests.

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References

1. National Institute of Alcohol Abuse and Alcoholism (NIAAA), National Institutes of Health. *Alcohol Facts and Statistics*. 2018. https://www.niaaa.nih.gov/publications/brochures-and-fact-sheets/alcohol-facts-and-statistics. Accessed January 27, 2020.
2. McCaul ME, Roach D, Hasin DS, et al. Alcohol and women: A brief overview. *Alcohol Clin Exp Res*. 2019;43(5):774-779. http://doi.org/10.1111/acer.13985.
3. Witbrodt J, Mulia N, Zemore SE, et al. Racial/ethnic disparities in alcohol-related problems: Differences by gender and level of

heavy drinking. *Alcohol Clin Exp Res*. 2014;38(6):1662-1670. http://doi.org/10.1111/acer.12398.
4. McCabe SE, West BT, Hughes TL, et al. Sexual orientation and substance abuse treatment utilization in the United States: Results from a national survey. *J Subst Abuse Treat*. 2013;44(1):4-12. http://doi.org/10.1016/j.jsat.2012.01.007.
5. Alvanzo AAH, Storr CL, Mojtabai R, et al. Gender and race/ethnicity differences for initiation of alcohol-related service use among persons with alcohol dependence. *Drug Alcohol Depend*. 2014;140:48-55. http://doi.org/10.1016/j.drugalcdep.2014.03.010.
6. Epstein EE, Menges D. Women and addiction. In: McCrady BS, Epstein EE, eds. *Addictions: A Comprehensive Guidebook*. New York, NY: Oxford University Press; 2013:788-818.
7. Substance Abuse and Mental Health Services Administration (SAMHSA), Center for Substance Abuse Treatment. *Substance Abuse Treatment: Addressing the Specific Needs of Women. A Treat Improvement Protocol TIP 51*. 2013. https://store.samhsa.gov/system/files/sma15-4426.pdf. Accessed January 27, 2020.
8. Oliva EM, Gregor A, Rogers J, et al. Correlates of specialty substance use disorder treatment among female patients in the Veterans Health Administration. *J Soc Work Pract Addict*. 2012;12(3):282-301. https://doi.org/10.1080/1533256X.2012.702620.
9. Khan S, Okuda M, Hasin DS, et al. Gender differences in lifetime alcohol dependence: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Alcohol Clin Exp Res*. 2013;37(10):1696-1705. https://doi.org/10.1111/acer.12158.
10. Kalpakci A, Sofuoglu M, Petrakis I, et al. Gender differences among Veterans with alcohol use disorder nationally in the Veterans Health Administration. *J Addict Dis*. August 2019:1-10. https://doi.org/10.1080/10550887.2019.1653739.
11. Pirard S, Sharon E, Kang SK, et al. Prevalence of physical and sexual abuse among substance abuse patients and impact on treatment outcomes. *Drug Alcohol Depend*. 2005;78(1):57-64. https://doi.org/10.1016/j.drugalcdep.2004.09.005.
12. Hien DA, Litt L, Cohen LC, et al. *Integrating Trauma Services for Women in Addictions Treatment*. New York, NY: American Psychological Association; 2009.
13. Wu L-T, Ringwalt CL. Alcohol dependence and use of treatment services among women in the community. *Am J Psychiatry*. 2004;161(10):1790-1797. https://doi.org/10.1176/ajp.161.10.1790.
14. Lale R, Sklar M, Wooldridge J, et al. Gender congruence moderates beliefs about the causes of alcohol dependence and major depression. *Int J Ment Health Addict*. 2014;12(4):395-405. https://doi.org/10.1007/s11469-013-9465-y.
15. Verissimo ADO, Grella CE. Influence of gender and race/ethnicity on perceived barriers to help-seeking for alcohol or drug problems. *J Subst Abuse Treat*. 2017;75:54-61. https://doi.org/10.1016/j.jsat.2016.12.013.
16. Rodriguez LM, Neighbors C, Knee CR. Problematic alcohol use and marital distress: An interdependence theory perspective. *Addict Res Theory*. 2014;22(4):294-312. https://psycnet.apa.org/doi/10.3109/16066359.2013.841890.
17. Tuchman E. Women and addiction: The importance of gender issues in substance abuse research. *J Addict Dis*. 2010;29(2):127-138. https://doi.org/10.1080/10550881003684582.
18. Gilbert PA, Pro G, Zemore SE, et al. Gender differences in use of alcohol treatment services and reasons for nonuse in a national sample. *Alcohol Clin Exp Res*. 2019;43(4):722-731. https://doi.org/10.1111/acer.13965.
19. Edlund MJ, Booth BM, Han X. Who seeks care where? Utilization of mental health and substance use disorder treatment in two national samples of individuals with alcohol use disorders. *J Stud Alcohol Drugs*. 2012;73(4):635-646. https://doi.org/10.15288/jsad.2012.73.635.
20. Manuel JI, Stebbins MB, Wu E. Gender differences in perceived unmet treatment needs among persons with and without co-occurring disorders. *J Behav Health Serv Res*. 2018;45(1):1-12. https://doi.org/10.1007/s11414-016-9530-y.
21. Grella CE. Treatment seeking and utilization among women with substance use disorders. In: Brady KT, Back SE, Greenfield SF, eds. *Women and Addiction: A Comprehensive Handbook*. New York, NY: The Guilford Press; 2009:307-322.
22. Green CA. Gender and use of substance abuse treatment services. *Alcohol Res Health*. 2006;29(1):55-62.
23. Greenfield SF, Brooks AJ, Gordon SM, et al. Substance abuse treatment entry, retention, and outcome in women: A review of the literature. *Drug Alcohol Depend*. 2007;86(1):1-21. https://doi.org/10.1016/j.drugalcdep.2006.05.012.
24. Green P, Watts D, Poole S, et al. Why patients sign out against medical advice (AMA): Factors motivating patients to sign out AMA. *Am J Drug Alcohol Abuse*. 2004;30(2):489-493. https://doi.org/10.1081/ada-120037390.
25. Bravo F, Gual A, Lligoña A, et al. Gender differences in the long-term outcome of alcohol dependence treatments: An analysis of twenty-year prospective follow up. *Drug Alcohol Rev*. 2013;32(4):381-388. https://doi.org/10.1111/dar.12023.
26. Bornstein K, Longinaker N, Bryant-Genevier M, et al. Sex differences in substance abuse treatment adherence in the United States. *Addict Disord Their Treat*. 2015;14(3):131-138. https://dx.doi.org/10.1016%2Fj.cpr.2017.10.012.
27. Rash CJ, Petry NM. Contingency management treatments are equally efficacious for both sexes in intensive outpatient settings. *Exp Clin Psychopharmacol*. 2015;23(5):369-376. https://doi.org/10.1037/pha0000035.
28. Litt MD, Kadden RM, Tennen H. Network Support treatment for alcohol dependence: Gender differences in treatment mechanisms and outcomes. *Addict Behav*. 2015;45:87-92. https://doi.org/10.1016/j.addbeh.2015.01.005.
29. Unger A, Jung E, Winklbaur B, et al. Gender issues in the pharmacotherapy of opioid-addicted women: Buprenorphine. In: *Women, Children, and Addiction*. Abingdon, UK: Routledge; 2014:113-126.
30. Agabio R, Pani PP, Preti A, et al. Efficacy of medications approved for the treatment of alcohol dependence and alcohol withdrawal syndrome in female patients: A descriptive review. *Eur Addict Res*. 2016;22(1):1-16. https://doi.org/10.1159/000433579.
31. Canidate SS, Carnaby GD, Cook CL, et al. A systematic review of naltrexone for attenuating alcohol consumption in women with alcohol use disorders. *Alcohol Clin Exp Res*. 2017;41(3):466-472. https://doi.org/10.1111/acer.13313.
32. Ashley OS, Marsden ME, Brady TM. Effectiveness of substance abuse treatment programming for women: A review. *Am J Drug Alcohol Abuse*. 2003;29(1):19-53. https://doi.org/10.1081/ada-120018838.
33. Sword W, Jack S, Niccols A, et al. Integrated programs for women with substance use issues and their children: A qualitative meta-synthesis of processes and outcomes. *Harm Reduct J*. 2009;6(1):32. https://doi.org/10.1186/1477-7517-6-32.
34. SAMHSA. *National Survey of Substance Abuse Treatment Services (N-SSATS): 2018. Data on Substance Abuse Treatment Facilities*. 2019. http://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSSATS-2018.pdf. Accessed January 27, 2020.

35. Timko C, Hoggatt KJ, Wu FM, et al. Substance use disorder treatment services for women in the Veterans Health Administration. *Womens Health Issues*. 2017;27(6):639-645. https://doi.org/10.1016/j.whi.2017.04.001.
36. Smith WB, Weisner C. Women and alcohol problems: A critical analysis of the literature and unanswered questions. *Alcohol Clin Exp Res*. 2000;24(8):1320-1321.
37. Greenfield SF, Grella CE. What is "women-focused" treatment for substance use disorders? *Psychiatr Serv*. 2009;60(7):880-882. https://doi.org/10.1176/ps.2009.60.7.880.
38. Greenfield SF, Pirard S. Gender-specific treatment for women with substance use disorders. In: Brady KT, Back SE, Greenfield SF, eds. *Women and Addiction: A Comprehensive Handbook*. New York, NY: The Guilford Press; 2009:289-306.
39. Neale J, Tompkins CNE, Marshall AD, et al. Do women with complex alcohol and other drug use histories want women-only residential treatment? *Addiction*. 2018;113(6):989-997. https://doi.org/10.1111/add.14131.
40. Bride BE. Single-gender treatment of substance abuse: Effect on treatment retention and completion. *Soc Work Res*. 2001;25(4):223-232. https://doi.org/10.1093/swr/25.4.223.
41. Giannitrapani KF, Huynh AK, Schweizer CA, et al. Patient-centered substance use disorder treatment for women Veterans. *J Mil Veteran Fam Health*. 2018;4(2):8-17. https://doi.org/10.3138/jmvfh.2017-0006.
42. Dahlgren L, Willander A. Are special treatment facilities for female alcoholics needed? A controlled 2-year follow-up study from a specialized female unit (EWA) versus a mixed male/female treatment facility. *Alcohol Clin Exp Res*. 1989;13(4):499-504. https://doi.org/10.1111/j.1530-0277.1989.tb00366.x.
43. Gjestad R, Franck J, Lindberg S, et al. Early treatment for women with alcohol addiction (EWA) reduces mortality: A randomized controlled trial with long-term register follow-up. *Alcohol Alcohol*. 2011;46(2):170-176. https://dx.doi.org/10.1093%2Falcalc%2Fagq097.
44. Grella CE. Women in residential drug treatment: Differences by program type and pregnancy. *J Health Care Poor Underserved*. 1999;10(2):216-229. https://doi.org/10.1353/hpu.2010.0174.
45. Grella CE, Joshi V, Hser YI. Program variation in treatment outcomes among women in residential drug treatment. *Eval Rev*. 2000;24(4):364-383. https://doi.org/10.1177/019384 1x0002400402.
46. Claus RE, Orwin RG, Kissin W, et al. Does gender-specific substance abuse treatment for women promote continuity of care? *J Subst Abuse Treat*. 2007;32(1):27-39. https://doi.org/10.1016/j.jsat.2006.06.013.
47. Niv N, Hser Y-I. Women-only and mixed-gender drug abuse treatment programs: Service needs, utilization and outcomes. *Drug Alcohol Depend.* 2007;87(2-3):194-201. https://doi.org/10.1016/j.drugalcdep.2006.08.017.
48. Prendergast ML, Messina NP, Hall EA, et al. The relative effectiveness of women-only and mixed-gender treatment for substance-abusing women. *J Subst Abuse Treat.* 2011;40(4):336-348. https://doi.org/10.1016/j.jsat.2010.12.001.
49. Kaskutas LA, Zhang L, French MT, et al. Women's programs versus mixed-gender day treatment: Results from a randomized study. *Addiction.* 2005;100(1):60-69. https://doi.org/10.1111/j.1360-0443.2005.00914.x.
50. McCrady BS, Epstein EE, Cook S, et al. A randomized trial of individual and couple behavioral alcohol treatment for women. *J Consult Clin Psychol.* 2009;77(2):243-256. https://doi.org/10.1037/a0014686.
51. Schumm JA, O'Farrell TJ, Kahler CW, et al. A randomized clinical trial of behavioral couples therapy versus individually based treatment for women with alcohol dependence. *J Consult Clin Psychol.* 2014;82(6):993-1004. https://doi.org/10.1037/a0037497.
52. O'Farrell TJ, Schumm JA, Murphy MM, et al. A randomized clinical trial of behavioral couples therapy versus individually-based treatment for drug-abusing women. *J Consult Clin Psychol.* 2017;85(4):309-322. http://doi.org/10.1037/ccp0000185.
53. McCrady BS, Epstein EE, Cook S, et al. What do women want? Alcohol treatment choices, treatment entry and retention. *Psychol Addict Behav.* 2011;25(3):521-529. https://doi.org/10.1037/a0024037.
54. Upshur C, Weinreb L, Bharel M, et al. A randomized control trial of a chronic care intervention for homeless women with alcohol use problems. *J Subst Abuse Treat.* 2015;51:19-29. https://doi.org/10.1016/j.jsat.2014.11.001.
55. Polcin DL, Nayak MB, Korcha R, et al. Heavy drinking among women receiving intensive motivational interviewing: 6-month outcomes. *J Psychoactive Drugs.* 2019;51(5):421-430. https://doi.org/10.1080/02791072.2019.1634302.
56. Connors GJ, Walitzer KS. Reducing alcohol consumption among heavily drinking women: Evaluating the contributions of life-skills training and booster sessions. *J Consult Clin Psychol.* 2001;69(3):447-456. https://doi.org/10.1037//0022-006x.69.3.447.
57. Walitzer KS, Connors GJ. Thirty-month follow-up of drinking moderation training for women: A randomized clinical trial. *J Consult Clin Psychol.* 2007;75(3):501-507. https://doi.org/10.1037/0022-006X.75.3.501.
58. Epstein EE, McCrady BS. *Overcoming Alcohol Use Problems: A Cognitive-Behavioral Treatment Program.* New York, NY: Oxford University Press; 2009.
59. Epstein EE, McCrady BS, Hallgren KA, et al. A randomized trial of female-specific cognitive behavior therapy for alcohol dependent women. *Psychol Addict Behav.* 2018;32(1):1-15. https://doi.org/10.1037/adb0000330.
60. Epstein EE, McCrady BS, Hallgren KA, et al. Individual versus group female-specific cognitive behavior therapy for alcohol use disorder. *J Subst Abuse Treat.* 2018;88:27-43. https://doi.org/10.1016/j.jsat.2018.02.003.
61. Olmstead TA, Graff FS, Ames-Sikora A, et al. Cost-effectiveness of individual versus group female-specific cognitive behavioral therapy for alcohol use disorder. *J Subst Abuse Treat.* 2019;100:1-7. https://doi.org/10.1016/j.jsat.2019.02.001.
62. Greenfield SF, Trucco EM, McHugh RK, et al. The Women's Recovery Group study: A Stage I trial of women-focused group therapy for substance use disorders versus mixed-gender group drug counseling. *Drug Alcohol Depend.* 2007;90(1):39-47. https://doi.org/10.1016/j.drugalcdep.2007.02.009.
63. Greenfield SF. *Treating Women with Substance Use Disorders: The Women's Recovery Group Manual.* New York, NY: The Guilford Press; 2016.
64. McHugh RK, Greenfield SF. Psychiatric symptom improvement in women following group substance abuse treatment: Results from the Women's Recovery Group study. *J Cogn Psychother.* 2010;24(1):26-36. https://doi.org/10.1891/0889-8391.24.1.26.
65. Greenfield SF, Sugarman DE, Freid CM, et al. Group therapy for women with substance use disorders: Results from the Women's Recovery Group Study. *Drug Alcohol Depend.* 2014;142:245-253. https://doi.org/10.1016/j.drugalcdep.2014.06.035.

66. Greenfield SF, Kuper LE, Cummings AM, et al. Group process in the single-gender Women's Recovery Group compared with mixed-gender Group Drug Counseling. *J Groups Addict Recover.* 2013;8(4):270-293. https://doi.org/10.1080/1556035X.2013.836867.
67. Sugarman DE, Wigderson SB, Iles BR, et al. Measuring affiliation in group therapy for substance use disorders in the Women's Recovery Group study: Does it matter whether the group is all-women or mixed-gender? *Am J Addict.* 2016;25(7):573-580. https://doi.org/10.1111/ajad.12443.
68. Valeri L, Sugarman DE, Reilly ME, et al. Group therapy for women with substance use disorders: In-session affiliation predicts women's substance use treatment outcomes. *J Subst Abuse Treat.* 2018;94:60-68. https://doi.org/10.1016/j.jsat.2018.08.008.
69. Sugarman DE, Meyer LE, Reilly ME, et al. Feasibility and acceptability of a web-based, gender-specific intervention for women with substance use disorders. *J Women's Health.* October 2019. https://doi.org/10.1089/jwh.2018.7519.
70. Najavits LM, Enggasser J, Brief D, et al. A randomized controlled trial of a gender-focused addiction model versus 12-step facilitation for women veterans. *Am J Addict.* 2018;27(3):210-216. https://doi.org/10.1111/ajad.12709.
71. Covington SS. *Helping Women Recover: A Program for Treating Addiction.* Rev ed. Hoboken, NJ: John Wiley & Sons; 2008.
72. Covington SS. *Beyond Trauma: A Healing Journey for Wom*en. Center City, MN: Hazelden Publishing; 2003.
73. Messina N, Grella CE, Cartier J, et al. A randomized experimental study of gender-responsive substance abuse treatment for women in prison. *J Subst Abuse Treat.* 2010;38(2):97-107. https://doi.org/10.1016/j.jsat.2009.09.004.
74. Saxena P, Messina NP, Grella CE. Who benefits from gender-responsive treatment? Accounting for abuse history on longitudinal outcomes for women in prison. *Crim Justice Behav.* 2014;41(4):417-432. https://doi.org/10.1177/0093854813514405.
75. Flanagan JC, Korte KJ, Killeen TK, et al. Concurrent treatment of substance use and PTSD. *Curr Psychiatry Rep.* 2016;18(8):70. https://doi.org/10.1007/s11920-016-0709-y.
76. Simpson TL, Lehavot K, Petrakis IL. No wrong doors: Findings from a critical review of behavioral randomized clinical trials for individuals with co-occurring alcohol/drug problems and posttraumatic stress disorder. *Alcohol Clin Exp Res.* 2017;41(4):681-702. https://doi.org/10.1111/acer.13325.
77. Najavits L. *Seeking Safety: A Treatment Manual for PTSD and Substance Abuse.* New York, NY: The Guilford Press; 2002.
78. Hien DA, Cohen LR, Miele GM, et al. Promising treatments for women with comorbid PTSD and substance use disorders. *Am J Psychiatry.* 2004;161(8):1426-1432. https://doi.org/10.1176/appi.ajp.161.8.1426.
79. Hien DA, Wells EA, Jiang H, et al. Multisite randomized trial of behavioral interventions for women with co-occurring PTSD and substance use disorders. *J Consult Clin Psychol.* 2009;77(4):607-619.
80. Morrissey JP, Ellis AR, Gatz M, et al. Outcomes for women with co-occurring disorders and trauma: Program and person-level effects. *J Subst Abuse Treat.* 2005;28(2):121-133. https://doi.org/10.1037/a0016227.
81. Gamble SA, Talbot NL, Cashman-Brown SM, et al. A pilot study of interpersonal psychotherapy for alcohol-dependent women with co-occurring major depression. *Subst Abus.* 2013;34(3):233-241. https://doi.org/10.1080/08897077.2012.746950.
82. Baker AL, Kavanagh DJ, Kay-Lambkin FJ, et al. Randomized controlled trial of cognitive-behavioural therapy for coexisting depression and alcohol problems: Short-term outcome. *Addiction.* 2010;105(1):87-99. https://doi.org/10.1111/j.1360-0443.2009.02757.x.
83. Adamson SJ, Sellman JD, Foulds JA, et al. A randomized trial of combined citalopram and naltrexone for nonabstinent outpatients with co-occurring alcohol dependence and major depression. *J Clin Psychopharmacol.* 2015;35(2):143-149. https://doi.org/10.1097/jcp.0000000000000287.
84. Rosenthal RN. Treatment of persons with substance use disorder and co-occurring other mental disorders. In: McCrady BS, Epstein EE, eds. *Addictions: A Comprehensive Guidebook.* New York, NY: Oxford University Press; 2013:659-707.
85. Dimeff LA, Linehan MM. Dialectical behavior therapy for substance abusers. *Addict Sci Clin Pract.* 2008;4(2):39-47. https://doi.org/10.1151/ascp084239.
86. Lee NK, Cameron J, Jenner L. A systematic review of interventions for co-occurring substance use and borderline personality disorders. *Drug Alcohol Rev.* 2015;34(6):663-672. https://doi.org/10.1111/dar.12267.
87. Longabaugh R, Magill M, Morgenstern J, et al. Mechanisms of behavior change in treatment for alcohol and other drug use disorders. In: McCrady BS, Epstein EE, eds. *Addictions: A Comprehensive Guidebook.* New York, NY: Oxford University Press; 2013:572-596.
88. Haver B, Gjestad R. Phobic anxiety and depression as predictor variables for treatment outcome. A LISREL analysis on treated female alcoholics. *Nord J Psychiatry.* 2005;59(1):25-30. https://doi.org/10.1080/08039480510018797.
89. Holzhauer CG, Epstein EE, Hayaki J, et al. Moderators of sudden gains after sessions addressing emotion regulation among women in treatment for alcohol use. *J Subst Abuse Treat.* 2017;83:1-9. https://doi.org/10.1016/j.jsat.2017.09.014.
90. Hallgren KA, Epstein EE, McCrady BS. Changes in hypothesized mechanisms of change before and after initiating abstinence in cognitive-behavioral therapy for women with alcohol use disorder. *Behav Ther.* 2019;50(6):1030-1041. https://doi.org/10.1016/j.beth.2019.01.009.
91. Hallgren KA, McCrady BS, Epstein EE. Trajectories of drinking urges and the initiation of abstinence during cognitive–behavioral alcohol treatment. *Addiction*. 2016;111(5):854-865. https://doi.org/10.1111/add.13291.
92. Holzhauer CG, Hildebrandt T, Epstein EE, et al. Mechanisms of change in female-specific and gender-neutral cognitive behavioral therapy for women with alcohol use disorder. *J Consult Clin Psychol.* February 20, 2020. https://doi.org/10.1037/ccp0000492.
93. Food and Drug Administration, National Institutes of Health, Department of Health and Human Services. *NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research.* 1994. https://grants.nih.gov/grants/guide/notice-files/not94-100.html. Accessed January 28, 2020.
94. NIAAA. *Mechanisms of Behavior Change Research Initiative: Strategic Research Plan.* 2006. https://www.niaaa.nih.gov/sites/default/files/publications/MechanismsofBehaviorChange2006.pdf. Accessed January 28, 2020.
95. NIAAA. *Mechanisms of Behavior Change in the Treatment of Alcohol Use Disorders* (R21). 2006. https://grants.nih.gov/grants/guide/rfa-files/RFA-AA-07-005.html. Accessed January 28, 2020.

96. Precision Medicine Initiative Working Group. *The Precision Medicine Initiative Cohort Program – Building a Research Foundation for 21st Century Medicine.* 2015. https://acd.od.nih.gov/documents/reports/DRAFT-PMI-WG-Report-9-11-2015-508.pdf. Accessed January 28, 2020.
97. Willenbring ML. The past and future of research on treatment of alcohol dependence. *Alcohol Res Health.* 2010;33(1-2):55-63.
98. Buckman JF, Vaschillo B, Vaschillo EG, et al. Improvement in women's cardiovascular functioning during treatment for alcohol use disorder. *Psychol Addict Behav.* 2019;33(8):659-668. https://doi.org/10.1037/adb0000524.
99. Bold KW, Epstein EE, McCrady BS. Baseline health status and quality of life after alcohol treatment for women with alcohol dependence. *Addict Behav.* 2017;64:35-41. https://doi.org/10.1016/j.addbeh.2016.08.014.
100. Epstein EE, McCrady BS, Cook S, et al. Non-ETOH drug use among women in outpatient treatment for alcohol dependence. *Drug Alcohol Depend.* 2015;146:e272. http://dx.doi.org/10.1016/j.drugalcdep.2014.09.205
101. NIAAA. *Notice of Special Interest on Development and Dissemination of Behavioral Treatments for AUD.* 2019. https://grants.nih.gov/grants/guide/notice-files/NOT-AA-19-010.html. Accessed January 28, 2020.
102. SAMHSA. *Guidance Document for Supporting Women in Co-Ed Settings.* 2016. https://store.samhsa.gov/system/files/sma16-4979.pdf. Accessed January 28, 2020.
103. Cucciare MA, Simpson T, Hoggatt KJ, et al. Substance use among women veterans: Epidemiology to evidence-based treatment. *J Addict Dis.* 2013;32(2):119-139. https://doi.org/10.1080/10550887.2013.795465.

ALCOHOL RESEARCH
Current Reviews

Alcohol Res. 2020;40(2):09 • https://doi.org/10.35946/arcr.v40.2.09

Published: 3 September 2020

Alcohol-Related Disparities Among Women: Evidence and Potential Explanations

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Although research on alcohol-related disparities among women is a highly understudied area, evidence shows that racial/ethnic minority women, sexual minority women, and women of low socioeconomic status (based on education, income, or residence in disadvantaged neighborhoods) are more likely to experience alcohol-related problems. These problems include alcohol use disorder, particularly after young adulthood, and certain alcohol-related health, morbidity, and mortality outcomes. In some cases, disparities may reflect differences in alcohol consumption, but in other cases such disparities appear to occur despite similar and possibly lower levels of consumption among the affected groups. To understand alcohol-related disparities among women, several factors should be considered. These include age; the duration of heavy drinking over the life course; the widening disparity in cumulative socioeconomic disadvantage and health in middle adulthood; social status; sociocultural context; genetic factors that affect alcohol metabolism; and access to and quality of alcohol treatment services and health care. To inform the development of interventions that might mitigate disparities among women, research is needed to identify the factors and mechanisms that contribute most to a group's elevated risk for a given alcohol-related problem.

KEY WORDS: alcohol problems; health disparities; minorities; cumulative disadvantage; life course; alcohol

INTRODUCTION

Although women consume less alcohol and drink less often than men,[1] women's drinking warrants serious attention from alcohol researchers and health care providers, in part because women are more susceptible to certain alcohol-related problems at a given level of consumption[2] and because women are less likely to receive help for problems with alcohol use.[3] While women may share many experiences and risk factors relevant to their alcohol use and associated problems, women are not a monolithic group. Multiple dimensions of social location (e.g., race/ethnicity, socioeconomic status, and sexual identity) profoundly shape women's lived experiences.[4] These can affect health and a wide range of health-related factors over the life course, such as social and environmental risk and health-promoting exposures, health behavior, resources that enhance health and help to manage disease, care-seeking, and the quality of health care received. Thus, unsurprisingly, among women there is heterogeneity of risk for problems related to drinking.

This article briefly reviews what is known about alcohol-related disparities among women and discusses mechanisms that could give rise to inequities in alcohol outcomes. In this article, disparity refers to social group differences in which groups that have greater social or economic advantages have more desirable health outcomes than groups without those advantages.[5] Research on alcohol-related disparities has focused on racial/ethnic and socioeconomic groups[6-8] and often has not been stratified by gender to examine disparities among women or men separately, as doing so would require very large samples for low-prevalence outcomes. Thus, this review reflects a predominant focus in the extant literature on race/ethnicity (often White, Black, and Latinx groups, with rare analysis of Latinx subgroups), socioeconomic status, and the limited study of disparities among women. Far less research has been conducted on sexual minority groups (defined by sexual orientation). Reflecting the work to date, unless otherwise stated, this review defines women based on physiological sex. Finally, this review focuses on problems associated with personal alcohol consumption and does not include the many secondary harms experienced because of other people's drinking.

DISPARITIES IN ALCOHOL-RELATED PROBLEMS

Identifying racial/ethnic and socioeconomic disparities in alcohol-related problems is not always a straightforward task, partly because of differential abstinence rates across racial/ethnic and socioeconomic groups. For example, in the National Epidemiologic Survey on Alcohol and Related Conditions-III (NESARC-III), the percentage of people who drank alcohol in the past year ranged from 62% to 75% across racial/ethnic groups and 56% to 81% across levels of education.[1] The National Alcohol Survey (NAS) reported 64% of heterosexual women and 78% of bisexual women drank alcohol in the past year.[9] In addition, race, ethnicity, and socioeconomic status are deeply intertwined in the United States.[10] In light of the above, the detection of alcohol-related disparities can be affected by the inclusion of abstainers in analyses and also by how investigators handle socioeconomic status when analyzing racial/ethnic differences. Although analytic decisions depend on research objectives (e.g., to establish general population rates, understand risk relationships, estimate residual racial/ethnic differences, or recognize the role of socioeconomic status in racial/ethnic differences), sensitivity analyses are always a useful option to gauge the effects of such decisions on study results and enhance

interpretation. Effort was made in this review to be attentive to such decisions.

Alcohol Use Disorder and Negative Consequences of Drinking

The following section provides a review of research on the prevalence and risk of alcohol-related problems in different subgroups of women defined by race/ethnicity, socioeconomic status, and sexual minority status. Problems examined in this literature include alcohol use disorder (AUD) and negative consequences of drinking. In nearly all of the studies reviewed, AUD was defined according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV),*[11] which includes and distinguishes alcohol abuse and alcohol dependence. In 2013, the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*[12] was released, which replaces DSM-IV alcohol abuse and dependence diagnoses with a single AUD diagnosis that is classified as mild, moderate, and severe.

Race and ethnicity

National survey data show greater prevalence of DSM-IV AUD among White women compared to other racial/ethnic groups. For example, in Wave 1 of the NESARC, which was conducted from 2001 to 2002, age group–specific rates of DSM-IV alcohol abuse and dependence among women (including abstainers) were consistently higher in White women compared to Black, Latina, and Asian/Pacific Islander women in nearly all of four age groups examined.[13] The exceptions were American Indian/Alaska Native (AIAN) women, whose prevalence of DSM-IV alcohol abuse and dependence was greater than that of White women in three of four age groups, and Black women, whose DSM-IV alcohol dependence prevalence was higher than that of White women at midlife (ages 45 to 64) and older (ages 65 and older). However, many of these differences did not appear to be statistically significant. Taking into account standard error, the clearest differences were observed among White, Black, and Latina women, the three largest groups. DSM-IV alcohol abuse prevalence was higher in White women compared to Black women before midlife (younger than age 45), and higher than DSM-IV alcohol abuse prevalence of Latinas in all but the oldest age group (ages 65 and older).

In the same NESARC survey, the prevalence of DSM-IV alcohol dependence was significantly higher only in young-adult, White women (ages 18 to 29) at 6% vs. 4% in young Black women and 4% in young Latina women.[13] At 9%, the prevalence of DSM-IV alcohol dependence among young AIAN women was highest of all, but it had a wide confidence interval. By contrast, in 2000, 2005, and 2010 NAS data, White, Black, and Latina women (including abstainers and not stratified by age) showed statistically nondistinguishable prevalence and odds of having DSM-IV alcohol dependence and two or more negative consequences of drinking.[14]

Because these studies were based on older data that, in some cases, were collected nearly 20 years ago, data from the 2017 National Survey on Drug Use and Health (NSDUH)[15] were analyzed to provide updated national estimates for women. As shown in Table 1, most of the significant racial/ethnic differences in DSM-IV alcohol dependence prevalence were no longer apparent when abstainers were excluded. When compared with White women who drink alcohol, only Asian women who drink had significantly lower rates of DSM-IV AUD, and AIAN women who drink had higher rates of DSM-IV AUD.

Table 1 2017 NSDUH 12-Month Prevalence of DSM-IV Alcohol Dependence and AUD Among Women

Category	Alcohol Dependence, % (Standard Error)		Alcohol Dependence or Abuse, % (Standard Error)	
	All Women (*N* = 22,567)	Drank in Past Year (*N* = 16,042)	All Women (*N* = 22,567)	Drank in Past Year (*N* = 16,042)
Race/Ethnicity				
White†	2.70 (0.14)	3.70 (0.20)	4.44 (0.15)	6.07 (0.22)
Black	1.86 (0.24)*	3.11 (0.41)	3.12 (0.31)**	5.21 (0.50)
AIAN	8.04 (1.26)**	16.21 (2.64)**	9.10 (1.32)**	18.35 (2.75)**
Native Hawaiian/Pacific Islander	2.11 (1.54)	4.46 (3.27)	2.90 (1.71)	6.11 (3.62)
Asian	1.29 (0.42)*	2.68 (0.85)	1.79 (0.46)**	3.71 (0.88)*
More Than One Race	4.91 (1.70)	7.44 (2.63)	6.70 (1.76)	10.15 (2.75)
Latina	1.72 (0.23)**	2.93 (0.42)	3.20 (0.28)**	5.46 (0.52)
Education				
Less Than High School	1.58 (0.24)**	3.92 (0.61)	2.11 (0.32)**	5.24 (0.79)
High School Graduate	1.60 (0.15)**	2.80 (0.27)	2.63 (0.19)**	4.61 (0.34)*
Some College	3.05 (0.27)	4.23 (0.39)	4.84 (0.32)	6.72 (0.45)
College Graduate†	2.69 (0.22)	3.38 (0.27)	4.74 (0.27)	5.96 (0.33)
Sexual Identity				
Heterosexual†	2.14 (0.11)	3.18 (0.17)	3.61 (0.12)	5.36 (0.19)
Lesbian	5.12 (1.33)**	6.31 (1.62)*	8.21 (1.69)*	10.12 (2.10)**
Bisexual	8.63 (1.02)**	10.68 (1.25)**	12.23 (1.11)**	15.12 (1.35)**

Note: Data are for women ages 18 and older. Percentages are weighted for sampling, and sample size (*N*) represents unweighted totals. Pairwise significance tests involve comparisons to the reference category using Pearson's chi-square test. *$p < 0.05$, **$p < 0.01$, † = reference category. *Source:* Data from Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality, October 2018.[15]

In studies excluding lifetime abstainers, there is some evidence of greater alcohol problems among racial/ethnic minority women who drink compared with White women who drink. For example, Grant and colleagues conducted a longitudinal analysis of NESARC Waves 1 and 2 from the early 2000s and found that at Wave 2, young White women had the greatest risk for DSM-IV alcohol dependence onset compared with young Black and Latina women.[16] However, the risk for young White women was lower than that for older minority women. Both Black and U.S.-born Latina women ages 40 and older had greater risk of DSM-IV alcohol dependence onset than young White women (adjusted *OR* = 1.71 and 2.08, respectively).[16] In addition, older Black and U.S.-born Latina women had more persistent alcohol dependence (adjusted *OR* = 2.73 and 1.36, respectively), and older U.S.-born Latina women had greater recurrence of dependence (among those with lifetime dependence prior to Wave 1). This elevated risk among older minority women was in marked contrast to similarly aged, White peers, whose risk for alcohol dependence onset, persistence, and recurrence was much lower than that of young White women. The racial/ethnic patterning of risk was the same when DSM-IV AUD was the outcome, except that disparities were also evident among younger minority women ages 30 to 39. In this age group, Black women had greater AUD onset, and U.S.-born Latinas had greater AUD persistence than young White women.

Notably, this NESARC study did not control for socioeconomic status indicators.[16] In a 2005 and 2010 combined NAS study of women who drink, which adjusted for demographics, education, and income and also rigorously controlled for heavy drinking, the only disparities found between Black and White women were in DSM-IV alcohol dependence (adjusted *OR* = 3.3), and this disparity held across the range of heavy drinking.[17] There was no significant disparity between Latina and White women in either negative consequences of drinking (an outcome similar to alcohol abuse) or DSM-IV alcohol dependence. (Due to sample size limitations of the study,[17] U.S.-born Latina women were not analyzed separately as they were in the NESARC study by Grant and colleagues.[16])

As noted, all of the research on AUD in demographic subgroups reviewed above, including the 2017 NSDUH data on AUD,[15] is based on the DSM-IV diagnostic criteria rather than the DSM-5 criteria. Thus, it is not clear whether these findings (especially those based on data collected from the early 2000s) accurately reflect DSM-5 AUD patterns among women, as the latter have not yet been examined. However, results from two recent NESARC-III studies of women and men combined suggest that the patterning of AUD prevalence across racial/ethnic, socioeconomic, and other demographic subgroups may be similar across DSM-IV and DSM-5 criteria.[18,19] For instance, AUD prevalence among White, Black, and Latinx study participants based on DSM-IV criteria was 13%, 13%, and 12%, respectively,[18] and the prevalence based on DSM-5 criteria was 14%, 14%, and 14%, respectively.[19] Similarly, for educational levels, the DSM-IV AUD prevalence was 10% for less than high school, 13% for high school, and 13% for some college or more,[18] and the prevalence based on DSM-5 criteria was 12%, 15%, and 14%, respectively.[19] These results suggest that the presence or absence of disparities in women's prevalence of DSM-5 AUD might reasonably be gauged by recent research that uses DSM-IV AUD criteria (for instance, as captured by the 2017 NSDUH). But confirmation is needed, as the NESARC-III analyses were not restricted to women.

Socioeconomic status

Similar to the findings for race/ethnicity, the 2017 NSDUH data show significant differences in DSM-IV alcohol dependence and AUD by educational attainment, but when abstainers are excluded, nearly all differences become nonsignificant (see Table 1).[15] Importantly, in a recent systematic review, Collins concluded that although groups with greater socioeconomic advantages (defined by income, education, and other indicators at the individual, family, or neighborhood levels) had similar or greater levels of alcohol consumption than those with fewer advantages, the groups with fewer socioeconomic advantages were at greater risk for alcohol-related problems.[8] This finding has been referred to as the "alcohol harm paradox"[20] and is similar to the phenomenon among some U.S. racial/ethnic minority groups, particularly Black persons, of having greater risk for alcohol-related problems than White persons despite drinking less.[21]

This socioeconomic status paradox has been studied mostly outside of the United States and has been observed for a variety of alcohol outcomes. A meta-analysis by Grittner and colleagues, drawing upon survey data from 25 countries, found that in several high-income countries, women who drink alcohol and who have less education were at greater risk for external drinking consequences (e.g., consequences affecting finances; work, school, or employment; close relationships; and risk of injury/fights).[22] In the full sample of countries, an inverse educational gradient was found when controlling for age and drinking pattern, as well as country-level, socioeconomic development factors.

The socioeconomic conditions of residential neighborhoods also are relevant. Analysis of the 2000 and 2005 combined NAS data found that women who drink alcohol and live in disadvantaged neighborhoods have twofold greater risk for alcohol problems (adjusted *OR* = 2.07 for two or more drinking consequences or DSM-IV alcohol dependence) than women who drink and live in more advantaged neighborhoods.[23]

This study controlled for individuals' education, income, unemployment status, and demographics.

A different study that used 2000 and 2005 combined NAS data further showed that among White women who drink alcohol, neighborhood disadvantage was associated with increased risk for negative consequences of drinking.[24] The authors noted that White women who drink and reside in disadvantaged (as compared to more advantaged) neighborhoods were challenged by greater family histories of alcohol problems, co-occurring drug use, and drinking to cope with stress, which are risk factors for alcohol problems.

Providing a context for such findings, a longitudinal study of women in poverty highlighted the distinctive stressors faced by women who drink and have low incomes.[25] Stressful life events and neighborhood stressors (e.g., crime, drug trafficking, and shootings) were common, and these in addition to economic stress, contributed to psychological distress and increased women's risk for developing problematic alcohol use.

Sexual minority women

In this article, sexual minority women, including bisexual women and lesbians, are defined based on sexual orientation. In a study by Wilsnack and colleagues, the investigators compared data collected from sexual minority women in the 2001 to 2002 Chicago Study of Health and Life Experience of Women (CHLEW) study with data collected from exclusively heterosexual women in the 2001 National Study of Health and Life Experiences of Women.[26] The investigators found higher prevalence of lifetime alcohol-related problems, alcohol dependence symptoms, and hazardous drinking among sexual minority women. Bisexual women were most likely to report alcohol problems, with 70% reporting lifetime problems in contrast to 29% of heterosexual women.

Similar disparities in hazardous drinking were found in a more recent wave of the CHLEW study (2010 to 2012) and in a 2000 to 2015 NAS analysis.[9] Additionally, a separate study by Drabble and colleagues that used 2000 NAS data found that lesbians had 7.1 times higher risk of meeting criteria for DSM-IV alcohol dependence (bisexual women had 6.4 times higher risk) than heterosexual women.[27] A recent study that used 2015 to 2017 NSDUH data indicated disparities in DSM-IV AUD rates as well.[28] In that study, bisexual women had 2.2 times higher odds than heterosexual women and 1.5 times higher odds than lesbian women of having past-year AUD after adjusting for demographic characteristics.[28]

Although this review focuses on sexual minority women, the newly emerging literature on alcohol use among gender minority women (i.e., noncisgender and nonbinary women) should be noted. A systematic review of transgender individuals (including gender minority women) by Gilbert and colleagues found estimates of binge drinking among transgender individuals ranging from 7% to 65%, with estimates of lifetime and past-year DSM-IV AUD prevalence at 26% and 11%, respectively.[29] More research is needed on these groups. As noted by Gilbert and colleagues, to facilitate research on alcohol use disparities among gender minority women and transgender individuals, new methods will be needed, as many of the current alcohol use measures to assess unsafe drinking rely on physiological sex-specific cut points.

Health, Morbidity, and Mortality

Disparities in alcohol-related health outcomes, morbidity, and mortality are studied less commonly than disparities in AUD and the negative consequences of drinking alcohol. Few studies focus on women; instead, studies typically include women and men and control for gender. Nonetheless, in analyses restricted to women, racial/ethnic and socioeconomic disparities in risk have been reported for some alcohol-related health conditions and outcomes. For example, based on suicide decedent data from the National Violent Death Reporting System, AIAN women had approximately twice the odds of acute alcohol intoxication relative to White women at the time of death.[30] Also, increased alcohol use is known to be associated with

mortality among people with HIV.[31] This risk disproportionately affects Black women, whose incidence rate for HIV far exceeds that of White women (estimated at 783.7 and 43.6 per 100,000 for Black and White women, respectively).[32]

Research also indicates socioeconomic differentials in alcohol-related morbidity and mortality. An English study of hospital admissions from 2010 to 2013 that examined wholly and partially alcohol-attributable conditions found the greatest socioeconomic disparities among women with wholly alcohol-attributable chronic and acute conditions.[33] These results suggest that socioeconomic status differences in harmful drinking patterns contribute to differential morbidity.

Applying a similar comparative approach, Probst and colleagues conducted a meta-analysis of 15 studies from 7 countries and found greater socioeconomic disparities in women's alcohol-attributable mortality than in their all-cause mortality.[34] Across different measures of socioeconomic status (e.g., individual-level education, occupation, employment status, or income), socioeconomically disadvantaged women had 1.8 times the relative risk of alcohol-attributable vs. all-cause mortality when compared to more advantaged women. Similarly, a Scottish study of women and men combined found that socioeconomically disadvantaged participants who drink moderately had much greater risk for alcohol-attributable harms (i.e., hospital admissions or deaths) compared to socioeconomically advantaged participants who drink moderately or even heavily, regardless of the socioeconomic status measure used and even after controlling for differences in binge drinking, obesity, smoking, and other risk factors.[20]

Other research has investigated disparities in the protective health effects of moderate drinking. Although protective effects for cardiovascular disease mortality and for diabetes onset have been found,[35,36] some studies indicate health benefits for Whites but not for racial/ethnic minorities.[37-39] Race/ethnicity differences in the protective effects of alcohol have also been observed in two studies of all-cause mortality. One study used NAS data[40] and the other was a gender-stratified study based on data from the National Health Interview Survey.[41] The latter study found that moderate drinking was associated with the lowest mortality among White women (a mortality rate of 40.1 per 1,000 person-years). In Black women, moderate drinking was associated with a mortality rate of 93.8 per 1,000 person-years), more than double the rate of White women with a similar drinking level and also higher than the mortality rate associated with high-risk drinking among Black women (67.6 per 1,000 person-years), although confidence intervals for Black women's rates were widely overlapping.[41]

In contrast to these disparities, the United States has seen a racial/ethnic crossover in liver cirrhosis mortality rates for women. Although rates for Black women were highest in 2000, they have since dropped, and rates for White, non-Latina women and for White, Latina women have risen, exceeding the rates for Black women.[42] These results are consistent with reports of increased consumption and alcohol problems among White women based on the 2000 and 2010 NAS survey series.[14,43]

POSSIBLE EXPLANATIONS FOR DISPARITIES

An obvious potential explanation for these disparities is that they reflect population differences in harmful drinking patterns. Sexual minority women, for instance, are more likely to drink alcohol, to drink to intoxication, and to drink heavily compared to exclusively heterosexual women (adjusted *OR* = 1.8 and 2.0 for intoxication and heavy drinking, respectively).[27] Yet, it is unlikely that consumption patterns alone account for disparities. Indeed, the finding of greater harm despite lower or similar levels of drinking lies at the heart of the alcohol harm paradox. As noted, the latter refers to socioeconomic disparities in alcohol outcomes but is similar to the phenomenon observed for some racial/ethnic minority groups of disparities in alcohol problems at the same level

of heavy drinking among both women and men. Related to this, it is important to note that previous research finding elevated alcohol consumption among AIAN relative to White individuals has been based on specific AIAN tribes or geographic-area subgroups, whose prevalence of alcohol use varies.[44] Recent analyses of the 2009 to 2013 NSDUH and the 2011 to 2013 Behavioral Risk Factor Surveillance System indicate that, nationally, AIAN and White participants had similar odds of binge drinking and heavy drinking (i.e., drinking five or more drinks on 5 or more days). Moreover, White participants had lower abstinence relative to AIAN participants, with an adjusted odds ratio for abstinence among White participants relative to AIAN participants of 0.64 (95% CI: 0.56, 0.73).[45]

Thus, consideration of other ways that disparities in alcohol-related problems can arise is needed. Recent research calls attention to potential explanations involving the life course, differential vulnerability, and access to care. As noted earlier, this review reflects a predominant focus in the literature on racial/ethnic and socioeconomic disparities. Future studies are needed to assess relevance to other disadvantaged social groups.

Harmful Drinking Patterns Over the Life Course

Reflecting core concepts of life-course developmental theory,[46] both the age at which heavy drinking occurs and the duration of heavy drinking across the life course are relevant to disparities in alcohol-related problems. This makes sense intuitively, as the longer a person engages in health risk behaviors, the greater the chances of experiencing related problems. Also, certain age periods are likely to pose more or less risk for different kinds of alcohol-related problems. Bouts of heavy drinking, for instance, are likely to be tolerated less and to have more consequences when coupled with greater responsibilities to others, such as family and employers.

Notably, three recent studies based on National Longitudinal Study of Adolescent to Adult Health data examined racial/ethnic differences in the heavy-drinking trajectories of young women, with somewhat mixed results (possibly reflecting methodological differences, such as adjustments for socioeconomic status).[47-49] Two studies showed that heavy drinking of young White women consistently exceeded that of Black women.[47,48] One study indicated that the rapidly declining trajectory of White women converged with the trajectory of Latina women by age 30,[47] and another showed a convergence of White, Latina, and Black women's trajectories by their early 30s.[49]

A fourth study based on the 1979 cohort of the National Longitudinal Study of Youth (NLSY) examined women's heavy-drinking trajectories from ages 21 to 51.[50] This study also found that heavy drinking among White women exceeded that of Black and Latina women in their early and mid-20s, but the trajectories of all 3 groups declined thereafter, with no significant racial/ethnic differences in heavy drinking between ages 30 to 51. However, sensitivity analyses excluding lifetime abstainers and women who never drank heavily showed a crossover in the heavy-drinking trajectories of Black and White women.[50] The trajectory for Black women rose during their early 20s, a period when White women's trajectory declined, thus causing a crossover at age 30. Thereafter, Black women's trajectory declined and reconverged with the flattening trajectory for White women at age 40. Consistent with these results, a 2010 NAS analysis of heavy drinking trajectories among women who reported ever drinking in their lifetime found that Black women, compared to White women, had twofold greater odds of persistent, frequent, heavy drinking (vs. declining heavy drinking) beyond their 20s and into their 40s (adjusted $OR = 2.65$, $p < .01$).[51]

Taken together, these life-course drinking studies highlight racial/ethnic differences in the heavy-drinking trajectories of women in their early and mid-20s, which are consistent with the greater DSM-IV AUD risk observed during this period among young White women. Importantly, early adulthood is a time when health is relatively robust, and many women have yet to take on large, adult responsibilities. Drinking trajectory studies

that extend beyond the 20s are rare, but there is some evidence of Black–White disparities in the age and duration of heavy drinking among women who reported ever drinking in their lifetime. These disparities were found for women in their 30s, possibly extending to their 40s.

Prospective studies beyond young adulthood are needed, especially for younger cohorts, as racial/ethnic differences in heavy drinking may be changing.[1,52] Nonetheless, the observed Black–White disparity in heavy drinking after young adulthood is consistent with the findings from a NESARC study of women who drink (described earlier), showing greater DSM-IV AUD onset among Black women in their 30s and 40s, as well as greater AUD persistence among Black women in their 40s and older, compared to White women in these same age groups as well as younger (ages 18 to 29).[16] These disparities are particularly significant when juxtaposed with other life-course findings. Namely, by midlife, there are striking racial differences in cumulative lifetime exposure to socioeconomic disadvantage,[53] and disparities in health become more pronounced.[5,54]

Cumulative Disadvantage

Population differences in exposure to health risk factors and their cumulative effects are an important mechanism in health disparities.[5] Cumulative disadvantage refers to the notion that social status positions such as race/ethnicity and socioeconomic status profoundly influence opportunities and resources over the life course and, thus, also affect exposures to health risk factors.[55]

Growing up in poverty in neighborhoods with inferior schools, greater crime and violence, and limited economic opportunities can lead to poor quality and low-paying jobs, a lack of health insurance, and ongoing exposure to stressors. Black women and men with low incomes are particularly affected by these factors due, in part, to racial residential segregation[56] and geographic inequalities of opportunity.[57] Consistent with this, research has indicated that a large majority of Black children who were raised in poor neighborhoods continue to reside in similar neighborhoods as adults.[58]

In an early articulation of the effects of cumulative disadvantage and its relationship to health disparities, Geronimus proposed the "weathering hypothesis" to account for the accelerated health deterioration of Black persons relative to White persons.[59] This is exemplified by high rates of chronic disease found in young and middle-aged Black women residing in low-income, urban areas, which contribute to their early mortality rates. According to the hypothesis, the widening racial health disparity seen through middle adulthood reflects the cumulative effect of adverse exposures from conception onward. These adverse exposures include chronic social stressors (e.g., discrimination), environmental hazards, inadequate health care access and treatment, and unhealthy behaviors. Notably, greater alcohol availability, targeted advertising, and less access to healthy food in low-income and minority neighborhoods can contribute to and aggravate unhealthy behaviors.[60-62]

Research has since shown that chronic, enduring stress affects the body's physiological stress response, with adverse effects on the cardiovascular, metabolic, and immune systems.[63] Moreover, the physiological consequences of chronic stress, which are referred to as allostatic load and assessed via biomarkers, have been found to be greater among poor and non-poor Black women than White women, and have been associated with accelerated aging.[64,65] Consistent with these findings, data from the 2017 National Health Interview Survey showed that 14% of Black women (and 13% of Latina women) reported fair or poor health, in contrast to 8% of White women.[66] Even when the sample was stratified by poverty status (i.e., poor, near poor, and not poor, with poor defined as having income below the federal poverty threshold), Black women and men tended to report worse health than White women and men.

As suggested, cumulative disadvantage can also affect health indirectly through risky health behaviors that people use to cope with stressors.[67]

A longitudinal study based on NESARC data found that the effect of poverty on heavy drinking incidence was worse for Black women who drink than for their Latina and White counterparts.[68] A different longitudinal study based on the 1979 NLSY cohort data reported that cumulative poverty across the life span was positively associated with onset and persistence of alcohol dependence symptoms after young adulthood (in a combined sample of women and men who drink).[69] Further, a study based on 2010 NAS data found that cumulative socioeconomic disadvantage partly explained the disparity in persistent heavy drinking until midlife between Black and White women.[51]

This confluence of disparities in cumulative disadvantage and health in middle adulthood provides an important backdrop for understanding disparities in alcohol problems after young adulthood. It raises the question of differential health vulnerability—the idea that certain social groups are more susceptible to health-related consequences when they are exposed to risk factors such as, in this case, heavy drinking.[70] To the extent that health "weathering" begins to accelerate after young adulthood and at a faster rate for demographic groups that have more enduring chronic stress, heavy drinking beyond young adulthood may contribute to alcohol-related health disparities at midlife and later. In keeping with this, a recent NLSY study by Kerr and colleagues found that among Black and Latina women, but not White women, diabetes onset was associated with a history of heavy drinking in the previous 10 years, even when controlling for health risk behaviors, socioeconomic status, and other demographics.[71]

Differential health vulnerability may reflect various mechanisms that require future study. It may be rooted in biological interactions with alcohol that affect health. For example, heavy drinking can exacerbate certain health conditions such as hypertension, type 2 diabetes, and chronic kidney disease, which are more prevalent among Black Americans. Also, as discussed by Jackson and colleagues, differential vulnerability may reflect unmeasured health risk behaviors like smoking and unhealthy eating, which may co-occur with heavy drinking and are thus potentially confounding variables.[41]

Alternatively, unhealthy behaviors could, in some instances, be effect modifiers that interact with alcohol to alter risk for health conditions. For instance, the aforementioned NLSY study by Kerr and colleagues found an interaction between alcohol and obesity for diabetes risk for women.[71] Bensley and colleagues' study of male, Veterans Health Administration patients who had HIV provides further illustration of this complexity.[31] Black patients with low-risk drinking (defined as a score of one to three on the Alcohol Use Disorders Identification Test consumption questions [AUDIT-C]) had greater mortality than White patients who had similar drinking levels, indicating differential vulnerability. The disparity was attenuated after adjusting for the greater presence of hypertension, hepatitis C, tobacco use, and other drug use among Black patients. To better understand alcohol-related disparities and the epidemiologic paradox of greater problems despite lower levels of drinking for some groups, research is needed to examine population differences in health and health behaviors and potential interactions with alcohol consumption patterns.

Other Social and Biological Factors

Studies have documented gene variants that are more prevalent among Black persons[21] that affect the metabolism of alcohol, leading to a buildup of acetaldehyde in the bloodstream. While the gene variants have been associated with lower rates of alcohol dependence and heavy drinking, experimental research by Pedersen and McCarthy has found that the variants also are associated with more intense subjective responses to alcohol.[72] Specifically, they found that Black participants experience greater stimulating effects from alcohol than White participants, even after controlling for differences in past-month alcohol use. Further, greater increases in stimulation are associated with more alcohol-related problems among Black participants. As the researchers suggested, this acute stimulation could contribute to disparities in

the negative consequences of drinking alcohol at a given level of consumption.[72]

In addition, Black women in this study experienced greater sedating effects from alcohol than White women. In view of the greater cumulative and chronic stress experienced by Black women compared with White women,[51,65] this finding of greater sedating effects of alcohol might be a factor in Black-White disparities in persistent heavy drinking and AUD among older women who drink.

Social position and sociocultural context also affect the likelihood of experiencing alcohol problems, particularly negative social consequences, at a given level of consumption. For years, researchers have called attention to the greater negative consequences of drinking borne by racial/ethnic minority groups who have less permissive drinking norms and are subject to greater societal scrutiny and stigmatization.[73,74] People with greater resources and higher status are better able to shield themselves from the negative consequences of drinking that others experience.[75] For example, negative consequences could be minimized at work (because of greater flexibility and autonomy and less scrutiny), in family duties (by paying for childcare or home-delivered meals and groceries), and when going out for the night (by hiring a driver).

These differential standards and consequences of drinking may be seen among women, perhaps more now than in the past when gendered roles and drinking norms were more similar across women. Reflecting on recent decades, Schmidt observed that social and economic changes resulting in greater freedoms for women have led to the "equal right to drink" only for women in the middle and upper classes.[76] By contrast, women with low incomes and women who receive welfare benefits, particularly racial/ethnic minority women, arguably have been more surveilled, stigmatized, and penalized for alcohol and other drug use.

Finally, stress experienced due to being a member of a stigmatized minority group may help to explain alcohol-related disparities between sexual minority women and exclusively heterosexual women. Minority stress theory applied to drinking behavior suggests that the heavy drinking patterns of sexual minority women (relative to heterosexual women) are related to the stress of holding one or more minority identities.[77,78]

Minority stress theory has been used in many studies. Research shows that sexual minority women experience stressors such as discrimination and harassment because of their sexual orientation, and that these women are more likely to report psychological distress than heterosexual women.[74] A study of sexual minority women and sexual minority stressors associated with substance use and mental health outcomes (e.g., unfair treatment, events of prejudice, and victimization) has provided further empirical support of this theory.[79] In this study, sexual minority stressors mediated the adverse effects of more masculine gender expression (i.e., a set of culturally assigned qualities to the category of masculine) on mental health and substance use outcomes. Other studies have found that sexual minority women experience additional stressors associated with increased alcohol use. In comparison to exclusively heterosexual women, sexual minority women are more likely to have experienced child sexual abuse, depression in their lifetime or in the past 12 months, and early onset of alcohol use.[26,80]

Together, this varied literature suggests that social and biological factors may contribute to alcohol-related disparities among women in several ways. These factors may increase exposure to high levels of stress and discrimination (and drinking in response), they may increase sensitivity to the physiological effects of alcohol, and they may increase exposure to punitive societal responses to an individual's own alcohol use.

Differential Access to and Quality of Care

Differences in access to care and in the quality of care received constitute another important explanation for disparities in alcohol-related problems. Although health care access and quality account for a relatively small percentage of the

variation in life expectancy in the United States—estimated at 10%[81]—health care is a valuable resource. Indeed, having a regular source of primary care has been associated with reduced racial/ethnic and socioeconomic disparities in health.[54]

The Institute of Medicine's report, *Unequal Treatment*, famously documented racial/ethnic disparities in the quality of health care received in the United States, even after accounting for differences in socioeconomic status, insurance, disease stage, comorbidities, and facility type.[82] Such findings have motivated the national goal of ensuring equitable access to high-quality care to mitigate disparities in early or delayed diagnosis, types of treatment, and care outcomes.[83] Part of the problem of health care disparities is structural, related to income, insurance, and the type and quality of care that is affordable and geographically accessible. Another part of the problem is social, related to implicit (unconscious) bias on the part of health care providers and how this bias affects patient-provider communication and interaction, treatment decisions, and health care outcomes.[84,85] Related to both structural and social factors, health care utilization also reflects patient perceptions, attitudes, and willingness to seek care. In the case of racial/ethnic disparities in alcohol-related care or treatment, cultural acceptability (including language compatibility) and perceived stigma toward people with AUD may be particularly relevant.[86,87]

Whereas considerable research has investigated racial/ethnic and gender disparities in the receipt of alcohol-related care, far less is known about disparities among women specifically. In a rare, gender-stratified analysis of alcohol treatment utilization, Zemore and colleagues' analysis of NAS data found racial/ethnic disparities in treatment use among women with a lifetime AUD.[88] When compared with White women, Latina and Black women were significantly less likely to obtain specialty alcohol treatment, even after controlling for survey year, age, socioeconomic status (i.e., education and income), and insurance status (adjusted $OR = 0.31$ and 0.38 among Latina and Black women, respectively; $p < .05$). Moreover, this disparity was also observed for Alcoholics Anonymous use (adjusted $OR = 0.38$ and 0.37 for Latina and Black women, respectively).[88] Other studies (using samples of women and men combined) have further shown disparities in treatment completion, which is an important predictor of post-treatment substance use and health outcomes.[89,90]

A variety of factors might contribute to racial/ethnic disparities in treatment use specifically among women. One factor is the stigma of AUD, which may be a particularly salient deterrent for social groups that have more conservative drinking norms and that might already be socially marginalized. Notably, there is evidence of more conservative drinking norms for Black women compared to those for White women[91] and less permissive attitudes toward Latina women's drinking, which tend to be held by less-acculturated Latina women.[92] The stigma of AUD could lead to concealment or denial of alcohol problems and to family concerns about privacy and pressure to not seek treatment. All of these issues may be magnified for women due to the more intense social control of women's drinking.

Other potential treatment barriers are a lack of childcare and concerns that children could be taken away. These concerns are not unfounded, given research showing that Black mothers who use alcohol or other drugs are reported to child protective services more often than similar White mothers.[93] In addition, women generally are more likely than men to experience treatment barriers because of transportation difficulties and inadequate insurance.[94] The latter may be particularly relevant to racial/ethnic minority women, as studies have found that Latinx and Black individuals are more likely than White individuals to report logistical and structural barriers.[95,96] Considering the pronounced racial/ethnic disparities in alcohol problems among women after young adulthood, additional disparities in alcohol-related care and treatment compound the problem. This large unmet need among minority women, which may reflect a variety of causes, must be addressed.

CONCLUSION

This review provides evidence of alcohol-related disparities among women. The research in this area is relatively sparse, but disparities in AUD prevalence, the negative consequences of drinking, and alcohol-related health, morbidity, and mortality outcomes are apparent. This review also highlights the importance of a life-course perspective for understanding disparities in alcohol problems. By examining what happens within and between social groups across the life span, the widening of social group differences in cumulative socioeconomic disadvantage, health, and alcohol-related problems—especially after young adulthood—becomes more noticeable. Future research is needed to examine how these various disparities may be interrelated.

Importantly, a life-course lens also requires attending to social roles and health as these change with age. Attention to such changes can help to advance understanding of how alcohol consumption results in negative consequences and why some groups are affected more than others. Finally, social position and sociocultural context remain important considerations because they can affect internal and external responses to drinking. Social position and sociocultural context also influence access to, use of, and the quality of alcohol-related and general health care. All these factors can affect the persistence of alcohol-related problems and the progression of disease.

In thinking about potential remedies, education emerges as one important factor. Some research has found that education, compared with income, is more strongly and negatively associated with the onset of disease (i.e., the likelihood that an individual will develop a chronic health condition). By contrast, income is a stronger predictor than education of how a disease progresses once an individual has the condition.[97] In light of the benefits of education for health and health behavior,[50,98] improving access to quality education at an early age and supporting higher educational attainment is an important strategy for improving health and addressing health disparities among racial/ethnic minorities and socioeconomically disadvantaged persons.

In addition, increasing insurance coverage and access to affordable, quality health care for underserved groups, a goal of the Patient Protection and Affordable Care Act, represents another crucial path to reducing health disparities. However, efforts devoted to improving health care access and quality will yield limited gains so long as stress and social stigmatization among minority populations persist, and profound differences in neighborhood conditions and available opportunities remain. These are the fundamental causes that need to be addressed to truly eliminate alcohol-related and general health disparities.

Acknowledgments

This article was supported by the National Institute on Alcohol Abuse and Alcoholism grant P50AA005595.

Financial Disclosure

The authors declare that they have no competing financial interests.

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References

1. Dawson DA, Goldstein RB, Saha TD, et al. Changes in alcohol consumption: United States, 2001–2002 to 2012–2013. *Drug Alcohol Depend*. 2015;148:56-61. https://doi.org/10.1016/j.drugalcdep.2014.12.016.
2. Erol A, Karpyak VM. Sex and gender-related differences in alcohol use and its consequences: Contemporary knowledge and future research considerations. *Drug Alcohol Depend*. 2015;156:1-13. https://doi.org/10.1016/j.drugalcdep.2015.08.023.
3. Weisner C, Schmidt L. Gender disparities in treatment for alcohol problems. *JAMA*. 1992;268(14):1872-1876. https://doi.org/10.1001/jama.1992.03490140080039.
4. Collins PH. *Black Feminist Thought: Knowledge, Consciousness, and the Politics of Empowerment*. New York, NY: Routledge; 1991.
5. Adler NE, Stewart J. Health disparities across the lifespan: Meaning, methods, and mechanisms. *Ann N Y Acad Sci*. 2010;1186(1):5-23. https://doi.org/10.1111/j.1749-6632.2009.05337.x.
6. Chartier K, Caetano R. Ethnicity and health disparities in alcohol research. *Alcohol Res Health*. 2010;33(1-2):152-160.
7. Chartier KG, Vaeth PAC, Caetano R. Focus on: Ethnicity and the social and health harms from drinking. *Alcohol Res*. 2013;35(2):229-237.
8. Collins SE. Associations between socioeconomic factors and alcohol outcomes. *Alcohol Res*. 2016;38(1):83-94.

9. Drabble LA, Trocki KF, Korcha RA, et al. Comparing substance use and mental health outcomes among sexual minority and heterosexual women in probability and non-probability samples. *Drug Alcohol Depend*. 2018;185:285-292. https://doi.org/10.1016/j.drugalcdep.2017.12.036.
10. Williams DR, Collins C. U.S. socioeconomic and racial differences in health: Patterns and explanations. *Annu Rev Sociol*. 1995;21(1):349-386. https://doi.org/10.1146/annurev.so.21.080195.002025.
11. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 1994.
12. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Publishing, Incorporated; 2013. https://doi.org/10.1176/appi.books.9780890425596.
13. Grant BF, Dawson DA, Stinson FS, et al. The 12-month prevalence and trends in DSM-IV alcohol abuse and dependence: United States, 1991–1992 and 2001–2002. *Drug Alcohol Depend*. 2004;74(3):223-234. https://doi.org/10.1016/j.drugalcdep.2004.02.004.
14. Zemore SE, Karriker-Jaffe KJ, Mulia N. Temporal trends and changing racial/ethnic disparities in alcohol problems: Results from the 2000 to 2010 National Alcohol Surveys. *J Addict Res Ther*. 2013;4(4):160. https://doi.org/10.4172/2155-6105.1000160.
15. Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. *2017 National Survey on Drug Use and Health: Public Use File Codebook*. Rockville, MD: U.S. Department of Health and Human Services; October 2018.
16. Grant JD, Vergés A, Jackson KM, et al. Age and ethnic differences in the onset, persistence and recurrence of alcohol use disorder. *Addiction*. 2012;107(4):756-765. https://doi.org/10.1111/j.1360-0443.2011.03721.x.
17. Witbrodt J, Mulia N, Zemore SE, et al. Racial/ethnic disparities in alcohol-related problems: Differences by gender and level of heavy drinking. *Alcohol Clin Exp Res*. 2014;38(6):1662-1670. https://doi.org/10.1111/acer.12398.
18. Grant BF, Chou P, Saha TD, et al. Prevalence of 12-month alcohol use, high-risk drinking, and DSM-IV alcohol use disorder in the United States, 2001–2002 to 2012–2013: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *JAMA Psychiatry*. 2017;74(9):911-923. https://doi.org/10.1001/jamapsychiatry.2017.2161.
19. Grant BF, Goldstein RB, Saha TD, et al. Epidemiology of DSM-5 alcohol use disorder: Results from the National Epidemiologic Survey on Alcohol and Related Conditions III. *JAMA Psychiatry*. 2015;72(8):757-766. https://doi.org/10.1001/jamapsychiatry.2015.0584.
20. Katikireddi SV, Whitley E, Lewsey J, et al. Socioeconomic status as an effect modifier of alcohol consumption and harm: Analysis of linked cohort data. *Lancet Public Health*. 2017;2(6):e267-e276. https://doi.org/10.1016/S2468-2667(17)30078-6.
21. Zapolski TCB, Pedersen SL, McCarthy DM, et al. Less drinking, yet more problems: Understanding African American drinking and related problems. *Psychol Bull*. 2014;140(1):188-223. https://doi.org/10.1037/a0032113.
22. Grittner U, Kuntsche S, Graham K, et al. Social inequalities and gender differences in the experience of alcohol-related problems. *Alcohol Alcohol*. 2012;47(5):597-605. https://doi.org/10.1093/alcalc/ags040.
23. Mulia N, Karriker-Jaffe KJ. Interactive influences of neighborhood and individual socioeconomic status on alcohol consumption and problems. *Alcohol Alcohol*. 2012;47(2):178-186. https://doi.org/10.1093/alcalc/agr168.
24. Karriker-Jaffe KJ, Zemore SE, Mulia N, et al. Neighborhood disadvantage and adult alcohol outcomes: Differential risk by race and gender. *J Stud Alcohol Drugs*. 2012;73(6):865-873. https://doi.org/10.15288/jsad.2012.73.865.
25. Mulia N, Schmidt L, Bond J, et al. Stress, social support and problem drinking among women in poverty. *Addiction*. 2008;103(8):1283-1293. https://doi.org/10.1111/j.1360-0443.2008.02234.x.
26. Wilsnack SC, Hughes TL, Johnson TP, et al. Drinking and drinking-related problems among heterosexual and sexual minority women. *J Stud Alcohol Drugs*. 2008;69(1):129-139. https://doi.org/10.15288/jsad.2008.69.129.
27. Drabble L, Midanik LT, Trocki K. Reports of alcohol consumption and alcohol-related problems among homosexual, bisexual and heterosexual respondents: Results from the 2000 National Alcohol Survey. *J Stud Alcohol*. 2005;66(1):111-120. https://doi.org/10.15288/jsa.2005.66.111.
28. Schuler MS, Collins RL. Sexual minority substance use disparities: Bisexual women at elevated risk relative to other sexual minority groups. *Drug Alcohol Depend*. 2020;206:107755. https://doi.org/10.1016/j.drugalcdep.2019.107755.
29. Gilbert PA, Pass LE, Keuroghlian AS, et al. Alcohol research with transgender populations: A systematic review and recommendations to strengthen future studies. *Drug Alcohol Depend*. 2018;186:138-146. https://doi.org/10.1016/j.drugalcdep.2018.01.016.
30. Kaplan MS, McFarland BH, Huguet N, et al. Acute alcohol intoxication and suicide: A gender-stratified analysis of the National Violent Death Reporting System. *Inj Prev*. 2013;19(1):38-43. https://doi.org/10.1136/injuryprev-2012-040317.
31. Bensley KM, McGinnis KA, Fiellin DA, et al. Racial/ethnic differences in the association between alcohol use and mortality among men living with HIV. *Addict Sci Clin Pract*. 2018;13(1):2. https://doi.org/10.1186/s13722-017-0103-z.
32. Hoover KW, Hu X, Porter S, et al. HIV diagnoses and the HIV care continuum among women and girls aged ≥13 years—39 states and the District of Columbia, 2015–2016. *J Acquir Immune Defic Syndr*. 2019;81(3):251-256. https://doi.org/10.1097/QAI.0000000000002023.
33. Sadler S, Angus C, Gavens L, et al. Understanding the alcohol harm paradox: An analysis of sex- and condition-specific hospital admissions by socio-economic group for alcohol-associated conditions in England. *Addiction*. 2017;112(5):808-817. https://doi.org/10.1111/add.13726.
34. Probst C, Roerecke M, Behrendt S, et al. Socioeconomic differences in alcohol-attributable mortality compared with all-cause mortality: A systematic review and meta-analysis. *Int J Epidemiol*. 2014;43(4):1314-1327. https://doi.org/10.1093/ije/dyu043.
35. Ronksley PE, Brien SE, Turner BJ, et al. Association of alcohol consumption with selected cardiovascular disease outcomes: A systematic review and meta-analysis. *BMJ*. 2011;342:d671. https://doi.org/10.1136/bmj.d671.
36. Knott C, Bell S, Britton A. Alcohol consumption and the risk of type 2 diabetes: A systematic review and dose-response meta-analysis of more than 1.9 million individuals from 38 observational studies. *Diabetes Care*. 2015;38(9):1804-1812. https://doi.org/10.2337/dc15-0710.
37. Fuchs FD, Chambless LE, Folsom AR, et al. Association between alcoholic beverage consumption and incidence of coronary heart disease in whites and blacks: The Atherosclerosis Risk in Communities Study. *Am J Epidemiol*. 2004;160(5):466-474. https://doi.org/10.1093/aje/kwh229.

38. Mukamal KJ, Chen CM, Rao SR, et al. Alcohol consumption and cardiovascular mortality among U.S. adults, 1987 to 2002. *J Am Coll Cardiol*. 2010;55(13):1328-1335. https://doi.org/10.1016/j.jacc.2009.10.056.
39. Kerr WC, Ye Y, Williams E, et al. Lifetime alcohol use patterns and risk of diabetes onset in the National Alcohol Survey. *Alcohol Clin Exp Res*. 2019;43(2):262-269. https://doi.org/10.1111/acer.13924.
40. Kerr WC, Greenfield TK, Bond J, et al. Racial and ethnic differences in all-cause mortality risk according to consumption patterns in the National Alcohol Surveys. *Am J Epidemiol*. 2011;174(7):769-778. https://doi.org/10.1093/aje/kwr147.
41. Jackson CL, Hu FB, Kawachi I, et al. Black-white differences in the relationship between alcohol drinking patterns and mortality among U.S. men and women. *Am J Public Health*. 2015;105(suppl 3):S534-S543. https://doi.org/10.2105/AJPH.2015.302615.
42. Yoon Y-H, Chen CM. *Surveillance Report #111: Liver Cirrhosis Mortality in the United States: National, State, and Regional Trends, 2000–2015*. Rockville, MD: National Institute on Alcohol Abuse and Alcoholism; April 2018.
43. Kerr WC, Mulia N, Zemore SE. U.S. trends in light, moderate, and heavy drinking episodes from 2000 to 2010. *Alcohol Clin Exp Res*. 2014;38(9):2496-2501. https://doi.org/10.1111/acer.12521.
44. Vaeth PAC, Wang-Scheig M, Caetano R. Drinking, alcohol use disorder, and treatment access and utilization among U.S. racial/ethnic groups. *Alcohol Clin Exp Res*. 2017;41(1):6-19. https://doi.org/10.1111/acer.13285.
45. Cunningham JK, Solomon TA, Muramoto ML. Alcohol use among Native Americans compared to Whites: Examining the veracity of the "Native American elevated alcohol consumption" belief. *Drug Alcohol Depend*. 2016;160:65-75. https://doi.org/10.1016/j.drugalcdep.2015.12.015.
46. Bronfenbrenner U, Evans GW. Developmental science in the 21st century: Emerging questions, theoretical models, research designs, and empirical findings. *Soc Dev*. 2000;9(1):115-125. https://doi.org/10.1111/1467-9507.00114.
47. Evans-Polce RJ, Vasilenko SA, Lanza ST. Changes in gender and racial/ethnic disparities in rates of cigarette use, regular heavy episodic drinking, and marijuana use: Ages 14 to 32. *Addict Behav*. 2015;41:218-222. https://doi.org/10.1016/j.addbeh.2014.10.029.
48. Keyes KM, Vo T, Wall MM, et al. Racial/ethnic differences in use of alcohol, tobacco, and marijuana: Is there a cross-over from adolescence to adulthood? *Soc Sci Med*. 2015;124:132-141. https://doi.org/10.1016/j.socscimed.2014.11.035.
49. Chen P, Jacobson KC. Developmental trajectories of substance use from early adolescence to young adulthood: Gender and racial/ethnic differences. *J Adolesc Health*. 2012;50(2):154-163. https://doi.org/10.1016/j.jadohealth.2011.05.013.
50. Mulia N, Karriker-Jaffe KJ, Witbrodt J, et al. Racial/ethnic differences in 30-year trajectories of heavy drinking in a nationally representative U.S. sample. *Drug Alcohol Depend*. 2017;170:133-141. https://doi.org/10.1016/j.drugalcdep.2016.10.031.
51. Mulia N, Tam T, Bond J, et al. Racial/ethnic differences in life-course heavy drinking from adolescence to midlife. *J Ethn Subst Abuse*. 2018;17(2):167-186. https://doi.org/10.1080/15332640.2016.1275911.
52. Williams E, Mulia N, Karriker-Jaffe KJ, et al. Changing racial/ethnic disparities in heavy drinking trajectories through young adulthood: A comparative cohort study. *Alcohol Clin Exp Res*. 2018;42(1):135-143. https://doi.org/10.1111/acer.13541.
53. Rank MR. Measuring the economic racial divide across the course of American lives. *Race Soc Probl*. 2009;1(2):57-66. https://doi.org/10.1007/s12552-009-9009-z.
54. Brown TH, O'Rand AM, Adkins DE. Race-ethnicity and health trajectories: Tests of three hypotheses across multiple groups and health outcomes. *J Health Soc Behav*. 2012;53(3):359-377. https://doi.org/10.1177/0022146512455333.
55. Hatch SL. Conceptualizing and identifying cumulative adversity and protective resources: Implications for understanding health inequalities. *J Gerontol B Psychol Sci Soc Sci*. 2005;60:130-134. https://doi.org/10.1093/geronb/60.Special_Issue_2.S130.
56. Williams DR, Mohammed SA, Leavell J, et al. Race, socioeconomic status, and health: Complexities, ongoing challenges, and research opportunities. *Ann N Y Acad Sci*. 2010;1186:69-101. https://doi.org/10.1111/j.1749-6632.2009.05339.x.
57. Osypuk TL, Acevedo-Garcia D. Beyond individual neighborhoods: A geography of opportunity perspective for understanding for racial/ethnic health disparities. *Health Place*. 2010;16(6):1113-1123. https://doi.org/10.1016/j.healthplace.2010.07.002.
58. Sharkey P. The intergenerational transmission of context. *Am J Soc*. 2008;113(4):931-969. https://doi.org/10.1086/522804.
59. Geronimus AT. Black/White differences in the relationship of maternal age to birthweight: A population-based test of the weathering hypothesis. *Soc Sci Med*. 1996;42(4):589-597. https://doi.org/10.1016/0277-9536(95)00159-X.
60. LaVeist TA, Wallace JM Jr. Health risk and inequitable distribution of liquor stores in African American neighborhood. *Soc Sci Med*. 2000;51(4):613-617. https://doi.org/10.1016/S0277-9536(00)00004-6.
61. Jones-Webb RJ, Karriker-Jaffe KJ. Neighborhood disadvantage, high alcohol content beverage consumption, drinking norms, and consequences: A mediation analysis. *J Urban Health*. 2013;90(4):667-684. https://doi.org/10.1007/s11524-013-9786-y.
62. Bower KM, Thorpe RJ Jr, Rohde C, et al. The intersection of neighborhood racial segregation, poverty, and urbanicity and its impact on food store availability in the United States. *Prev Med*. 2014;58:33-39. https://doi.org/10.1016/j.ypmed.2013.10.0103.
63. McEwen BS, Seeman T. Protective and damaging effects of mediators of stress. Elaborating and testing the concepts of allostasis and allostatic load. *Ann N Y Acad Sci*. 1999;896:30-47. https://doi.org/10.1111/j.1749-6632.1999.tb08103.x
64. Geronimus AT, Hicken M, Keene D, et al. "Weathering" and age patterns of allostatic load scores among Blacks and Whites in the United States. *Am J Public Health*. 2006;96(5):826-833. https://doi.org/10.2105/AJPH.2004.060749.
65. Geronimus AT, Hicken MT, Pearson JA, et al. Do U.S. Black women experience stress-related accelerated biological aging? A novel theory and first population-based test of Black–White differences in telomere length. *Hum Nat*. 2010;21(1):19-38. https://doi.org/10.1007/s12110-010-9078-080.
66. Centers for Disease Control and Prevention, National Center for Health Statistics. National Health Interview Survey. Table P-1a: Age-Adjusted Percent Distribution (With Standard Errors) of Respondent-Assessed Health Status, by Selected Characteristics: United States, 2017 (page 3). Hyattsville, MD: National Center for Health Statistics; 2017. https://ftp.cdc.gov/pub/Health_Statistics/NCHS/NHIS/SHS/2017_SHS_Table_P-1.pdf. Accessed August 28, 2018.
67. Boardman JD, Alexander KB. Stress trajectories, health behaviors, and the mental health of Black and White young adults. *Soc Sci Med*. 2011;72(10):1659-1666. https://doi.org/10.1016/j.socscimed.2011.03.024.

68. Glass JE, Rathouz PJ, Gattis M, et al. Intersections of poverty, race/ethnicity, and sex: Alcohol consumption and adverse outcomes in the United States. *Soc Psychiatry Psychiatr Epidemiol*. 2017;52(5):512-524. https://doi.org/10.1007/s00127-017-1362-4.
69. Lui CK, Mulia N. A life course approach to understanding racial/ethnic differences in transitions into and out of alcohol problems. *Alcohol Alcohol*. 2018;53(4):487-496. https://doi.org/10.1093/alcalc/agy015.
70. Diderichsen F, Evans T, Whitehead M. The social basis of disparities in health. In: Evans T, Whitehead M, Diderichsen F, et al, eds. *Challenging Inequities in Health: From Ethics to Action*. New York, NY: Oxford University Press; 2001:12-23. https://doi.org/10.1093/acprof:oso/9780195137408.003.0002
71. Kerr WC, Williams E, Li L, et al. Alcohol use patterns and risk of diabetes onset in the 1979 National Longitudinal Survey of Youth cohort. *Prev Med*. 2018;109:22-27. https://doi.org/10.1016/j.ypmed.2018.01.010.
72. Pedersen SL, McCarthy DM. Differences in acute response to alcohol between African Americans and European Americans. *Alcohol Clin Exp Res*. 2013;37(6):1056-1063. https://doi.org/10.1111/acer.12068.
73. Caetano R, Clark CL. Hispanics, Blacks and Whites driving under the influence of alcohol: Results from the 1995 National Alcohol Survey. *Accid Anal Prev*. 2000;32(1):57-64. https://doi.org/10.1016/S0001-4575(99)00049-4.
74. Herd D. Predicting drinking problems among Black and White men: Results from a national survey. *J Stud Alcohol*. 1994;55(1):61-71. https://doi.org/10.15288/jsa.1994.55.61.
75. Room R. Stigma, social inequality and alcohol and drug use. *Drug Alcohol Rev*. 2005;24(2):143-155. https://doi.org/10.1080/09595230500102434.
76. Schmidt LA. The equal right to drink. *Drug Alcohol Rev*. 2014;33(6):581-587. https://doi.org/10.1111/dar.12215.
77. Meyer IH. Prejudice, social stress, and mental health in lesbian, gay, and bisexual populations: Conceptual issues and research evidence. *Psychol Bull*. 2003;129(5):674-697. https://doi.org/10.1037/0033-2909.129.5.674.
78. Hatzenbuehler ML. How does sexual minority stigma "get under the skin"? A psychological mediation framework. *Psychol Bull*. 2009;135(5):707-730. https://doi.org/10.1037/a0016441.
79. Lehavot K, Simoni JM. The impact of minority stress on mental health and substance use among sexual minority women. *J Consult Clin Psychol*. 2011;79(2):159-170. https://doi.org/10.1037/a0022839.
80. Hughes T. Alcohol use and alcohol-related problems among sexual minority women. *Alcohol Treat Q*. 2011;29(4):403-435. https://doi.org/10.1080/07347324.2011.608336.
81. Kaplan RM, Milstein A. Contributions of health care to longevity: A review of 4 estimation methods. *Ann Fam Med*. 2019;17(3):267-272. https://doi.org/10.1370/afm.2362.
82. Institute of Medicine (U.S.) Committee on Understanding and Eliminating Racial and Ethnic Disparities in Health Care. *Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care*. Washington, DC: Institute of Medicine, National Academies Press; 2003. https://doi.org/10.17226/12875.
83. Institute of Medicine. *Crossing the Quality Chasm: A New Health System for the 21st Century*. Washington, DC: Institute of Medicine, National Academies Press; 2001. https://doi.org/10.17226/10027.
84. Tajeu GS, Cherrington AL, Andreae L, et al. "We'll get to you when we get to you": Exploring potential contributions of health care staff behaviors to patient perceptions of discrimination and satisfaction. *Am J Public Health*. 2015;105(10):2076-2082. https://doi.org/10.2105/AJPH.2015.302721.
85. Hall WJ, Chapman MV, Lee KM, et al. Implicit racial/ethnic bias among health care professionals and its influence on health care outcomes: A systematic review. *Am J Public Health*. 2015;105(12):e60-e76. https://doi.org/10.2105/AJPH.2015.302903.
86. Keyes KM, Hatzenbuehler ML, McLaughlin KA, et al. Stigma and treatment for alcohol disorders in the United States. *Am J Epidemiol*. 2010;172(12):1364-1372. https://doi.org/10.1093/aje/kwq304.
87. Guerrero EG, Marsh JC, Khachikian T, et al. Disparities in Latino substance use, service use, and treatment: Implications for culturally and evidence-based interventions under health care reform. *Drug Alcohol Depend*. 2013;133(3):805-813. https://doi.org/10.1016/j.drugalcdep.2013.07.027.
88. Zemore SE, Murphy RD, Mulia N, et al. A moderating role for gender in racial/ethnic disparities in alcohol services utilization: Results from the 2000 to 2010 National Alcohol Surveys. *Alcohol Clin Exp Res*. 2014;38(8):2286-2296. https://doi.org/10.1111/acer.12500.
89. Arndt S, Acion L, White K. How the states stack up: Disparities in substance abuse outpatient treatment completion rates for minorities. *Drug Alcohol Depend*. 2013;132(3):547-554. https://doi.org/10.1016/j.drugalcdep.2013.03.015.
90. Saloner B, Lê Cook B. Blacks and Hispanics are less likely than Whites to complete addiction treatment, largely due to socioeconomic factors. *Health Aff (Millwood)*. 2013;32(1):135-145. https://doi.org/10.1377/hlthaff.2011.0983.
91. Herd D. Racial differences in women's drinking norms and drinking patterns: A national study. *J Subst Abuse*. 1997;9:137-149. https://doi.org/10.1016/S0899-3289(97)90012-2.
92. Zemore SE. Re-examining whether and why acculturation relates to drinking outcomes in a rigorous, national survey of Latinos. *Alcohol Clin Exp Res*. 2005;29(12):2144-1253. https://doi.org/10.1097/01.alc.0000191775.01148.c0.
93. Roberts SC, Nuru-Jeter A. Universal screening for alcohol and drug use and racial disparities in child protective services reporting. *J Behav Health Serv Res*. 2012;39(1):3-16. https://doi.org/10.1007/s11414-011-9247-x.
94. Tuchman E. Women and addiction: The importance of gender issues in substance abuse research. *J Addict Dis*. 2010;29(2):127-138. https://doi.org/10.1080/10550881003684582.
95. Schmidt LA, Ye Y, Greenfield TK, et al. Ethnic disparities in clinical severity and services for alcohol problems: Results from the National Alcohol Survey. *Alcohol Clin Exp Res*. 2007;31(1):48-56. https://doi.org/10.1111/j.1530-0277.2006.00263.x.
96. Verissimo AD, Grella CE. Influence of gender and race/ethnicity on perceived barriers to help-seeking for alcohol or drug problems. *J Subst Abuse Treat*. 2017;75:54-61. https://doi.org/10.1016/j.jsat.2016.12.013.
97. Herd P, Goesling B, House JS. Socioeconomic position and health: The differential effects of education versus income on the onset versus progression of health problems. *J Health Soc Behav*. 2007;48(3):223-238. https://doi.org/10.1177/002214650704800302.
98. Cutler DM, Lleras-Muney A. Understanding differences in health behaviors by education. *J Health Econ*. 2010;29(1):1-28. https://doi.org/10.1016/j.jhealeco.2009.10.003.

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ALCOHOL RESEARCH
Current Reviews

Alcohol Res. 2020;40(2):10 • https://doi.org/10.35946/arcr.v40.2.10

Published: 2 July 2020

Alcohol and Liver Function in Women

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Alcohol-related liver disease generally has been ascribed to men because men reportedly consume alcohol at an increased rate and quantity as compared to women. Recent literature has reported, however, that rates of liver disease attributed to alcohol use by women have increased, largely due, in part, to the increased number of women who consume alcohol regularly. This increase is a paramount concern, as women are more susceptible than men to the effects of alcohol-related liver injury. Health care providers should make efforts to counsel women on the risks of excess alcohol consumption to prevent further increase in alcohol-related liver disease and its associated complications.

KEY WORDS: alcohol; estrogen; liver disease; women

EPIDEMIOLOGY

The prevalence of alcohol use disorder is increasing, and one of the most devastating complications is end-stage liver disease. Interestingly, the consequences of alcohol use do not affect all heavy-drinking individuals with the same frequency. Only 15% of people who drink heavily develop cirrhosis from heavy alcohol consumption.[1] Certain populations, including those with genetic predispositions (e.g., presence of the *PNPLA3* genotype) and women, are more susceptible to end-stage effects of alcohol-related liver injury.

Historically, alcohol-associated liver injury has been reported to be more prevalent in men, despite women's increased susceptibility to the detrimental effects of alcohol.[2] This difference in prevalence largely is due to the fact that men generally consume more alcohol than women. However, a recent study that examined the presence of alcohol-related liver disease from 2009 to 2015 demonstrated increased incidence (50%) of alcohol-related liver injury in women, as compared to a 30% increase among men during the same time period.[3] The increase in alcohol-related liver injury among women appears to parallel the increase in alcohol consumption observed in women.

A study examining alcohol use patterns in the United States from 2001 to 2002, as compared with 2012 to 2013, reported an 80% increase in

heavy alcohol consumption among women and a 30% increase among men.[4] Similar patterns have been seen globally, with a Japanese study noting a twofold to fourfold increase in alcohol consumption among women from 1968 to 1987.[5] In this study, the rates of alcohol consumption in men remained static. A meta-analysis examining the effects of alcohol use and cirrhosis reported that cirrhosis was more frequent in women versus men, despite similar amounts of alcohol consumption.[6]

MECHANISTIC FACTORS

Previous studies have shown that, when controlling for the amount of alcohol consumed and for body weight, women had increased levels of blood alcohol when compared with men.[7] This increase likely is due to decreased body water content in women, thus leading to a smaller volume of distribution. Moreover, women have reduced gastric alcohol dehydrogenase compared with men and therefore impaired first-pass metabolism, resulting in increased susceptibility to injury.[7] Additional studies also have shown gender differences in alcohol metabolism by hepatic enzymes such as cytochrome P450 2E1, with lower levels in women due to regulation of growth hormone.[8] The role of estrogen is also a culprit.

Kupffer cells reside within hepatic sinusoids and play a role in clearance of foreign compounds within the liver. Activation of Kupffer cells leads to cytokine release and subsequent hepatic inflammation.[9] Rat models have shown that estrogen exposure increases Kupffer cell susceptibility to endotoxin. When animals that received exogenous estrogen were studied, increased Kupffer cell sensitization to lipopolysaccharide was observed.[10] Additional animal models have demonstrated that increased endotoxin release related to Kupffer cell activation resulted in more severe hepatic injury and necrosis.[11] In fact, estrogen blockade in mouse models has been shown to attenuate alcohol-related injury in females.[12]

IMPLICATIONS

These factors likely account for studies showing that women, compared to men, are more susceptible to liver disease with less alcohol consumption, and that women have a faster progression to cirrhosis over a shorter time period. In a study conducted in Australia, the rate of progression to cirrhosis for women was 13.5 years, as compared to 20 years for men, when controlling for less alcohol consumption among the women.[13] More vexing is that although alcohol abstinence has been linked to fibrosis regression, reports show that among people who had cirrhosis and then abstained from alcohol, women had lower 5-year survival rates than men.[14]

Current recommendations from the "Dietary Guidelines for Americans 2015–2020" advise that women should not consume more than 14 grams of alcohol daily, and men should not consume more than 28 grams of alcohol daily.[15] The relative risk of alcohol-related liver disease increases in women who drink any more than one drink per day. Recently, the Million Women Study in the United Kingdom published prospective data and reported observed liver disease patterns among women from 1996 to 2001.[16]

An interesting observation from the Million Women Study is that people who reported drinking daily were more susceptible to liver injury than those who reported binge drinking.[16] Thus, recommendations from this study advise that women abstain from drinking daily. This study also noted that women who drank alcohol with meals were less susceptible to alcohol-related injury than those who drank without eating. A possible explanation for this finding is the increased metabolism of alcohol for those who drank with meals as compared to the metabolism of those who did not drink with meals.

The effects of alcohol consumption outside of meals appear to coincide with the observation that women with eating disorders (e.g., bulimia, anorexia) are more susceptible to alcohol-related liver injury than women with no eating disorder.[17,18] These findings may be explained by the nutritional deficiencies associated with eating

disorders, which are hepatotoxic independent of the effects of alcohol. Other studies have shown that increases in alcohol-related liver disease coincide with obesity.[1] Thus, the presence of eating disorders is not the only risk factor that implicates accelerated progression of alcohol-related liver disease. In a study examining risk factors for liver disease in both men and women, an increased waist-to-hip ratio (a measure of fat distribution) portended a worse prognosis for development of severe liver disease.[1]

OBESITY AND ALCOHOL USE

A possible explanation for the paradoxical discrepancy between alcohol-related liver injury in people with eating disorders and the recent observed increase in those with obesity may be due to the overlap of non-alcoholic fatty liver disease co-existing with alcohol-related liver disease, thus explaining the latter.

In a non–gender focused study, researchers replaced alcoholic beverages with non-alcoholic beverages to examine the effects on hepatic triglyceride fat content.[19] Individuals who received a sugary beverage as a substitute for alcohol, as compared with those who received a non-sugary beverage, had increased hepatic triglyceride fat content. Even more intriguing was that the hepatic triglyceride levels for those who consumed the sugary beverage were comparable to the levels observed for those who consumed the alcoholic beverage. The effects of non-alcoholic beverages on the liver warrant further study, but these results may explain the increase of cirrhosis in patients with concomitant alcohol use and obesity.

MANAGEMENT

Abstinence for individuals with alcohol-related liver injury is paramount to preventing liver-related complications. Although liver disease progression may persist even with abstinence, prevention of further hepatic damage is crucial. After enrolling in alcohol treatment programs, women had higher rates of abstinence than men.[20] However, women are less likely to use face-to-face counseling and pharmacologic therapy to prevent relapse because of family/childcare barriers and a perceived stigma associated with attending programs.[21]

Moreover, if a woman experiences complications of liver disease and needs a transplant, she is often disadvantaged. A recent study that examined early liver transplantation across multiple centers within the United States reported that few women undergo early liver transplantation for alcoholic hepatitis.[22] In addition, few women with any type of alcohol-related liver disease receive transplants. In a retrospective study of individuals evaluated for transplantation for alcohol-related liver disease, men were more likely than women to be listed for transplantation.[23] Also, of all the participants listed, men were more likely than women to receive a transplant.

The lack of proper counseling for alcohol use disorder must be addressed, as studies have demonstrated increased risk of relapse of harmful drinking among women with alcohol-related liver disease who received transplants.[24] This increased relapse for women is problematic, as it has been associated with a higher incidence of recurrent disease for women than for men.

Determining why women are drinking more and exceeding the drinking observed among men is imperative. Several hypotheses include the paradigm shift of women assuming male gender roles, for example, more women are working outside the home and fewer women are having children.[25] Another hypothesis is that the increasing stress of family and work balance for women leads to the use of alcohol to manage stress.[26] In addition, alcohol advertisements targeted toward females have increased, beginning with advertisements for wine coolers in the early 2000s[27] to the advertisements for "female-friendly" drinks such as wine in the current decade, and have made alcohol use more socially acceptable. Increased alcohol use may inadvertently be used to manage stress.

Research shows that the association between problematic drinking and post-traumatic stress

disorder, anxiety, and depression is stronger for women than for men.[28] Moreover, women are more likely to use alcohol to regulate negative reinforcement, whereas for men, investigators have speculated that drinking results in positive reinforcement.

FUTURE AREAS OF RESEARCH

It is quite evident from currently available literature that women, compared to men, have an increased risk of end-stage liver disease from alcohol use. Although it has been established that women should consume less alcohol than men, observations vary as to whether binge drinking or moderate daily drinking (i.e., not exceeding 14 grams per day) is more likely to lead to end-stage liver disease. Future studies should be conducted to provide more detailed recommendations, although in the interim, health care practitioners should advise women to consume no more than one drink per day.

In addition, the Million Women Study's observation that women who did not eat meals while consuming alcohol had increased alcohol-related liver injury needs further corroborative evidence. Currently available literature also indicates that women with obesity should be advised to avoid drinking heavily and to avoid substituting alcohol with beverages that have high sugar content, as these beverages may lead to further hepatic fibrosis despite alcohol abstinence.

Moreover and more significantly, public awareness of current hazardous drinking is needed, as many women are unaware they are increasing their risk of liver disease. Public policies need to minimize alcohol advertising targeted toward women.

CONCLUSION

Although alcohol-related liver injury previously has not been linked to women, it is paramount to educate women about the dangers of consuming alcohol given that women are more susceptible than men to injury after consuming less alcohol. Globally, alcohol consumption has increased, particularly among women. Safe drinking habits, including not exceeding 14 grams of alcohol consumption in a day, not drinking without eating meals, and avoiding daily drinking, should be recommended. If alcohol use disorder is identified, adequate and appropriate counseling and pharmacologic therapy should be provided. Additionally, further study into the neurobiologic basis leading to alcohol use disorder should be made by clinicians and researchers.

Financial disclosure
The authors declare that they have no competing financial interests.

References

1. Sahlman P, Nissinen M, Puukka P, et al. Genetic and lifestyle risk factors for advanced liver disease among men and women. *J Gastroenterol Hepatol*. 2020;35(2):291-298. https://doi.org/10.1111/jgh.14770.
2. Delker E, Brown Q, Hasin DS. Alcohol consumption in demographic subpopulations: An epidemiologic overview. *Alcohol Res*. 2016;38(1):7-15.
3. Mellinger JL, Shedden K, Winder GS, et al. The high burden of alcoholic cirrhosis in privately insured persons in the United States. *Hepatology*. 2018;68(3):872-882. https://doi.org/10.1002/hep.29887.
4. Grant BF, Chou SP, Saha TD, et al. Prevalence of 12-month alcohol use, high-risk drinking, and DSM-IV alcohol use disorder in the United States, 2001–2002 to 2012–2013: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *JAMA Psychiatry*. 2017;74(9):911-923. https://doi.org/10.1001/jamapsychiatry.2017.2161.
5. Yamauchi M, Ohata M. [The incidence of alcoholic liver disease in Japan]. *Nihon Rinsho*. 2002;60(suppl 1):220-225.
6. Rehm J, Taylor B, Mohapatra S, et al. Alcohol as a risk factor for liver cirrhosis: A systematic review and meta-analysis. *Drug Alcohol Rev*. 2010;29(4):437-445. https://doi.org/10.1111/j.1465-3362.2009.00153.x.
7. Frezza M, di Padova C, Pozzato G, et al. High blood alcohol levels in women. The role of decreased gastric alcohol dehydrogenase activity and first-pass metabolism. *N Engl J Med*. 1990;322(2):95-99. https://doi.org/10.1056/NEJM199001113220205.
8. Agrawal AK, Shapiro BH. Intrinsic signals in the sexually dimorphic circulating growth hormone profiles of the rat. *Mol Cell Endocrinol*. 2001;173(1-2):167-181. https://doi.org/10.1016/S0303-7207(00)00401-9.

9. Dixon LJ, Barnes M, Tang H, et al. Kupffer cells in the liver. *Compr Physiol*. 2013;3(2):785-797.
10. Ikejima K, Enomoto N, Iimuro Y, et al. Estrogen increases sensitivity of hepatic Kupffer cells to endotoxin. *Am J Physiol*. 1998;274(4):G669-G676. https://doi.org/10.1152/ajpgi.1998.274.4.G669.
11. Thurman RG. II. Alcoholic liver injury involves activation of Kupffer cells by endotoxin. *Am J Physiol*. 1998;275(4):G605-G611. https://doi.org/10.1152/ajpgi.1998.275.4.G605.
12. Järveläinen HA, Lukkari TA, Heinaro S, et al. The antiestrogen toremifene protects against alcoholic liver injury in female rats. *J Hepatol*. 2001;35(1):46-52. https://doi.org/10.1016/S0168-8278(01)00050-2.
13. Wilkinson P, Kornaczewski A, Rankin JG, et al. Physical disease in alcoholism. Initial survey of 1,000 patients. *Med J Aust*. 1971;1(23):1217-1223. https://doi.org/10.5694/j.1326-5377.1971.tb50304.x.
14. Powell WJ Jr, Klatskin G. Duration of survival in patients with Laennec's cirrhosis. Influence of alcohol withdrawal, and possible effects of recent changes in general management of the disease. *Am J Med*. 1968;44(3):406-420. https://doi.org/10.1016/0002-9343(68)90111-3.
15. U.S. Department of Health and Human Services, U.S. Department of Agriculture. *Dietary Guidelines for Americans 2015–2020*. 8th ed. December 2015. https://health.gov/dietaryguidelines/2015/guidelines. Accessed February 10, 2020.
16. Simpson RF, Hermon C, Liu B, et al. Alcohol drinking patterns and liver cirrhosis risk: Analysis of the prospective UK Million Women Study. *Lancet Public Health*. 2019;4(1):e41-e48. https://doi.org/10.1016/S2468-2667(18)30230-5.
17. Cuellar RE, Tarter R, Hays A, et al. The possible occurrence of "alcoholic hepatitis" in a patient with bulimia in the absence of diagnosable alcoholism. *Hepatology*. 1987;7(5):878-883. https://doi.org/10.1002/hep.1840070514.
18. Platis IE, Carpenter LL, Vojvoda D, et al. Possible acceleration of alcoholic cirrhosis in a patient with bulimia. *Int J Eat Disord*. 1996;20(4):439-442. https://doi.org/10.1002/(SICI)1098-108X(199612)20:4<439::AID-EAT13>3.0.CO;2-T.
19. van Eekelen E, Beulens JWJ, Geelen A, et al. Consumption of alcoholic and sugar-sweetened beverages is associated with increased liver fat content in middle-aged men and women. *J Nutr*. 2019;149(4):649-658. https://doi.org/10.1093/jn/nxy313.
20. Erol A, Karpyak VM. Sex and gender-related differences in alcohol use and its consequences: Contemporary knowledge and future research considerations. *Drug Alcohol Depend*. 2015;156:1-13. https://doi.org/10.1016/j.drugalcdep.2015.08.023.
21. Verissimo AD, Grella CE. Influence of gender and race/ethnicity on perceived barriers to help-seeking for alcohol or drug problems. *J Subst Abuse Treat*. 2017;75:54-61. https://doi.org/10.1016/j.jsat.2016.12.013.
22. Lee BP, Mehta N, Platt L, et al. Outcomes of early liver transplantation for patients with severe alcoholic hepatitis. *Gastroenterology*. 2018;155(2):422-430.e1.
23. McElroy LM, Likhitsup A, Winder GS, et al. Gender disparities in patients with alcoholic liver disease evaluated for liver transplantation. *Transplantation*. 2020;104(2):293-298. https://doi.org/10.1097/TP.0000000000002843.
24. Zeair S, Cyprys S, Wisniewska H, et al. Alcohol relapse after liver transplantation: Younger women are at greatest risk. *Ann Transplant*. 2017;22:725-729. https://doi.org/10.12659/AOT.905335.
25. Keyes KM, Grant BF, Hasin DS. Evidence for a closing gender gap in alcohol use, abuse, and dependence in the United States population. *Drug Alcohol Depend*. 2008;93(1-2):21-29. https://doi.org/10.1016/j.drugalcdep.2007.08.017.
26. Johnson RA, Gerstein DR. Initiation of use of alcohol, cigarettes, marijuana, cocaine, and other substances in US birth cohorts since 1919. *Am J Public Health*. 1998;88(1):27-33. https://doi.org/10.2105/AJPH.88.1.27.
27. Jernigan DH, Ostroff J, Ross C, et al. Sex differences in adolescent exposure to alcohol advertising in magazines. *Arch Pediatr Adolesc Med*. 2004;158(7):629-634. https://doi.org/10.1001/archpedi.158.7.629.
28. Peltier MR, Verplaetse TL, Mineur YS, et al. Sex differences in stress-related alcohol use. *Neurobiol Stress*. 2019;10:100149. https://doi.org/10.1016/j.ynstr.2019.100149.

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Alcohol Res. 2020;40(2):11 • https://doi.org/10.35946/arcr.v40.2.11

Published: 18 June 2020.

Alcohol's Effects on Breast Cancer in Women

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Globally, more than 2 million new cases of breast cancer are reported annually. The United States alone has more than 496,000 new cases every year. The worldwide prevalence is approximately 6.8 million cases. Although many risk factors for breast cancer are not modifiable, understanding the role of the factors that can be altered is critical. Alcohol consumption is a modifiable factor. Studies of alcohol in relation to breast cancer incidence have included hundreds of thousands of women. Evidence is consistent that intake, even intake of less than 10-15 grams per day, is associated with increased risk of this disease. In addition, evidence, although less extensive, shows that possible early indicators of risk, such as benign breast disease and increased breast density, are associated with alcohol consumption. Evidence is less strong for differences based on geographic region, beverage type, drinking pattern, or breast cancer subtype. Some studies have examined the association between alcohol and recurrence or survival after a breast cancer diagnosis. These findings are less consistent. Public awareness of alcohol as a risk factor for breast cancer is low, and public health measures to increase that awareness are warranted.

KEY WORDS: alcohol drinking; breast cancer incidence; breast cancer survival; drinking pattern; women

INTRODUCTION

In 1987, the *New England Journal of Medicine* published two reports about alcohol consumption and breast cancer risk.[1,2] In the two reports, both prospective cohorts, alcohol consumption, even at modest levels of intake, was associated with risk of breast cancer. An accompanying editorial indicated that based on the existing epidemiologic studies, approximately 17 at the time, one could conclude "despite variations in study design, population, culture and language of the country of origin, and methods of determining the amount of alcohol ingested, most investigations have found at least a small increase in risk with increases in intake, particularly among premenopausal women."[3] Since those landmark papers were published, studies have been conducted among hundreds of thousands of women. Findings of an association between

alcohol consumption and an increase in breast cancer risk for women have persisted.

SCOPE OF THE PROBLEM

Breast cancer affects more than 2 million women each year around the world.[4] The age-adjusted rate is 46.3 new cases of this disease per year for every 100,000 women. In the United States, more than 496,000 new cases are diagnosed every year, and the age-adjusted incidence is 84.8 per 100,000 women. Globally, 626,679 deaths from breast cancer occur annually, and in the United States, close to 89,000 deaths were reported. The age-adjusted breast cancer mortality rates are 13.0 deaths per 100,000 women globally, and 12.6 deaths per 100,000 women in the United States. It is estimated that the prevalence of breast cancer around the world is 6.8 million cases.

ALCOHOL AND BREAST CANCER INCIDENCE

A large body of research provides evidence that alcohol is a risk factor for incidence of breast cancer. The World Cancer Research Fund and the American Institute for Cancer Research (WCRF-AICR) collaborated to organize a continuous systematic review of dietary factors in relation to cancer.[5] The WCRF-AICR reports include examinations of alcohol and breast cancer. In a 2018 update, they concluded that, based on the existing literature (16 prospective studies of premenopausal breast cancer and 34 of postmenopausal disease), alcohol consumption is a "probable cause" and a "convincing cause" for premenopausal and postmenopausal breast cancer, respectively. The meta-analysis showed that for a 10-gram increase in alcohol consumed per day on average, risk increased 5% among premenopausal women and 9% among postmenopausal women. A standard drink contains approximately 14 grams of alcohol.[6]

As noted in the 1987 editorial in the *New England Journal of Medicine*, an association between alcohol and breast cancer was found across geographic locations for a range of beverage types consumed and for a variety of drinking patterns.[3] Most of the studies on alcohol and breast cancer have been conducted in North America and Europe, but there are some from other locations.

The WCRF-AICR meta-analysis reported some differences by location.[5] For premenopausal breast cancer, the summary meta-analysis was significant only for North America. Results were similar in magnitude but not statistically significant for analyses of findings from Europe and Asia. For postmenopausal cancer, in the meta-analysis of dose-response, the association was statistically significant only for studies of Europe and North America.

In a study that pooled data from 20 cohorts in the United States, Canada, Europe, Australia, and Japan, no significant heterogeneity was found among studies, although the association between alcohol and breast cancer was stronger for the North American cohorts than for the others.[7] Even within regions, there can be considerable differences in quantities of alcohol consumption, types of beverages consumed, and intensities of drinking (e.g., frequency of binge drinking, drinking with meals or not). For example, within Europe, drinking patterns vary considerably. In a study of 335,000 women in Europe, of whom 11,600 had invasive breast cancer, a significant, 4% increase in risk was shown for each additional 10 grams of alcohol consumed per day.[8]

Studies of individual European countries, including Italy,[9] France (among postmenopausal but not premenopausal women),[10] and the United Kingdom,[11] but not Greece,[12] also reported evidence of increased risk. In a case-control study of more than 2,000 cases and 2,000 controls from 3 countries in sub-Saharan Africa, an association between alcohol consumption and risk was reported, despite considerable differences in the prevalence of alcohol consumption in those countries.[13] In South America, studies in Brazil reported some evidence of an association.[14,15] For studies in Asia, where women's alcohol consumption generally is lower, results have been inconsistent.[16-20]

Few studies have examined the association between alcohol and breast cancer by race/ethnicity. The African American Breast Cancer Epidemiology and Risk (AMBER) Consortium, a pooled analysis of studies of African American women, found a J-shaped association between alcohol consumption and breast cancer risk.[21] The magnitude of the association for higher intakes of alcohol was similar to results reported in other studies of women of European descent.

Overall, there is strong evidence that alcohol increases breast cancer risk. Evidence is strongest for North America and Europe, where more studies have been conducted, but other regions also show some evidence of a similar association. Much additional research has been done regarding the details of the alcohol consumption (e.g., beverage type, drinking pattern, the participant's age at the time of consumption) and the details of the breast cancer (e.g., tumor subtype). These findings are less consistent.

Variability in findings may be a function of the small sample size of some studies, for instance, in those studies that examined associations between alcohol consumption for breast cancer by subtype (e.g., estrogen receptor–positive or –negative). In addition, alcohol consumption can be difficult to assess for a variety of reasons, including difficulty recalling usual intake, change in consumption over the lifetime, and response bias. In this context, the consistency of the findings regarding overall risk of breast cancer associated with alcohol consumption is noteworthy.

Beverage Type

Several studies of alcohol and risk examined whether there are differences depending on the beverage consumed: wine, beer, or spirits. The pooled analysis of 20 cohorts reported no difference in risk based on the beverage type.[7] The Million Women Study in the United Kingdom reported similar associations for those who drank wine only and for those who consumed other drinks.[11] In the WCRF-AICR meta-analysis, only beer was associated with a statistically significant increase in risk among premenopausal women, and only wine was associated with risk among postmenopausal women.[5] However, in all of the studies, there was an indication of increased risk with each of the beverages, even if not statistically significant. In addition, the evidence was that there was not a statistical difference of the association with each of the three types of beverage for both premenopausal and postmenopausal analyses. Some studies provided evidence of a stronger effect for a particular beverage, but most of the evidence pointed to effects from any alcoholic beverage.

Drinking Pattern

When examining the effects of alcohol consumption on health and disease, how participants consumed the alcohol must be considered. Not only the absolute quantity consumed, but also the intensity of consumption may have biological effects. For example, the effects of an average consumption of seven drinks per week may differ for consumption of one drink daily and for seven drinks on one day once per week.

Just a few studies have examined drinking intensity. In the Nurses' Health Study I (NHS), binge drinking (defined as six or more drinks in one day) was associated with increased risk, even after adjusting for total consumption.[22] The frequency of alcohol consumption was not associated with risk in that cohort after adjusting for total consumption. In the Sister Study, a cohort of women with a family history of breast cancer, self-report of ever binge drinking (defined as four or more drinks in one sitting) or ever having blacked out while drinking were associated with increased breast cancer risk.[23] These associations were not adjusted for overall alcohol intake.

Even among people who drink lightly, evidence of increased risk has been reported. In a systematic review of light drinking, which used the World Health Organization definition of less than 21 grams of alcohol consumed per day, Shield and colleagues found consistent evidence of increased risk.[24] In a meta-analysis, Choi and colleagues found statistically significant increases in risk of 4%, 9%, and 13% for individuals who drank less than 0.5 drinks per day, less than or

equal to 1 drink per day, and 1 to 2 drinks per day, respectively; in this analysis, one drink was defined as 12.5 grams of alcohol.[25] There is no evidence of a lower threshold for an effect of alcohol consumption on risk of breast cancer. Collectively, results from these studies on intake indicate that drinking pattern may affect risk, as drinks per drinking day are associated with increased risk even after adjusting for total intake.

Breast Cancer Subtype

Breast cancer can be classified into subtypes by tumor markers. The subtypes may have different risk factors, and they are different in terms of aggressiveness, treatment, and prognosis. A number of studies have examined the association between alcohol consumption and invasive breast cancer by subtype.

In the European Prospective Investigation into Cancer and Nutrition (EPIC) study, which examined a cohort of more than 360,000 women from 23 centers in 10 countries in Europe, the association between alcohol consumption and risk was stronger for women with estrogen receptor–positive tumors than for those with estrogen receptor–negative tumors.[26] In a report on postmenopausal breast cancer from the Million Women Study in the United Kingdom, no heterogeneity by estrogen receptor status was found for the association between alcohol consumption and risk.[27] A pooled analysis of 20 cohort studies, which comprised more than 1 million women, reported no difference in the associations of alcohol and estrogen receptor–positive tumors or of alcohol and estrogen receptor–negative tumors.[7] Finally, in the systematic review by the WCRF-AICR, the findings for postmenopausal cancer indicated an increase in risk for estrogen receptor–positive tumors but not for estrogen receptor–negative tumors.[5]

In one study, alcohol consumption and risk of human epidermal growth factor receptor 2 (HER2)–positive and triple-negative breast cancers were compared to risk of estrogen receptor–positive tumors.[28] Alcohol consumption was associated with a lower risk of HER2-positive tumors and no difference in the risk of triple-negative tumors, as compared to its association with risk for estrogen receptor–positive tumors. In an analysis of data from the AMBER Consortium of African American women, the association between alcohol consumption and risk was stronger for estrogen receptor–negative, progesterone receptor–negative, and HER2-negative tumors than for tumors with positive receptor status.[21] Overall, findings from studies of associations between alcohol consumption and breast cancer subtypes have been inconsistent.

Period of Exposure

Alcohol consumption patterns generally vary during the life span, and effects of exposures may differ depending on the stage of breast development when the drinking occurred. A number of studies have examined risk associated with alcohol consumption at particular time periods, especially during adolescence and early adulthood.

The NHS II, a prospective study of women ages 24 to 44 at baseline, reported an 11% increase in breast cancer risk associated with consumption of 10 grams of alcohol per day between menarche and first pregnancy, adjusting for subsequent intake.[29] A similar increase in risk was observed for consumption of alcohol after the first pregnancy, adjusting for intake before that time. In NHS I, a cohort of women ages 30 to 55 at baseline, there was an 8% increase in risk associated with 10 grams of alcohol consumed per day between ages 18 and 40, even after adjusting for consumption after age 40.[22] For consumption after age 40, there was a 7% increase in risk, after adjusting for earlier intake.

Benign breast disease is associated with increased breast cancer risk and may be an early indicator of risk. In the NHS II, evidence indicated a 15% increase in risk of benign breast disease for each additional 10 grams per day of alcohol consumed during adolescence.[30] Another study of young women reported a 50% increase in risk of benign breast disease for each additional drink per day during the period of ages 9 to 15.[31] In one study, associations for alcohol with risk

were similar for pre-cancerous conditions as for invasive breast cancer.[32]

The EPIC cohort study examined the association between risk and alcohol consumption for parous women before their first, full-term pregnancy compared with women who did not begin drinking until after their first pregnancy.[8] Point estimates were similar but there was a significant association only for those who started drinking before their first pregnancy. In addition to intake during adolescence and young adulthood, even exposure to alcohol *in utero* may predispose to increased risk. Evidence from animal models indicates that ethanol exposure *in utero* can lead to increased breast tumorigenesis in the adult offspring when exposed to carcinogens.[33]

These studies indicate that the association of lifetime alcohol consumption with breast cancer risk may be different depending on when the alcohol was consumed. Evidence shows, with some inconsistency among studies, that consumption in adolescence and before a first pregnancy may particularly affect risk.

Breast Density

Breast density is a measure of breast tissue from radiography. It is associated with subsequent breast cancer and is one of the strongest breast cancer risk factors.[34,35] Understanding factors related to increased density may provide insight into early stages of carcinogenesis. A number of cross-sectional analyses have shown that alcohol consumption is associated with increased breast density. In a study in Germany, consumption of more than 10 grams of alcohol per day was associated with increased risk of high mammographic density.[36] Similarly, increases in risk of increased breast density were associated with alcohol drinking in Japan,[37] Sweden,[38] and the United States in Hawaii[39] and New York City.[40] There was a nonsignificant association in a study in China.[41]

In some studies, the association between alcohol consumption and risk varied depending on other breast cancer risk factors. In the Swedish study, the association was strongest for the group that also had other factors that predicted increased risk of breast cancer.[38] In a multicultural population in New York City, the association was strongest among individuals who had lower body mass index.[40] In a study of Mexican women, alcohol use was associated with increased breast density.[42] In a study of NHS II participants, no association was found between breast density and alcohol consumption.[43] A meta-analysis of studies reported an association between increased breast density and higher levels of alcohol consumption.[35] Although these reported findings are not consistent, effects of alcohol consumption on breast density may be one mechanism for the associations with risk for breast cancer.

Diet

A number of studies have examined alcohol consumption in concert with other known breast cancer risk factors. In particular, there has been study of interactions of alcohol with other dietary factors such as folate and other B vitamins, which play a role in alcohol metabolism. Alcohol negatively affects folate status, impacting folate absorption and metabolism and increasing folate excretion.[44] A systematic review reported evidence of interaction between alcohol and folate in relation to breast cancer risk.[45] Breast cancer risk decreased with increased folate consumption among individuals who drank heavily but not lighter drinkers.

Several recent studies examined plasma folate as a measure of vitamin status. In the NHS II, there was an interaction between alcohol and plasma vitamin concentrations, with a trend toward plasma folate being protective for breast cancer risk among individuals who consumed greater amounts, but not among those consuming lesser amounts of alcohol.[46] However, in the NHS I, plasma folate was not associated with breast cancer risk and did not vary by alcohol consumption.[47]

Further, in the EPIC cohort study in Europe, no interaction was found for alcohol and plasma folate consumption in relation to breast cancer risk.[48] This study found some evidence of an interaction of alcohol and plasma vitamin B_{12} consumption in

relation to breast cancer risk; vitamin B_{12} also is a cofactor in one-carbon metabolism. A study that examined the Women's Health Study cohort found no interaction between plasma concentrations of B vitamins and alcohol consumption in relation to risk.[49] A systematic review found evidence for an association between higher levels of folate consumption and decreased risk of breast cancer among participants with moderate or high alcohol intake.[50] Collectively, these results show that diet, particularly vitamins related to one-carbon metabolism, may modify the association between alcohol and the risk for breast cancer.

Genetic Factors

Several studies have examined genetic variation in the association between alcohol consumption and breast cancer risk. There have been several studies of the genes that code for the alcohol dehydrogenases (ADH), which are critical enzymes for alcohol metabolism. In a cohort in the Netherlands, variants in the genes for ADH were not associated with breast cancer risk nor did they modify the risk associated with alcohol consumption.[51] The NHS I reported similar findings; the association between alcohol consumption and risk for breast cancer was not modified by genetic variation in ADH.[52] There was, however, evidence that an association between alcohol and steroid hormone levels differed depending on ADH genotype.

A Danish cohort study examined variation in the *CYP19A1* gene, which codes for aromatase, an enzyme important to estrogen metabolism.[53] Although these researchers found an interaction of genetic variation with blood steroid hormones with acute alcohol consumption, they found no evidence of an association of the genetic variant with breast cancer risk. Among women who have the *BRCA1* or *BRCA2* genes, mutations that confer a particularly elevated risk of breast cancer, alcohol was not associated with breast cancer risk.[54] Overall, the evidence for genetic factors modifying the association between alcohol consumption and the risk for breast cancer is not strong.

Other Potential Modifying Factors

Understanding of whether other factors modify the observed association between alcohol consumption and breast cancer is another area of active research. In a pooled analysis, alcohol was positively associated with risk among both nulliparous and parous women.[55] Point estimates of risk were similar and not significantly different for the two groups. There is some evidence of a stronger association between alcohol and breast cancer risk among women receiving hormone therapy as compared to those not receiving hormone therapy, particularly the risk for estrogen receptor–positive breast cancer.[56] Further examination of modifying factors such as other dietary factors, body mass index, level of physical activity, and smoking is warranted.

ALCOHOL AND SURVIVAL AFTER DIAGNOSIS

Although most of the research regarding the association between consuming alcohol and the risk for breast cancer has focused on incidence, some studies have examined the effects of alcohol on survival after a breast cancer diagnosis. Studies used different time frames (before or after diagnosis) for the alcohol consumption and different outcome measures, such as breast cancer recurrence, breast cancer–specific survival, and all-cause mortality. Most studies did not distinguish by breast cancer subtype, which can affect prognosis.

A meta-analysis of 11 studies found evidence of improved survival after breast cancer diagnosis among individuals who reported any prediagnostic alcohol consumption, when compared with those who reported none.[57] The association differed somewhat by the estrogen receptor status of the tumor, with some evidence of reduced all-cause mortality for women with estrogen receptor–negative disease and no association with mortality in those with estrogen receptor–positive disease. Studies of lifetime alcohol intake found no association with all-cause mortality or

death from breast cancer (breast cancer–specific mortality).[58,59]

In the National Institutes of Health (NIH)-AARP Diet and Health Study cohort, alcohol consumption at the study baseline was not statistically significantly associated with breast cancer–specific survival.[60] In the Women's Health Initiative, there was no association between prediagnostic alcohol consumption and breast cancer–specific or all-cause mortality.[61] There was some evidence of decreased breast cancer–specific mortality for estrogen receptor–negative tumors. Among breast cancer patients from the Moffitt Cancer Center, self-reported alcohol consumption one year before diagnosis was associated with improved breast cancer–free survival.[62] Another study of women in the United States reported that prediagnostic alcohol intake was associated with an increased risk of breast cancer–specific mortality.[63]

Alcohol consumption pattern may affect mortality as well as incidence. In a study in western New York among women who had postmenopausal breast cancer, drinking intensity before diagnosis was associated with prognosis.[59] Participants who drank four or more drinks per drinking occasion had increased mortality from breast cancer and from all causes, and participants who drank fewer drinks per drinking occasion had decreased mortality from both breast cancer and all causes.

Few studies have examined alcohol consumption following a breast cancer diagnosis. One study reported an increased risk of breast cancer recurrence with alcohol consumption after diagnosis among premenopausal but not postmenopausal women.[64] In another study, investigators found no association between postdiagnostic intake and breast cancer–specific mortality.[63] There was better overall survival for those with greater postdiagnostic alcohol consumption. Findings regarding alcohol consumption and prognosis after a breast cancer diagnosis are not consistent. More research is needed to examine alcohol consumption, including patterns of consumption, following diagnosis.

More analyses regarding breast cancer subtype and treatment are required to better understand a possible role of alcohol consumption following diagnosis. Recent studies examining alcohol consumption and the efficacy of breast cancer treatments have not found any effect of alcohol consumption on radiotherapy[65] or on adjuvant hormone therapy.[62] More data regarding in-depth analysis of alcohol consumption both before and after diagnosis are needed, along with more research examining the total amount of alcohol consumed, drinking patterns in relation to outcomes, and the effects of drinking alcohol during treatment.

MECHANISMS FOR ALCOHOL EFFECTS

The role of alcohol consumption in breast carcinogenesis is a complex process likely acting through a number of mechanisms. Although alcoholic beverages contain a variety of compounds, for breast carcinogenesis, alcohol itself appears to be the more important carcinogen,[66] consistent with the finding that overall, risk does not differ based on the type of beverage consumed. However, much is not understood regarding the underlying mechanisms for alcohol and breast carcinogenesis. Potential mechanisms include oxidative stress, cell proliferation, effects on hormones, particularly steroid hormones, and effects on one-carbon metabolism.

Alcohol likely contributes to carcinogenesis partly through oxidation from alcohol metabolism and through oxidative stress from production of the alpha-hydroxyethyl radical, a reactive oxygen species.[67] Alcohol is metabolized to acetaldehyde, classified as a carcinogen by the International Agency for Research on Cancer (IARC), part of the World Health Organization, in 2010.[67] Although production of acetaldehyde from alcohol primarily occurs in the liver, it also occurs in breast tissues.

There is in vivo evidence that acetaldehyde can concentrate in mammary cells following a single exposure. In an animal model, acetaldehyde accumulated and persisted in higher concentrations

in breast tissue than in blood.[68] Adverse effects of acetaldehyde include DNA adduct formation, oxidation, and altered DNA methylation.[67] Further, in vitro, at low concentrations, alcohol can increase cell proliferation, including proliferation of breast cells.[69] Higher concentrations of alcohol and red wine exposure may reduce cell proliferation.

In addition to the carcinogenic effects of alcohol consumption and acetaldehyde on breast tissue, alcohol consumption's effects on hormones also may contribute to cancer in the breast. There are both acute and chronic effects of alcohol on steroid hormone level. At doses of even 15 to 30 grams of alcohol per day, serum estrogens increase.[24] In one study of premenopausal women, alcohol consumption was associated with plasma estrogens, but not androgens, when measured during the luteal phase. Neither hormone was associated with alcohol during the follicular phase.[70] In that same cohort, urinary estradiol measured at the mid-luteal phase was more than 20% higher in women who drank more than 15 grams per day, when compared with those who did not drink.[71] Further, a mediation analysis provided evidence that changes in hormones associated with alcohol consumption may explain part of the relationship between alcohol and breast cancer.[72]

Altered DNA methylation also contributes to carcinogenesis. Alcohol significantly affects one-carbon metabolism, including DNA methylation, in part by effects on folate status, as discussed previously. Studies that examined DNA methylation in breast tumors made comparisons based on drinking history and found differences by the amount of alcohol consumption.[73,74] Another study found some evidence of these differences in normal, noncancerous breast tissues.[75] Alcohol's effects on estrogen also may play a role in altered DNA methylation. There is evidence that higher concentrations of the steroid hormone affect DNA methylation.[24]

Other possible mechanisms for an effect of alcohol on carcinogenesis in general and breast cancer in particular are still emerging. For example, the microbiome in the mouth and gut may affect breast cancer risk,[76,77] and alcohol can affect the microbiome.[78,79] Alcohol likely has other effects on breast carcinogenesis, including effects on metastasis, angiogenesis, and cancer stem cells, affecting both cancer initiation and tumor aggressiveness.[80]

Alcohol's effects on oxidative stress, cell proliferation, steroid hormones, and one-carbon metabolism may explain, in part, the observed associations with breast cancer risk. Additional research is needed regarding these and other mechanisms, including research on those specific to tumor subtypes and mechanisms for exposures following a breast cancer diagnosis.

PUBLIC AWARENESS OF RISK

A limited number of studies have examined public understanding of alcohol and breast cancer. In a study of women attending a breast screening clinic in the United Kingdom, only 19% were aware that alcohol consumption is a breast cancer risk factor.[81] Among university students in a survey conducted in 23 countries around the world, overall, 3.3% were aware of alcohol consumption as a breast cancer risk factor.[82] Although awareness was highest in the United States, only 10% of students correctly identified alcohol consumption as a risk factor.

Awareness tends to be greater among women who have been diagnosed with breast cancer, with resulting lower alcohol intake in that group. In a systematic review, 62% to 97% of participants adhered to recommendations to limit alcohol consumption in a study of women completing initial treatment for breast cancer.[83] These studies were conducted primarily in the United States; a small number of participants were in Europe. In spite of the strength of the overall evidence connecting alcohol consumption to breast cancer,[5,67] there is little public awareness of alcohol consumption as a breast cancer risk factor.

RECOMMENDATIONS

Reduction of alcohol consumption could measurably affect the burden of disease related to breast cancer. Based on global data of the prevalence of alcohol consumption and of the incidence rate of breast cancer, an estimated 144,000 new cases of breast cancer and 38,000 breast cancer deaths annually are accounted for by alcohol consumption, which is 8.6% of all incidence and 7.3% of mortality.[24] The magnitude of effect of a decrease in consumption in a particular region depends on the prevalence of alcohol consumption in that region. For example, in Australia, it has been estimated that any regular consumption of alcohol accounts for 12.6% and 6.6% of premenopausal and postmenopausal breast cancer, respectively.[84] Alcohol consumption accounts for 12% of breast cancer in the United Kingdom.[11] In the United Kingdom, regular consumption of each additional drink per day accounts for 11 additional breast cancers per 1,000 women in their lifetime, up to age 75.[11] As further indication of the effect, one estimate is that the increase in cancer risk for drinking one bottle of wine per week is approximately equivalent to smoking 10 cigarettes per week, with breast cancer accounting for most of that increase.[85]

Although the evidence is strong for an increase in breast cancer with alcohol consumption, some areas of research still require further attention. A better understanding of the roles of drinking pattern, or drinking intensity, in relation to total consumption is needed. More studies of alcohol consumption and breast cancer subtypes would help increase insight into the relationship. A clearer understanding of the effects of exposures in early life, including *in utero* exposure, is warranted. Examination of how other breast cancer risk factors (e.g., physical activity, body mass index, smoking, reproductive history) interact with alcohol consumption in relation to both breast cancer risk and prognosis is needed. More studies of the association by race/ethnicity, by age at diagnosis, and conducted in regions outside of Europe and North America would contribute to our understanding. Additional research linking epidemiological information with biological information regarding the role of alcohol in carcinogenesis could enhance the ability to leverage this important relationship toward prevention efforts.[44] Further, additional study is needed of the effects of alcohol consumption, both before and after diagnosis, on breast cancer recurrence, breast cancer–specific mortality, and overall mortality.

Given the strength of the evidence linking alcohol to breast cancer, increasing awareness of risk is critical. It is time for a clear public health message identifying the role of alcohol in breast carcinogenesis and indicating that that there is no apparent lower threshold of effect. Consumption levels of less than one drink per day are associated with increased risk. Further, drinking alcohol affects risk at all phases of life, including early and late life. The science is consistent and clear, but awareness is low. It is time for a focus on developing public understanding of alcohol, which is a very common exposure, and its connection with increased risk of breast cancer.

Acknowledgments

This article was supported in part by the New York State Department of Health award C33916GG.

Financial disclosure

The author declares no competing financial interests.

Publisher's note

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References

1. Willett WC, Stampfer MJ, Colditz GA, et al. Moderate alcohol consumption and the risk of breast cancer. *New Engl J Med*. 1987;316(19):1174-1180. https://doi.org/10.1056/nejm198705073161902.
2. Schatzkin A, Jones DY, Hoover RN, et al. Alcohol consumption and breast cancer in the epidemiologic follow-up study of the First National Health and Nutrition Examination Study. *New Engl J Med.* 1987;316(19):1169-1173. https://doi.org/0.1056/NEJM198705073161901.

3. Graham S. Alcohol and breast cancer. *New Engl J Med*. 1987;316:1121-1123. https://doi.org/10.1056/NEJM198711123172010.
4. World Health Organization, International Agency for Research on Cancer (IARC). GLOBOCAN 2018. http://gco.iarc.fr/today/data/factsheets/cancers/39-All-cancers-fact-sheet.pdf. 2019. Accessed March 16, 2020.
5. World Cancer Research Fund, American Institute for Cancer Research. *Continuous Update Project Expert Report. Diet, Nutrition, Physical Activity and Breast Cancer: A Global Perspective*. https://www.wcrf.org/dietandcancer/about.
6. National Institute on Alcohol Abuse and Alcoholism. *What is a standard drink?* https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/what-standard-drink. Accessed July 25, 2019.
7. Jung S, Wang M, Anderson K, et al. Alcohol consumption and breast cancer risk by estrogen receptor status: In a pooled analysis of 20 studies. *Int J Epidemiol*. 2016;45(3):916-928. https://doi.org/10.1093/ije/dyv156.
8. Romieu I, Scoccianti C, Chajès V, et al. Alcohol intake and breast cancer in the European prospective investigation into cancer and nutrition. *Int J Cancer*. 2015;137(8):1921-1930. https://doi.org/10.1002/ijc.29469.
9. Masala G, Bendinelli B, Assedi M, et al. Up to one-third of breast cancer cases in post-menopausal Mediterranean women might be avoided by modifying lifestyle habits: The EPIC Italy study. *Breast Cancer Res Treat*. 2017;161(2):311-320. https://doi.org/10.1007/s10549-016-4047-x.
10. Fagherazzi G, Vilier A, Boutron-Ruault M-C, et al. Alcohol consumption and breast cancer risk subtypes in the E3N-EPIC cohort. *Eur J Cancer Prev*. 2015;24(3):209-214. https://doi.org/10.1097/CEJ.0000000000000031.
11. Allen NE, Beral V, Casabonner D, et al. Moderate alcohol intake and cancer incidence in women. *J Natl Cancer Inst*. 2009;101(5):296-305. https://doi.org/10.1093/jnci/djn514.
12. Trichopoulou A, Bamia C, Lagiou P, et al. Conformity to traditional Mediterranean diet and breast cancer risk in the Greek EPIC (European Prospective Investigation into Cancer and Nutrition) cohort. *Am J Clin Nutr*. 2010;92(3):620-625. https://doi.org/10.3945/ajcn.2010.29619.
13. Qian F, Ogundiran T, Hou N, et al. Alcohol consumption and breast cancer risk among women in three sub-Saharan African countries. *PLoS One*. 2014;9(9):e106908. https://doi.org/10.1371/journal.pone.0106908.
14. De Menezes RF, Bergmann A, de Aguiar SS, et al. Alcohol consumption and the risk of cancer in Brazil: A study involving 203,506 cancer patients. *Alcohol*. 2015;49(7):747-751. https://doi.org/10.1016/j.alcohol.2015.07.001.
15. Vieira R, Tobar JSS, Dardes R, et al. Alcohol consumption as a risk factor for breast cancer development: A case-control study in Brazil. *Asian Pac J Cancer Prev*. 2018;19(3):703-707. https://doi.org/10.22034/APJCP.2018.19.3.703.
16. Nagata C, Mizoue T, Tanaka K, et al. Alcohol drinking and breast cancer risk: An evaluation based on a systematic review of epidemiologic evidence among the Japanese population. *Jpn J Clin Oncol*. 2007;37(8):568-574. https://doi.org/10.1093/jjco/hym062.
17. Li Y, Yang H, Cao J. Association between alcohol consumption and cancers in the Chinese population—A systematic review and meta-analysis. *PLoS One*. 2011;6(4):e18776. https://doi.org/10.1371/journal.pone.0018776.
18. Lee SM, Park JH, Park HJ. Breast cancer risk factors in Korean women: A literature review. *Int Nurs Rev*. 2008;55(3):355-359. https://doi.org/10.1111/j.1466-7657.2008.00633.x.
19. Suzuki R, Iwasaki M, Inoue M, et al. Alcohol consumption-associated breast cancer incidence and potential effect modifiers: The Japan Public Health Center-based Prospective Study. *Int J Cancer*. 2010;127(3):685-695. https://doi.org/10.1002/Ijc.25079.
20. Kawai M, Minami Y, Kakizaki M, et al. Alcohol consumption and breast cancer risk in Japanese women: The Miyagi cohort study. *Breast Cancer Res Treat*. 2011;128(3):817-825. https://doi.org/10.1007/s10549-011-1381-x.
21. Williams LA, Olshan AF, Hong CC, et al. Alcohol intake and breast cancer risk in African American women from the AMBER Consortium. *Cancer Epidemiol Biomarkers Prev*. 2017;26(5):787-794. https://doi.org/10.1158/1055-9965.EPI-16-0792.
22. Chen WY, Rosner B, Hankinson SE, et al. Moderate alcohol consumption during adult life, drinking patterns, and breast cancer risk. *JAMA*. 2011;306(17):1884-1890. https://doi.org/10.1001/jama.2011.1590.
23. White AJ, DeRoo LA, Weinberg CR, et al. Lifetime alcohol intake, binge drinking behaviors and breast cancer risk. *Am J Epidemiol*. 2017;186(5):541-549. https://doi.org/10.1093/aje/kwx118.
24. Shield KD, Soerjomataram I, Rehm J. Alcohol use and breast cancer: A critical review. *Alcohol Clin Exp Res*. 2016;40(6):1166-1181. https://doi.org/10.1111/acer.13071.
25. Choi Y-J, Myung S-K, Lee J-H. Light alcohol drinking and risk of cancer: A meta-analysis of cohort studies. *Cancer Res Treat*. 2018;50(2):474-487. https://doi.org/10.4143/crt.2017.094.
26. Assi N, Rinaldi S, Viallon V, et al. Mediation analysis of the alcohol-postmenopausal breast cancer relationship by sex hormones in the EPIC cohort. *Int J Cancer*. 2020;146(3):759-768. https://doi.org/10.1002/ijc.32324.
27. Key TJ, Balkwill A, Bradbury KE, et al. Foods, macronutrients and breast cancer risk in postmenopausal women: A large UK cohort. *Int J Epidemiol*. 2019;48(2):489-500. https://doi.org/10.1093/ije/dyy238.
28. Baglia ML, Cook LS, Mei-Tzu C, et al. Alcohol, smoking, and risk of HER2-overexpressing and triple-negative breast cancer relative to estrogen receptor-positive breast cancer. *Int J Cancer*. 2018;143(8):1849-1857. https://doi.org/10.1002/ijc.31575.
29. Liu Y, Colditz G, Rosner B, et al. Alcohol intake between menarche and first pregnancy: A prospective study of breast cancer risk. *J Natl Cancer Inst*. 2013;105(20):1571-1578. https://doi.org/10.1093/jnci/djt213.
30. Liu Y, Tamimi RM, Berkey CS, et al. Intakes of alcohol and folate during adolescence and risk of proliferative benign breast disease. *Pediatrics*. 2012;129(5):e1192-e1198. https://doi.org/10.1542/peds.2011-2601.
31. Berkey CS, Willett WC, Frazier AL, et al. Prospective study of adolescent alcohol consumption and risk of benign breast disease in young women. *Pediatrics*. 2010;125(5):e1081-e1087. https://doi.org/10.1542/peds.2009-2347.
32. Mullooly M, Khodr ZG, Dallal CM, et al. Epidemiologic risk factors for in situ and invasive breast cancers among postmenopausal women in the National Institutes of Health-AARP Diet and Health Study. *Am J Epidemiol*. 2017;186(12):1329-1340. https://doi.org/10.1093/aje/kwx206.
33. Cohick WS, Crismale-Gann C, Stires H, et al. Fetal alcohol exposure and mammary tumorigenesis in offspring: Role of the estrogen and insulin-like growth factor systems. *Adv Exp Med Biol*. 2015;815:403-424. https://doi.org/10.1007/978-3-319-09614-8_24.
34. Bond-Smith D, Stone J. Methodological challenges and updated findings from a meta-analysis of the association between mammographic density and breast cancer. *Cancer Epidemiol Biomarkers Prev*. 2019;28(1):22-31. https://doi.org/10.1158/1055-9965.EPI-17-1175.

35. Ziembicki S, Zhu J, Tse E, et al. The association between alcohol consumption and breast density: A systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2016;26(2):170-178. https://doi.org/10.1158/1055-9965.EPI-16-0522.
36. Voevodina O, Bilich C, Arand B, et al. Association of Mediterranean diet, dietary supplements and alcohol consumption with breast density among women in South Germany: A cross-sectional study. *BMC Public Health*. 2013:13:203. https://doi.org/10.1186/1471-2458-13-203.
37. Okamoto T, Ito A. Association between alcohol consumption and mammographic density: A hospital-based cross-sectional study. *Breast Cancer*. 2019;26(4):478-484. https://doi.org/10.1007/s12282-019-00946-7.
38. Trinh T, Christensen SE, Brand JS, et al. Background risk of breast cancer influences the association between alcohol consumption and mammographic density. *Br J Cancer*. 2015;113(1):159-165. https://doi.org/10.1038/bjc.2015.185.
39. Maskarinec G, Takata Y, Pagano I, et al. Alcohol consumption and mammographic density in a multiethnic population. *Int J Cancer.* 2006;118(10):2579-2583. https://doi.org/10.1002/ijc.21705.
40. Quandt Z, Flom JD, Tehranifar P, et al. The association of alcohol consumption with mammographic density in a multiethnic urban population. *BMC Cancer*. 2015;15:1094. https://doi.org/10.1186/s12885-015-1094-3.
41. Sung H, Ren J, Li J, et al. Breast cancer risk factors and mammographic density among high-risk women in urban China. *NPJ Breast Cancer*. 2018;4:3. https://doi.org/10.1038/s41523-018-0055-9.
42. Rice MS, Bertrand KA, Lajouns M, et al. Reproductive and lifestyle risk factors and mammographic density in Mexican women. *Ann Epidemiol.* 2015;25(11):868-873. https://doi.org/10.1016/j.annepidem.2015.08.006.
43. Liu Y, Tamimi RM, Colditz GA, et al. Alcohol consumption across the life course and mammographic density in premenopausal women. *Breast Cancer Res Treat*. 2018;167:529-535. https://doi.org/10.1007/s10549-017-4517-9.
44. Zakhari S, Hoek JB. Epidemiology of moderate alcohol consumption and breast cancer: Association or causation? *Cancers*. 2018;10(10):349. https://doi.org/10.3390/cancers10100349.
45. Chen P, Li C, Li X, et al. Higher dietary folate intake reduces the breast cancer risk: A systematic review and meta-analysis. *Br J Cancer*. 2014;110:2327-2338. https://doi.org/10.1038/bjc.2014.155.
46. Houghton S, Eliassen AH, Zhang SM, et al. Plasma B-vitamins and one-carbon metabolites and the risk of breast cancer in younger women. *Breast Cancer Res Treat*. 2019;176(1):191-203. https://doi.org/10.1007/s10549-019-05223-x.
47. Houghton S, Eliassen AH, Zhang SM, et al. Plasma B-vitamin and one-carbon metabolites and the risk of breast cancer before and after folic acid fortification in the United States. *Int J Cancer*. 2019;144(8):1929-1940. https://doi.org/10.1002/ijc.31934.
48. Matejcic M, de Batlle J, Ricci C, et al. Biomarkers of folate and vitamin B12 and breast cancer risk: Report from the EPIC cohort. *Int J Cancer*. 2017;140(6):1246-1259. https://doi.org/10.1002/ijc.30536.
49. Lin J, Lee I-M, Cook NR, et al. Plasma folate, vitamin B-6, vitamin B-12 and risk of breast cancer in women. *Am J Clin Nutr.* 2008;87(3):734-743. https://doi.org/10.1093/ajcn/87.3.734.
50. Zeng J, Wang K, Ye F, et al. Folate intake and the risk of breast cancer: An up-to-date analysis of prospective studies. *Eur J Clin Nutr*. 2019;73(12):1657-1660. https://doi.org/10.1038/s41430-019-0394-0.
51. Hahn M, Simons CCJM, Weijenberg MP, et al. Alcohol drinking, ADH1B and ADH1C genotypes and the risk of postmenopausal breast cancer by hormone receptor status: The Netherlands Cohort Study on diet and cancer. *Carcinogenesis*. 2018;39(11):1342-1351. https://doi.org/10.1093/carcin/bgy101.
52. Hines LM, Hankinson SE, Smith-Warner SA, et al. A prospective study of the effect of alcohol consumption and ADH3 genotype on plasma steroid hormone levels and breast cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2000;9(10):1099-1105.
53. Kopp TI, Jensen DM, Ravn-Haren G, et al. Alcohol-related breast cancer in postmenopausal women—effect of *CYP19A1*, *PPARG* and *PPARGC1A* polymorphisms on female sex-hormone levels and interaction with alcohol consumption and NSAID usage in a nested case-control study and a randomized controlled trial. *BMC Cancer*. 2016;16:283. https://doi.org/10.1186/s12885-016-2317-y.
54. Cybulski C, Lubinski J, Huzarski T, et al. Prospective evaluation of alcohol consumption and the risk of breast cancer in *BRCA1* and *BRCA2* mutation carriers. *Breast Cancer Res Treat*. 2015;151(2):435-441. https://doi.org/10.1007/s10549-015-3393-4.
55. Schonfeld SJ, Pfeiffer RM, Lacey JV Jr, et al. Hormone-related risk factors and postmenopausal breast cancer among nulliparous women: An aggregated study. *Am J Epidemiol*. 2011;173(5):509-517. https://doi.org/10.1093/aje/kwq404.
56. Hvidtfeldt UA, Tjonneland A, Keiding N, et al. Risk of breast cancer in relation to combined effects of hormone therapy, body mass index, and alcohol use, by hormone-receptor status. *Epidemiology*. 2015;26(3):353-361. https://doi.org/10.1097/EDE.0000000000000261.
57. Ali AMG, Schmidt MK, Bolla MK, et al. Alcohol consumption and survival after a breast cancer diagnosis: A literature-based meta-analysis and collaborative analysis of data for 29,239 cases. *Cancer Epidemiol Biomarkers Prev*. 2014;23(6):934-945. https://doi.org/10.1158/1055-9965.EPI-13-0901.
58. Zeinomar N, Thai A, Cloud AJ, et al. Alcohol consumption and breast cancer-specific and all-cause mortality in women diagnosed with breast cancer at the New York site of the Breast Cancer Family Registry. *PLoS One*. 2017;12(12):e0189118. https://doi.org/10.1371/journal.pone.0189118.
59. Weaver AM, McCann SE, Nie J, et al. Alcohol intake over the life course and breast cancer survival in Western New York exposures and breast cancer (WEB) study: Quantity and intensity of intake. *Breast Cancer Res Treat*. 2013;139(1):245-253. https://doi.org/10.1007/s10549-013-2533-y.
60. Cifu G, Arem H. Adherence to lifestyle-related cancer prevention guidelines and breast cancer incidence and mortality. *Ann Epidemiol*. 2018;28(11):767-773. https://doi.org/10.1016/j.annepidem.2018.09.002.
61. Lowry SJ, Kapphahn K, Chlebowski R, et al. Alcohol use and breast cancer survival among participants in the Women's Health Initiative. *Cancer Epidemiol Biomarkers Prev*. 2016;25(8):1268-1273. https://doi.org/10.1158/1055-9965.EPI-16-0151.
62. Kowalski A, Striley CW, Varma DS, et al. Interactions between alcohol consumption and adjuvant hormone therapy in relation to breast cancer-free survival. *J Breast Cancer*. 2018;21(2):158-164. https://doi.org/10.4048/jbc.2018.21.2.158.
63. Newcomb PA, Kampman E, Trentham-Dietz A, et al. Alcohol consumption before and after breast cancer diagnosis: Associations with survival from breast cancer, cardiovascular disease, and other causes. *J Clin Oncol.* 2013;31(16):1939-1946. https://doi.org/10.1200/JCO.2012.46.5765.
64. Kwan ML, Kushi LH, Weltzien E, et al. Alcohol consumption and breast cancer recurrence and survival among women with early-stage breast cancer: The Life After Cancer Epidemiology study. *J Clin Oncol*. 2010;28(29):4410-4416. https://doi.org/10.1200/JCO.2010.29.2730.

65. DiMarzio P, Peila R, Dowling O, et al. Smoking and alcohol drinking effect on radiotherapy associated risk of second primary cancer and mortality among breast cancer patients. *Cancer Epidemiol*. 2018;57:97-103. https://doi.org/10.1016/j.canep.2018.10.002.
66. Lachmeier DW, Przybylski MC, Rehm J. Comparative risk assessment of carcinogens in alcoholic beverages using the margin of exposure approach. *Int J Cancer*. 2012;131(6):E995-E1003. https://doi.org/10.1002/ijc.27553.
67. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Alcohol consumption and ethyl carbamate. *IARC Monogr Eval Carcinog Risks Hum*. 2010;96:3-1383.
68. Castro GD, Delgado de Layno MA, Fanelli SL, et al. Acetaldehyde accumulation in rat mammary tissue after an acute treatment with alcohol. *J Appl Toxicol.* 2008;28(3):315-321. https://doi.org/10.1002/jat.1281.
69. Chen S, Yi Y, Xia T, et al. The influences of red wine in phenotypes of human cancer cells. *Gene*. 2019;702:194-204. https://doi.org/10.1016/j.gene.2018.10.049.
70. Hirko KA, Spiegelman D, Willett WC, et al. Alcohol consumption in relation to plasma sex hormones, prolactin, and sex hormone-binding globulin in premenopausal women. *Cancer Epidemiol Biomarkers Prev*. 2014;23(12):2943-2953. https://doi.org/10.1158/1055-9965.EPI-14-0982.
71. Hartman TJ, Sisti JS, Hankinson SE, et al. Alcohol consumption and urinary estrogens and estrogen metabolites in premenopausal women. *Horm Cancer*. 2016;7(1):65-74. https://doi.org/10.1007/s12672-015-0249-7.
72. Assi N, Rinaldi S, Viallon V, et al. Mediation analysis of the alcohol-postmenopausal breast cancer relationship by sex hormones in the EPIC cohort. *Int J Cancer*. 2019;146(3):759-768. https://doi.org/10.1002/ijc.32324.
73. Tao MH, Marian C, Shields PG, et al. Alcohol consumption in relation to aberrant DNA methylation in breast tumors. *Alcohol*. 2011;45(7):689-699. https://doi.org/10.1016/j.alcohol.2010.11.006.
74. Christensen BC, Kelsey KT, Zheng S, et al. Breast cancer DNA methylation profiles are associated with tumor size and alcohol and folate intake. *PLoS Genet*. 2010;6(7):e1001043. https://doi.org/10.1371/journal.pgen.1001043.
75. Wilson LE, Xu Z, Harlid S, et al. Alcohol and DNA methylation: An epigenome-wide association study in blood and normal breast tissue. *Am J Epidemiol*. 2019;188(6):1055-1065. https://doi.org/10.1093/aje/kwz032.
76. Xuan C, Shamonki JM, Chung A, et al. Microbial dysbiosis is associated with human breast cancer. *PLoS One*. 2014;9(1):e83744. https://doi.org/10.1371/journal.pone.0083744.
77. Freudenheim JL, Genco RJ, LaMonte MJ, et al. Periodontal disease and breast cancer: Prospective cohort study of postmenopausal women. *Cancer Epidemiol Biomarkers Prev*. 2016;25(1):43-50. https://doi.org/10.1158/1055-9965.EPI-15-0750.
78. Genco RJ, Borgnakke WS. Risk factors for periodontal disease. *Periodontol 2000*. 2013;62(1):59-94. https://doi.org/10.1111/j.1600-0757.2012.00457.x.
79. Engen PA, Green SJ, Voigt RM, et al. The gastrointestinal microbiome. Alcohol effects on the composition of intestinal microbiota. *Alcohol Res*. 2015;37(2):223-236.
80. Wang Y, Xu M, Ke Z, et al. Cellular and molecular mechanisms underlying alcohol-induced aggressiveness of breast cancer. *Pharmacol Res*. 2017;115:299-308. https://doi.org/10.1016/j.phrs.2016.12.005.
81. Sinclair J, McCann M, Sheldon E, et al. The acceptability of addressing alcohol consumption as a modifiable risk factor for breast cancer: A mixed method study within breast screening services and symptomatic breast clinics. *BMJ Open*. 2019;9(6):e027371. https://doi.org/10.1136/bmjopen-2018-027371.
82. Peacey V, Steptoe A, Davidsdottir S, et al. Low levels of breast cancer risk awareness in young women: An international survey. *Eur J Cancer.* 2006;42(15):2585-2589. https://doi.org/10.1016/j.ejca.2006.03.017.
83. Tjon-A-Joe S, Pannekoek S, Kampman E, et al. Adherence to diet and body weight recommendations among cancer survivors after completion of initial cancer treatment: A systematic review of the literature. *Nutr Cancer.* 2019;71(3):367-374. https://doi.org/10.1080/01635581.2018.1540713.
84. Arriga ME, Vajdic CM, Canfell K, et al. The preventable burden of breast cancers for premenopausal and postmenopausal women in Australia: A pooled cohort study. *Int J Cancer*. 2019;145(9):2383-2394. https://doi.org/10.1002/ijc.32231.
85. Hydes TJ, Burton R, Inskip H, et al. A comparison of gender-linked population cancer risks between alcohol and tobacco: How many cigarettes are there in a bottle of wine? *BMC Public Health*. 2019;19(1):316. https://doi.org/10.1186/s12889-019-6576-9.

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ALCOHOL RESEARCH
Current Reviews

Alcohol Res. 2020;40(2):12 • https://doi.org/10.35946/arcr.v40.2.12

Published: 6 August 2020

Effects of Alcohol on the Cardiovascular System in Women

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Cardiovascular disease (CVD) is a leading cause of morbidity and mortality for women. This review summarizes the relationship between alcohol consumption and common CVDs in women and highlights potential differences from men. Except for risk of hypertension, no sex-related effects of alcohol consumption on the risk for coronary heart disease and stroke have been reported, and data on the sex-related effects on risk for peripheral arterial disease are limited. For women, alcohol consumption has a J-shaped relationship with hypertension. About 1 to 2 standard drinks per day is associated with lower risk for the development of hypertension, whereas for men, the relationship is relatively linear. In the area of alcoholic cardiomyopathy, the prevalence is greater for men, but women may develop alcoholic cardiomyopathy at a lower lifetime level of alcohol consumption. Overall, data support that 1 to 2 standard drinks per day for women and men is associated with a lower risk of CVD, and higher daily amounts may increase the risk of CVD.

KEY WORDS: alcohol; cardiovascular disease; hypertension; stroke; women

INTRODUCTION

Biologic sex is an important determinant of health and disease. Over the past several decades, research has revealed sex differences in the epidemiology, risk, clinical manifestations, pathophysiology, and progression of many diseases, including cardiovascular disease (CVD) and alcohol-induced pathologies. CVD is the leading cause of morbidity and mortality for women.[1] Therefore, understanding the potential interaction between sex and alcohol consumption on the cardiovascular system is important. This review presents the effects of alcohol consumption on the cardiovascular system in women, focusing on prevalent cardiovascular conditions such as

hypertension, coronary heart disease (myocardial infarction), stroke, and peripheral arterial disease. The cardiovascular disorders are briefly defined, sex differences in the prevalence and prognosis of the disorders are discussed, followed by examination of the sex differences in alcohol's effects on those conditions. This review also reports on the sex differences in the prevalence, clinical manifestations, and outcomes associated with alcoholic cardiomyopathy.

METHODS

The relationship between alcohol consumption and CVD has been extensively investigated, and women have been included in many of these studies. However, results for women and men often have not been presented separately. Studies have been experimental, such as short-term clinical trials, and longitudinal, using participants from ongoing population cohorts such as the Nurses' Health Study and the Framingham Heart Study. Data from these studies have allowed for the completion of several comprehensive systematic reviews and meta-analyses of alcohol use and its relationships with hypertension, myocardial infarction, stroke, and peripheral arterial disease.

This review summarizes data from meta-analyses and from longitudinal studies. Results were included in this discussion if they were reported for men and women separately. Data were summarized from studies that examined alcohol consumption by either standard drinks or by grams per unit of ethanol per day or week. Studies varied in the way they measured and categorized alcohol consumption, making comparisons sometimes challenging. Most studies reviewed reported alcohol consumption in grams of ethanol per day or week and defined a standard drink as 12 to 15 grams of alcohol.

Drinking patterns, particularly binge drinking, have emerged as an important modifier of the relationship between alcohol and cardiovascular risk. For a review of the sex differences in binge drinking on cardiovascular function, see the 2017 review by Piano and colleagues.[2]

BLOOD PRESSURE AND HYPERTENSION

The current blood pressure guidelines published in 2018 define hypertension as systolic blood pressure (SBP) greater than 130 mm Hg or diastolic blood pressure (DBP) greater than 80 mm Hg.[3] In many of the studies reviewed for this article, hypertension was defined as SBP greater than 140 mm Hg or DBP greater than 90 mm Hg. The effects of alcohol consumption on blood pressure in women are important to consider, because hypertension is a leading cause of cardiovascular morbidity and mortality.[1] From 2015 to 2016, the overall prevalence of hypertension (SBP > 140 mm Hg) among adults was 29.0% and was similar for men (30.2%) and women (27.7%).[4] For adults ages 18 to 59, hypertension prevalence is greater for men than for women. However, women older than age 60 have greater prevalence (66.8%) of hypertension than men older than age 60 (58.5%). In the United States, experts have estimated that alcohol consumption accounts for 10% of the population burden of hypertension.[3]

The effects of single episodes of alcohol consumption have not been investigated in women. Studies that included men have reported that consuming alcohol (1 to 2 standard drinks) in a single episode was associated with transient blood pressure increases that ranged from 4 to 7 mm Hg SBP and from 4 to 6 mm Hg DBP.[5-7] In healthy women, an episode of low to moderate alcohol consumption (1 to 2 standard drinks, or 12 to 14 grams of ethanol) more than likely would have no appreciable effect on blood pressure.

Clinical studies and randomized clinical trials have been designed to examine the short-term effects of alcohol consumption, but only one study included women.[8-12] In a crossover study, Mori and colleagues examined the effects of different levels of alcohol consumption on ambulatory, 24-hour blood pressure levels among healthy, premenopausal women ages 20 to 45 ($N = 24$).[12] Blood pressure was measured after a 4-week period during which participants consumed different amounts of red wine: 42 to 73 grams of alcohol

per week (0.5 to 1.0 drink per day) vs. 146 to 218 grams of alcohol per week (2 to 3 drinks per day). Awake SBP was 2.3 mm Hg higher and DBP was 1.3 mm Hg higher for women who consumed more alcohol (2 to 3 drinks per day) than for women who consumed less (0.5 to 1.0 drink per day) or no alcohol. For the women who consumed less, the red wine showed no effect on blood pressure. These findings suggest 2 to 3 drinks per day have a mild pressor effect on blood pressure in women.

Findings from two meta-analyses support an association between alcohol consumption and the risk of developing hypertension (SBP > 140 mm Hg), and that sex is a modifier of this relationship.[13,14] In a meta-analysis of 18 cohort studies, Roerecke and colleagues found that for women (with a mean age of 46.7), compared to abstainers, consumption of 1 to 2 drinks per day was not associated with increased hypertension risk.[14] However, hypertension risk was elevated for women who consumed 3 or more drinks per day, with a relative risk (RR) of 1.42, 95% confidence interval (CI) [1.22, 1.66]. However, for men, compared to abstainers, any level of alcohol consumption increased the risk for hypertension.

In another meta-analysis conducted several years earlier, Briasoulis and colleagues reported that women ages 30 to 55 who consumed less than 10 grams of alcohol (less than 1 drink) per day, compared to abstainers, showed a significant reduction in RR for hypertension (RR = 0.87, 95% CI [0.82, 0.92]).[13] These investigators also reported a "trend toward decreased risk of hypertension" for women participants who consumed 1 to 2 drinks per day (RR = 0.9, 95% CI [0.87, 1.04]). For women, the increased risk for hypertension emerged at alcohol consumption levels of 21 to 30 grams (2 drinks) per day and 31 to 40 grams (2 to 3 drinks) per day. Men who consumed less alcohol showed a trend toward increased risk for hypertension, and a significant increase in risk of hypertension was shown among men who consumed 31 to 40 grams per day (RR = 1.77, CI [1.39, 2.26]) or more than 50 grams (about 4 drinks) per day (RR = 1.62, CI [1.31, 1.87]). Results from another meta-analysis also found a linear relationship for men and a J-shaped relationship for women.[15]

Roerecke and colleagues also conducted a meta-analysis to examine the effects of a reduction in alcohol consumption on blood pressure.[16] Data were analyzed from 36 clinical trials, and the main analysis included men (n = 2,464) and women (n = 401) together, with a subgroup analysis for sex differences. Although trial characteristics (e.g., length of trial and blood pressure assessment method) differed among the studies, for individuals who drank more than 2 drinks per day, a reduction in alcohol consumption was associated with a reduction in blood pressure. Blood pressure reductions were greatest for individuals who consumed 6 or more drinks per day at baseline.

These same authors estimated the reduction in blood pressure that might be achieved by 50% of people in the United Kingdom who consume more than 2 drinks per day.[16] Using pooled effect sizes from a subgroup analyses for sex and amount of alcohol, the authors estimated the proportional difference, or the magnitude of SBP reduction, would be a 4.4% reduction for men and a 1.2% reduction for women among men and women with SBP greater than 140 mm Hg.

These results and the examination of daily alcohol consumption indicate the relationship between alcohol and blood pressure is different for men (linear) and for women (J-shaped). For men, all levels of alcohol consumption are associated with increased blood pressure and risk of hypertension.[14] For women, the J-shaped relationship indicates that 1 to 2 drinks per day has no effect[14] or a lowering effect[13] on blood pressure, whereas more than 2 drinks per day increases the risk of hypertension. All these meta-analyses included women before and after menopause; therefore, speculation about the potential effect of hormones on these sex differences is difficult.

CORONARY HEART DISEASE

Coronary heart disease is defined as a disease that results from coronary artery disease or

myocardial infarction. The terms "coronary heart disease" and "coronary artery disease" are often used interchangeably. Across all age groups, the prevalence of coronary heart disease and myocardial infarction is greater for men than for women.[1] However, the difference in prevalence between men and women narrows with advancing age.[1,17] Most women are older when they present with their first myocardial infarction (the mean age is 71.8). Regardless of age, more women than men die within 1 to 5 years after a first myocardial infarction.[17]

Many epidemiologic studies have examined the relationship between coronary heart disease (and myocardial infarction) and alcohol use. Ronksley and colleagues have conducted the most comprehensive meta-analysis, which incorporated 84 studies over the past 30 years.[18] Among those studies, 52% included women. In the analysis, active drinkers were defined using a wide range of alcohol consumption categories, from less than 2.5 grams per day (less than 0.5 drink) to more than 60 grams per day (5 or more drinks). For comparison, the reference group was nondrinkers. These investigators reported that for men and women ages 15 to 90, any amount of alcohol consumption compared to none was associated with a reduced RR for occurrence of coronary heart disease and mortality (for men: RR = 0.71, 95% CI [0.66, 0.77] and RR = 0.77, 95% CI [0.72,0.82], respectively; for women: RR = 0.71, 95% CI [0.66, 0.77] and RR= 0.78, 95% CI [0.64, 0.94], respectively).

In an analysis that used data from the international Interheart case-control study, which included a population of women and men with a mean age of 58, Leong and colleagues examined the relationship between alcohol consumption of 1 drink or more per day during the year before a myocardial infarction.[19] Women who had at least 1 drink were less likely to have a myocardial infarction (*OR* = 0.73, 95% CI [0.61, 0.88]) compared to men who had at least 1 drink (*OR* = 0.92, 95% CI [0.84, 1.00]). Because alcohol use was defined as the consumption of any alcoholic beverage within the previous 12 months, this analysis did not allow for determining any dose response or specific level of alcohol consumption associated with the reduced risk in women or men.

Collectively, based on these data, there are no sex-related effects of alcohol consumption on the risk for occurrence of coronary heart disease or for coronary heart disease mortality. The results reported by Ronksley and colleagues suggest a wide range of daily alcohol consumption levels are associated with a reduced risk of incidence of coronary heart disease and coronary heart disease mortality in women and men.[18] The lack of specific alcohol intake categories in the Interheart study disallows understanding either the lower or upper limits for alcohol consumption associated with myocardial infarction risk.

Neither study's findings provide specific guidance for understanding the frequency or regularity of consuming different daily levels of alcohol within a designated time period, for example, per week or month. More than likely, more than 2 to 3 drinks per day, every day, may be associated with a different risk profile when compared to consuming 2 to 3 drinks per day, but only 2 to 3 times per week. Finally, consuming 5 or more drinks per day could be considered a binge pattern, which is associated with increased risk of CVD.[2]

STROKE

The two main types of stroke are ischemic and hemorrhagic. Both types are associated with a marked reduction in cerebral blood and oxygenation and involve ischemic cell death. Approximately 90% of strokes are ischemic and arise from a decrease or blockage of cerebral blood flow, whereas about 10% of strokes are due to intracerebral hemorrhage.[1] Stroke is the most common cerebrovascular disease and the second-leading cause of death worldwide. Each year, approximately 55,000 more women than men have a stroke. For women younger than age 75, stroke incidence rates are lower than they are for men, although for women older than age 75, incidence rates exceed those for men older than age 75. A similar age-related trend

is found for stroke-associated mortality rates, which are similar for women and men younger than age 45. Women between ages 45 and 74 have lower stroke mortality than men, but as age advances, mortality rates tend to be higher for women compared to age-matched men.

Among a Swedish cohort of men and women, Larsson and colleagues examined the association between alcohol consumption and risk of different stroke subtypes.[20] The reference group included nondrinkers, never drinkers, and occasional drinkers. Among women and men, no statistically significant association was found between any level of alcohol consumption (i.e., less than 1 to more than 21 drinks per week) and the risk of ischemic stroke. For men and women, only the higher level of alcohol consumption (more than 21 drinks per week) was associated with increased risk of intracerebral hemorrhagic stroke. For women but not men, all levels of alcohol consumption were significantly and positively associated with subarachnoid hemorrhagic stroke. As the authors noted, at the highest level of alcohol consumption and among this cohort of women, the number of cases of all stroke subtypes ($n = 2$ to $n = 11$) was low, which affects the power of these associations.

In this same study, a meta-analysis was conducted and included 27 prospective studies, of which the majority controlled for potential confounders such as age, sex, smoking, body mass index, and diabetes mellitus.[20] In the subgroup analysis, 2 drinks or fewer per day for women was associated with a lower risk for ischemic stroke (RR = 0.80, 95% CI [0.83, 0.95]). No effect was shown for intracerebral hemorrhagic stroke (RR = 0.95, 95% CI [0.76, 1.19]), and a modest increase was shown for subarachnoid hemorrhagic stroke (RR = 1.38, 95% CI [1.01, 1.85]). More than 2 drinks per day for women was associated with increased RR for all stroke subtypes. Similar findings were reported for men. For women compared to men, more than 2 drinks per day appeared to be a greater RR for intracerebral and subarachnoid hemorrhagic stroke, but no sex differences were found in the RR values for all stroke subtypes.

Zheng and colleagues conducted a meta-analysis of prospective observational studies (23 studies including 18 cohorts) and examined the association of alcohol intake and the risk of cardiovascular outcomes, which included total stroke (ischemic and all hemorrhagic strokes) and ischemic stroke.[21] For men and women, less than 15 grams per day of alcohol had no effect on the risk for total stroke, whereas for both men and women, this low daily amount of alcohol consumption had similar significant reductions in the risk for ischemic stroke (about 17% to 24%). For women but not for men, moderate alcohol consumption (15 to 30 grams per day) was associated with a reduction of risk for total stroke and ischemic stroke. However, the RR ratio (women to men) was not significantly different, indicating no sex difference. For men and women, heavy alcohol consumption had no significant effect on total or ischemic stroke risk.

Jimenez and colleagues examined the relationship of alcohol and the risk of stroke for women enrolled in the prospective Nurses' Health Study.[22] Women (with a mean age of 46) free of CVD at baseline were followed between 1980 and 2006. Women who reported light (up to 4.9 grams per day) to moderate (5.0 to 14.8 grams per day) alcohol consumption had a lower risk of stroke compared to abstainers. Consumption of 30 to 45 grams per day had no effect on stroke risk, whereas consumption exceeding 36 grams per day (about 3 drinks) was associated with greater risk of stroke. Similar results were obtained after a multivariate analysis controlled for many key variables, such as age, aspirin use, hormone replacement therapy, and smoking. However, as the authors noted, the confidence limits were wide, because only a few events were at the higher end of the alcohol intake range. Few women in this study consumed more than 45 grams per day, limiting the power to investigate that level of alcohol consumption on stroke risk.

Collectively, based on the data reviewed, there are no sex-related differences of alcohol consumption on the risk for total stroke or stroke subtypes. Findings from these studies suggest a

J-shaped relationship for alcohol use and stroke risk for both men and women, with 1 to 2 drinks being not harmful for women and perhaps reducing the risk for certain stroke subtypes.[20,21] Reported findings for higher levels of alcohol consumption are similar for men and women; that is, exceeding 3 drinks per day or 21 drinks per week may increase the risk of all types of stroke, particularly hemorrhagic stroke.

PERIPHERAL ARTERIAL DISEASE

Peripheral arterial disease is an atherosclerotic, occlusive disease of the lower limbs affecting 202 million individuals worldwide.[1] Unlike the other CVDs discussed in this article, less is known about peripheral arterial disease in women compared to men.[23] Many population-based prevalence studies of peripheral arterial disease have not noted prevalence separately for women. Overall, the disease progression, pathophysiology, and symptoms in women have been poorly characterized. For men and women, prevalence of peripheral arterial disease increases with age, reaching 25% for women older than age 80. Investigators often use the ankle brachial index (ABI), which is calculated by dividing the SBP at the ankle by the SBP at the arm, as a metric for diagnosing peripheral arterial disease. Hirsch and colleagues used the ABI test and reported that the severity of peripheral arterial disease for women was similar to the severity associated with men.[23]

Compared to the relationships between alcohol consumption and coronary heart disease or stroke, the relationship between alcohol consumption and peripheral arterial disease has been examined less often. Consequently, no meta-analyses or systematic reviews have been reported. More than a decade ago, two large prospective studies examined the effects of alcohol consumption on peripheral arterial disease.[24,25] The Strong Heart Study was conducted in the United States, and the Rotterdam study was done in Europe, and both used an ABI value of less than 0.9 as an indicator for the presence of peripheral arterial disease.

In the Strong Heart Study, which enrolled only American Indian participants, current alcohol drinking was inversely associated with peripheral arterial disease prevalence for men and women, after controlling for other factors.[24] Because more specific information was not provided about levels or amounts of alcohol consumption and only American Indians were included, the generalizability of the findings is limited.

In the Rotterdam study, however, results were similar.[25] This study enrolled 1,489 men and 2,486 women who were age 55 or older and were free from CVD at baseline. These studies found that the risk of peripheral arterial disease (assessed by an ABI of less than 0.9) was significantly reduced (22% to 36%) for women who reported consuming 10 to 20 grams of ethanol, or less than 2 drinks, per day (*OR* = 0.66, 95% CI [0.43, 1.00]) or more than 20 grams per day (*OR* = 0.64; 95% CI [0.41, 1.01]). A nonsignificant association was found for men. However, risk was not lowered for women smokers, men smokers, or men nonsmokers, suggesting that alcohol consumption may lower risk of peripheral arterial disease for women who do not smoke.

These findings suggest there are sex-related effects of alcohol consumption on the risk for peripheral arterial disease.[24,25] For women, unlike for men, low to moderate drinking levels may reduce the risk of peripheral arterial disease. Many studies have examined alcohol and the other CVDs, but a dearth of studies have examined alcohol and peripheral arterial disease. Therefore, more research on the effect of alcohol consumption on peripheral arterial disease in women is warranted.

ALCOHOLIC CARDIOMYOPATHY

The term "alcoholic cardiomyopathy" describes a heart muscle disease found in individuals with a history of heavy, long-term, alcohol consumption. Alcoholic cardiomyopathy is characterized by a dilated left ventricle, normal or reduced left ventricle wall thickness, increased left ventricle mass, and (in advanced stages) a reduced left

ventricle ejection fraction (less than 40%).[26] In studies of alcoholic cardiomyopathy, women have been excluded or underrepresented. In part, this may relate to differences and overall lower alcohol consumption and prevalence of alcohol use disorders in women compared to men.

At a population level, the exact prevalence of alcoholic cardiomyopathy, especially among women, remains unknown. Two decades ago, cross-sectional studies that estimated the frequency of alcoholic cardiomyopathy among individuals with a diagnosis of idiopathic dilated cardiomyopathy generally excluded women.[27-29] Using a large, nationally representative database of inpatients, Mogos and colleagues recently estimated that the prevalence of new or existing alcoholic cardiomyopathy was 68 per 100,000, or 1 for every 1,471 inpatient hospitalizations.[30] Among this inpatient population, a greater percentage of men than women had alcoholic cardiomyopathy (the male to female ratio was 8 to 1).

Some reports indicated that women with alcohol dependence developed alcoholic cardiomyopathy after consuming less alcohol over a shorter period than age-matched men with alcohol dependence.[31] However, for women and men, the exact amount and duration of alcohol consumption associated with the development of alcoholic cardiomyopathy remains unknown. Also, the point at which alcohol-induced abnormalities appear during the course of an individual's lifetime of drinking is not well-established and is highly individualized, suggesting either protective or adverse interaction effects because of genetic or lifestyle modifications.[26]

Urbano-Márquez and colleagues prospectively enrolled a cohort of women with alcoholic cardiomyopathy and specifically examined myocardial structural characteristics (e.g., ventricular dimensions and mass).[32] In this study, asymptomatic women (n = 50) and men (n = 100) with alcoholic cardiomyopathy had similar changes in echocardiographic parameters reflecting myocardial function and structure, suggesting similar alcohol-induced, global myocardial changes. Women had a total lifetime dose of ethanol (14.2 ± 5.4 g/kg of body weight) that was less than the dose for men (23.1 ± 12.4 g/kg of body weight), leading to the idea that women may be more vulnerable to the development of alcoholic cardiomyopathy.

Recently, Mogos and colleagues examined sex differences in the distribution of co-occurring conditions among men and women with alcoholic cardiomyopathy.[30] Women with alcoholic cardiomyopathy, compared to men with the same condition, were significantly more likely to have co-occurring anemia (28.3% vs. 19.2%), heart failure with preserved ejection fraction (3.2% vs. 2.5%), thyroid disorders (10.5% vs. 4.7%), and asthma (5.1% vs. 2.5%). Women were also more likely than men to experience co-occurring alcoholic cardiomyopathy and depression or anxiety. Conversely, men with alcoholic cardiomyopathy were more likely than women to also have hyperlipidemia (19.5% vs. 15.5%), heart failure with reduced ejection fraction (18.6% vs. 15.2%), diabetes mellitus (18.0% vs. 13.6%), and renal disease (21.8% vs. 18.4%).

Findings from the study suggest sex differences in certain co-occurring conditions among men and women with alcoholic cardiomyopathy.[30] Prevalence of alcoholic cardiomyopathy is greater for men compared to women, and women may develop the condition after shorter lifetime alcohol consumption. Women with alcoholic cardiomyopathy experienced more anxiety and depression; however, these findings are similar to those found in the general population.[33] Nonetheless, co-occurring conditions are important considerations when treating women who have alcoholic cardiomyopathy.

CONCLUSION

Many studies have included women in the examination of the effects of alcohol on the cardiovascular system. Excluding alcoholic cardiomyopathy and other alcohol-induced diseases such as liver disease,[34] low to moderate alcohol consumption does not adversely affect cardiovascular risk in women. Although consumption of 2 to 3 drinks per day may exert a pressor effect on blood pressure in women,[12] low

to moderate levels of daily alcohol consumption (1 to 2 drinks per day) have been associated with no increased risk of hypertension.[14]

Furthermore, with the exception of hypertension, sex-specific differences have not been found in the relationship between alcohol and cardiovascular risk. Results from these studies have been informative, but a lack of data remains for understanding the safe or risk-reducing weekly limits of alcohol consumption for women.

Results from some of the studies pose a bit of conundrum. Zheng and colleagues reported that moderate levels of alcohol consumption in women were associated with a lower risk for total stroke and ischemic stroke, but this same level of alcohol for women, compared to men, has been reported to have a significant 10% increase in the risk of total mortality.[21]

What might the recommended levels of alcohol consumption for women be? The answer lies in the recent, large-scale, international study by Wood and colleagues.[35] These investigators analyzed individual participant data from three large, international sources (including about 600,000 current drinkers). These investigators found the threshold for the lowest risk for all-cause mortality (i.e., mortality related to any condition or event) for men and women was about 100 grams of alcohol (about 7 drinks) per week. Furthermore, women who reported drinking more than the U.K. or U.S. recommended weekly limits of 112 grams per week[36] and 98 grams per week,[37] respectively, had a shorter life expectancy (by about 1.1 to 1.5 years) at age 40, compared with women who reported drinking less than these thresholds.[35]

Alcohol consumption remains a major risk factor for global burden of disease.[38] For women who consume alcoholic beverages, the Dietary Guidelines for Americans recommend drinking in moderation—up to one drink per day.[37] The Guidelines also recommend that individuals who do not drink alcohol not start drinking for any reason.

Acknowledgments

This article was supported by the National Institutes of Health grant R21AA024535.

Financial disclosure

The authors declare that they have no competing financial interests.

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References

1. Benjamin EJ, Muntner P, Alonso A, et al. Heart disease and stroke statistics—2019 update: A report from the American Heart Association. *Circulation*. 2019;139(10):e56-e528. PMID: 30700139.
2. Piano MR, Mazzuco A, Kang M, et al. Cardiovascular consequences of binge drinking: An integrative review with implications for advocacy, policy, and research. *Alcohol Clin Exp Res*. 2017;41(3):487-496. PMID: 28067964.
3. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: Executive summary: A report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Hypertension*. 2018;71(6):1269-1324. PMID: 29133354.
4. Fryar CD, Ostchega Y, Hales CM, et al. Hypertension prevalence and control among adults: United States, 2015–2016. *NCHS Data Brief*. 2017;(289):1-8. PMID: 29155682.
5. Potter JF, Watson RD, Skan W, et al. The pressor and metabolic effects of alcohol in normotensive subjects. *Hypertension*. 1986;8(7):625-631. PMID: 3522422.
6. Seppa K, Sillanaukee P. Binge drinking and ambulatory blood pressure. *Hypertension*. 1999;33(1):79-82. PMID: 9931085.
7. Rosito GA, Fuchs FD, Duncan BB. Dose-dependent biphasic effect of ethanol on 24-h blood pressure in normotensive subjects. *Am J Hypertens*. 1999;12(2):236-240. PMID: 10090355.
8. Bau PF, Bau CH, Naujorks AA, et al. Early and late effects of alcohol ingestion on blood pressure and endothelial function. *Alcohol*. 2005;37(1):53-58. PMID: 16472719.
9. Chiva-Blanch G, Urpi-Sarda M, Ros E, et al. Dealcoholized red wine decreases systolic and diastolic blood pressure and increases plasma nitric oxide: Short communication. *Circ Res*. 2012;111(8):1065-1068. PMID: 22955728.
10. Zilkens RR, Burke V, Hodgson JM, et al. Red wine and beer elevate blood pressure in normotensive men. *Hypertension*. 2005;45(5):874-879. PMID: 15837829.
11. Puddey IB, Beilin LJ, Vandongen R. Regular alcohol use raises blood pressure in treated hypertensive subjects. A randomised controlled trial. *Lancet*. 1987;1(8534):647-651. PMID: 2882082.

12. Mori TA, Burke V, Beilin LJ, et al. Randomized controlled intervention of the effects of alcohol on blood pressure in premenopausal women. *Hypertension*. 2015;66(3):517-523. PMID: 26123682.
13. Briasoulis A, Agarwal V, Messerli FH. Alcohol consumption and the risk of hypertension in men and women: A systematic review and meta-analysis. *J Clin Hypertens (Greenwich)*. 2012;14(11):792-798. PMID: 23126352.
14. Roerecke M, Tobe SW, Kaczorowski J, et al. Sex-specific associations between alcohol consumption and incidence of hypertension: A systematic review and meta-analysis of cohort studies. *J Am Heart Assoc*. 2018;7(13):e008202. PMID: 29950485.
15. Taylor B, Irving HM, Baliunas D, et al. Alcohol and hypertension: Gender differences in dose-response relationships determined through systematic review and meta-analysis. *Addiction.* 2009;104(12):1981-1990. PMID: 19804464.
16. Roerecke M, Kaczorowski J, Tobe SW, et al. The effect of a reduction in alcohol consumption on blood pressure: A systematic review and meta-analysis. *Lancet Public Health*. 2017;2(2):e108-e120. PMID: 29253389.
17. Mehta LS, Beckie TM, DeVon HA, et al. Acute myocardial infarction in women: A scientific statement from the American Heart Association. *Circulation*. 2016;133(9):916-947. PMID: 26811316.
18. Ronksley PE, Brien SE, Turner BJ, et al. Association of alcohol consumption with selected cardiovascular disease outcomes: A systematic review and meta-analysis. *BMJ*. 2011;342:d671. PMID: 21343207.
19. Leong DP, Smyth A, Teo KK, et al. Patterns of alcohol consumption and myocardial infarction risk: Observations from 52 countries in the Interheart case-control study. *Circulation*. 2014;130(5):390-398. PMID: 24928682.
20. Larsson SC, Wallin A, Wolk A, et al. Differing association of alcohol consumption with different stroke types: A systematic review and meta-analysis. *BMC Med*. 2016;14(1):178. PMID: 27881167.
21. Zheng YL, Lian F, Shi Q, et al. Alcohol intake and associated risk of major cardiovascular outcomes in women compared with men: A systematic review and meta-analysis of prospective observational studies. *BMC Public Health*. 2015;15:773. PMID: 26264040.
22. Jimenez M, Chiuve SE, Glynn RJ, et al. Alcohol consumption and risk of stroke in women. *Stroke*. 2012;43(4):939-945. PMID: 22403048.
23. Hirsch AT, Allison MA, Gomes AS, et al. A call to action: Women and peripheral artery disease: A scientific statement from the American Heart Association. *Circulation*. 2012;125(11):1449-1472. PMID: 22343782.
24. Fabsitz RR, Sidawy AN, Go O, et al. Prevalence of peripheral arterial disease and associated risk factors in American Indians: The Strong Heart Study. *Am J Epidemiol.* 1999;149(4):330-338. PMID: 10025475.
25. Vliegenthart R, Geleijnse JM, Hofman A, et al. Alcohol consumption and risk of peripheral arterial disease: The Rotterdam study. *Am J Epidemiol*. 2002;155(4):332-338. PMID: 11836197.
26. Piano MR, Phillips SA. Alcoholic cardiomyopathy: Pathophysiologic insights. *Cardiovasc Toxicol*. 2014;14(4):291-308. PMID: 24671642.
27. McKenna CJ, Codd MB, McCann HA, et al. Alcohol consumption and idiopathic dilated cardiomyopathy: A case control study. *Am Heart J*. 1998;135(5):833-837. PMID: 9588413.
28. Gavazzi A, De Maria R, Parolini M, et al. Alcohol abuse and dilated cardiomyopathy in men. *American J Cardiol*. 2000;85(9):1114-1118. PMID: 10781762.
29. Fauchier L, Babuty D, Poret P, et al. Comparison of long-term outcome of alcoholic and idiopathic dilated cardiomyopathy. *Eur Heart J*. 2000;21(4):306-314. PMID: 10653678.
30. Mogos MF, Salemi JL, Phillips SA, et al. Contemporary appraisal of sex differences in prevalence, correlates, and outcomes of alcoholic cardiomyopathy. *Alcohol Alcohol*. 2019;54(4):386-395. PMID: 31206165.
31. Fernández-Solà J, Estruch R, Nicolás JM, et al. Comparison of alcoholic cardiomyopathy in women versus men. *Am J Cardiol*. 1997;80(4):481-485. PMID: 9285662.
32. Urbano-Márquez A, Estruch R, Fernández-Solà J, et al. The greater risk of alcoholic cardiomyopathy and myopathy in women compared with men. *JAMA*. 1995;274(2):149-154. PMID: 7596003.
33. Altemus M, Sarvaiya N, Neill Epperson C. Sex differences in anxiety and depression clinical perspectives. *Front Neuroendocrinol*. 2014;35(3):320-330. PMID: 24887405.
34. Guy J, Peters MG. Liver disease in women: The influence of gender on epidemiology, natural history, and patient outcomes. *Gastroenterol Hepatol*. 2013;9(10):633-639. PMID: 24764777.
35. Wood AM, Kaptoge S, Butterworth AS, et al. Risk thresholds for alcohol consumption: Combined analysis of individual-participant data for 599,912 current drinkers in 83 prospective studies. *Lancet*. 2018;391(10129):1513-1523. PMID: 29676281.
36. Kalinowski A, Humphreys K. Governmental standard drink definitions and low-risk alcohol consumption guidelines in 37 countries. *Addiction*. 2016;111(7):1293-1298. PMID: 27073140.
37. Dietary Guidelines for Americans, 2015-2020. Washington, DC, US Department of Health and Human Services. https://www.dietaryguidelines.gov/
38. GBD 2016 Alcohol Collaborators. Alcohol use and burden for 195 countries and territories, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2018;392(10152):1015-1035. PMID: 30146330.

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Current Reviews

Alcohol Res. 2020;40(2):13 • https://doi.org/10.35946/arcr.v40.2.13

Published: 16 July 2020

Sleep and Alcohol Use in Women

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Sleep disturbance is common among individuals with alcohol use disorder (AUD). Insomnia not only is a pathway toward alcohol consumption but also is related to increased risk of relapse, psychosocial impairment, decreased quality of life, and suicidal ideation in individuals with AUD. Few studies examining sleep disturbance and alcohol use have explored how this relationship differs between men and women. Historically, studies of AUD have included few, if any, women in their samples. However, women are increasingly consuming alcohol at an earlier age and at higher rates, and the effect of alcohol on women's mental and physical health is expected to rise. This narrative review consolidates findings from studies that have reported the effects of acute and chronic alcohol use on sleep among women. Additional research is needed to investigate sex differences in this area. Such research should consider the modifying effects of age, lifetime alcohol use, and psychiatric co-occurrence, as well as the effectiveness of combined interventions for AUD and sleep disturbance.

KEY WORDS: adolescence; alcohol use disorder; circadian; sex differences; slow wave sleep; substance use

INTRODUCTION

Sleep disturbance is one of the most common complaints of individuals with alcohol use disorder (AUD), with prevalence estimates ranging from 36% to 91%.[1] Insomnia in particular has been associated with multiple aspects of AUD: relapse to drinking, psychosocial impairment (e.g., employment problems, social conflict, and impulse control), decreased quality of life, suicidal ideation, and insufficient sleep duration. (For

definitions of insomnia and other technical terms, see the box **Glossary of Sleep Terms.**) Sleep disturbance can serve as a pathway to increased alcohol use, in part because alcohol can be used as a sleep aid to reduce time to sleep onset. However, even acute alcohol consumption increases sleep disruption throughout the night, and tolerance to the sedating qualities of alcohol accumulates quickly.[2] In people with AUD, chronic alcohol use is related to changes in sleep structure that persist into abstinence. For abstinent individuals with AUD, this persistent sleep disturbance is a risk factor for relapse.[1] Once relapse occurs, the cycle repeats, as continued consumption of alcohol perpetuates sleep disturbance.

Historically, studies of AUD and sleep have mostly included men. Although women with AUD have been recruited for a handful of studies,[3-7] women have largely been underrepresented in the research that examines the relationship between sleep and alcohol use. Sex differences in the effects of alcohol are dependent on the interaction of many biopsychosocial factors. Sleep intertwines with several of these relationships: alcohol disrupts sleep, and sleep disturbance relates to increased risk of psychiatric co-occurrence, alcohol misuse, and relapse to AUD. In addition, sleep is a modifiable behavior.[8,9] Thus, understanding how sleep problems relate to problematic alcohol use and the extent to which this relationship differs between men and women can inform the development of targeted methods for prevention and treatment of AUD.

This narrative review aims to stimulate new research in this area by consolidating findings from studies that have reported effects of acute and chronic use of alcohol on sleep among women. First, an overview of sex differences in sleep disorders is provided, followed by considerations for how sex may modify the relationship between alcohol use and sleep. (For consistency, both biological and psychological/sociological/cultural factors are referred to as "sex"-related throughout the review.) The review concludes by providing treatment considerations and directions for future research.

SEX DIFFERENCES IN SLEEP

Sleep is a universal process across species and is a behavioral state that is essential to physical and mental health in humans. Changes in brain activity throughout the night demarcate different stages of sleep. This neuronal activity, along with muscle activity and eye movements, can be measured via polysomnography (PSG) to provide an objective measure of sleep. Sleep is divided into stages (N1, N2, and N3) of non–rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep.[10] Throughout the night, sleep follows a cyclical pattern. Each cycle begins with stage N1, and the majority of time is spent in stage N2 before progression to stage N3 (deep sleep) and eventually to REM sleep. Each cycle lasts approximately 90 minutes. More detailed analysis of the sleep electroencephalogram (EEG) is possible with spectral analysis to determine activity during sleep within a specific frequency band (e.g., slow wave activity).

PSG provides a detailed, objective measure of sleep architecture and quality but is mainly confined to the laboratory. Actigraphy (usually measured with devices worn on the wrist) relies on an accelerometer to measure patterns of activity from which sleep–wake states can be estimated.[11] Actigraphy is useful for objective assessments of sleep outside the laboratory environment. Self-perception of sleep quality is also valuable and can be measured over many nights with questionnaires or sleep diaries.

Glossary of Sleep Terms

Actigraphy: An objective measure of sleep quantity and circadian patterns that uses an accelerometer (generally worn like a wristwatch) to detect sleep–wake activity over several days or weeks.

Apnea-hypopnea index: An index used to indicate the severity of sleep apnea that is represented by the number of apnea and hypopnea events per hour of sleep.

Circadian period: The amount of time for a cyclical process to return to the same phase (e.g., from one day's waking to the next day's waking).

Circadian preference/ chronotype: An individual's tendency towards relatively earlier or relatively later sleep and activity patterns, typically measured via preferred timing (i.e., morningness versus eveningness) or self-reported actual timing (i.e., early versus late chronotype).

Circadian rhythm: An endogenous 24-hour rhythm, typically measured via levels of melatonin or by core body temperature.

Circadian timing: The timing of biological processes that follow a circadian rhythm (e.g., sleepiness, wakefulness, melatonin, body temperature).

Hypopnea: The partial blockage of air, resulting in decreased airflow and oxygen saturation.

Insomnia: A sleep disorder characterized by difficulty falling asleep or staying asleep, causing distress or impairment in daytime functioning.

K-complex: A high-voltage delta frequency EEG event seen in NREM sleep that occurs when large numbers of healthy neurons fire in a synchronized manner.

Non–rapid eye movement (NREM) sleep: The sleep stage characterized by slower, higher amplitude EEG activity, regular breathing and heart rate, muscle tone (i.e., low-level contraction), and a lack of eye movement; consists of stages N1, N2, and N3.

Polysomnography (PSG): A test conducted to study sleep and diagnose sleep disorders using a multitude of physiological measures, including measures of brain activity, blood oxygen levels, heart rate, breathing, and muscle movements.

Rapid eye movement (REM) sleep: The sleep stage characterized by low-amplitude, high-frequency EEG activity, rapid eye movement, irregular respiration and heart rate, and muscle atonia.

Sleep apnea: A sleep disorder in which breathing is repeatedly interrupted during sleep.

Sleep architecture: The structural organization of sleep, such as cyclical alternation of NREM and REM sleep stages.

Sleep behavior: Self-report measures from questionnaires that typically ask about sleep over a period of weeks or months.

Sleep-disordered breathing: An umbrella term that encompasses breathing disorders and respiratory abnormalities that occur during sleep, including sleep apnea and snoring.

Sleep efficiency: The total number of minutes of sleep divided by the number of minutes in bed.

Sleep electroencephalogram (EEG): A recording of brain activity during sleep.

Sleep onset latency: The number of minutes to fall asleep after the lights are turned off.

Sleep timing: The times of day an individual goes to sleep and wakes up.

Slow wave activity: EEG activity in the delta (slow wave) band (0.5 Hz to 4.0 Hz), typically averaged separately for NREM and REM sleep for the entire night.

Slow wave sleep: The deepest stage of NREM sleep (stage N3), characterized by more than 20% delta wave EEG activity.

Stage N1: The lightest stage of sleep, which occurs right after falling asleep; characterized by low-voltage, fast EEG activity.

Stage N2: The intermediate stage of sleep that follows stage N1; characterized by theta activity (4-7 Hz), K-complexes, and bursts of faster activity on EEG.

Stage N3: The deepest stage of sleep; characterized by high-amplitude slow waves on EEG.

Total sleep time: The total number of minutes asleep.

Total wake time: The total number of minutes awake during the sleep period.

Wake after sleep onset: The number of minutes awake after falling asleep.

Differences in Sleep Measures

Women tend to have better sleep quality, as measured by PSG, than men. Women have less total wake time, shorter sleep onset latency, better sleep efficiency, and a larger percentage of slow wave sleep and slow wave activity (for definitions of these sleep measurements, see the box **Glossary of Sleep Terms**).[12] The prevalence of sleep-disordered breathing is 9% among women versus 24% in men. However, women with sleep-disordered breathing are more likely to present with initial symptoms of insomnia or fatigue rather than the typical symptoms associated with sleep-disordered breathing, such as snoring, daytime sleepiness, and witnessed apneic events.[13]

Although PSG is considered the gold standard of sleep measurement, it has limitations. PSG cannot capture habitual sleep duration under naturalistic settings and may miss subcortical brain activity (particularly in regions shown to be involved in conscious awareness) that may be more prominent in individuals with insomnia than in those who sleep well.[14] Although not yet examined, possible sex differences in subcortical brain activity during sleep may explain the finding that women report poorer subjective sleep quality than men despite having better PSG-based sleep quality.

When using subjective measures, women report more sleep problems than men, including disrupted and insufficient sleep, poor sleep quality, difficulty falling asleep, frequent night awakenings, and time awake during the night.[15,16] Women also have a 40% greater risk of insomnia[12] and report earlier sleep timing (i.e., bedtime and wake time) than men.[17] Potential reasons for sex differences in sleep are described briefly in this review. For more detailed discussions, see the reviews by Mong and Cusmano[12] and Krishnan and Collop.[13]

Biological Differences

Sex steroids (i.e., testosterone in men and estrogen and progestins in women) modulate sleep differently. Generally, women's sleep is more sensitive to changes in ovarian steroids.[12] For example, sex hormones modulate the orexin/hypocretin system, which plays an important part in regulating sleep and wake states.[18] Therefore, fluctuations in ovarian steroids in women (e.g., puberty, menstrual cycle, menopausal transition) are associated with changes in sleep and circadian rhythms[19] and increased prevalence of sleep disturbance.[20,21] In addition, among men and women with similar sleep timing and duration, women have a shorter circadian period and earlier circadian timing of endogenous temperature and melatonin rhythms.[12] (For definitions of these circadian terms, see the box **Glossary of Sleep Terms.**) This mismatch in sleep timing and circadian timing can cause sleep disturbance, such as problems with sleep maintenance and/or early morning awakening, which, in part, may underlie women's increased risk for insomnia.

Psychosocial Differences

Among women, those with more anxiety and more perceived nighttime awakenings also report worse subjective sleep quality, despite a lack of objectively measured sleep disturbance.[12] Anxiety and depression are both more prevalent among women and are strongly associated with insomnia. The risk of affective disorders increases at the onset of puberty, especially among girls.[22]

ALCOHOL AND SLEEP

Sex differences occur in sleep continuity and sleep architecture measures as well as in the prevalence of sleep disorders like insomnia and obstructive sleep apnea. Sex differences also have been reported in alcohol use patterns, biological effects of alcohol, and risk factors for heavy alcohol use. Alcohol use likely affects sleep systems differently in men and women, and pathways that link sleep disturbances with subsequent heavy alcohol use also may differ according to sex. In this section, we review the evidence for sex differences in bidirectional relationships between sleep quality and alcohol use (although directionality is not always clear when based on findings from observational or cross-sectional studies).

Sleep and wake states are regulated by complex patterns of neurotransmitter release and

neural activation, many of which are affected by alcohol.[23] Individuals who have trouble sleeping may initiate alcohol use as a sleep aid. Because alcohol affects the gamma-aminobutyric acid (GABA) neurotransmitter system, alcohol acts as a sedative and reduces time to sleep onset, increases slow wave sleep, and suppresses REM sleep in the first half of the night.

Alcohol has acute neurotoxic effects that affect receptors important for sleep generation. As alcohol metabolizes (at 7 grams per hour, on average), its sedating benefits diminish.[24] Later in the night, sleep becomes more disrupted and awakenings are more frequent. Thus, the effects of alcohol on sleep differ depending on which half of the night is examined. Chronic alcohol exposure damages nerve cells and fibers, reducing the likelihood of synchronized neuronal firing across the cortex, which is necessary for slow wave sleep. With prolonged use, neurotransmitter systems adapt and modulate their release, which can increase sleep disruption and change sleep architecture, sometimes permanently.[23,25]

Studies (mostly among men) indicate that these changes in sleep structure persist during abstinence, and disturbed sleep is a risk factor for relapse.[1] Therefore, sleep disturbance has been suggested as a target for treatment, potentially decreasing the risk of problematic alcohol use while also increasing the likelihood of abstinence.

Sleep Architecture

This section examines studies (which included women participants) of both the acute and chronic effects of alcohol on sleep architecture. To the extent possible, results from experimental studies are emphasized.

Effects of acute alcohol use

First, we present studies that primarily used PSG to examine the acute effects of alcohol on sleep architecture. These experiments provide some evidence of directionality in the relationship between alcohol use and subsequent sleep quality. One of the first studies to investigate the effect of acute alcohol use on sleep, specifically in young women, was conducted by Williams and colleagues.[26] As part of this double-blind trial, 11 healthy women (ages 18 to 21) completed several nights of PSG an hour after consuming a beverage with either 0.00, 0.50, or 0.75 grams of alcohol per kilogram of body weight (g/kg). Results were consistent with previous findings reported for men. As the alcohol dose increased, sleep onset latency decreased. A significant decrease in the percentage of REM sleep was found, which was most apparent in the first 3 hours of the night. Also, a dose-dependent increase in slow wave sleep during the first half of the night was found, followed by a decrease in slow wave sleep in the second half of the night. Furthermore, these women demonstrated a dose-dependent increase in the percentage of stage N1 sleep, with increased minutes spent in stage N1 sleep in the second half of the night.

A later study conducted by Van Reen and colleagues examined the extent that a moderate dose of alcohol (0.49 g/kg), compared to placebo, consumed an hour before bedtime affected the sleep and sleep EEG of 7 women (ages 22 to 25).[27] Similar to the findings reported for men,[23] this study reported that alcohol consumption led to an increase in slow wave sleep (in the first 2 hours) and an overall decrease in REM sleep.[27] Also, frontal EEG power during NREM sleep in the alpha range (9 to 11 Hz) increased relative to placebo following alcohol consumption.

In a direct evaluation of sex differences, Arnedt and colleagues performed PSG for 93 healthy adults (ages 21 to 31, 59 were female) following alcohol intoxication.[28] For this double-blind, randomized trial, all participants received alcohol on one night and placebo on another night, 1 week apart. Participants were given either placebo or alcohol (1.2 g⁄kg for men and 1.1 g⁄kg for women) 1 to 2.5 hours before bed. The alcohol dose was adjusted for weight and sex such that breath alcohol concentration (BrAC) levels were equivalent in men and women. At bedtime on the alcohol night, women reported higher ratings of sleepiness than men. Despite reaching equivalent BrACs, sleep continuity was more disrupted in women than in

men. For women, the total sleep time decreased by 20 minutes relative to the placebo night, and the wake after sleep onset time increased by 15 minutes. In addition, among women participants, the frequency of awakenings increased, and overall sleep efficiency decreased by 4% after alcohol intoxication. In men, no significant differences in sleep continuity measures (i.e., sleep onset latency, total sleep time, sleep efficiency, frequency of nighttime awakenings, and wake after sleep onset) between the placebo and alcohol conditions were reported. For both sexes, sleep architecture variables differed for the alcohol condition compared to the placebo condition—alcohol use increased slow wave sleep and decreased REM sleep.

Chan and colleagues also examined the effects of acute alcohol consumption (a mean dose of 0.828 g/kg an hour before bedtime) on the sleep architecture of 24 older adolescents (ages 18 to 21, 12 were female).[29] They found main effects of alcohol on sleep, dependent on halves of the night. In the first half of the night, participants experienced fewer arousals, less stage N1 sleep, increased slow wave sleep, and reduced REM sleep. In the second half of the night, they experienced less sleep efficiency and more time awake after sleep onset. These researchers did not find evidence for an interaction between sex and alcohol.

Effects of chronic alcohol use

The following studies are observational, such that they examine sleep among individuals with a history of chronic alcohol use in the context of many other variables. Individuals in these studies vary regarding the duration of their abstinence at the time of study, their co-occurring disorders, and their lifetime alcohol use. When participants were examined early (at less than 1 month) during recovery, the effects on sleep may have reflected the effects of withdrawal more than any chronic effects of heavy alcohol use. When participants were examined later during recovery, withdrawal effects would have subsided. Therefore, the associations observed do not prove causality in these relationships, but they provide a starting point to stimulate further research that may better distinguish directionality.

Colrain and colleagues collected sleep architecture and EEG measures from 42 abstinent participants (mean age of 49, 15 were women) with long-term AUD and from 42 control participants (mean age of 51, 23 were women).[5] Overall, women had better sleep efficiency, fewer periods of in-bed awake time, and more slow wave activity during NREM sleep than men. There were main effects of AUD for some sleep measures. For example, individuals with AUD had less slow wave sleep and slow wave activity during NREM sleep and more stage N1 and REM sleep than controls.

Despite a lack of significant interaction between sex and diagnosis, women with AUD and women control participants had similar amounts of NREM slow wave activity, whereas men with AUD had substantially lower NREM slow wave activity than men control participants.[5] Women with AUD had lower levels of lifetime alcohol consumption and longer periods of sobriety when compared with the men who had AUD in this study. Although greater estimated lifetime alcohol consumption was related to a lower percentage of slow wave sleep in men, this measure was not related to the percentage of slow wave sleep in women. This study did not investigate sex interaction effects, and the samples of women and men with AUD were unequal sizes, had varying lengths of sobriety, and had different levels of lifetime alcohol exposure.

Using the same sample, Colrain and colleagues examined K-complex incidence and amplitude during sleep.[6] K-complexes are high-voltage, delta frequency events that occur during NREM sleep when large numbers of healthy neurons fire together at the same time. They provide a sensitive measure of typical, healthy, brain aging. In this study, participants with AUD had both reduced K-complex incidence and amplitude. Men and women also showed the same pattern of AUD-related change in K-complex amplitude, despite women having less lifetime alcohol consumption.

In a sample that included 26 participants (ages 32 to 63, 10 were women) with alcohol dependence who were in subacute withdrawal from alcohol and 23 control participants (ages 24 to 61, 9 were women), overall, women spent a larger proportion of time awake during the sleep period, and they had shorter time to REM sleep.[7] The relationships between sleep parameters and group did not vary by sex; however, this analysis may have been underpowered because of the sample size. The investigators noted that the distribution of sex across groups was not equal.

A population-based study of sleep among 400 Swedish women (ages 20 to 70) found that women who self-reported alcohol dependence had longer sleep onset latency, reduced REM sleep, and more stage N2 sleep compared to women who did not report alcohol dependence.[30] In addition, alcohol dependence was related to decreased time spent in REM sleep and increased sleep onset latency, independent of age, body mass index, apnea-hypopnea index, smoking, and hypertension.

Summary

Sleep is a complex neurological function, and the extent that it may be affected after a single night of alcohol compared to chronic alcohol misuse can differ. Thus, sex differences in the acute effects of alcohol may not necessarily coincide with sex differences in the chronic effects of alcohol. The single experimental study that examined sex differences in the effect of acute alcohol consumption found sex differences in objectively measured sleep among healthy subjects (with equivalent BrAC levels before sleep), with women showing more disrupted sleep than men.[28]

Sex differences in alcohol pharmacokinetics may underlie these differences. Even at equivalent starting points, BrAC levels decline more rapidly for women than for men.[28] As alcohol metabolizes, alcohol metabolites disrupt sleep. Chronic alcohol misuse leads to changes in brain macrostructure and microstructure that can manifest as sleep disturbance.[25] Few studies have examined sleep in both men and women during recovery from AUD, and those studies have not had sample sizes large enough to statistically examine sex differences.

Further study is needed to examine potential sex differences in sleep among individuals with AUD who are abstinent. Dose effects, time in recovery, and the effects of interaction between age and sex should be considered. Sleep structure changes across age, and these changes vary by sex.[31] For example, women have a greater amount of slow wave activity than men, and although men tend to show a decrease in slow wave activity with age, women do not show the same pattern of decline.[12]

Sleep Physiology

Limited experimental work has examined whether the effects of alcohol on the functioning of physiological systems (e.g., respiratory or cardiovascular) during sleep differ according to sex.

Effects of acute alcohol use

In an investigation of the acute effects of alcohol, Block and colleagues monitored breathing and oxygenation during sleep for 78 participants (20 were men ages 20 to 40 years, 20 were men ages 40 years and older, 20 were women ages 20 to 40, and 18 were postmenopausal women ages 51 to 66) following consumption of 2 milliliters of alcohol per kilogram of body weight.[32] Men in both groups had more oxygen desaturation episodes across the night and greater severity of desaturation, but no effect of alcohol on breathing or oxygenation was found for either group of women. As expected, postmenopausal women had significantly more episodes of apnea and oxygen desaturation than premenopausal women, although this difference was unrelated to alcohol consumption.

A large, observational study of 1,420 men and women (mean age of 51, 645 were women) demonstrated similar findings.[33] Men showed increased likelihood of sleep-disordered breathing for each drink consumed per day (measured via a self-report questionnaire), whereas no association between minimal to moderate alcohol consumption and sleep-disordered breathing

was found for women. The investigators posited that circulating progesterone may protect young women in particular from the depressant effects of alcohol and consequent sleep apnea and oxygen desaturation,[32,34] and that hormonally mediated increased ventilatory drive and anatomical differences may also protect women from sleep-disordered breathing events.[33,35,36] Since alcohol had no effect on breathing for postmenopausal women, other nonhormonal factors may have played a role in the sex differences related to sleep-disordered breathing and alcohol consumption.

Effects of chronic alcohol use

A study of 24 patients with chronic AUD who were recently abstinent (10 were women ages 25 to 58) compared with 24 control participants (10 were women ages 25 to 58) showed that both males and females with AUD had a high number of observed apneic/hypopneic episodes, and this result did not differ by sex.[37] The researchers concluded that women with AUD were as likely as men with AUD to have a sleep-related breathing disorder.

In a study investigating autonomic nervous system functioning during sleep, de Zambotti and colleagues found that patients with AUD who were recently sober (n = 14, 7 were women ages 28 to 54) compared with healthy control participants (n = 16, 8 were women ages 30 to 62) had elevated heart rates, reduced total heart rate variability, and reduced high-frequency activity (a measure of vagal functioning) across the night.[4] Together, this pattern of findings indicates disrupted autonomic nervous system functioning during the night, providing compelling evidence of impaired cardiovascular functioning during sleep. Effects did not differ by sex, and women with AUD, despite having less lifetime alcohol consumption, were affected to the same extent as men with AUD. In a follow-up investigation across the first few months of abstinence, as the duration of abstinence increased, individuals with AUD showed substantial recovery in heart rate and vagal functioning during sleep, although examination of any modifying effect by sex was not possible in this small sample.[3]

Periodic limb movements can also contribute to disturbed sleep. Aldrich and Shipley found that periodic limb movements were more likely to occur at a clinically significant frequency among adults ages 19 to 81 who self-reported consuming 2 or more drinks per day (heavy users, n = 112, 24 were women) when compared with adults who consumed less than 2 drinks per day (abstainers and light to moderate users, n = 872, 317 were women).[38] In addition, women who were heavy users were more likely to report symptoms of periodic limb movements than women who were light users, whereas no difference was observed between the two groups of men.

Summary

For physiological measures, the evidence from one large, experimental study suggests that acute alcohol consumption does not affect women's breathing during sleep to the same extent it does for men, who demonstrate more oxygen desaturation events during the night. Also, among men, self-reported alcohol use is positively associated with greater likelihood of sleep-disordered breathing, although this relationship is not observed in women. However, women with AUD are just as likely as men to have sleep-disordered breathing.[37]

Women may be more susceptible to periodic limb movements, and alcohol use could be a potential trigger of these movements. Also, women who experience periodic limb movements may self-medicate with alcohol. One study with a small sample size suggested that chronic alcohol use may affect cardiovascular functioning in women more than it does in men, as women and men did not differ in these measures despite women having less lifetime alcohol consumption.

These results are consistent with other studies that have demonstrated that women are at greater risk of alcohol-induced cardiomyopathy and peripheral neuropathy despite fewer years of drinking and lower quantities of alcohol consumption.[39] Given that two of these studies examined men and women early during their recovery,[4,37] some of the effects found could reflect

residual withdrawal effects of alcohol. Further longitudinal studies across a period of recovery among men and women with AUD are needed to separate effects of alcohol withdrawal and chronic heavy alcohol use on sleep as well as on physiological measurements taken during sleep.

Self-Reported Sleep Behavior

Many individuals report using alcohol as a sleep aid,[40,41] even though the use of alcohol to help initiate sleep can further perpetuate sleep disturbance. In women older than age 60, using alcohol to sleep and shorter sleep onset latency each are associated with greater risk for alcohol misuse.[42] However, moderate alcohol use is associated with fewer insomnia symptoms in women, but not in men, older than age 65.[43]

In a study of healthy men and women, self-reported insomnia symptoms at baseline were associated with greater odds of heavy drinking at a 5-year follow-up.[44] Likewise, heavy drinking and binge drinking at baseline were associated with greater odds of insomnia symptoms at a 5-year follow-up. Although results specific to sex were not reported, the investigators noted that these associations were similar among men and women but reached statistical significance only for women.

Some epidemiological studies have considered associations between alcohol use and insomnia symptoms among women in midlife and after menopause, an age group in which sleep problems are common. Blümel and colleagues reported that troublesome drinking (assessed with the Brief Scale of Abnormal Drinking) in a group of women ages 40 to 59 was strongly associated with increased risk for insomnia symptoms more than other factors, including mood and vasomotor symptoms, education level, and use of hypnotics.[45] In contrast, frequency of alcohol use (i.e., not currently, occasionally, or regularly in the past week) was not associated with sleep disturbances in a group of postmenopausal women ($N = 322$, ages 60 to 70).[46] These findings show that relationships between alcohol use and insomnia for women may differ depending on whether frequency of alcohol use or troublesome drinking are examined.

A large, longitudinal study of 9,941 Norwegian adults (53.6% were women) found that men reporting high levels of alcohol consumption at baseline were at higher risk of reporting sleeplessness at a follow-up 13 years later.[47] Similarly, men who experienced sleeplessness at baseline also were at higher risk of reporting high levels of alcohol consumption at the follow-up, demonstrating the bidirectionality of associations between sleep problems and alcohol use. In contrast, no such relationships were found for women.

A population-based study of 3,450 French adults (52.4% were women ages 18 to 64) reported that drug use for insomnia (prescription or nonprescription) was associated with alcohol misuse among men but not among women.[48] The only study of insomnia prevalence among individuals in treatment for AUD found that women and men reported similar rates of insomnia symptoms, despite a larger prevalence of insomnia among women in the general population.[49] Also, insomnia symptoms at baseline were significantly associated with relapse to AUD for both men and women.

The extant data are mixed regarding whether women show differential risk for associations between self-reported sleep disturbance and alcohol use. However, these observational studies, which rely entirely on self-report methods to measure both alcohol use and sleep disturbance, use different questionnaires and, in some cases, use measures limited to a single item. More research is needed to characterize the relationship between sleep behavior and alcohol use among women, especially studies that help distinguish sleep problems as predictors of relapse and alcohol use as a predictor of insomnia. Further investigation should use more comprehensive, frequent measures of sleep behavior (e.g., sleep diaries) potentially combined with objective measures (e.g., actigraphy) and measures of alcohol consumption to better characterize sex differences in these relationships.

Sleep as a Predictor of Adolescent Alcohol Use

As early as childhood, self-reported sleep problems are related to onset of substance use in adolescence.[50] In the first prospective study of sex differences in this relationship, Wong and colleagues found that sleep problems in childhood were a significant predictor of onset of drinking in both boys and girls but at earlier ages for boys (8 to 14) than girls (15 to 17).[51] In a large, community-based sample of 7,507 children and adolescents in Hong Kong (48.5% were females ages 6 to 17), Zhang and colleagues found that boys with insomnia symptoms were more likely to report regular consumption of alcohol (sometimes or often), whereas no such relationship was found for girls.[52]

In a population-based study of 4,187 Finnish adolescents (51.8% were females ages 11 to 15), perceived tiredness was related to increased likelihood of drinking and smoking for boys, but for girls it was only related to an increased likelihood of smoking.[53] In contrast, in a large sample of 13,381 U.S. adolescents (48.8% were females ages 12 to 17), there was a stronger relationship between subjective sleep problems and substance use in general (i.e., use of cigarettes, alcohol, or illicit drugs) for girls than for boys.[54]

Unpublished data from Hasler and colleagues (2017) suggest that in a sample of 729 adolescents (368 were females ages 12 to 21) from the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA) study, females with worse sleep quality were more likely to report binge alcohol use at baseline. However, males with worse sleep quality at baseline were at a greater risk of worsening binge alcohol use a year later.

Emerging data from longitudinal studies that track sleep patterns in adolescents before the onset of alcohol use suggest there may be sex differences in the relationships between sleep behaviors and alcohol use.[50] However, further data are required before definitive conclusions can be reached. Such work is needed to determine sex differences in the directionality of the relationships between substance use and sleep and circadian factors, as well as the underlying mechanisms of these relationships.

Sleep and Circadian Timing

Circadian rhythm disturbance can underlie sleep problems, and alcohol use alters many circadian functions (e.g., blood pressure, body temperature, hormone release).[55] Proper assessments of melatonin level, cortisol level, or body temperature, which are validated methods for measuring circadian rhythm, require rigorous laboratory protocols conducted over multiple hours to days and, thus, are not always feasible. Measurements of circadian preference (i.e., morningness-eveningness), chronotype, or sleep timing can serve as proxies for direct measures of circadian patterns of sleep–wake activity. To our knowledge, no studies have directly examined whether sex moderates the relationship between alcohol use and circadian rhythms in humans. One preclinical study that used mice with a knockout of adenosine equilibrative nucleotide transporter type 1 (ENT1), which is associated with both AUD and circadian/sleep disruptions, showed that circadian rhythm disruption increased alcohol consumption in male but not female mice,[56] suggesting that further investigation of sex differences in this area is warranted in humans.

Although more bona fide circadian research is needed, proxies for circadian rhythm, such as eveningness and late chronotype, consistently are associated with more alcohol use and problems with alcohol.[57] On average, women tend towards a relatively earlier sleep and activity pattern (i.e., morningness/early chronotype), which theoretically might lower the risk of alcohol use associated with circadian factors.

Hasler and colleagues investigated the effect of sleep timing on response to alcohol among 148 young adults (50 were women ages 21 to 35).[58] In males (White males only) but not in females, later sleep timing and greater eveningness preference were associated with a greater self-reported stimulating effect of alcohol immediately following alcohol consumption. In addition, greater variability in sleep duration was related to

greater sedation following alcohol consumption for both men and women. Further work is needed to examine links between circadian factors and heavy alcohol use, particularly among adolescents, to establish potential sex-specific predictors of alcohol use.

CLINICAL CONSIDERATIONS AND TREATMENT

Some sleep abnormalities may predate the effects of alcohol and also may differ between men and women. In addition, the prevalence of different sleep disorders must be taken into consideration. As already described, women are 40% more likely to develop insomnia than men.[20] Individuals may be vulnerable to the development of insomnia for a variety of reasons.[1] Predisposing factors such as genetics (e.g., *CLOCK* gene polymorphism or family history of AUD), childhood trauma, and childhood sleep problems increase an individual's risk of developing insomnia. Precipitating factors are stress-promoting events that trigger acute insomnia. Perpetuating factors are maladaptive compensatory behaviors, such as reading in bed or drinking alcohol, used to cope with sleep difficulty. Screening women for sleep problems may help providers intervene before problematic use of alcohol develops or may increase the likelihood of maintaining abstinence.

Pathways toward alcohol use vary developmentally, and sleep characteristics during childhood and adolescence predict risk for onset of alcohol use and misuse.[59] Childhood sleep problems are related to the onset of alcohol use in adolescence; therefore, treating sleep problems early in life may confer some benefit by delaying the onset of alcohol use. Furthermore, sleep disorders often manifest during reproductive transitions (e.g., puberty, pregnancy, menopause).

Females tend to develop insomnia after puberty, and the later sleep timing that occurs during puberty is positively associated with alcohol use.[16] Addressing the sleep disturbances of pregnant women is especially important. Alcohol consumption during pregnancy acutely affects fetal sleep behavior, and research suggests that prenatal alcohol exposure is related to persistent sleep disruption in affected children.[60] For many women, sleep disturbance and complaints of insomnia increase during and after the menopause transition.[12] The sleep changes related to aging, hormonal fluctuations, and psychological adjustment may contribute to women in this age group being particularly vulnerable to developing AUD.[61]

Improved understanding of the mechanisms by which these hormones modulate sleep may help guide development of novel therapies for treatment of problematic alcohol use. Such studies will help health care providers make informed decisions about medications (and dosages) and behavioral interventions that will be effective for treating sleep problems among women with AUD.

Cognitive behavioral therapy for insomnia is the first line of treatment for insomnia and is equally effective for men and women.[8,62] This nonpharmacological treatment method focuses on behaviors, cognitions, and associations that contribute to poor sleep.[63] The therapy uses a combination of sleep restriction (i.e., limiting time spent awake in bed), stimulus control, sleep hygiene (that is, healthy sleep habits such as consistent bed and wake times, comfortable bedroom environment, or avoiding caffeine and alcohol before bedtime), and cognitive therapy to address distorted beliefs about sleep. Up to 80% of patients benefit from this therapy, and treatment effects are maintained at follow-up a year later.[9] Pharmacotherapy is the next evidence-based approach for treatment of sleep disturbance, and it often is used in conjunction with cognitive behavioral therapy for insomnia, although it can be contraindicated for individuals with AUD.

Although women tend to have better long-term treatment outcomes than men, they are less likely to receive services specifically for alcohol-related issues, and they are more likely to seek treatment in settings that are not alcohol specific.[39] Educating health care providers in the primary

care setting to screen women for AUD and sleep problems may help reduce the stigma many women face when seeking appropriate treatment for AUD.

In addition, management of sleep problems is not typically a first line of treatment for individuals with AUD, despite the association between insomnia symptoms and increased risk of relapse. Sleep is a modifiable behavior that, if improved, may have downstream benefits for other health outcomes.[23] Medication trials (e.g., trazodone, gabapentin, quetiapine) have shown mixed efficacy and can be contraindicated in individuals with AUD, whereas behavioral treatments for insomnia consistently have been more effective in treating sleep problems, with moderate to large effect sizes.[1]

Treating sleep problems early may reduce risk for subsequent AUD. Considering that for women depressive symptoms predict alcohol consumption, cognitive behavioral therapy for both insomnia and depression may help prevent problematic alcohol use with two points of intervention. Although cognitive behavioral therapy for insomnia has not been shown to differentially improve alcohol outcomes,[64,65] more randomized controlled trials are warranted. This therapy has already shown promise as a treatment for insomnia among individuals with AUD, and men and women with no AUD respond to the therapy equally well.[66] It will be valuable for future studies to investigate the utility of cognitive behavioral therapy for insomnia and of other treatments that aim to improve sleep in individuals with AUD, as well as to examine whether these treatments are equally effective in men and women.

FUTURE DIRECTIONS AND CONCLUSION

Suggested areas for future research on sex differences related to alcohol and sleep include examination of:

- Alcohol's neurotoxic effects on circuits important for sleep generation
- Sleep during sustained abstinence from alcohol
- Cardiovascular functioning at night following alcohol use
- Alcohol use and its relationships with circadian misalignment and shiftwork
- Hormonal change and reproductive phase (e.g., puberty, the menstrual cycle, pregnancy, menopause) effects on alcohol use and sleep
- Other demographic factors (e.g., age, race, ethnicity, socioeconomic status) and how they affect alcohol use and sleep
- Longitudinal studies of sleep before initiation of alcohol use and across the course of recovery in individuals with AUD who are abstinent
- Cognitive behavioral therapy for insomnia and other treatment efficacy and effectiveness in improving sleep for individuals with AUD

Women historically have been underrepresented in research studies on alcohol use and sleep. Although AUD currently is more prevalent among men, the male/female differences in patterns of alcohol consumption are converging. Now, more than ever, sex differences need to be considered in all aspects of alcohol research. Only a small body of literature has investigated sex differences or interactions with sex in relation to sleep outcomes and alcohol use, making it challenging to draw definitive conclusions from the research thus far. Sleep and alcohol use vary by race and ethnicity,[67] and further research examining these characteristics in the context of sex differences is needed.

In addition to understanding sex differences in the relationship between alcohol and sleep, understanding the consistencies in the effects of alcohol on sleep among men and women is important. Alcohol has the same detrimental effects on many aspects of sleep and sleep physiology, regardless of sex. Given that sleep disturbance is so commonly reported by individuals with AUD, and the strong associations among sleep, daytime functioning, and mental and physical health, understanding how these relationships might differ in women compared to men is crucial to developing targeted and appropriate treatment recommendations.

Acknowledgments

This article was supported by National Institutes of Health grants F31AA027148, R01AA025626, R01AA026249, U01AA021696, and U01DA041022. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Financial Disclosure

The authors declare no competing financial interests.

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References

1. Chakravorty S, Chaudhary NS, Brower KJ. Alcohol dependence and its relationship with insomnia and other sleep disorders. *Alcohol Clin Exp Res*. 2016;40(11):2271-2282. https://doi.org/10.1111/acer.13217.
2. Roehrs T, Roth T. Insomnia as a path to alcoholism: Tolerance development and dose escalation. *Sleep*. 2018;41(8). https://doi.org/10.1093/sleep/zsy091.
3. de Zambotti M, Willoughby AR, Baker FC, et al. Cardiac autonomic function during sleep: Effects of alcohol dependence and evidence of partial recovery with abstinence. *Alcohol*. 2015;49(4):409-415. https://doi.org/10.1016/j.alcohol.2014.07.023.
4. de Zambotti M, Baker FC, Sugarbaker DS, et al. Poor autonomic nervous system functioning during sleep in recently detoxified alcohol-dependent men and women. *Alcohol Clin Exp Res*. 2014;38(5):1373-1380. https://doi.org/10.1111/acer.12384.
5. Colrain IM, Turlington S, Baker FC. Impact of alcoholism on sleep architecture and EEG power spectra in men and women. *Sleep*. 2009;32(10):1341-1352. https://doi.org/10.1093/sleep/32.10.1341.
6. Colrain IM, Crowley KE, Nicholas CL, et al. The impact of alcoholism on sleep evoked delta frequency responses. *Biol Psychiatry*. 2009;66(2):177-184. https://doi.org/10.1016/j.biopsych.2008.10.010.
7. Feige B, Scaal S, Hornyak M, et al. Sleep electroencephalographic spectral power after withdrawal from alcohol in alcohol-dependent patients. *Alcohol Clin Exp Res*. 2007;31(1):19-27. https://doi.org/10.1111/j.1530-0277.2006.00260.x.
8. Morin CM, Culbert JP, Schwartz SM. Nonpharmacological interventions for insomnia: A meta-analysis of treatment efficacy. *Am J Psychiatry*. 1994;151(8):1172-1180. https://doi.org/10.1176/ajp.151.8.1172.
9. Smith MT, Perlis ML, Park A, et al. Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia. *Am J Psychiatry*. 2002;159(1):5-11. https://doi.org/10.1176/appi.ajp.159.1.5.
10. American Academy of Sleep Medicine. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications*. Darien, IL: American Academy of Sleep Medicine; 2007.
11. de Zambotti M, Cellini N, Goldstone A, et al. Wearable sleep technology in clinical and research settings. *Med Sci Sports Exerc*. 2019;51(7):1538-1557. https://doi.org/10.1249/MSS.0000000000001947.
12. Mong JA, Cusmano DM. Sex differences in sleep: Impact of biological sex and sex steroids. *Philos Trans R Soc Lond B Biol Sci*. 2016;371(1688):20150110. https://doi.org/10.1098/rstb.2015.0110.
13. Krishnan V, Collop NA. Gender differences in sleep disorders. *Curr Opin Pulm Med*. 2006;12(6):383-389. https://doi.org/10.1097/01.mcp.0000245705.69440.6a.
14. Kay DB, Karim HT, Soehner AM, et al. Subjective-objective sleep discrepancy is associated with alterations in regional glucose metabolism in patients with insomnia and good sleeper controls. *Sleep*. 2017;40(11). https://doi.org/10.1093/sleep/zsx155.
15. Lindberg E, Janson C, Gislason T, et al. Sleep disturbances in a young adult population: Can gender differences be explained by differences in psychological status? *Sleep*. 1997;20(6):381-387. https://doi.org/10.1093/sleep/20.6.381.
16. Zhang B, Wing YK. Sex differences in insomnia: A meta-analysis. *Sleep*. 2006;29(1):85-93. https://doi.org/10.1093/sleep/29.1.85.
17. Roenneberg T, Kuehnle T, Juda M, et al. Epidemiology of the human circadian clock. *Sleep Med Rev*. 2007;11(6):429-438. https://doi.org/10.1016/j.smrv.2007.07.005.
18. Silveyra P, Cataldi NI, Lux-Lantos V, et al. Gonadal steroids modulated hypocretin/orexin type-1 receptor expression in a brain region, sex and daytime specific manner. *Regul Pept*. 2009;158(1-3):121-126. https://doi.org/10.1016/j.regpep.2009.08.002.
19. Baker FC, Driver HS. Circadian rhythms, sleep, and the menstrual cycle. *Sleep Med*. 2007;8(6):613-622. https://doi.org/10.1016/j.sleep.2006.09.011.
20. Mallampalli MP, Carter CL. Exploring sex and gender differences in sleep health: A Society for Women's Health Research Report. *J Womens Health (Larchmt)*. 2014;23(7):553-562. https://doi.org/10.1089/jwh.2014.4816.
21. Baker FC, de Zambotti M, Colrain IM, et al. Sleep problems during the menopausal transition: Prevalence, impact, and management challenges. *Nat Sci Sleep*. 2018;10:73-95. https://doi.org/10.2147/NSS.S125807.
22. Camhi SL, Morgan WJ, Pernisco N, et al. Factors affecting sleep disturbances in children and adolescents. *Sleep Med*. 2000;1(2):117-123. https://doi.org/10.1016/s1389-9457(99)00005-2.
23. Koob GF, Colrain IM. Alcohol use disorder and sleep disturbances: A feed-forward allostatic framework. *Neuropsychopharmacology*. 2020;45(1):141-165. https://doi.org/10.1038/s41386-019-0446-0.
24. Cederbaum AI. Alcohol metabolism. *Clin Liver Dis*. 2012;16(4):667-685. https://doi.org/10.1016/j.cld.2012.08.002.
25. Colrain IM, Nicholas CL, Baker FC. Alcohol and the sleeping brain. *Handb Clin Neurol*. 2014;125:415-431. https://doi.org/10.1016/B978-0-444-62619-6.00024-0.
26. Williams DL, MacLean AW, Cairns J. Dose-response effects of ethanol on the sleep of young women. *J Stud Alcohol*. 1983;44(3):515-523. https://doi.org/10.15288/jsa.1983.44.515.
27. Van Reen E, Jenni OG, Carskadon MA. Effects of alcohol on sleep and the sleep electroencephalogram in healthy young women. *Alcohol Clin Exp Res*. 2006;30(6):974-981. https://doi.org/10.1111/j.1530-0277.2006.00111.x.

28. Arnedt JT, Rohsenow DJ, Almeida AB, et al. Sleep following alcohol intoxication in healthy, young adults: Effects of sex and family history of alcoholism. *Alcohol Clin Exp Res*. 2011;35(5):870-878. https://doi.org/10.1111/j.1530-0277.2010.01417.x.
29. Chan JK, Trinder J, Andrewes HE, et al. The acute effects of alcohol on sleep architecture in late adolescence. *Alcohol Clin Exp Res*. 2013;37(10):1720-1728. https://doi.org/10.1111/acer.12141.
30. Sahlin C, Franklin KA, Stenlund H, et al. Sleep in women: Normal values for sleep stages and position and the effect of age, obesity, sleep apnea, smoking, alcohol and hypertension. *Sleep Med*. 2009;10(9):1025-1030. https://doi.org/10.1016/j.sleep.2008.12.008.
31. Redline S, Kirchner HL, Quan SF, et al. The effects of age, sex, ethnicity, and sleep-disordered breathing on sleep architecture. *Arch Intern Med*. 2004;164(4):406-418. https://doi.org/10.1001/archinte.164.4.406.
32. Block AJ, Hellard DW, Slayton PC. Effect of alcohol ingestion on breathing and oxygenation during sleep: Analysis of the influence of age and sex. *Am J Med*. 1986;80(4):595-600. https://doi.org/10.1016/0002-9343(86)90813-2.
33. Peppard PE, Austin D, Brown RL. Association of alcohol consumption and sleep disordered breathing in men and women. *J Clin Sleep Med*. 2007;3(3):265-270. https://doi.org/10.5664/jcsm.26795.
34. Block AJ, Boysen PG, Wynne JW, et al. Sleep apnea, hypopnea and oxygen desaturation in normal subjects: A strong male predominance. *N Engl J Med*. 1979;300(10):513-517. https://doi.org/10.1056/NEJM197903083001001.
35. Collop NA, Adkins D, Phillips BA. Gender differences in sleep and sleep-disordered breathing. *Clin Chest Med*. 2004;25(2):257-268. https://doi.org/10.1016/j.ccm.2004.01.002.
36. Bixler EO, Vgontzas AN, Lin HM, et al. Prevalence of sleep-disordered breathing in women: Effects of gender. *Am J Respir Crit Care Med*. 2001;163(3):608-613. https://doi.org/10.1164/ajrccm.163.3.9911064.
37. Le Bon O, Verbanck P, Hoffmann G, et al. Sleep in detoxified alcoholics: Impairment of most standard sleep parameters and increased risk for sleep apnea, but not for myoclonias—A controlled study. *J Stud Alcohol*. 1997;58(1):30-36. https://doi.org/10.15288/jsa.1997.58.30.
38. Aldrich MS, Shipley JE. Alcohol use and periodic limb movements of sleep. *Alcohol Clin Exp Res*. 1993;17(1):192-196. https://doi.org/10.1111/j.1530-0277.1993.tb00747.x.
39. Erol A, Karpyak VM. Sex and gender-related differences in alcohol use and its consequences: Contemporary knowledge and future research considerations. *Drug Alcohol Depend*. 2015;156:1-13. doi: https://doi.org/10.1016/j.drugalcdep.2015.08.023.
40. Johnson EO, Roehrs T, Roth T, et al. Epidemiology of alcohol and medication as aids to sleep in early adulthood. *Sleep*. 1998;21(2):178-186. https://doi.org/10.1093/sleep/21.2.178.
41. Kaneita Y, Uchiyama M, Takemura S, et al. Use of alcohol and hypnotic medication as aids to sleep among the Japanese general population. *Sleep Med*. 2007;8(7-8):723-732. https://doi.org/10.1016/j.sleep.2006.10.009.
42. Stevenson JS, Masters JA. Predictors of alcohol misuse and abuse in older women. *J Nurs Scholarsh*. 2005;37(4):329-335. https://doi.org/10.1111/j.1547-5069.2005.00057.x.
43. Jaussent I, Dauvilliers Y, Ancelin ML, et al. Insomnia symptoms in older adults: Associated factors and gender differences. *Am J Geriatr Psychiatry*. 2011;19(1):88-97. https://doi.org/10.1097/JGP.0b013e3181e049b6.
44. Haario P, Rahkonen O, Laaksonen M, et al. Bidirectional associations between insomnia symptoms and unhealthy behaviours. *J Sleep Res*. 2013;22(1):89-95. https://doi.org/10.1111/j.1365-2869.2012.01043.x.
45. Blümel JE, Cano A, Mezones-Holguín E, et al. A multinational study of sleep disorders during female mid-life. *Maturitas*. 2012;72(4):359-366. https://doi.org/10.1016/j.maturitas.2012.05.011.
46. Seib C, Anderson D, Lee K. Prevalence and correlates of sleep disturbance in postmenopausal women: The Australian Healthy Aging of Women (HOW) study. *J Womens Health (Larchmt)*. 2014;23(2):151-158. https://doi.org/10.1089/jwh.2013.4472.
47. Rognmo K, Bergvik S, Rosenvinge JH, et al. Gender differences in the bidirectional relationship between alcohol consumption and sleeplessness: The Tromsø study. *BMC Public Health*. 2019;19(1):444. https://doi.org/10.1186/s12889-019-6801-6.
48. Peretti-Watel P, Legleye S, Baumann M, et al. Fatigue, insomnia and nervousness: Gender disparities and roles of individual characteristics and lifestyle factors among economically active people. *Soc Psychiatry Psychiatr Epidemiol*. 2009;44(9):703-709. https://doi.org/10.1007/s00127-008-0487-x.
49. Brower KJ, Aldrich MS, Robinson EA, et al. Insomnia, self-medication, and relapse to alcoholism. *Am J Psychiatry*. 2001;158(3):399-404. https://doi.org/10.1176/appi.ajp.158.3.399.
50. Claudatos S, Baker FC, Hasler BP. Relevance of sleep and circadian rhythms to adolescent substance use. *Curr Addict Rep*. 2019;6(4):504-513. https://doi.org/10.1007/s40429-019-00277-9.
51. Wong MM, Brower KJ, Zucker RA. Childhood sleep problems, early onset of substance use and behavioral problems in adolescence. *Sleep Med*. 2009;10(7):787-796. https://doi.org/10.1016/j.sleep.2008.06.015.
52. Zhang J, Chan NY, Lam SP, et al. Emergence of sex differences in insomnia symptoms in adolescents: A large-scale school-based study. *Sleep*. 2016;39(8):1563-1570. https://doi.org/10.5665/sleep.6022.
53. Tynjälä J, Kannas L, Levälahti E. Perceived tiredness among adolescents and its association with sleep habits and use of psychoactive substances. *J Sleep Res*. 1997;6(3):189-198. https://doi.org/10.1046/j.1365-2869.1997.00048.x.
54. Johnson EO, Breslau N. Sleep problems and substance use in adolescence. *Drug Alcohol Depend*. 2001;64(1):1-7. https://doi.org/10.1016/s0376-8716(00)00222-2.
55. Sarkar DK. Circadian genes, the stress axis, and alcoholism. *Alcohol Res*. 2012;34(3):362-366.
56. Jia YF, Vadnie CA, Ho AM, et al. Type 1 equilibrative nucleoside transporter (ENT1) regulates sex-specific ethanol drinking during disruption of circadian rhythms. *Addict Biol*. July 2019:e12801. https://doi.org/10.1111/adb.12801.
57. Pieters S, Van Der Vorst H, Burk WJ, et al. Puberty-dependent sleep regulation and alcohol use in early adolescents. *Alcohol Clin Exp Res*. 2010;34(9):1512-1518. https://doi.org/10.1111/j.1530-0277.2010.01235.x.
58. Hasler BP, Wallace ML, White SJ, et al. Preliminary evidence that real world sleep timing and duration are associated with laboratory-assessed alcohol response. *Alcohol Clin Exp Res*. 2019;43(7):1575-1584. https://doi.org/10.1111/acer.14076.
59. Hasler BP, Franzen PL, de Zambotti M, et al. Eveningness and later sleep timing are associated with greater risk for alcohol and marijuana use in adolescence: Initial findings from the National Consortium on Alcohol and Neurodevelopment in Adolescence study. *Alcohol Clin Exp Res*. 2017;41(6):1154-1165. https://doi.org/10.1111/acer.13401.
60. Inkelis SM, Thomas JD. Sleep in infants and children with prenatal alcohol exposure. *Alcohol Clin Exp Res*. 2018;42(8):1390-1405. https://doi.org/10.1111/acer.13803.

61. Milic J, Glisic M, Voortman T, et al. Menopause, ageing, and alcohol use disorders in women. *Maturitas*. 2018;111:100-109. https://doi.org/10.1016/j.maturitas.2018.03.006.
62. Suh S, Cho N, Zhang J. Sex differences in insomnia: From epidemiology and etiology to intervention. *Curr Psychiatry Rep*. 2018;20(9):69. https://doi.org/10.1007/s11920-018-0940-9.
63. Brooks AT, Wallen GR. Sleep disturbances in individuals with alcohol-related disorders: A review of cognitive-behavioral therapy for insomnia (CBT-I) and associated non-pharmacological therapies. *Subst Abuse*. 2014;8:55-62. https://doi.org/10.4137/SART.S18446.
64. Arnedt JT, Conroy DA, Armitage R, et al. Cognitive-behavioral therapy for insomnia in alcohol dependent patients: A randomized controlled pilot trial. *Behav Res Ther*. 2011;49(4):227-233. https://doi.org/10.1016/j.brat.2011.02.003.
65. Currie SR, Clark S, Hodgins DC, et al. Randomized controlled trial of brief cognitive-behavioural interventions for insomnia in recovering alcoholics. *Addiction*. 2004;99(9):1121-1132. https://doi.org/10.1111/j.1360-0443.2004.00835.x.
66. Trauer JM, Qian MY, Doyle JS, et al. Cognitive behavioral therapy for chronic insomnia: A systematic review and meta-analysis. *Ann Intern Med*. 2015;163(3):191-204. https://doi.org/10.7326/M14-2841.
67. Hasler BP, Pedersen SL. Sleep and circadian risk factors for alcohol problems: A brief overview and proposed mechanisms. *Curr Opin Psychol*. 2019;34:57-62. https://doi.org/10.1016/j.copsyc.2019.09.005.