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THE JOURNAL OF THE NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

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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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Associations Between Socioeconomic Factors and Alcohol Outcomes

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Socioeconomic status (SES) is one of the many factors influencing a person's alcohol use and related outcomes. Findings have indicated that people with higher SES may consume similar or greater amounts of alcohol compared with people with lower SES, although the latter group seems to bear a disproportionate burden of negative alcohol-related consequences. These associations are further complicated by a variety of moderating factors, such as race, ethnicity, and gender. Thus, among individuals with lower SES, members of further marginalized communities, such as racial and ethnic minorities and homeless individuals, experience greater alcohol-related consequences. Future studies are needed to more fully explore the underlying mechanisms of the relationship between SES and alcohol outcomes. This knowledge should be applied toward the development of multilevel interventions that address not only individual-level risks but also economic disparities that have precipitated and maintained a disproportionate level of alcohol-related consequences among more marginalized and vulnerable populations.

Key words: Alcohol consumption; alcohol-related problems; alcohol-related consequences; special populations; socioeconomic status; socioeconomic factors; economic disparities; racial minority; ethnic minority; homeless

According to the World Health Organization (2014), alcohol consumption is responsible for approximately 5.9 percent of deaths worldwide and a global loss of 139 million disability-adjusted life-years. The alcohol-related disease burden is precipitated in part by acute intoxication, which decreases reaction time, perception and motor skills, and inhibitions and is thereby associated with an increased risk for traffic accidents, self-inflicted injuries, suicide, falls, drownings, alcohol poisoning, and interpersonal violence. Longer-term effects of alcohol consumption also contribute to the disease burden by way of various medical conditions (e.g., cancer, cardiovascular disease, and liver cirrhosis) and psychiatric disorders (e.g., depression and alcohol use disorder [AUD]). Given the strong positive association between alcohol use and negative alcohol-related consequences, it is important to understand social determinants of these alcohol outcomes.

The quantity and frequency of a person's alcohol use, the resulting negative alcohol-related consequences (also known as alcohol-related problems), and his or her risk of AUD are determined by a variety of influences. These include higher-level chrono- and macrolevel factors, such as historical time and geopolitical context, as well as meso-, micro-, and individual-level factors, such as community context, family/peer influences, biological predisposition, effects of prenatal alcohol exposure, psychological factors, and sociodemographic features (e.g., gender, age, race, ethnicity, culture, religious affiliation, and socioeconomic status [SES]) (Edwards 2000; Gately 2008). These factors, which operate within various systems and levels, interact and transact over time to determine alcohol-related outcomes, such as drinking patterns and negative alcohol-related consequences (Gruenewald et al. 2014; Holder 1998).

This article focuses on one particular aspect of this complex set of systems, namely the relationship between SES—including income/economic factors, educational level, employment status, and housing status—and alcohol-related outcomes. It synthesizes data primarily obtained from English-language systematic reviews and meta-analyses that were based on studies conducted in the past decade involving adult populations (for a summary of these reviews and meta-analyses, see table 1). In some cases, these analyses were limited to studies from only one country, whereas other analyses were

cross-national. In any case, caution must be used when interpreting these findings, because the cultural and political contexts in which these phenomena occur can differ widely. In addition, this article reviews some larger, population-based studies (see table 2), particularly those that were not addressed within the included reviews and which directly assess the association between SES and alcohol consumption and related outcomes. Although most of the studies only included adults, a few also involved adolescents when meta-analyses and reviews did not exclude such studies.

Across the studies discussed in this article, SES has been operationalized on various levels (e.g., individual, area/neighborhood, and national levels) using a variety of parameters, such as personal income and debt, family or household income, educational level, employment status, and housing status; neighborhood or area disadvantage; and gross national income. Although these variables often are interrelated, this article addresses economic, income, and educational factors; employment status; and housing status in separate sections to facilitate interpretation of the overall findings.

Alcohol-related variables evaluated in this article, which were assessed either cross-sectionally or longitudinally, include the following:

- Alcohol use, which is operationalized either continuously (e.g., by quantity and/or frequency of alcohol use or heavy episodic drinking [HED],[1] defined as consuming four or more drinks per episode for women and five or more drinks per episode for men), or dichotomously by alcohol-use status (e.g., ever-drinker, heavy drinker, heavy episodic drinker);
- Presence of AUD; and
- Alcohol-related problems, including alcohol-related mortality.

It is important to keep in mind that these are outcomes at the individual level; however, alcohol use and misuse certainly also have consequences at the familial, community, or societal levels. A discussion of these consequences is outside of the scope of this article.

The article first summarizes cross-sectional perspectives on the associations of socioeconomic variables such as income, economic factors, and educational level with the quantity and frequency of alcohol use as well as negative alcohol-related consequences. In addition, it reviews the findings of longitudinal analyses regarding the associations between SES and alcohol-related outcomes before focusing on studies assessing two specific socioeconomic variables—i.e., employment status and housing—and their relationship with alcohol outcomes and touching on the effects of changes in SES on alcohol use and its consequences. A discussion of the limitations of the existing research and future directions concludes the review. Note that in some of the studies discussed, alcohol-related variables have been collapsed with other drug-related variables (e.g., any alcohol or other drug [AOD] use, alcohol and nicotine dependence), and this is noted accordingly.

Cross-Sectional Associations Between SES Variables and Alcohol Outcomes

Quantity and Frequency of Alcohol Use

In the past decade, several population-based studies, but no meta-analyses or systematic reviews, have assessed the cross-sectional relationship between snapshots of SES and quantity and/or frequency of alcohol use. These studies typically have focused on either individual-level (e.g., personal income, debt, or education) or area-level (e.g., neighborhood median income or economic disparities in a given region) SES variables.

The Centers for Disease Control and Prevention (CDC) (2012) conducted a population-based study of the association between HED and several SES-related variables among adults (N = 457,677) in 48 States and Washington, DC. The findings indicated that people who did not graduate from high school and had a low income had the lowest prevalence of HED. In fact, HED prevalence increased with household income and was highest among those with a household income greater than $75,000 a year. However, among those respondents who did engage in HED, those who reported the lowest educational and income levels reported the highest frequency of HED and the highest quantity consumed per occasion (CDC 2012). Another population-based study conducted in New York City at the neighborhood level yielded similar findings (Galea et al. 2007). Specifically, the neighborhoods with the highest income and with the greatest income disparities showed the highest prevalence of alcohol use as well as greater frequency of drinking. Similarly, analysis of data from a large, population-based survey called the Panel Study of Income Dynamics demonstrated that three indicators of family-background SES—income, wealth, and parental education—predicted alcohol use in young adults (Patrick et al. 2012). Young adults with the highest family-background SES reported greater alcohol use, and those with greater family wealth reported higher monthly HED prevalence. It is conceivable, however, that other factors, such as regional differences or personal characteristics (e.g., religiosity) may influence these associations.

A few studies have examined alternative operationalizations of individual-level SES by looking at each participant's subjective assessment of his or her social status (Finch et al. 2013) or personal unsecured debt (Richardson et al. 2013). Finch and colleagues

[1] The terms "heavy episodic drinking" and "binge drinking" have sometimes been used synonymously. The latter, however, has fallen out of favor with some alcohol researchers and treatment professionals because it can be confused with a longer-term and more extreme alcohol-use period than is typically referred to as a heavy drinking episode.

Table 1 Summary of Meta-Analyses and Reviews of Cross-National Studies Reporting on the Association Between Socioeconomic Status (SES) and Alcohol Outcomes

Authors	Type	Number of Studies Included	Variables Analyzed	Main Findings Regarding the Association Between SES and Alcohol Outcomes
Bryden et al. 2013	Systematic review	48	Association between community-level social factors and alcohol use among adults and adolescents	• Findings were inconclusive for associations between alcohol use and deprivation, poverty, income, unemployment, social disorder, and crime. • Social-capital characteristics (e.g., social support, community cohesion, social participation, supportiveness) may protect against alcohol use.
Fazel et al. 2008	Meta-analysis	29 (n = 5,684)	Prevalence of psychiatric disorders among homeless people	• Prevalence of psychiatric disorders varied greatly among studies. • The most common psychiatric disorders were alcohol dependence (prevalence 8.1 to 58.5 percent) and drug dependence (prevalence 4.5 to 54.2 percent).
Grittner et al. 2012	Meta-analysis	Survey data from 42,655 individuals in 25 countries participating in the Gender, Alcohol and Culture: An International Study (GENACIS)	Association of country-level characteristics and individual SES and individual alcohol-related consequences	• Lower gross national income was associated with more social problems in men. • Lower educational attainment was associated with more reported alcohol-related consequences at comparable drinking levels in both men and women.
Karriker-Jaffe 2011	Systematic review	41; 34 studies used for main analysis	Association between area-level disadvantage and substance use	• Strong evidence suggested that substance-use outcomes cluster by geographic area. • There was limited/conflicting support that area-level disadvantage is associated with increased substance use. • The association between area-level disadvantage and substance use seemed to vary according to age, ethnicity, size of area examined, type of SES measure, specific outcome analyzed, and analysis techniques.
Probst et al. 2014	Meta-analysis	15	Association between SES and alcohol-related mortality vs. all-cause mortality	• For both men and women, lower SES was associated with 1.5- to 2-times-higher alcohol-related mortality compared with all-cause mortality. • Alcohol consumption and SES interacted to lead to greater harm in people with lower SES even at comparable levels of alcohol consumption.
Richardson et al. 2013	Meta-analysis	65, including 5 studies (n = 26,706) assessing problem drinking	Association between personal, unsecured debt and health outcomes (eg, various mental disorders, suicide attempt or completion, problem drinking, drug dependence)	• Most studies found that more debt is related to worse health (i.e., increased odds of mental disorders, alcohol and drug dependence, suicide attempt or completion). • A significant relationship existed between debt and problem drinking (odds ratio = 2.68).
Wiles et al. 2007	Systematic review	19 longitudinal studies	Association between childhood SES and alcohol use later in life	• Evidence indicated only weak and inconsistent associations between lower childhood SES and later alcohol use and abuse.

(2013) found that subjective social status was not associated with level of alcohol use; however, consistent with the findings of other studies, personal and household income were positively correlated with alcohol-use quantity and frequency as well as frequency of HED. Richardson and colleagues (2013) conducted a meta-analysis of 65 studies examining the effects of personal, unsecured debt on various health outcomes, including 5 studies that included alcohol-related outcomes. The findings from those studies indicated that personal, unsecured debt was associated with 2.68 times higher odds of "problem drinking," which was variously defined as higher quantity/frequency of alcohol use, HED, or presence of AUD.

In another review of 41 studies, Karriker-Jaffe (2011) examined whether area-level disadvantage (i.e., the effects of living in a certain neighborhood, zone, county, or country) was associated with increased AOD use. The studies included in the analysis assessed the impact of a wide range of area-level SES effects. The review concluded that residents in a given area were relatively similar in their AOD use (i.e., AOD-use outcomes clustered by geographic area). However, the studies reviewed provided only limited and conflicting support for the hypothesis that area-level disadvantage was associated with increased AOD use, with some effects supporting the hypothesis and others pointing in the opposite direction (i.e., indicating that area affluence was associated with increased alcohol use). A wide range of factors related to the populations studied (e.g., age and ethnicity), the size of the areas examined, the specific SES measures used, the specific outcomes evaluated, and the analytic techniques employed all seemed to influence the association between SES and AOD use. Similarly, in a review of 48 studies, Bryden and colleagues (2013) reported inconclusive findings regarding the association between alcohol use and various measures of SES (e.g., neighborhood deprivation, poverty, income levels, and unemployment). The analyses did, however, offer area-level corroboration of the conclusions from individual-level studies because there was some indication that adults living in higher-income areas reported greater alcohol use. The findings also indicated a protective effect of the level of community participation and involvement on alcohol use.

Another population-based study (Karriker-Jaffe et al. 2012) that used data from the 2000 U.S. Census and the 2000 and 2005 National Alcohol Surveys (NAS) (N = 13,864) examined relationships between neighborhood disadvantage (i.e., low levels of education, employment, and income/financial assets) and several parameters, including levels of abstinence, heavy drinking, and negative alcohol-related consequences. Analyses using various models incorporating both individual-level and neighborhood-level measures indicated that individual-level SES had the strongest impact on drinking patterns and consequences. When such individual-level factors were removed from the models, neighborhoods with lower SES were characterized by greater prevalence of alcohol abstinence compared with neighborhoods with higher SES, although among those who did drink, neighborhood disadvantage was associated with heavy drinking and negative alcohol-related consequences. These associations were moderated by various demographic characteristics, such as race/ethnicity and gender. Thus, African-American and Hispanic men were excluded from the protective effect of neighborhood disadvantage on risk of any drinking. Furthermore, neighborhood disadvantage was associated with reduced heavy drinking for European Americans but with increased heavy drinking for African Americans.

To some extent the racial/ethnic differences may be the result of different levels of exposure to social disadvantage. Thus, in a separate analysis of data from the 2005 NAS (Mulia et al. 2008) that compared the relationship among social disadvantage, stress, and alcohol use among Black, Hispanic, and White Americans, the investigators found that for all three racial/ethnic groups, exposure to social disadvantage (e.g., greater poverty, unfair treatment, racial or ethnic stigma) was associated with problem drinking. However, Blacks and Hispanics reported greater exposure to social disadvantage than Whites, which may account for higher rates of problem drinking.

Additional analyses of data from the 2000 U.S. Census and 2000 and 2005 NAS (Mulia and Karriker-Jaffe 2012) further identified interactions between individual-level and neighborhood SES that influenced alcohol consumption and related problems. Among men, living in a neighborhood with higher SES was associated with higher odds of heavy drinking and intoxication only among those with a low individual SES compared with men with a middle or higher SES living in the same advantaged neighborhoods. In contrast, neighborhood disadvantage was associated with an increased risk for alcohol-related problems in women, and individual-level SES did not seem to influence this association.

Alcohol-Related Harm and AUD

Studies have shown a strong association between SES and alcohol-related mortality, the most severe form of alcohol-related harm. In a meta-analysis of 15 studies capturing data on approximately 133 million people worldwide, Probst and colleagues (2014) examined the association between SES (operationalized as a pooled measure reflecting occupation, employment status, income, and education) and alcohol-related mortality as well as all-cause mortality. The analyses found that lower SES increased the risk of alcohol-related mortality by 66 percent for men and 78 percent for women compared with all-cause mortality.

Additional studies have supported these findings. In a recent study involving data from the U.S. Health and Retirement survey (N = 8,037), being in the most disadvantaged SES

Table 2 Summary of the Design and Main Findings of Population-Based Studies Concerning the Association Between Socioeconomic Status (SES) and Alcohol Outcomes

Authors	Type; Country of Study	Number of Participants	Variables Analyzed	Main Findings Regarding the Association Between SES and Alcohol Outcomes
Berg et al. 2013	Longitudinal; Finland	1,334	Association between drinking trajectories and adult health and socioeconomic disadvantage	• Among Finnish men, those with a steady high or increasing drinking trajectory had an increased risk of experiencing health and economic disadvantage. • Among Finnish women, those with a steady high drinking trajectory had an increased risk of almost all health and economic disadvantages.
Blomgren et al. 2004	Cross-sectional; Finland	1.1 million	Association between individual-level and area-level SES characteristics and alcohol-related mortality	• Individual-level socioeconomic and cultural factors were protective against alcohol-related mortality. • Some, but not all, area-level factors were protective against alcohol-related mortality. • Individual-level SES factors had a greater impact than area-level factors.
Centers for Disease Control and Prevention 2012	Cross-sectional; United States	457,677	Prevalence, frequency, and intensity of heavy episodic drinking (HED) and influence of various sociodemographic variables	• Overall prevalence of HED was 17.1 percent; among binge drinkers the average frequency was 4.4 episodes per month and the average intensity was 7.9 drinks per occasion. • With respect to household income, binge-drinking prevalence was highest among those with the highest income (> $75,000), but frequency and intensity were highest among those with the lowest income (< $25,000).
Collins et al. 2012	Longitudinal; United States	95	Association between project-based Housing First and alcohol-use trajectories among homeless people	• Time spent in low-barrier, non–abstinence-based, permanent, supportive housing (Housing First model) was associated with declining alcohol use. • Greater number of months spent in housing predicted additional decreases in alcohol use.
Compton et al. 2014	Cross-sectional; United States	Ca. 405,000	Association between employment status and alcohol and other drug outcomes	• Unemployment was associated with higher rates of heavy alcohol use, past-year alcohol and other drug abuse/dependence, and past-month tobacco and illicit drug use. • Marked increases in unemployment rates during the recent recession did not moderate these associations.
Fothergill and Ensminger 2006	Longitudinal; United States	1,242	Association between childhood/adolescent antecedents and adult alcohol and drug problems in African Americans	• Educational attainment was associated with reduced risk of substance-use problems.
Galea et al. 2007	Cross-sectional; United States	1,355	Association between neighborhood income and income distribution and prevalence and frequency of alcohol and other drug use	• Neighborhoods with both the highest income and the highest income maldistribution had the highest prevalence of alcohol use. • On an individual level, both high neighborhood income and income maldistribution were associated with greater likelihood of alcohol use as well as with greater frequency of alcohol use.

Table 2 Summary of the Design and Main Findings of Population-Based Studies Concerning the Association Between Socioeconomic Status (SES) and Alcohol Outcomes *(continued)*

Authors	Type; Country of Study	Number of Participants	Variables Analyzed	Main Findings Regarding the Association Between SES and Alcohol Outcomes
Karriker-Jaffe et al. 2012	Cross-sectional; United States	13,864	Association between neighborhood disadvantage and alcohol outcomes (drinking, heavy drinking, alcohol-related consequences, dependence)	• Neighborhood disadvantage was significantly associated with increased abstinence among all groups except for African-American and Hispanic/Latino men. • Neighborhood disadvantage was inversely associated with heavy drinking for White drinkers but positively associated with heavy drinking for African-American drinkers. • Neighborhood disadvantage was marginally associated with elevated alcohol-related consequences among those who do drink, particularly among African-American men and White women.
Karriker-Jaffe et al. 2013	Cross-sectional; United States	13,997	Association between State-level income inequality (Black–White and Hispanic–White poverty ratios) and alcohol outcomes	• Higher Black–White poverty ratios were associated with higher levels of light and heavy drinking among Whites and Blacks. • Higher Black–White poverty ratios were associated with increased alcohol-related consequences and dependence for Blacks. • Higher Hispanic–White poverty ratios were associated with higher levels of light drinking by Whites and Hispanics. • Higher Hispanic–White poverty ratios were associated with increased alcohol-related consequences and dependence for Hispanics.
Melchior et al. 2006	Longitudinal; France	20,570	Association between socioeconomic trajectory and mortality	• Steadily disadvantaged SES or downward SES trajectory increased risk of premature all-cause mortality. • Alcohol consumption was one of the factors explaining this association.
Mulia and Karriker-Jaffe 2012	Cross-sectional; United States	8,728	Association between neighborhood and individual SES and alcohol use and alcohol-related problems	• For men with low SES, living in a neighborhood with a high SES was associated with increased risk drinking, intoxication, and alcohol-related problems. • For women, living in a neighborhood with low SES was associated with increased risk of alcohol problems, but no interactions existed with individual SES.
Mulia et al. 2008	Cross-sectional; United States	6,631	Association between social disadvantage (poverty level, frequency of unfair treatment, racial/ethnic stigma consciousness) and alcohol outcomes (drinking, at-risk drinking, problem drinking)	• Blacks and Hispanics reported greater exposure to social disadvantage than Whites. • In all groups, exposure to social disadvantage was associated with problem drinking. • Frequent unfair treatment, high racial stigma, and extreme disadvantage was associated with 2 to 6 times greater experience of alcohol problems. • The association can be partially explained by psychological distress.
Mulia et al. 2014	Cross-sectional; United States	5,382	Association between types of economic loss and alcohol outcomes	• Severe economic loss (job, housing) was positively associated with negative drinking consequences, alcohol dependence, and, marginally, with intoxication. • Moderate economic loss (retirement savings, reduced hours/wages, trouble paying bills) was unassociated with alcohol outcomes. • Gender and age moderated these associations.

Table 2 Summary of the Design and Main Findings of Population-Based Studies Concerning the Association Between Socioeconomic Status (SES) and Alcohol Outcomes *(continued)*

Authors	Type; Country of Study	Number of Participants	Variables Analyzed	Main Findings Regarding the Association Between SES and Alcohol Outcomes
Murphy et al. 2014	Cross-sectional; United States	5,307	Association between housing instability and alcohol outcomes (social, legal, work-related, health, injuries/accidents) during the 2007–2009 U.S. recession	• Both unstable and lost housing were associated with more alcohol problems and alcohol dependence symptoms. • Perceived family support moderated the associations. Greater family support was associated with fewer alcohol problems, irrespective of housing instability. • Job loss was not associated with alcohol outcomes if housing instability was included in the analysis.
Nandi et al. 2014	Cross-sectional; United States	8,037	Associations between SES, health behaviors (drinking, smoking, physical inactivity), and all-cause mortality	• Being in the subpopulation with the lowest SES was associated with increased mortality. • Drinking, smoking, and physical inactivity accounted for about two-thirds of the increased mortality risk.
Patrick et al. 2012	Cross-sectional; United States	1,203	Association between family SES (income, wealth, parental education) and substance use (drinking, smoking, marijuana use) in young adults	• Alcohol and marijuana use in young adults were associated with higher family SES. • HED in young adults was most strongly predicted by greater family wealth. • Smoking in young adults was associated with lower family SES.
Platt et al. 2010	Longitudinal; United States	6,787	Association between drinking trajectories and various personal characteristics in older adults	• Alcohol consumption declined for most adults studied, with substantial variation in the rate of decline; in a minority, alcohol consumption increased. • High SES (affluence, high educational attainment) was associated with increasing alcohol consumption over time.
Poonawalla et al. 2014	Longitudinal; United States	1,356	Association of changes in family income with adolescent alcohol use and smoking	• Family income trajectory was associated with past-year alcohol use at age 15 and ever-smoking at age 15. • Children of families with declining SES were more likely to drink than were children from the most advantaged and most disadvantaged families.
Popovici and French 2013	Cross-sectional; United States	43,093	Association between employment status and alcohol outcomes	• Job loss during the past year was positively associated with average daily alcohol consumption, frequency of HED, and alcohol abuse or dependence.
Tompsett et al. 2013	Longitudinal; United States	371	Association between substance abuse, affiliation with substance-using peers, and homelessness	• Recent homelessness and affiliation with alcohol-using friends was associated with increased risk of alcohol abuse. • The influence of alcohol-using friends on alcohol abuse decreased over time. • The duration of initial homelessness did not influence substance abuse over time.
Zemore et al. 2013	Cross-sectional; United States	5,382	Associations among race/ethnicity, economic loss, and drinking	• After experiencing severe economic loss, Blacks were more likely to experience alcohol-related problems and alcohol dependence compared with Whites. • The associations between economic loss and alcohol outcomes were weak/ambiguous for Hispanics.

quartile was associated with a 2.84 times greater risk of all-cause mortality than being in the most advantaged quartile. Mediating factors, including alcohol use, smoking, and physical inactivity, significantly and collectively accounted for 68 percent of this all-cause mortality (Nandi et al. 2014). Further, a Finnish study of men ages 25–64 showed that individual-level socioeconomic (i.e., higher education and occupation status) and cultural (i.e., being part of the Swedish-speaking minority) factors were protective against alcohol-related mortality. As with the association with alcohol use discussed earlier, these factors typically dwarfed the influence of area-level factors (Blomgren et al. 2004). Thus, neither area-level median income nor income inequality was associated with alcohol-related mortality. Nevertheless, some area-level SES variables (i.e., percentage of manual laborers and unemployment) were significant risk factors for alcohol-related mortality when explored on their own.

Other investigators have focused on negative alcohol-related consequences beyond mortality. A meta-analysis of cross-sectional surveys conducted across 25 countries (N = 42,655) indicated that men and women with less education were more likely to report negative alcohol-related consequences than their more educated counterparts—even after controlling for drinking patterns (Grittner et al. 2012). In addition, men from countries with lower gross national incomes reported more societal consequences of drinking compared with men from countries with higher gross national incomes (Grittner et al. 2012). Again, these effects of SES-related variables on negative alcohol-related consequences may be moderated by other individual-level factors, such as race and ethnicity. A recent population-based study in the United States (N = 13,997) that explored socioeconomic disparity by race and ethnicity (Karriker-Jaffe et al. 2013) determined that in States with greater between-race income inequality, African-American and Latino/Hispanic individuals were at greater risk for negative alcohol-related consequences and alcohol dependence than were European-American individuals.

Finally, Lee and colleagues (2013) evaluated the relationship between SES and AUD in a study (N = 808) of substance-use (i.e., alcohol, nicotine, and cannabis) and psychiatric-disorder (i.e., depression and anxiety) latent classes. The study identified four groups of participants: those with virtually no symptoms of mental health or substance-use problems, those with symptoms of licit-substance use disorders (mostly alcohol and nicotine dependence), those with mental health disorder symptoms, and those with comorbid symptoms of all five mental health and substance-use indicators. The analysis suggested that the relationship between SES and AUD is not simply unidirectional but that effects actually occur in both directions. Thus, the investigators found that people who did not earn their high school diploma by age 21 were more than twice as likely to belong to the alcohol- and nicotine-dependence group and six times more likely to belong to the comorbid-symptoms group compared with those who had achieved a higher educational attainment. At the same time, people with greater alcohol- and nicotine-dependence symptoms or comorbid symptomatology achieved lower wealth accumulation at age 30 compared with people with low overall symptom experience (Lee et al. 2013). Taken together, these findings indicate a strong, bidirectional relationship between SES and alcohol-related harm. Specifically, people with lower SES tend to experience more negative alcohol-related consequences than people with higher SES. Further, people with greater experience of negative alcohol-related consequences tend to have lower income.

Longitudinal Associations Between SES and Alcohol Outcomes

Looking beyond static and cross-sectional relationships of SES and alcohol use and its consequences is important for understanding developmental changes in alcohol-related variables as a function of changing SES and vice versa. These associations have been studied using a variety of strategies. A few studies have examined the relationship between childhood SES and later alcohol use and related outcomes, often without identifying a clear association. For example, a systematic review of 19 international longitudinal studies of childhood SES and alcohol use in adulthood only revealed weak and inconsistent associations between childhood SES and later drinking (Wiles et al. 2007). Another 25-year longitudinal study that followed African-American children through young adulthood (N = 1,242) found no significant direct effects of childhood SES (i.e., parental education and family income) on later AOD problems (Fothergill and Ensminger 2006). However, the study did identify significant indirect effects of lower SES, such that lower SES predicted fewer years of education, which in turn increased the risk for AOD problems.

Poonawalla and colleagues (2014) used a different approach by conceptualizing SES not as static but as a trajectory of its own. Using latent-class growth analysis of data from the Study of Early Child Care and Youth Development survey (N = 1,356 families), these investigators examined the relationship between childhood SES trajectories and alcohol-use prevalence at age 15. The analyses indicated that family-level economic downturns predicted past-year drinking at age 15. Similarly, a French occupational cohort study (N = 20,570) suggested that downward or steadily disadvantaged SES trajectories along with alcohol and tobacco use predicted greater later all-cause mortality (Melchior et al. 2006).

A third approach used in longitudinal analyses is to follow the alcohol trajectories of participants and relate these to SES. Such studies have yielded mixed findings. Platt and colleagues (2010) focused on U.S. adults over age 50, assessing their alcohol use as

well as a variety of demographic, socioeconomic, and other characteristics. The study found that alcohol use generally tended to decrease over time in this population. However, the investigators identified a minority (2.2 percent) of individuals with increasing alcohol use. This group was largely characterized by greater affluence, European-American race, male gender, nonmarried status, lower levels of religiosity, and good-to-excellent health, thus suggesting that increased alcohol use was associated with higher SES. Conversely, a Finnish study following participants (N = 1,334) from ninth grade through adulthood found that people with increasing and heavy-drinking trajectories from ages 16 through 42 had greater socioeconomic difficulties at age 42, even after controlling for baseline SES (Berg et al. 2013).

Associations Between Specific Socioeconomic Variables and Alcohol Use

Employment Status

Compared with various measures of SES discussed in many of the above studies (e.g., neighborhood disadvantage, personal income, household income, and education), the association of employment status with alcohol use is less equivocal. Thus, a systematic review of five studies suggested that adult unemployment was associated with increased levels of alcohol use (Bryden et al. 2013). It should be noted, however, that the review included only a relatively small number of studies and that those studies primarily involved adolescents.

A few population-based studies have corroborated these findings. Popovici and French (2013) conducted a fixed-effect analysis of data from waves 1 and 2 of the population-based National Epidemiologic Survey of Alcohol and Related Consequences (NESARC) (N = 43,093). The investigators found that past-year unemployment was associated with increases in average daily alcohol quantity, HED frequency, and probability of an AUD diagnosis. Compton and colleagues (2014) analyzed the associations between unemployment and heavy drinking and AUD using data from the U.S. National Survey on Drug Use and Health between 2002 and 2010, taking into consideration the economic downturn during that time period. The analyses indicated that unemployment was significantly associated with heavier alcohol use and AUD and that this association was nearly independent of gender, age, or race/ethnicity. This association did not significantly differ between the periods before and after the economic downturn of 2008.

Housing Status

Homelessness may be viewed as an extreme form of socioeconomic disadvantage and marginalization.[2] The top reasons for homelessness include lack of sufficient income, loss of employment, and increased expenses, as well as lack of affordable housing (Mojtabai 2005; Tessler et al. 2001).

In addition to socioeconomic disadvantage, homeless individuals are disproportionately affected by other problems. For example, the prevalence of alcohol use among homeless individuals has been estimated to be as high as 80 percent (Velasquez et al. 2000), which is substantially higher than in the general population. A meta-analysis of international studies determined a mean alcohol-dependence prevalence of 38 percent among homeless individuals (Fazel et al. 2008), which is 10 times the prevalence of alcohol dependence in the general U.S. population (Grant et al. 2004). Chronically homeless people also often have severe and persistent psychiatric, medical, and substance-use disorders (Collins et al. 2012; Fazel et al. 2008; Hwang 2001; Mackelprang et al. 2014; Martens 2001). Together, these factors lead to greater mortality, including increased alcohol-related mortality, in the homeless population (Hawke et al. 2007; Hwang et al. 2009; O'Connell 2005) as well as an increased burden on the health care and criminal justice systems (Larimer et al. 2009; World Health Organization 2011).

Several studies have suggested that housing status and alcohol outcomes may share a complex longitudinal association that is apparent across the lifespan. For example, a study of 370 adolescents indicated that recent homelessness was the strongest predictor of subsequent substance abuse (Tompsett et al. 2013). In addition, a within-subject analysis involving the older and more severely affected end of the homeless population (i.e., chronically homeless individuals with alcohol dependence) showed that alcohol use and negative alcohol-related consequences seemed to decrease as a function of time spent in housing (Collins et al. 2012). Thus, homelessness seems to precipitate substance abuse, and the provision of adequate and low-barrier housing to people affected by homelessness may in turn reduce negative alcohol-related consequences.

Effects of Changes in SES on Alcohol Use and Its Consequences

As indicated previously, not only overall SES but also changes in SES may have an impact on people's alcohol use and its consequences. The economic recession that affected the United States between 2007 and 2009[3] has afforded researchers an opportunity to study the consequences of such

[2] The U.S. Federal Government defines homelessness as lacking a fixed, regular, and adequate nighttime residence; having a primary nighttime dwelling that is not a regular sleeping accommodation; living in a supervised shelter or transitional housing; exiting an institution that served as temporary residence when the individual had previously resided in a shelter or place not meant for human habitation; or facing imminent loss of housing when no subsequent residence is identified and insufficient resources/support networks exist (Homeless Emergency and Rapid Transition to Housing [HEARTH] Act of 2009).

[3] The National Bureau of Economic Research (2015) has officially dated the recession as lasting from December 2007 to July 2009; however, individual studies may refer to slightly different time periods.

economic downturns. Mulia and colleagues (2014) used data from the 2009–2010 NAS (N = 5,382) to assess the association between economic loss and alcohol consumption, intoxication, negative alcohol-related consequences, and alcohol dependence. The analyses found that severe economic loss, such as loss of a job or housing, was associated with greater experience of negative alcohol-related consequences, alcohol dependence, and intoxication, whereas moderate economic loss, such as loss of retirement savings or reduced work hours or wages, had no such impact.

Several sociodemographic characteristics, such as gender, age, and race/ethnicity, moderated these associations. For example, women affected by economic loss showed increased alcohol consumption, whereas men showed increased intoxication, drinking consequences, and alcohol dependence (Mulia et al. 2014). Additional analyses of the same dataset determined that the association between exposure to severe economic loss and alcohol consumption and related consequences differed among Blacks, Hispanics, and Whites. Thus, not only were Blacks and Hispanics more likely than Whites to experience economic loss, such as job loss or housing problems, but Blacks also had a significantly higher risk than Whites of experiencing two or more negative alcohol-related consequences and alcohol dependence when experiencing severe economic loss (Zemore et al. 2013). For Hispanics, in contrast, only weak and ambiguous associations existed between economic loss and alcohol outcomes.

Other less concrete factors, such as informal social support systems, also may influence the association between changes in SES and alcohol use and alcohol-related negative consequences. When researchers examined the effects of housing instability (e.g., difficulties paying rent or mortgage as well as loss of housing) on alcohol use during the 2007–2009 recession, they confirmed the findings described earlier that housing instability was associated with more negative alcohol-related consequences and increased risk of alcohol dependence (Murphy et al. 2014). This association was modified by perceived family support—that is, respondents who thought that they had greater support from their families reported fewer alcohol-related consequences compared with respondents with less perceived support. These observations further underscore that the relationships between SES and alcohol use and related consequences are highly complex and influenced by a multitude of interacting factors.

Limitations

The existing research reviewed here has some important limitations that deserve mention. First, some of these meta-analyses, reviews, and studies have conflated measures of alcohol use (e.g., quantity/frequency measures) with measures of negative alcohol-related consequences. For example, in their analysis, Richardson and colleagues (2013) combined higher levels of alcohol use (i.e., greater quantity and HED frequency) with AUD symptomatology into one construct of "problem drinking," even though none of the studies they included in their meta-analysis used designated measures of negative alcohol-related consequences. Future research should more clearly differentiate between these measures and terms to avoid confusion, because heavier drinking does not necessarily translate into a greater experience of negative alcohol-related consequences or problem drinking.

Second, relatively few meta-analyses have comprehensively explored the associations between various conceptualizations of SES and alcohol outcomes. Therefore, the current overview and many of the reviews cited within rely on subjective assessments of the literature. Given the number of studies that have been conducted in this area, this approach is an inefficient way to synthesize such a complex body of research (Borenstein et al. 2009). Therefore, future research should involve more comprehensive meta-analyses to more rigorously analyze the association between SES and various operationalizations of alcohol use and related outcomes (e.g., quantity/frequency, experience of negative alcohol-related consequences, and presence of AUD). Such meta-analyses also should consider the moderation of these associations by other factors, such as race, ethnicity, gender, housing status, or drinking status. A more comprehensive approach would help better understand the relationship between SES and alcohol outcomes and their repercussions for more marginalized groups in our society.

Summary and Future Directions

This review has summarized the current state of knowledge regarding the associations between SES and alcohol use and its negative consequences, based on a variety of study approaches (e.g., cross-sectional vs. longitudinal studies, meta-analyses vs. summary reviews, population-based vs. individual-level studies). The literature on the cross-sectional associations between alcohol use and individual- and area-level income and economic factors mostly has supported a positive relationship between SES and alcohol use, such that individuals with higher SES (or living in areas with higher SES) engage in more frequent and heavier drinking. However, this relationship may be moderated by other individual-level variables, such as drinking status, gender, race, and ethnicity (CDC 2012; Karriker-Jaffe et al. 2012). Therefore, future studies should clarify these associations by simultaneously examining the roles of these factors, particularly within meta-analyses that could capitalize on increased power to identify significant moderating effects.

In contrast to the findings for alcohol use, cross-sectional analyses have indicated that SES is inversely related to negative alcohol-related consequences, including alcohol-related

mortality. In other words, although people with lower SES may be less likely to drink and may be consuming less alcohol overall, they are more negatively affected by its effects. Findings to date suggest that economic disparities and their secondary effects are moderating the relationship between alcohol use and the experience of negative alcohol-related consequences; however, the exact nature of these complex relationships requires further exploration.

Research on the long-term associations between SES and alcohol outcomes has shown inconsistent correlations between snapshots of childhood SES and later alcohol outcomes. In contrast, a relatively consistent, inverse association seems to exist between long-term trajectories of SES and alcohol outcomes, with downward SES trajectories predicting heavier subsequent drinking and greater negative alcohol-related consequences. Further studies involving more sophisticated longitudinal analytic methods (e.g., cross-lagged panel modeling) are needed to more explicitly test and establish the nature of the complex transactional dependencies between the trajectories of SES and alcohol outcomes over time.

Two of the numerous factors that can be used to operationalize and assess SES are employment and housing status, and the relationship of these two factors with alcohol use and related outcomes sometimes has been evaluated separately from more general SES studies. Such studies have indicated that among adults, unemployment is associated with increased drinking and elevated risk for AUD. Interestingly, this relationship has not seemed to be affected by the economic downturn in 2008 (Compton et al. 2014). Taking a cue from the longitudinal literature discussed above, however, future studies should focus on evaluating the effects of changing employment status on alcohol outcomes and negative alcohol-related consequences.

Although homelessness may be considered a more extreme form of socioeconomic disadvantage, its effects on individuals go beyond those of SES. The literature on housing status and alcohol outcomes shows an unequivocal and clinically significant association between homelessness and increases in alcohol use, negative alcohol-related consequences, and AUD prevalence. In recent years, research efforts have begun to shed light on the relationship between homelessness and alcohol outcomes (U.S. Department of Health and Human Services 2007). However, more research is necessary to fully assess and address the needs of this marginalized population, which is multiply affected by psychiatric, medical, and substance-use disorders and disproportionately uses high-cost health care and criminal justice services.

Taken together, the findings discussed in this review suggest that although individuals with higher SES may consume similar or greater amounts of alcohol compared with individuals with lower SES, the latter group seems to bear a disproportionate burden of negative alcohol-related consequences. Future studies—particularly rigorous meta-analyses—are needed to more fully explore the mechanisms underlying these relationships. This research can contribute to data gathered in the context of larger public health efforts, including the Healthy People 2020 Initiative, which seeks to assess health disparities in the U.S. population by tracking rates of death, chronic and acute conditions, and health-related behaviors for various marginalized subpopulations (U.S. Department of Health and Human Services 2010). This knowledge should be applied toward the development of multilevel interventions that address not only individual-level risks but also economic disparities at higher levels that have precipitated and maintained a disproportionate level of negative alcohol-related consequences among more marginalized and vulnerable populations. Such interventions would fit well in the context of larger public health efforts (e.g., Affordable Care Act; HHS Action Plan to Reduce Racial and Ethnic Health Disparities) that are aiming to increase access to health care among people with low SES, create more preventative health programs, and improve quality of care for people seeking health care services in lower-SES areas (U.S. Department of Health and Human Services 2010, 2011).

Acknowledgments

This work was supported by a treatment development grant from the National Institute on Alcohol Abuse and Alcoholism (R34–AA–022077; principal investigator: Dr. Collins). Dr. Susanne Hiller-Sturmhöfel contributed helpful edits to and suggestions for the final draft.

Financial Disclosure

The author declares that she has no competing financial interests.

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Alcohol Use and Related Problems Along the United States–Mexico Border

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The southern border the United States shares with Mexico has been of particular interest to alcohol researchers because of the presence of multiple risk factors conducive to alcohol-related problems. The border region spans 2,000 miles and is home to more than 7 million U.S. residents of predominantly Mexican-American ethnicity.

Compared with other areas of the United States, border residents have higher rates of poverty, undereducation, and unemployment (Gerber 2009; Soden 2006). They also are at elevated risk for multiple negative health outcomes, including tuberculosis, hepatitis A, diabetes, and liver disease (Centers for Disease Control and Prevention 2008*a,b*; Pan American Health Organization 2007; Texas Comptroller of Public Accounts 2003) and are differentially affected by crime related to illegal drug trafficking (Office of National Drug Control Policy 2011).

The border also separates two distinct geopolitical areas with long-standing differences in alcohol policy. In Mexico, the legal drinking age is 18, compared with 21 in the United States, and alcohol is comparatively inexpensive. The many Mexican bars within walking distance of the border cater primarily to people in younger age-groups who travel from U.S. border towns to Mexico specifically to capitalize on the cheap alcohol and easier access (Lange and Voas 2000; Lange et al. 2002).

Consistent with the risk factors described above, early studies of alcohol use within border populations showed that border residents were at higher risk for some alcohol outcomes compared with people who do not live near the border. However, the findings varied depending on the following factors:

- The populations studied—for example, Texas versus California;
- The comparison group used—for example, U.S. Hispanics versus U.S. Mexican Americans; and
- The specific alcohol outcome in question—for example, alcohol use versus alcohol-related problems (Substance Abuse and Mental Health Services Administration 2004; Wallisch 1998; Wallisch and Spence 2006; see also Harrison and Kennedy 1996; Holck et al. 1984).

Demonstrating the difficulties of finding good comparison groups, one study (Wallisch and Spence 2006) showed that, compared with more densely populated areas, rates of binge drinking and alcohol dependence tend to be higher in colonias, which are unregulated and sparsely populated settlements within the U.S. border region that often lack basic public services.

In more recent studies, researchers have drawn samples from geographic areas spanning the entire border region, and they have shifted the focus to comparisons between more ethnically homogeneous subgroups on and off the border, with the goal of clarifying the precise risk conferred by living in the border region. In general, these studies find that drinking levels are higher in U.S. border regions, regardless of ethnicity, compared with non-border regions and are particularly elevated among younger age-groups (Caetano et al. 2012; Liu 2012). Similar patterns

are seen for alcohol-problem outcomes such as abuse, dependence, and social problems (Caetano et al. 2013*c*; Vaeth et al. 2012). Despite these findings of generally higher levels of alcohol use and related problems, in general, rates of driving under the influence do not differ on and away from the border (Caetano et al. 2013*b*), and border residents do not report more treatment seeking for alcohol-related problems than non–border residents (Reingle et al. 2014). Both findings, however, are consistent with risks that primarily are restricted to younger age-groups in the region, particularly considering that younger age-groups have not had time to consume large cumulative quantities of alcohol that lead to chronic alcohol problems and typically precede treatment seeking.

One factor that clearly contributes to elevated alcohol-related risks along the U.S. side of the border is the ability to temporarily cross into Mexico to drink. This leads to generally higher annual levels of drinking and alcohol-related problems on the U.S. side of the border, particularly among younger age-groups who deliberately exploit Mexico's lower legal drinking age. For example, among current drinkers living on the U.S. side of the border, those who reported any drinking in Mexico in the past year tended to be younger and reported significantly more alcohol intake (measured in volume), higher rates of binge drinking, and higher rates of alcohol problems than those who reported drinking only in the United States (Caetano et al. 2013*a*; Clapp et al. 2001). Many of these individuals cross the border on foot, spend the evening patronizing the local bars, and return to their cars on the U.S. side in the early hours of the morning (Lange and Voas 2000). When bars in the border city of Juárez, Mexico, shifted to an earlier closing time (from 5 a.m. to 2 a.m.), the percentage of people crossing back into the United States with a positive blood alcohol content dropped by 89 percent (Voas et al. 2002). A second factor associated with higher alcohol-related risks among U.S. border residents seems to be drinking in bars, as opposed to elsewhere, whether on the Mexico side or the U.S. side of the border. Among U.S. border residents, more than 75 percent report not traveling to Mexico at all in the past year, and young adult border residents report more drinking than other groups, regardless of whether they cross into Mexico to drink (Caetano et al. 2012, 2013*a*). Surprisingly, young adult border residents who reported not traveling to Mexico to drink actually reported slightly higher rates of past-year bar attendance (75 percent) than those who reported drinking in Mexico (69 percent), both of which were higher than rates of past-year bar attendance among non-border young adults (59 percent). Moreover, the specific pattern of differences on and off the border in drinking (Mills et al. 2012, 2014) and acute alcohol problems are precisely mirrored in, and are statistically explained by, patterns of bar attendance across these areas. These effects cannot be attributed to age or border/non-border differences in the ways people think about drinking (e.g., more liberal drinking attitudes) or perceptions of broad neighborhood characteristics (e.g., perceptions of violence). Bar attendance seems to be a key contributing factor to elevated alcohol-related risks among the border region's younger population. Therefore, future research would benefit from identifying characteristics of these on-premise alcohol outlets in border areas, including their geographic distribution (Berke el at. 2010; Pollack et al. 2005; Romley et al. 2007) and characteristics of their clientele (Graham et al. 2006).

In sum, U.S. residents living near the country's border with Mexico are at higher risk for alcohol use and related consequences. This risk is accentuated among young people and is tightly connected to this group's higher frequency of bar attendance, whether on the U.S. or Mexico side of the border. Travelling to Mexico to drink—a major focus of early border research—contributes to this risk but falls short of fully explaining it. U.S. policymakers should be aware that high levels of alcohol-related risks on the border are not simply a south-of-the-border phenomenon. To a large extent, they reflect factors within U.S. borders that are under their direct control.

Financial Disclosure

The authors declare that they have no competing financial interests.

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Alcohol Use Patterns Among Urban and Rural Residents

Demographic and Social Influences

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Rates of alcohol use and alcohol use disorder (AUD) vary with geographic location. Research on risks for AUD associated with living in a rural versus urban setting is complicated by the varied systems used to classify geographic location. Studies comparing the prevalence of heavier or binge drinking and AUD based on a dichotomous urban/rural classification have mixed findings when compared with those using more detailed urban-to-rural categories. In addition, urban/rural residence interacts with other demographic factors such as age, U.S. region, and race/ethnicity to affect alcohol use. Social and cultural factors help explain the relationship between geographic location and alcohol use. However, this area of research could be improved by the use of standardized definitions as well as the analysis of a more complete urban-to-rural continuum (e.g., urban, suburban, and rural areas). Having a better understanding of how geographic characteristics influence alcohol use would help inform and improve prevention and treatment efforts.

Key words: Alcohol use, abuse, and dependence; alcohol use patterns; alcohol use disorder; geographic location; urban society; rural society; risk and protective factors; demographic risk and protective factors; cultural risk and protective factors; environmental risk and protective factors; social influences

Geographic location can be an important factor in determining a person's level of risk for alcohol-related problems. Certain factors associated with living in an urban or rural area may increase risk, while others may be protective. For example, the availability of alcohol, norms for acceptable drinking behaviors, demographic characteristics, and economic factors all vary with respect to geographic area and may influence drinking behaviors. The National Institute on Alcohol Abuse and Alcoholism's (NIAAA) Health Disparities Strategic Plan 2009–2013 (NIAAA 2009) recognized that differences exist due to location and called attention to addressing the impacts of alcohol use and its consequences on rural populations. This article represents a partial response to that call and examines rates of alcohol use and alcohol use disorder (AUD) in urban versus rural locations. Consideration is also given to how U.S. region, race/ethnicity, and age intersect with these drinking patterns, as well as other social and cultural factors that characterize place of residence. Both government documents and peer-reviewed journal articles were used to examine this topic. This article considers how more delineated categories on an urban-to-rural continuum could better characterize the relationships between geographic location, alcohol consumption, and AUD and improve prevention and treatment efforts.

Definitions of Urban versus Rural Population Areas

Defining and characterizing urban and rural population areas can be a complicated task. There are over two dozen definitions of "rural" used by U.S. government agencies (Bucholtz 2008). Three examples of such definitions are presented in table 1. These definitions have been applied in alcohol studies (with some of the related results reviewed in this article) and have implications for defining the percentage of the U.S. population that live in an urban versus a rural area. For example, according to the U.S. Census Bureau (USCB) and using its urban area, urban cluster, and rural area classifica-

tions, approximately 80.7 percent of the U.S. population in 2010 lived in an urban community, with the remainder (19.3 percent) living in a rural area (USCB 2013). The Office of Management and Business (OMB) employs a different 3-group urban-to-rural classification (OMB 2010, 2013), which defines Core Based Statistical Areas (CBSA) as metropolitan, micropolitan, or non-core based. The CBSA classification has been used to define a rural area in two ways: (1) living outside of both a metropolitan and a micropolitan county, or (2) only living outside of a metropolitan county. Based on these two definitions, in 2010 approximately 6.3 percent or 16.3 percent of Americans, respectively, lived in a rural area (Mackun and Wilson 2011). The United States Department of Agriculture (USDA), through the Economic Research Service (ERS), has also developed multiple methods of categorizing non-metropolitan counties, one of which is referred to in table 1 (USDA 2013*b*). According to the USDA denition of metropolitan versus non-metropolitan areas, in 2012, approximately 14.7 percent of the U.S. population lived in a non-metropolitan area (USDA 2013*a*).

These definitions exemplify the potential difficulties involved in defining urban or rural settings, and the possibility of organizing geographic data into categories based on a variety of urban/rural thresholds. These varied definitions complicate the study of how urban and rural areas are associated with patterns of alcohol use in the United States. For example, population estimates of alcohol use and AUD from the Substance Abuse and Mental Health Services Administration annual household surveys (from 1971 to 2001 called the National Household Survey on Drug Abuse [NHSDA], and from 2002 to the present called the National Survey on Drug Use and Health [NSDUH]) cannot be readily compared across urban and rural categories. The NHSDA defined urban and rural residence through a dichotomous metropolitan versus non-metropolitan classification using OMB definitions (SAMHSA 2003*a*), whereas the NSDUH uses the expanded 9-category classification based on the Rural/Urban Continuum Codes (RUCC) and updated OMB standards for defining a metropolitan area. Given the periodic updates of these definitions by government agencies, it can even be difficult to compare surveys

Table 1 Three Classifications of Urban-to-Rural Geographic Locations

Government Agency	Primary Geographic Area	Basis of Classification	Urban-to-Rural Categories
U.S. Census Bureau (USCB)	Census tract	Population density	Three-tier classification system: (1) Urban areas are census tracts with populations of 50,000 people or more; (2) urban clusters are census tracts with populations from 2,500 to 49,999; and (3) rural areas are all other census tracts outside urban areas and urban clusters.[1]
Office of Management and Budget (OMB)	County	Population clusters; and urbanized cores	Counties are designated as a Core Based Statistical Area (CBSA) or a non-CBSA area. CBSA areas are subdivided into Metropolitan Statistical Areas (MSA), or counties with an urbanized core of 50,000 residents or more; and Micropolitan Statistical Areas, or counties with a population cluster of between 10,000 and 49,999 residents. Frequently, MSA is used when discussing this classification system rather than CBSA.[2]
U.S. Department of Agriculture (USDA), and Economic Research Service (ERS)	County	Rural/Urban Continuum Codes (RUCC)	OMB's Metropolitan/non-Metropolitan Statistical Area categories are further divided. Metropolitan Statistical Areas are divided into three subcategories based on USCB population estimates; and non-metropolitan (i.e., Micropolitan Statistical Area and non-CBSA area) are divided into six subcategories, based on proximity to a Metropolitan Statistical Area. Metropolitan subcategories include (1) metro counties of 1 million population or more; (2) metro counties of 250,000 to 1 million; and (3) metro counties of less than 250,000. Non-metropolitan subcategories include: (1) non-metro county with urban population of 20,000 or more adjacent to a metro area; (2) non-metro county with urban population of 20,000 or more not adjacent to a metro area; (3) non-metro county with urban population between 2,500 and 19,999 adjacent to a metro area; (4) non-metro county with urban population between 2,500 and 19,999 not adjacent to a metro area; (5) rural county with urban population less than 2,500 adjacent to a metro area; and (6) rural county with urban population less than 2,500 not adjacent to a metro area.[3]

NOTE: Urban-to-rural classifications were based on information from the following sources: [1]USCB 2012; [2]OMB 2010, 2013; and [3]USDA 2013*a,b*.

from year to year (e.g., changes made from the 2002 to the 2003 NSDUH surveys) (SAMHSA 2004).

According to the 2002 NSDUH, prevalence rates of past-year alcohol use were highest for those living in large (72.9 percent) and small metropolitan areas (70.2 percent) compared with non-metropolitan areas (61.6 percent) (SAMHSA 2003*b*). Data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) for 2001–2002 used OMB's CBSA system to define geographic residence. One report identified past-year alcohol use rates using a dichotomous urban (67.2 percent) versus rural (58.4 percent) delineation (Dawson et al. 2011). Both surveys show higher rates of drinking in metropolitan areas. However, the utility is compromised, because the two surveys do not use consistent definitions and classifications to define place and are not entirely comparable. These surveys do use the same U.S. region classification based on USCB's state groupings (i.e., Northeast, Midwest, South, and West), enabling region-based estimates to be compared between the surveys.

Variations in Rates of Alcohol Use and AUD Across the Urban-to-Rural Continuum

Despite these varying definitions, epidemiologic studies have attempted to characterize geographic differences in prevalence rates of alcohol use and AUD (either reporting lifetime or past 12-month AUD rates or rates of alcohol dependence) in the adult U.S. population over the past 20 years. According to data from the 1991–1992 National Longitudinal Epidemiologic Survey (NLAES) (using an older version of OMB's metropolitan statistical area/non-metropolitan statistical area classification), the residents in urban areas compared with rural areas (odds ratio = 1.22) were more likely to report lifetime alcohol use. Among drinkers, however, urban and rural residents had similar risks for lifetime alcohol dependence (Grant 1997).

Using 2001–2002 NESARC data, Dawson and colleagues (2011) reported, as shown above, that prevalence rates of past-year drinking in the adult population were higher for urban residents compared with rural ones. However, the rates of past-year heavy episodic drinking (i.e., 5 or more drinks on any day for men, and 4 or more drinks on any day for women) were similar for residents living in both locations (23.7 and 23.2 percent for urban and rural residents, respectively). The 12-month AUD rates among urban and rural residents (8.4 percent and 8.8 percent, respectively) were also similar. Another analysis of NESARC data found that the lifetime prevalence of an AUD was somewhat lower for urban residents (29.6 percent) than for rural ones (33.3 percent) (Hasin et al. 2007).

Further, Borders and Booth (2007) used 2001–2002 NESARC data and a 3-tiered (urban, suburban, and rural) classification of residence based on OMB's CBSA definitions. They found that rates of abstinence were lowest for suburban residents (31.3 percent) compared with urban (35.4 percent) and rural (41.7 percent) residents. However, rural drinkers were significantly more likely than suburban drinkers to report exceeding the recommended daily drinking limits (more than 4 drinks for men and more than 3 drinks for women) (suburban: 34.5 percent; urban: 37.4 percent; and rural: 40.0 percent). Urban drinkers were more likely than suburban drinkers to report drinking more than 14 drinks for men and more than 7 drinks for women in a typical week (i.e., exceeding recommended weekly drinking limits) (suburban: 14.9 percent; urban: 17.1 percent; and rural: 16.7 percent). Rural drinkers (15.1 percent) were also significantly more likely than suburban drinkers (11.6 percent) to report a past-year AUD, with rates for urban drinkers (14.0 percent) falling in between.

The 2011 and 2012 NSDUH (SAMHSA 2013) include more current data, although these findings are not easily comparable with NLAES and NESARC. For adults ages 18 and older in 2011, the prevalence of past 12-month AUD was higher in large metropolitan areas (7.1 percent) and small metropolitan areas (7.0 percent) than in non-metropolitan areas (4.9 percent). In 2012, these rates remained higher for residents in metropolitan areas (large metropolitan: 7.4 percent; small metropolitan: 7.4 percent), but the past 12-month AUD rate for residents in non-metropolitan areas increased from the previous year to 6.1 percent. Recent treatment admissions data, based on the 2009 Treatment Episode Data Set (TEDS), showed other differences by urban and rural locations using, the National Center for Health Statistics (NCHS) standards and based on census data and Metropolitan Statistical Areas (MSAs) (Eberhardt et al. 2001; NCHS 2014). For example, persons admitted to treatment in rural areas (49.5 percent) were more likely to report alcohol as their primary drug of abuse compared with persons admitted in urban areas (36.1 percent) (SAMHSA 2012).

Although these studies are difficult to compare, the ones reviewed here suggest that rates of alcohol use are higher for urban versus rural residents and that rates of AUD tend to be similar across rural and urban environments. However, there is some indication that a more detailed evaluation of the urban-to-rural continuum will yield more nuanced relationships with alcohol use and AUD across geographic areas, particularly when suburban residence is separated from and compared with rural and urban residence.

Interactions Between Rural/Urban and Other Demographics

To understand an individual's alcohol-related risk profile, it is important to consider the interaction of a number of demographic characteristics with

geographic setting. The sections below examine U.S. region, race/ethnicity, and age as factors that interact with rural/urban setting to influence risk.

U.S. Regions

The Southern U.S. region consistently has the lowest rates of alcohol use. The 1991–1992 NLAES showed the lowest rates of lifetime drinking among Southern residents, followed by residents of the Midwest, West, and Northeast (Grant 1997). Drinkers in the West and Midwest were more likely than Southern drinkers to report lifetime alcohol dependence, whereas drinkers in the Northeast were less likely to report such dependence compared with those in the South. Similarly, based on survey data from the 1993 Behavioral Risk Factor Surveillance System (BRFSS), residence in the deep South (Alabama, Georgia, Louisiana, and Mississippi) was the single greatest predictor of past-month abstinence compared with other regionally representative states (New York, Illinois, Colorado, and California) (Lindquist et al. 1999). Further analysis of AUD based on the 2001–2002 NESARC showed that the Midwest (35.3 percent) and West (32.6 percent) had higher percentages of residents with a lifetime AUD compared with the Northeast (27.1 percent) and South (27.0 percent) (Hasin et al. 2007). NSDUH data from 2012 also showed that those living in the West had the highest past 12-month AUD rate at 8.0 percent, followed by the Midwest (7.7 percent), Northeast (6.8 percent), and South (6.5 percent). For residents in the South, the 2012 past 12-month AUD rate was significantly higher than in 2011 (5.7 percent), whereas the rates for other U.S. regions showed little change from the previous year (SAMHSA 2013). Researchers suggest that a relationship exists in the South between the high levels of Protestant religiosity, which encourages abstinence, and lower drinking and AUD rates (Booth and Curran 2006; Lindquist et al. 1999; Michalak et al. 2007). Religiosity and other social and cultural factors that are associated with geographic location and alcohol use are reviewed in a later section.

Using 2001–2002 NESARC data, Borders and Booth (2007) examined the intersection between urban, suburban, and rural residence and U.S. regions in predicting alcohol use and AUD. Residents from the rural South were most likely to abstain from drinking; they had the highest past-year abstinence rate at 52.1 percent compared with the next highest rate at 39.0 percent for urban Northeast residents. The lifetime abstinence rate was also highest in the rural South (27.5 percent) but lowest in the rural Northeast (9.2 percent). The urban Midwest (29.4 percent) had the highest percentage of residents exceeding daily drinking limits, and the rural South had the lowest percentage (17.3 percent). Residents in the urban West (18.3 percent) were more likely to exceed weekly drinking limits, whereas residents in the suburban Midwest were least likely to (12.7 percent). Urban Midwest drinkers also reported the highest prevalence of past 12-month AUD (12.4 percent), followed by drinkers in the rural Midwest (11.0 percent) and rural West (10.3 percent). The lowest rate of past 12-month AUD was reported by residents in the rural South (6.7 percent).

These regional urban-to-rural comparisons based on the NESARC set the rural South and the urban Midwest at opposite endpoints of the continuum from less risky to more risky drinking and AUD. The ranking of other locations in between these points is less consistent. Eberhardt and colleagues (2001) examined data from multiple government agencies (CDC, SAMHSA, DHHS) about rural and urban health. They reported within-region comparisons for heavy alcohol use (i.e., 5 or more drinks in one day) between metropolitan and non-metropolitan residents using MSAs. For example, in both the Northeast and West, adults ages 18 to 49 who lived in small metropolitan and non-metropolitan areas had higher rates of past-year heavy drinking than those who lived in large metropolitan areas within those same regions. It was also found that men in metropolitan areas were more likely to engage in heavy drinking (56 percent) compared to non-metropolitan areas (48 to 52 percent). However, it is unclear to what degree including a well-defined suburban classification would have altered the results.

Race and Ethnicity

The intersection of race and ethnicity with urban and rural location is another important comparison for understanding the alcohol use patterns of U.S. subpopulations. Data from several different reports generated using 2010 census data reveal concentrations of racial/ethnic groups across certain geographic areas (Ennis et al. 2011; Hixson et al. 2011, 2012; Hoeffel et al. 2012; Norris et al. 2012; Rastogi et al. 2011). The U.S. population of rural residents has shifted some; for example, the percentage of Hispanics living in rural areas has increased (in 1980, 3 percent; and in 2006, 6 percent) (Economic Research Service, n.d.). Rural residents in 2012 were 78 percent White, 9 percent Hispanic, and 8 percent Black, while urban residents were 44 percent White, 27 percent Black, and 17 percent Hispanic (Housing Assistance Council 2012). American Indian reservations are often in rural areas; however, only 22 percent of American Indians/Alaska Natives live on a reservation, on trust land, or in other designated areas (Norris et al. 2012).

Some studies examining the rates of alcohol use and AUD among race/ethnic groups by urban and rural location have mixed results. Booth and Curran (2006) studied Blacks and Whites in six Southern states and showed that rural residence (i.e., living outside of an MSA) was protective for alcohol use in both Blacks and Whites. Urban Blacks had higher abstinence

rates (63.0 percent) than urban Whites (49.9 percent) over the past 28 days, while rural residents of both groups had similar abstinence rates (66.8 percent and 65.5 percent, respectively). Blacks in urban areas also had lower rates of current problem drinking compared with Whites in urban areas (6.1 percent versus 10.0 percent), but similar rates to Whites in rural areas (6.0 percent and 6.9 percent, respectively). Diala and colleagues (2004) examined lifetime AUD rates across urban-to-rural locations for Blacks and Whites using the 1990–1992 National Comorbidity Survey. Blacks were less likely than Whites to report a lifetime AUD in rural areas (i.e., counties with less than 2,500 population) and urban areas (i.e., counties with a city of 50,000 or more population), but both groups had a similar likelihood in large metropolitan areas (i.e., counties with 100,000 or more population and a central city). Differences in the findings between these two studies may be attributed to the different definitions of urban/rural residence used by each study or the samples: Southern residents versus U.S. adults.

Using 2003 NSDUH data, Van Gundy (2006) compared past 12-month AUD rates for several races/ethnicities by urban versus rural location in two age groups. For young adults age 18 to 25, Whites were significantly more likely to report an AUD when living in an urban area (i.e., metropolitan area; 20.0 percent) versus a rural one (i.e., non-adjacent metropolitan area; 17.9 percent). The rates among Blacks in that age group were similar in urban (9.9 percent) and rural environments (10.5 percent). AUD rates declined with older age for all racial and ethnic groups. Among Blacks age 26 and older, those in urban areas had significantly higher rates (6.8 percent) of AUD compared with those in rural areas (3.0 percent). The difference in AUD rates among Whites was less dramatic ranging from 6.2 percent (urban) to 5.5 percent (rural). The AUD rate for Whites was similar to that of Blacks in urban areas in this 26-and-older age group; yet in rural areas, AUD rates were lowest for Blacks compared with other racial/ethnic groups. AUD rates were not significantly different among Hispanics or Asians/Pacific Islanders by urban or rural setting in either the 18-to-25 age group (Hispanics: 15.3 percent urban, 15.0 percent rural; and Asians/Pacific Islanders: 14.4 percent urban, 20.2 percent rural) or the 26-and-older age group (Hispanic: 6.6 percent urban, 8.3 percent rural; and Asians/Pacific Islanders: 3.6 percent urban, 5.8 percent rural). Bigger sample sizes could be needed to identify significant differences in some of these race/ethnicity-by-age subgroups.

Van Gundy (2006) also reported no significant differences in the 12-month AUD rates between American Indians living in urban and rural areas, either for individuals ages 18 to 25 (urban 24.9 percent; rural 20.2 percent) or ages 26 and older (urban 16.6 percent; rural 13.9 percent). An earlier study suggested that there is little difference in the quantity of alcohol consumed by urban and rural American Indians, but that urban American Indians tend to drink more frequently (Weisner et al. 1984). Other studies have examined alcohol use for American Indians living in different U.S. regions, including the Southwest and Plains regions that comprise parts of the West, Midwest, and South. O'Connell and colleagues (2005) examined drinking patterns across four groups: (1) reservation-based Southwestern Indians (SW-AI); (2) reservation-based Northern Plains Indians (NP-AI); (3) American Indians who were geographically dispersed (NLAES-AI); and (4) the U.S. general population excluding American Indians (NLAES-GP). Sixty percent of the NLAES-AI group lived in urban areas, while the reservation-based American Indian groups were primarily rural residents (O'Connell et al. 2005). Comparisons of American Indians living on and off reservation areas overlap some with rural versus urban comparisons; however, rural reservations have unique characteristics not shared with rural areas more generally. Reservation-based American Indians (SW-AI and NP-AI) showed a general pattern not only of high-quantity drinking (e.g., higher rates of drinking 5 or more drinks in 1 day and being intoxicated in the past year), but also of low-frequency drinking (e.g., lower rates of drinking monthly and drinking more than 8 days in a month). NP-AI males and females, in particular, were most likely to report high-quantity drinking. Several studies report that American Indians are less likely than the general U.S. population to be current drinkers; however, there is variability in the drinking rates and quantity of consumption by region and tribal affiliation (Beauvais 1998; May 1996; Szlemko et al. 2006; Young and Joe 2009).

Underage Drinking in Urban and Rural Areas

Using NSDUH data, rates of underage drinking can be compared across urban-to-rural locations. Pemberton and colleagues (2008) reported on past-month alcohol use and binge drinking based on the 2002–2006 NSDUH for 12- to 20-year-olds. County types were categorized by a 4-level urban-to-rural continuum, including metropolitan areas both large (with a population of 1 million or more) and small (less than 1 million population), as well as urbanized (20,000 or more population) and rural (less than 20,000) non-metropolitan areas. Past-month alcohol use was similar across location categories—i.e., large metropolitan (27.5 percent), small metropolitan (30.1 percent), urbanized non-metropolitan (31.3 percent), and rural non-metropolitan (28.1 percent). Prevalence rates for binge drinking were also similar by location (large metropolitan 17.7 percent; small metropolitan 20.8 percent; urbanized non-metropolitan 22.2 percent; and rural non-metropolitan 19.8 percent). Conversely, Lambert and colleagues (2008) used

2002–2004 NSDUH data for individuals ages 12 to 17 and reported significantly higher rates of past-month alcohol use and binge drinking when comparing four rural categories to one combined metropolitan category. These rates were highest in the most rural category (i.e., medium to small rural areas with a population less than 20,000 and not adjacent to a metropolitan area). Findings were less consistent for young adults ages 18 to 25 when comparing rural and urban areas.

Table 2 presents urban/rural prevalence rates based on 2002–2006 NSDUH data for Whites, Blacks, and Hispanics between ages 12 and 20 (Pemberton et al. 2008). In metropolitan areas, underage Whites were more likely to engage in binge drinking than Hispanics, while in urbanized non-metropolitan areas the rates between Whites and Hispanics were similar, and in rural non-metropolitan areas Hispanics had higher rates than Whites. Comparable differences were observed for rates of past-year AUD between Whites and Hispanics across urban/rural areas. Underage Blacks had higher rates of binge alcohol use and past-year AUD in urbanized non-metropolitan areas than in other areas; however, prevalence rates of binge drinking and AUD were lower for Blacks than Whites and Hispanics, regardless of urban/rural category.

Past-year AUD rates, reported by Van Gundy (2006) and based on the 2003 NSDUH, included additional race/ethnic groups. Comparisons were made based on an urban and rural dichotomy and in a smaller age group of youth ages 12 to 17. These data seem to similarly distinguish rural Hispanic youth as a potential risk group. Hispanics who live in rural areas (8.9 percent) were significantly more likely to report an AUD than those who live in urban areas (4.9 percent). Asian/Pacific Islanders reported higher rates of AUD in rural (11.4 percent) compared with urban (4.1 percent) areas, but this difference did not reach statistical significance. All other ethnic groups (i.e., Whites, Blacks, and American Indians/Alaska Natives) reported similar past-year rates of AUD in urban and rural areas.

Beyond Rural vs. Urban: Social and Cultural Characteristics of Geographic Locations

Understanding the relationship between alcohol use and geographic location requires more than assessing population density and proximity to a metropolitan area. A number of social and cultural factors are related to alcohol use patterns and also characterize urban and rural settings. These include religious cultural practices, community and family relationships, economic conditions, the availability of alcohol, and the enforcement of alcohol laws, among others. One mechanism that links these characteristics to drinking is the potential to control (increase or decrease) access to alcohol for residents in an area, but they may alternatively represent potential buffers or stressors that influence alcohol use.

Social relationships in a community may influence drinking behaviors. As previously mentioned, lower alcohol use rates in the Southern states have been attributed to higher participation in religions that encourage abstinence. A 2000 National Alcohol Survey study found that higher levels of religiosity and the religious proscription of drinking are significantly associated with drinking behaviors, particularly higher abstinence levels (Michalak et al. 2007). Community social capital, defined as neighborhood attachment, supportiveness, or participation, is also protective for problem drinking (Bryden et al. 2013). The family environment in particular, including parental monitoring, parental approval, and communication style, has a strong influence on drinking patterns among youth (Nash et al. 2005). Van Gundy (2006), for example, reported a 4-percent increase in alcohol abuse

Table 2 Prevalence of Underage Binge Drinking and Alcohol Use Disorder (AUD) by Urban to Rural Area and Race/Ethnicity (Percentage)

	Metropolitan Area*	Urbanized Non-metropolitan Area	Rural Non-metropolitan Area
Binge Alcohol Use			
Whites	22.9	23.6	20.7
Blacks	9.0	14.2	10.4
Hispanics	17.0	21.1	24.7
AUD			
Whites	10.9	12.1	10.0
Blacks	4.4	7.8	4.9
Hispanics	8.4	11.3	12.5

NOTE: *Metropolitan included both large and small metropolitan areas. Percentages were from the 2002–2006 NSDUH for youth ages 12 to 20 (Pemberton et al. 2008). Binge alcohol use was in the past 30 days and alcohol use disorder in the past year.

among rural youth when either the mother or father were absent from the home.

The economic conditions in a geographic area may be associated with local rates of alcohol use. Karriker-Jaffe (2011) reported varied relationships between alcohol outcomes and area-level socioeconomic status. Neighborhood disadvantage was associated with more heavy alcohol use in adults, while neighborhood advantage was associated with more alcohol use among underage drinkers. The qualities of the built environment, where someone lives, are also associated with alcohol use. Bernstein and colleagues (2007) reported that residents living in urban areas characterized by substandard buildings (stairway, window, or heating problems) were more likely to report heavy drinking. Community disorder more generally, defined by population density, crime, etc., was positively associated with alcohol use in adolescents and adults (Bryden et al. 2013).

Both the perceived and actual availability of alcohol from formal and informal sources can influence the prevalence of drinking and related problems (Treno et al. 2008). In adolescents, greater exposure to alcohol advertising was associated with increased drinking and a greater likelihood of alcohol use (Bryden et al. 2012). In assessing the relationship between alcohol outlet density (AOD) and specific area-level demographic characteristics, Berke and colleagues (2010) examined urban, suburban, large town, and rural geographic locations. In urban areas, AOD was associated with poverty, education, and Black and Hispanic race/ethnicity, but there were no associations for these characteristics with AOD in suburban areas, large towns, and rural areas. AOD predicted higher rates of binge drinking in urban areas at densities greater than 80 alcohol outlets per square mile (Ahern et al. 2013). The retail mix in a geographic area may also matter (i.e., higher binge drinking rates were reported in areas with liquor stores only versus areas with food stores only) (Shimotsu et al. 2013).

Other means of controlling the availability of alcohol in a geographic area include alcohol taxation and the enforcement of alcohol laws. There is evidence to support the use of price and tax policies; higher alcohol prices and taxes are associated with reductions in problems associated with binge and heavy drinking, including alcohol-related crash facilities (Elder et al. 2010). Jackson and colleagues (2014) reported that both the perceived enforcement of liquor laws and the level of funding for enforcement are associated with lower levels of alcohol use. Paschall and colleagues (2012) similarly showed that funding for underage drinking enforcement across various size cities in California was associated with a lower frequency of alcohol use in adolescents, but that AOD and the level of adult drinking in the area had positive correlations with adolescent drinking. Finally, Ying and colleagues (2013) recommended, to be most effective, that alcohol laws and policies (e.g., zero tolerance, open container, minimum legal drinking age, and blood alcohol content) should be adapted to the characteristics of the area where they are implemented.

Implications for Prevention and Treatment

The urban/rural patterns of alcohol use and area-level characteristics described above may have implications for developing intervention strategies. First, the reviewed research identifies potential at-risk subpopulations to target for intervention. Urban residents showed lower rates of abstinence; but more specifically, Midwest residents in urban areas had higher rates of heavier drinking and AUD. By both race/ethnicity and age, there was some evidence that White young adults and older Black adults had higher AUD rates in urban areas. Conversely, rural residence was associated with higher AUD rates for underage Hispanic drinkers, and underage drinking appeared to be higher in the most rural U.S. areas. American Indians had high AUD rates in both urban and rural settings, but reservation-based American Indians in the Northern Plains were at greater risk.

Second, the reviewed research may suggest potential strategies for reducing risky alcohol use in a geographic area, including at individual, community, and policy levels. For example, knowledge of the level of religiosity, the community and family relationships, and the social drinking norms of a population could be used to further target at-risk groups or to conceptualize intervention and prevention strategies. A computerized training program for 12-year-olds living in an urban setting showed positive effects (e.g., lower alcohol use and binge drinking and fewer drinking friends) that held over the course of 7 years compared to the control group (Schinke et al. 2010). Though not specifically addressed, this may have implications for rural underage drinking reduction; computerized intervention methods may be a cost-effective option for rural and sparsely populated areas. Geographic areas characterized by greater socioeconomic disadvantage and disorder could be targeted for community-level interventions to address these conditions and to reduce problem alcohol use through the building of social capital. Policy-level interventions to reduce AOD or to change the mix of retail options in a community may be of particular importance in urban areas, while alcohol taxation and law enforcement are more generally effective at reducing heavy drinking and drinking-related problems across geographic locations.

It also is important to consider whether the availability of treatment services matches the need in urban and rural areas. Lenardson and Gale (2007) used data from the 2004 National Survey of Substance Abuse Treatment Services to comparatively describe treatment facilities in urban and rural locations. Fewer facilities

and treatment beds are located in rural areas. Approximately 9 percent of all surveyed treatment facilities were located in a non-metropolitan area that is not adjacent, 12 percent in an adjacent non-metropolitan area, and 79 percent in a metropolitan area. Differences in the types of services offered by treatment facilities in urban and rural locations may also influence access to treatment services. Lenardson and Gale (2007) also reported that non-metropolitan treatment facilities were less likely than metropolitan ones to offer detoxification (15.4 percent versus 22.4 percent), transitional housing (7.6 percent versus 10.9 percent), and day treatment/partial hospitalization programs (9.4 percent versus 15.2 percent). Non-metropolitan counties also had a lower percentage of facilities offering substance abuse specialty services (51.9 percent) compared with metropolitan facilities (64.3 percent). It is unclear to what extent that the treatment needs in rural and urban areas are or are not being met according to this reported availability of services. However, given that the reviewed studies showed similar rural and urban AUD rates or higher rates among some segments of the rural population, it seems inconsistent that the need for treatment would be less in rural areas than urban ones. This apparent discrepancy between treatment availability and treatment need in rural areas could require a policy-level intervention.

Recommendations

Conducting alcohol studies on urban and rural populations is complicated by the various methods of defining these terms. The definitions have changed over time and are different across surveys, complicating direct comparisons between studies. Consistent and clearly stated definitions of what is meant by urban, suburban, or rural are important for understanding the relationship of these geographic locations to drinking patterns, as well as their implications for prevention and treatment needs. A dichotomous urban/rural classification may inappropriately aggregate data such that it masks the risky drinking behaviors of populations living in urban or rural areas compared with suburban locations. Future studies need to go beyond a rural/urban dichotomy to more fully examine the urban-to-rural continuum. For example, Kuo and Porter (1998) completed a demographic study and examined seven subgroups of Asian/Pacific Islanders in urban, suburban, and rural areas and across regions. Borders and Booth (2007) also offer an example of how to examine alcohol use patterns by intersecting regional and urban, suburban, and rural locations. Further study of differences in drinking and risks for AUD across the urban-suburban-rural continuum could present a more contextualized understanding of the relationship between alcohol use and geographic context.

Acknowledgments

Work on this publication was supported in part by NIAAA at the National Institutes of Health (NIH) under Award Number K01–AA–021145 (with Dr. Chartier as principal investigator). The content is solely the responsibility of the authors and does not necessarily represent the official views of NIH.

Financial Disclosure

The authors declare that they have no competing financial interests.

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Biology, Genetics, and Environment

Underlying Factors Influencing Alcohol Metabolism

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Gene variants encoding several of the alcohol-metabolizing enzymes, alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH), are among the largest genetic associations with risk for alcohol dependence. Certain genetic variants (i.e., alleles)—particularly the ADH1B*2, ADH1B*3, ADH1C*1, *and* ALDH2*2 *alleles—have been associated with lower rates of alcohol dependence. These alleles may lead to an accumulation of acetaldehyde during alcohol metabolism, which can result in heightened subjective and objective effects. The prevalence of these alleles differs among ethnic groups;* ADH1B*2 *is found frequently in northeast Asians and occasionally Caucasians,* ADH1B*3 *is found predominantly in people of African ancestry,* ADH1C*1 *varies substantially across populations, and* ALDH2*2 *is found almost exclusively in northeast Asians. Differences in the prevalence of these alleles may account at least in part for ethnic differences in alcohol consumption and alcohol use disorder (AUD). However, these alleles do not act in isolation to influence the risk of AUD. For example, the gene effects of* ALDH2*2 *and* ADH1B*2 *seem to interact. Moreover, other factors have been found to influence the extent to which these alleles affect a person's alcohol involvement, including developmental stage, individual characteristics (e.g., ethnicity, antisocial behavior, and behavioral undercontrol), and environmental factors (e.g., culture, religion, family environment, and childhood adversity).*

Key words: Alcohol dependence; alcohol use disorder (AUD); alcohol metabolism; alcohol-metabolizing enzymes; genetic factors; environmental factors; biological factors; gene variants; alcohol dehydrogenase (ADH); aldehyde dehydrogenase (ALDH); alleles; acetaldehyde; Asians; Caucasians; Africans; Asian-American; African-American

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Epidemiological studies have demonstrated that drinking patterns and the prevalence of alcohol-related adverse consequences, including alcohol use disorder (AUD), differ substantially among racial/ethnic groups in the United States. For example, analyses comparing drinking patterns and their consequences among Whites, Blacks, Asians, and Hispanics found the following: Whites have the highest risk and Asians have the lowest risk of AUD among these ethnic groups; Hispanics have higher rates and Asians have lower rates of heavy drinking than do Whites; and Hispanics and Blacks are more likely to have health and social problems from drinking than are Whites and Asians (Chartier and Caetano 2010). Other studies have found subgroup differences within racial/ethnic groups for alcohol-related problems; for example, individuals of Korean ancestry have higher rates of AUD than those of Chinese ancestry (Helzer et al. 1990; Luczak et al. 2004).

These differences among racial/ethnic/ancestry groups result from a variety of biological, genetic, and environmental influences, some of which relate to the metabolism of alcohol and are explored in this article. Genes encoding several variants of alcohol-metabolizing enzymes are among the largest genetic associations with the risk for alcohol dependence (Li 2000). This article briefly reviews how alcohol is metabolized in the body and describes ethnic differences in some of the genes encoding the enzymes involved in alcohol metabolism, as well as the mechanism by which these genes are thought to give rise to differences in rates of alcohol dependence. The article also summarizes what is known about

potential individual and environmental influences that may moderate the effects of these gene variants.

Alcohol Metabolism

The key enzymes involved in alcohol metabolism in the liver are alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH). ADH mediates (i.e., catalyzes) the oxidation of beverage alcohol (ethanol) into acetaldehyde. Acetaldehyde then is further metabolized by ALDH into acetate. These two reactions need to be properly coordinated in the body because accumulation of acetaldehyde can lead to heightened responses as well as unpleasant reactions, such as flushing, nausea, vomiting, hypotension, and/or rapid heartbeat (i.e., tachycardia). Variant forms of several ADH and ALDH enzymes exist and are encoded by an individual's genes. These variants (i.e., alleles) produce enzymes with different properties, resulting in potential differences in the rates with which alcohol or acetaldehyde are metabolized. As a result, these variants also may influence a person's response to alcohol, drinking behavior, and consequent risk of developing an AUD. People possessing certain ADH or ALDH alleles have significantly lower rates of alcohol dependence. The following sections review four of the best-studied ADH and ALDH variants—*ADH1B*2* (rs1229984), *ADH1B*3* (rs2066702), *ADH1C*1* (rs698), and *ALDH2*2* (rs671)—and their associations with a variety of alcohol-related factors or phenotypes. The table reports the allele frequencies of these genes in different populations.

ADH Variants

To date, seven different ADH genes—*ADH1A, ADH1B, ADH1C, ADH4, ADH5, ADH6,* and *ADH7*—have been identified clustered together on the long arm of chromosome 4 (Edenberg 2007). Of these, the *ADH1A*, *ADH1B*, and *ADH1C* genes encode the majority of the ADH enzymes that metabolize alcohol in the liver. Several genome-wide association studies of alcohol dependence have found significant results in the region of chromosome 4q that includes the ADH gene cluster in a variety of ethnically diverse samples (e.g., Gelernter et al. 2014). The ADH gene with the largest effect size with alcohol dependence is *ADH1B*. Significant associations have been found for the *ADH1B*2* allele and alcohol dependence in Asian populations (Li et al. 2012*a*; Luczak et al. 2006*a*), as well as in European and African-American populations (Bierut et al. 2012; Whitfield 1997, 2002). Whitfield (2002) found that Europeans with one *ADH1B*2* allele were about half as likely (odds ratio [OR] = 0.47) to be alcohol dependent as individuals without this genetic variant (*ADH1B*1/*1* genotype). In a large meta-analysis of Asian, European, African, Hispanic, and Native-American samples, individuals with an *ADH1B*2* allele overall were about half as likely to be alcohol dependent

Table Gene Frequencies of Specific Alleles of the Genes Encoding Alcohol Dehydrogenase (ADH) and Aldehyde Dehydrogenase (ALDH) in Different Ethnic Populations

Allele	rs Number	Frequency in Different Populations		
ADH1B*2	***rs1229984***		**A allele**	**G allele**
		European	0.000–0.008	0.992–1.000
		Asian	0.739–0.771	0.229–0.261
		Sub-Saharan African	0.000	1.000
		African American	0.000	1.000
ADH1B*3	***rs2066702***		**C allele**	**T allele**
		European	1.000	0.000
		Asian	1.000	0.000
		Sub-Saharan African	0.500–0.783	0.217–0.500
		African American	0.733	0.267
ADH1C*1	***rs698***		**C allele**	**T allele**
		European	0.523–0.527	0.473–0.477
		Asian	0.927–0.975	0.025–0.073
		Sub-Saharan African	0.938–0.958	0.042–0.062
		African American	0.800	0.200
ALDH2*2	***rs671***		**C allele**	**T allele**
		European	0.000	1.000
		Asian	0.110–0.282	0.718–0.890
		Sub-Saharan African	0.000	1.000
		African American	0.000	1.000

SOURCE: dbSNP Database (www.ncbi.nlm.nih.gov/snp).

as those without this genetic variant (OR = 0.49) (Li et al. 2012*a*). The protective association is also greater for individuals with two *ADH1B*2* alleles (Li et al. 2012*a*; Luczak et al. 2006*a*). When subgroup analyses were conducted, the associations were larger in Asian populations (Li et al. 2012*a*). This is likely a result of the combined effects of the *ADH1B*2* and *ALDH2*2* alleles, as expanded upon below (Luczak et al. 2006*a*).

A second *ADH1B* gene variant, the *ADH1B*3* allele, has been related to lower rates of alcohol dependence in many but not all association studies (Edenberg 2007; Edenberg et al. 2006, 2010; Ehlers et al. 2001, 2007; Gizer et al. 2011; Luo et al. 2006; Wall et al. 1997*a*). Significant associations for the *ADH1B*3* allele and alcohol dependence primarily have been found in individuals of African ancestry where this genetic variant is most prevalent (Edenberg et al. 2006; Luo et al. 2006).

A variant of the *ADH1C* gene, the *ADH1C*1* allele, also has been well studied with respect to alcohol dependence, but the results have been inconsistent because of limited sample sizes, ethnic variation, and the close proximity of the *ADH1B* and *ADH1C* genes. Some studies showed that *ADH1C*1* and *ADH1B*2* are in linkage disequilibrium, suggesting that associations of *ADH1C*1* with alcohol dependence may be attributed to correlation with *ADH1B*2* (Borras et al. 2000; Chen et al. 1999*a*; Osier et al. 1999). A large meta-analysis of Asian, European, African, and Native-American samples found that individuals with an *ADH1C*1* allele overall were about one-third as likely to be alcohol dependent as those without this genetic variant (OR = 0.66) and also demonstrated a larger effect (OR = 0.48) in Asian populations (Li et al. 2012*b*). Furthermore, linkage disequilibrium analyses located the *ADH1C* gene in a different haplotype block than the *ADH1B* gene, suggesting the associations may be independent of one another, even though the two genes are close together.

The proposed mechanism by which these ADH alleles lead to lower rates of alcohol dependence relate to differences in the characteristics of the enzymes that they ultimately encode. The *ADH1B*2* and *ADH1B*3* alleles are thought to encode enzymes that oxidize ethanol at an increased rate compared with enzymes encoded by the more common *ADH1B*1* allele, resulting in faster acetaldehyde production. Because this increased production may lead to the accumulation of acetaldehyde and potentially more intense and/or unpleasant alcohol reactions (e.g., a flushing response), people carrying these alleles may be less likely to drink alcohol, particularly at high levels, and accordingly they also may be less likely to develop an AUD (Wall 2005; Wall et al. 2013). Similarly, the *ADH1C*1* allele is thought to encode an enzyme that accelerates the conversion rate of alcohol into acetaldehyde relative to the *ADH1C*2* allele and thus may lead to acetaldehyde buildup after alcohol consumption, thereby promoting reduced alcohol consumption and ultimately protection against AUD (Li et al. 2012*b*).

The findings assessing this proposed mechanism of action—that *ADH1B* and *ADH1C* variations reduce alcohol dependence risk through elevated acetaldehyde levels, heightened responses to alcohol, and reduced drinking—have been inconsistent. *ADH1B*2*, *ADH1B*3*, and *ADH1C*1* have not been associated with elevations in acetaldehyde, although acetaldehyde is difficult to measure in the low concentrations expected from these alleles. Many but not all studies have found that *ADH1B*2* is associated with increased sensitivity to alcohol (i.e., increased flushing and associated symptoms; see Wall et al. 2013 for review). The *ADH1B*3* allele has been associated with a faster rate of alcohol elimination and a more intense response to alcohol in individuals of African ancestry (McCarthy et al. 2010; Thomasson et al. 1995).

ALDH Variants

The acetaldehyde generated by the ADH-mediated oxidation of ethanol is further oxidized by two main ALDH enzymes—ALDH1 and ALDH2—encoded by different genes. With regard to ALDH, the *ALDH2*2* allele has shown the largest association with alcohol dependence. A meta-analysis of studies of Asian samples (Luczak et al. 2006*a*) indicated that having one *ALDH2*2* allele was associated with a four- to fivefold reduction in alcohol dependence (OR = 0.22), and having two *ALDH2*2* alleles was associated with an eight- to ninefold reduction in alcohol dependence (OR = 0.12). This meta-analysis also examined the effect of *ALDH2*2* and *ADH1B*2* alleles in combination on the risk for alcohol dependence (Luczak et al. 2006*a*). In *ALDH2*1/*1* individuals (i.e., *ALDH2*1* homozygotes), one *ADH1B*2* allele was associated with about one-fourth (OR = 0.26) and two *ADH1B*2* alleles were associated with about one-fifth (OR = 0.20) the risk of alcohol dependence compared with individuals with no *ADH1B*2* alleles. In *ALDH2*1/*2* individuals (people who carry one *ALDH2*2* allele and one *ALDH2*1* allele; i.e., who are heterozygous), one *ADH1B*2* allele was associated with about one-sixth (OR = 0.17) and two *ADH1B*2* alleles were associated with about one-eleventh (OR = 0.09) the risk of alcohol dependence compared with individuals with no *ADH1B*2* alleles. These results suggest both *ALDH2* and *ADH1B* each contribute unique protective effects on alcohol dependence, and the level of protection may be even stronger in conjunction than alone (i.e., a gene × gene interaction exists).

A similar mechanism of action has been proposed for how *ALDH2*2* results in lower rates of alcohol dependence (Wall 2005; Wall et al. 2013). According to this model, *ALDH2*2*

encodes a deficient protein subunit that has low or no activity. As a result, acetaldehyde generated by the actions of ADH cannot be readily metabolized and accumulates in the body. Consistent with this assumption, in vitro and in vivo studies have demonstrated that compared with the enzyme activity generated in cells or organisms homozygous for *ALDH2*1* (i.e., *ALDH2*1/*1* genotype), those who are heterozygous show only 12 to 20 percent of the enzyme activity and elevated acetaldehyde levels, and those who are homozygous for *ALDH2*2* show no enzyme activity and even higher acetaldehyde levels (Bosron and Li 1986; Wall et al. 1997*b*). Consequently, people who are homozygous for *ALDH2*2* experience acetaldehyde buildup even after consuming only small amounts of alcohol. As a result, these individuals rarely consume large amounts of alcohol, and there are very few documented cases of people with this genotype having alcohol dependence (Chen et al. 1999*b*; Luczak et al. 2004).

Because of the accumulation of acetaldehyde, people carrying the *ALDH2*2* allele are thought to experience heightened responses to alcohol. This has been confirmed in self-report and alcohol-challenge studies. Thus, in self-report studies *ALDH2*2* has been related to indicators of alcohol sensitivity, such as alcohol-induced flushing and other symptoms (e.g., nausea, headaches, and palpitations). Similarly, numerous alcohol-challenge studies found that people who are heterozygous for *ALDH2*2* experience flushing as well as changes in pulse rate, hormone levels, psychomotor performance, and neurophysiological reactivity compared with people homozygous for *ALDH2*1* who had the same blood alcohol concentrations. People who are homozygous for *ALDH2*2* experience even more intense subjective and objective reactions to alcohol (see Wall et al. 2013).

As a result of this heightened sensitivity to alcohol, people with the *ALDH2*2* allele may have lower positive and higher negative expectancies about alcohol's effects. Alcohol expectancies are thought to be mediators between the biological factors that determine the physiological consequences of alcohol consumption and a person's actual alcohol use. Thus, people who are highly sensitive to alcohol's unpleasant effects because they carry the *ALDH2*2* allele may be less likely to drink because they do not expect alcohol to have pleasant, reinforcing effects and instead may expect it to have unpleasant, aversive ones. Several studies examining the association between *ALDH2*2* and alcohol expectancies support this hypothesis. Two studies (McCarthy et al. 2000, 2001) found that *ALDH2*2* was associated with reduced positive expectancies but was unrelated to negative expectancies. In another analysis (Hendershot et al. 2009*b*), people with *ALDH2*2* alleles reported greater negative expectancies and thought that alcohol had greater physiological effects than did people without the allele.

The greater sensitivity to alcohol and the resulting altered alcohol expectancies then are likely to lead to lower rates of drinking and of heavy drinking. Thus, several studies have found that people with one *ALDH2*2* allele showed lower quantity and frequency of alcohol use and engaged in less binge drinking than did people without this allele; the presence of two *ALDH2*2* alleles exacerbated these effects (see Wall et al. 2013). Reduced consumption, in turn, leads to fewer alcohol-related adverse consequences, as indicated by lower scores on questionnaires measuring hazardous alcohol use and alcohol-related problems (Hendershot et al. 2009*a*, 2011). Similarly, hangovers and blackouts as consequences of heavy drinking also are inversely associated with *ALDH2*2* (Luczak et al. 2006*b*; Wall et al. 2000). A longitudinal study found that *ALDH2*2* changes the association between alcohol consumption and problems over time, with *ALDH2*2* group differences in alcohol-related problems fully accounted for by differences in frequency of binge drinking (Luczak et al. 2014).

Similar to the results from meta-analyses showing that the *ALDH2* and *ADH1B* genes may have an interactive effect on alcohol dependence (Luczak et al. 2006*a*), some self-report and alcohol-challenge data in Asians suggest that the effects of *ADH1B*2* may be stronger in individuals with *ALDH2*1/*2* genotype (e.g., Chen et al. 1999*b*; Cook et al. 2005; Luczak et al. 2006*b*; Takeshita et al. 1996, 2001). For example, in one study of Asians who carried the *ADH1B*2* allele, a heightened sensitivity to alcohol was reported only if they also carried the *ALDH2*2* allele, whereas no increase in sensitivity was reported by people carrying *ADH1B*2* in combination with only *ALDH2*1* alleles (Luczak et al. 2011). Similarly, an alcohol-challenge study only found an increased response to alcohol in people with *ADH1B*2* who also were heterozygous for *ALDH2*2* (Cook et al. 2005). These results suggest that the effects of *ADH1B*2* may be felt more strongly in Asians who already have some heightened sensitivity to alcohol from possessing one *ALDH2*2* allele, but additional research is needed to confirm these findings.

Ethnic Differences in Prevalence of *ADH1B*, *ADH1C*, and *ALDH2* Alleles

Prevalence of ADH1B and ADH1C Alleles

The *ADH1B*2* allele is found in 80 percent or more of northeast Asians (i.e., Chinese, Japanese, and Koreans) and about 50 percent of Russians and Jews, but only in 10 percent or less of Caucasians of European ancestry (Goedde et al. 1992; Osier et al. 2002). However, within the large Asian ethnic group, variations in the prevalence of the *ADH1B*2* allele exist among subpopulations (Eng et al. 2007).

The *ADH1B*3* allele is found predominantly in people of African ancestry (about 30 percent) and in much lower prevalence in certain Native Americans (i.e., Mission Indians), likely because of admixture (Bosron et al. 1983; Edenberg et al. 2006; Wall et al. 1997*a*, 2003). This allele rarely has been found in Asians and Whites.

The *ADH1C*1* allele varies substantially across different populations. It is highly prevalent in Asian and African groups (80 percent or more) and lower in Caucasians of European ancestry (about 50 percent) (Eng et al. 2007; Li et al. 2012*b*).

Prevalence of ALDH2 Alleles

*ALDH2*2* is found almost exclusively in northeastern Asian populations, albeit with varying prevalences among different Asian ethnicities (see Eng et al. 2007). For example, among Han Chinese, overall approximately one-third of individuals possess at least one *ALDH2*2* allele, with different studies determining prevalence ranging from 20 to 47 percent of participants. In contrast, *ALDH2*2* was much less commonly found among Chinese and Taiwanese natives. Studies of Japanese identified prevalence rates of 41 to 52 percent for the *ALDH2*2* allele, whereas analyses of Koreans found *ALDH2*2* prevalence of 29 to 37 percent. In other Asian ethnicities (e.g., Thais), the *ALDH2*2* allele is much less common and is found only in 10 percent or less of individuals. In all cases, only a small proportion of the individuals were homozygous for this allele (about 5 percent); most were heterozygous (Eng et al. 2007).

Moderators of the Effects of *ADH1B*2* and *ALDH2*2*

Although the studies described above demonstrate that *ADH1B* and *ALDH2* variants influence the risk of AUD, it also is clear these genes and their alleles do not act in isolation. The effects of the *ADH1B*2* allele on a person's risk of AUD also depend on the person's *ALDH2* genotype. Thus, Asians who carry the *ALDH2*2* allele show a greater protective effect (i.e., a lower risk of alcohol dependence) from the *ADH1B*2* allele than do people who only carry the functional *ALDH2*1* allele (Luczak et al. 2006*a*). However, numerous additional factors may influence the extent to which *ALDH2*2* and *ADH1B*2* affect a person's risk of alcohol involvement and AUD. Even the design of the studies assessing the associations between genotypes and AUD risk may influence the results. Thus, results from a meta-analysis study found that both the diagnostic system used in a study and the recruitment strategy used to identify study participants moderated the effects of *ALDH2*2* on risk of alcohol dependence (Luczak et al. 2006*a*). For example, studies that used the more stringent criteria of the *International Code of Diseases, 10th Edition* (ICD–10) to establish an AUD diagnosis rather than the less stringent criteria of the *Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised* (DSM–III–R) revealed a greater protective effect of *ALDH2*2*. Similarly, studies in which participants were recruited from treatment settings showed greater protective effects of *ALDH2*2* than did studies involving recruitment of community samples, Thus, these findings demonstrate the importance of methodological issues that must be considered when examining the influence of moderators of gene effects. Only by accounting for these potential moderators will researchers be able to further understand the influences of these alleles and their interactions with other variables on alcohol-related behaviors and the risk of AUD. Other possible moderators of these gene effects include the following:

- Developmental stage;
- Individual characteristics, such as ethnicity, antisocial behavior, and behavioral undercontrol; and
- Environmental factors, such as culture, religion, family environment, and childhood adversity.

These factors are discussed in the following sections. Because *ALDH2*2* has the largest effect on alcohol dependence and because it is found almost exclusively in Asian populations, most of this discussion will focus on this gene and these ethnic groups.

Developmental Stage

The magnitude of *ALDH2*2* effects on alcohol use phenotypes has been shown to change over the course of development. In particular, associations of *ALDH2*2* with alcohol-related measures become stronger over the course of adolescence and young adulthood as alcohol use increases (Doran et al. 2007; Irons et al. 2007, 2012; Luczak et al. 2014). These findings are consistent with twin studies and studies of other candidate genes where genetic influences on alcohol phenotypes increase with age (Dick et al. 2006; Rose and Dick 2005).

Furthermore, although *ALDH2*2* protects against the development of alcohol dependence, the protection is not complete. In the presence of alcohol dependence or at lower levels of alcohol use, individuals with *ALDH2*2* alleles are more vulnerable to alcohol-related pathologies—particularly head and neck cancers, but also liver disease, pancreatitis, and Alzheimer's disease—consistent with a role of acetaldehyde in the pathogenesis of organ damage (Brennan et al. 2004; Brooks et al. 2009; Hao et al. 2011; Lewis and Smith 2005; Yang et al. 2010; Zhang et al. 2010; Zintzaras et al. 2006). Thus, the influence of *ALDH2*2* seems to change over the course of drinking; that is, *ALDH2*2* is protective at one stage of alcohol use (i.e., progression to heavy drinking) but becomes a risk factor at another stage (i.e., progression to alcohol-related medical problems). Prospective studies are needed to determine how

gene effects may change over the lifespan.

Individual Characteristics

Ethnicity

A study comparing Korean Americans and Chinese Americans examined whether differences in the prevalence of the *ALDH2*2* allele mediated ethnic differences in AUD and whether the effect of *ALDH2*2* was moderated by ethnicity (Luczak et al. 2004). These analyses found that *ALDH2*2* was a significant mediator of protection against alcohol dependence across different ethnic groups. However, no significant interaction existed between *ALDH2*2* and ethnicity. Another study, in contrast, found an interaction between *ALDH2*2*, ethnicity (i.e. Korean vs. Chinese), and alcohol dependence (Luczak et al. 2001). Chinese with an *ALDH2*2* allele were about one-quarter as likely to be alcohol dependent as those without the allele, whereas among the Koreans those with *ALDH2*2* were half as likely to be alcohol dependent. This finding suggests that *ALDH2*2* may have a stronger protective effect in Chinese than in Koreans. However, additional studies are needed to further explore this issue to conclusively determine the interplay between *ALDH2*2* and ethnicity, as well as other factors that might underlie ethnic differences.

Antisocial Behavior

Antisocial behavior and conduct disorder (CD) consistently have been identified as risk factors for alcohol use and AUD (see Krueger et al. 2002; Waldman and Slutske 2000). In both genders, symptoms of antisocial behavior and CD precede alcohol-related problems (Disney et al. 1999; Slutske et al. 1998). The prevalence of antisocial behavior as indicated by a diagnosis of antisocial personality disorder (ASPD) and CD differs among men and women and also shows racial/ethnic differences. In all populations studied, the prevalence for these conditions is significantly higher among men than among women (e.g., Lee et al. 1990; Luczak et al. 2004). Ethnic differences have been demonstrated particularly among Asian populations. For example, the rates of ASPD were substantially higher among South Koreans (1.6 percent) (Lee et al. 1990) than among Taiwanese (0.1 to 0.2 percent) (Hwu et al. 1989). Similarly, the prevalence of CD was higher among Korean-American college students (29 percent of men and 2 percent of women) than among Chinese-American college students (9 percent of men and 2 percent of women) (Luczak et al. 2004).

Several studies have analyzed whether differences in prevalence of protective alleles of alcohol-metabolizing enzymes and ASPD/CD could account for differences in the prevalence of AUD in different populations. A study assessing the relationship between *ALDH2*2*, CD, and alcohol dependence in Korean Americans and Chinese Americans found that although CD was a significant mediator of alcohol dependence, no significant interaction existed between CD and *ALDH2*2*. In other words, both *ALDH2*2* and CD influenced the risk of alcohol dependence, but these effects were independent of each other (Luczak et al. 2004). Other studies, however, have suggested that ASPD might interact with *ALDH2*2* to influence alcohol dependence. A study comparing *ALDH2* and *ADH1B* allele status in Taiwanese with and without ASPD and/or alcohol dependence found that *ALDH2*2* showed reduced association with alcohol dependence in people with ASPD compared with people without ASPD. *ADH1B*2* also no longer showed any association with alcohol dependence in antisocial alcoholics (Lu et al. 2005). Another study found that the prevalence of ASPD was higher in alcoholics with the *ALDH2*2* allele than in alcoholics without this allele (Iwahashi 1995). These findings suggest that the protective effects of *ALDH2*2* may be less strong in people with more antisocial behavior.

Behavioral Undercontrol

One of the personality traits known to predict alcohol and other drug use and abuse is behavioral undercontrol, a personality trait characterized by impulsivity, sensation seeking, and disinhibition (Sher et al. 2000). It also can explain, at least in part, the association between CD and AUD discussed above—that is, people with behavioral undercontrol also are more likely to be diagnosed with CD (Slutske et al. 2002). Researchers have investigated whether the increase in AUD risk conferred by behavioral undercontrol interacts with the reduction in risk conferred by *ALDH2*2*. One study (Doran et al. 2007) examined whether *ALDH2* status and the levels of behavioral undercontrol influenced the risk of binge drinking over a 2-week period in 18- to 29-year-old college students. The study found that, as expected, *ALDH2*2* reduced the risk of binge drinking, whereas behavioral undercontrol increased binge-drinking frequency. However, behavioral undercontrol did not seem to moderate the effects of *ALDH2*2*; instead, the effects of both factors were additive. This finding may be explained by the fact that behavioral undercontrol seems to act primarily at the level of alcohol use initiation (i.e., people with high levels of impulsivity and sensation seeking may be particularly likely to try alcohol and other drugs). In contrast, *ALDH2*2* influences not alcohol use initiation but continued use (i.e., people with *ALDH2*2* are less likely to continue using alcohol because they experience more intense effects).

Environmental Factors

Culture

Cultural influences, such as societal beliefs regarding alcohol use, which

are shaped by traditions, religious beliefs, and other philosophies widely acknowledged within a society, also shape drinking behaviors. For example, both Chinese and Korean cultures are influenced by Confucian philosophy, which emphasizes drinking in moderation (Bond and Hwang 1986; Cheng 1980). In addition, however, in Korean culture it also is important, especially for men, to socialize and drink heavily, which may result in greater acceptance of heavy drinking and alcohol problems (Cho and Faulkner 1993; Higuchi et al. 1996; Park et al. 1998*a,b*). Such cultural differences may contribute to the observed higher prevalence of AUD in people of South Korean heritage compared with those of Chinese or Taiwanese heritage (Helzer et al. 1990; Luczak et al. 2004). However, as mentioned previously, differences in the prevalence of *ALDH2*2* and *ADH1B*2* between different Asian ethnic groups also may account for at least part of the difference in AUD prevalence.

Further support for the relationship between culture and drinking behavior comes from observations that changes in cultural influences over time also may be followed by changes in drinking behaviors. Such developments, which have been observed in several Asian countries, also may moderate the influence of biological protective factors such as *ALDH2*2*. For example, a Japanese study found that between 1979 and 1992, when alcohol consumption became more culturally accepted and social pressure to drink increased, the proportion of Japanese patients who received treatment for alcohol dependence and carried the *ALDH2*2* allele increased from 2.5 percent to 13 percent, indicating that the protective effects of *ALDH2*2* had declined (Higuchi et al. 1994). Along the same lines, increasing acculturation of Asian Americans to American culture led to more heavy drinking and binge drinking (Hendershot et al. 2005). However, the extent of this effect was influenced by ethnicity. Thus, greater levels of acculturation in the United States may increase binge-drinking risk among people of Chinese origin but not among those of Korean origin.

Religion

Higher levels of religious behavior (e.g., commitment, affiliation, and service attendance, primarily with Christian religions) have been associated with lower alcohol use and related problems in the United States (e.g., Cochran et al. 1988; Midanik and Clark 1994; Wechsler et al. 1998). Similar analyses have been conducted with Asian and Asian-American populations, with different results depending on the population studied. Thus, whereas religious affiliation and involvement, particularly with Protestant denominations, was related to lower rates of alcohol involvement among Korean Americans (Lubben et al. 1989), the findings were inconsistent for Chinese Americans (Chi et al. 1988, 1989). In another study, religious affiliation as measured by service attendance was related to lower rates of binge drinking in Koreans regardless of their religion; among Chinese, however, such a relationship was found only among those affiliated with Western religions (Luczak et al. 2003).

Because twin studies have identified gene–environment interactions of religiosity with alcohol use behavior (Heath et al. 1999; Koopmans et al. 1999), researchers also have investigated potential interactions with *ALDH2*2* status. These analyses found that religiosity moderated the association of *ALDH2*2* with binge drinking (Luczak et al. 2003). Specifically, religious service attendance was related to binge drinking only in people homozygous for *ALDH2*1*, but not in those with at least one *ALDH2*2* allele, suggesting that the protective effect of *ALDH2*2* may be less strong in people with higher levels of religiosity.

Family Environment

Adoption studies can be especially informative for disentangling genetic influences from those of social environment. In particular, studies of adoptees can help determine if effects may be due to genetic factors or modeling behavior in the adoptive family environment. A study of adopted adolescents and young adults of Asian descent found that the effect of *ALDH2*2* was moderated by environmental influences of parental alcohol use and misuse as well as sibling alcohol use. Specifically, high parental alcohol use and misuse reduced the protective effect of *ALDH2*2* on alcohol phenotypes, whereas low parental alcohol use and misuse enhanced the effect of the allele (Irons et al. 2012). In a similar fashion, sibling alcohol use also appeared to moderate the effect of *ALDH2*2* on an adoptee's drinking behavior (Irons et al. 2007).

Childhood Adversity

Many but not all studies have shown that exposure to adverse events in childhood, such as sexual, emotional, and physical abuse, is a risk factor for developing an AUD in adulthood (Keyes et al. 2011). In a sample of Israeli adults with a relatively high prevalence of the *ADH1B*2* allele (47 percent either heterozygous or homozygous), a history of childhood adversity moderated the influence of *ADH1B*2* on alcohol-related phenotypes (Meyers et al. 2015). There was a stronger effect of *ADH1B*2* on AUD severity and the maximum number of drinks consumed in a day in individuals who had a history of childhood adversity compared with those who did not. Thus, *ADH1B*2* seems to exert a stronger effect in individuals whose risk for drinking is increased by their childhood adversity, although longitudinal studies are needed to confirm this finding.

Conclusions

Variations in the alcohol-metabolizing enzymes ADH and ALDH and the genes encoding them are associated with alcohol-related behaviors and the risk of AUD. In particular, the *ADH1B*2*, *ADH1B*3*, *ADH1C*1,* and *ALDH2*2* alleles have shown protective associations with alcohol dependence. The *ADH1B*2*, *ADH1C*1*, and *ALDH2*2* alleles have high prevalence in Asian populations and the *ADH1B*3* and *ADH1C*1* alleles in African populations, which may contribute to the differences in AUD prevalence observed among larger racial groups (i.e., Whites, Blacks, and Asians). Moreover, the prevalence of these alleles varies among different Asian subpopulations and may account at least in part for the different rates of AUD among those populations.

However, it also is clear that these alleles alone cannot explain all the differences in AUD prevalence between racial and ethnic groups; individual and environmental factors also play a role. In studies of Asian populations, some of these factors demonstrate additive effects to those imparted by *ADH1B*2* and *ALDH2*2*. In other cases, however, these additional factors interact with and moderate the effects of these alleles. In addition, a gene–gene moderating effect appears to exist between *ADH1B*2* and *ALDH2*2*, such that among people of Asian descent the effects of *ADH1B*2* may be larger in those who also carry *ALDH2*2*. Further exploration of the interactions between various genetic, individual, and environmental factors influencing drinking behavior and thus risk of AUD is necessary to fully understand how drinking behavior is shaped across developmental stages, which individual characteristics place people at risk for alcohol-related problems or AUD, when and where individuals are at most or least risk, and how preventive measures and interventions can reduce risk.

Financial Disclosure

The authors declare that they have no competing financial interests.

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Religious Affiliation and Spiritual Practices: An Examination of the Role of Spirituality in Alcohol Use and Alcohol Use Disorder

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"And be not drunk with wine, wherein is excess; but be filled with the Spirit" (Ephesians 5:18).

Religious affiliation, spirituality, and spiritual practices often have been studied as protective factors in the prevention and treatment of hazardous alcohol consumption (defined as drinking at a level that causes significant problems in functioning or that increases potential harms) and alcohol use disorder (AUD). Specifically, researchers have been interested in whether spirituality and spiritual practices, commonly associated with personal transformation, may also help in personal transformation of substance use behaviors. Personal transformation may involve elements—such as mindfulness and acceptance of a problem—that form the bases of behavioral treatments for substance use disorders, including AUD. Therefore, researchers are interested in whether spirituality can have a positive influence on AUD recovery. This sidebar reviews some of the recent research that evaluates the role of spirituality in the etiology, maintenance, and treatment of hazardous drinking and AUD, as well as the efficacy of spiritual practices, including meditation and prayer, in reducing alcohol use and preventing relapse following treatment for an AUD. It also discusses results from qualitative studies that have examined life experiences and spirituality as key sources of support among individuals who have recovered from an AUD. Finally, it mentions opportunities for integrating spiritual beliefs and practices into existing empirically supported treatments for hazardous drinking and AUD.

Spirituality and the Development of AUD

The importance of religiosity, religious experiences, and spiritual practices in the etiology and maintenance of AUD has been cited in the research literature for over 70 years (with seminal publications by Rice 1942 and Seliger 1947). Early publications described the potential benefits of religious practices in the treatment of "alcohol addiction" (Rice 1942, p. 393), although others noted that religious affiliation and early religious activity (e.g., attending church with parents) were not entirely protective against the development of AUD (Shalloo 1941; Walters 1957).

In an attempt to identify aspects of spirituality that may more or less protect against hazardous drinking and the development of AUD, more recent work has disentangled various dimensions of spirituality (e.g., Kendler et al. 2003) and identified potential mediators of the association between such dimensions and alcohol use (e.g., Drerup et al. 2011; Johnson et al. 2008). For example, Kendler and colleagues (2003) used a factor analysis of 78 items drawn from numerous sources to identify the following seven dimensions of spirituality that individuals engage in: (1) general religiosity; (2) social religiosity; (3) involvement of God; (4) forgiveness; (5) God as judge; (6) unvengefulness; and (7) thankfulness. Each was uniquely associated with the occurrence of a variety of psychiatric disorders in the general population. Of relevance to the current article, Kendler and colleagues (2003) found that greater general religiosity, social religiosity, belief in the involvement of God in a person's life, belief in God as

judge, and thankfulness all were significantly associated with a decreased risk for alcohol dependence.

Studies also have examined mediators of the associations between spirituality and alcohol use. For example, alcohol beliefs (including drinking motives and alcohol expectancies), social influences, and spiritual well-being all have been shown to significantly mediate the association between religious involvement and alcohol use among college students (Galen and Rogers 2004; Johnson et al. 2008) and among adults in the general population (Drerup et al. 2011). Alcohol use attitudes also mediate the association between religiosity and the frequency of alcohol use among adolescents such that higher rates of religious behavior were related to lower levels of alcohol use (Vaughan et al. 2011). In addition, degree of religiosity has been shown to moderate the association between perceived drinking norms and alcohol use, suggesting that greater focus on religion may buffer the effects of perceived drinking norms on heavy alcohol use behavior (Neighbors et al. 2013). Thus, involvement in religious activities or communities may exert a preventive influence on people, tempering the impact of other societal attitudes or pressures.

Religiosity and Spirituality in Recovery From AUD

In addition to the aforementioned associations between reduced alcohol use and religion and spirituality, some evidence suggests that religion and spirituality may be associated with recovery from AUD for some individuals. For example, Sobell and colleagues (1993) interviewed individuals who had successfully recovered from substance use disorders and identified 10 major themes that were key to their success. One of these was having had a religious experience (Cunningham et al. 1994; Sobell et al. 1993). Cunningham and colleagues (1994) asked individuals at two different treatment facilities if each of these 10 themes preceded their own recovery and to rate how important each was to their decision to seek treatment. Although other reasons for seeking treatment (e.g., weighing the pros and cons of continued alcohol use) were more frequently endorsed by participants, those who cited a religious experience as a reason for seeking treatment rated that experience as just as important as other reasons behind their decision (i.e., approximately a 4 out of 5 in degree of importance); (Cunningham et al. 1994). Although these findings were reported two decades ago, they represent seminal work. More recent research has found similar associations between spiritual experiences and religiosity and AUD recovery (e.g., Dawson et al. 2012; Matzger et al. 2005). Thus, for some people, religious experiences may be an important aspect of treatment seeking and AUD recovery.

Underscoring the potential power of religious and spiritual experiences for some individuals, research has identified such experiences as important among individuals who recover from AUD and other substance use disorders without treatment. For example, Tuchfeld (1981) examined intensive interviews with 51 individuals who had spontaneously remitted from AUD. Among 13 of these individuals, "religious conversion or experience" was a factor associated with their resolution of AUD (p. 632). Similarly, Ludwig (1985) examined interviews among 29 individuals with AUD and found that "spiritual–mystical experiences" were associated with the initiation of abstinence from alcohol among individuals who recovered from AUD without treatment (p. 53). Finfgeld (2000) reviewed extant qualitative findings on self-resolution of substance use problems and found that a common theme of recovery was a reinvestment in oneself that often included involvement in religious activities.

More recently, Matzger and colleagues (2005) collected data from 659 adults with AUD and evaluated the reasons they gave that were associated with reduced drinking and sustained remission from problem drinking. Among both general-public and treatment-seeking participant groups, "undergoing a spiritual awakening" (p. 1637) was one of the predictors of sustained remission. Accordingly, existing research suggests that religious and spiritual experiences are associated with AUD recovery among both treatment-seeking and non–treatment-seeking populations.

Changing Spirituality to Reduce Alcohol Use and Treat AUD

The majority of research conducted on spirituality and alcohol use has been focused on engagement in 12-step programs, such as Alcoholics Anonymous (AA). The AA program holds the belief that recovery is reached through spiritual experiences and an awakening to one's higher power. To better understand the relationship between AA and drinking, researchers have examined spiritual growth as a change mechanism in AA. In a group of new members of

AA, spiritual growth was found to mediate the effects of AA on increased abstinence and decreased drinking intensity such that spiritual growth was related to increased abstinence (Tonigan et al. 2013). In another study (Kelly et al. 2011), the effect of AA attendance on improved alcohol outcomes (including abstinence and drinking intensity) was partially mediated by increases in spirituality. Importantly, greater AA involvement (defined as engaging in AA-related activities, obtaining a sponsor, etc.) has been shown to be a stronger predictor of drinking outcomes and increased spiritual experience than AA attendance alone (Krentzman et al. 2013).

Changes in a person's spirituality also may influence drinking behavior independent of his or her AA involvement. To examine this possibility, researchers have measured changes in spirituality and religious participation among individuals with AUD both with and without AA involvement (Robinson et al. 2011). Results indicated that, independent of AA involvement, 6-month increases in private spiritual or religious practices and forgiveness of self were the strongest predictors of improved drinking outcomes. Changes in daily spiritual experiences, purpose in life, a general measure of forgiveness, and negative religious coping (defined as conflict, question, and doubt regarding issues of God and faith) were also significantly associated with drinking outcomes. The findings suggest that spirituality operates independently of a 12-step framework. Therefore, looking broadly at spiritual practices—both within and outside of AA—could help researchers understand what life changes people are making when they increase their spiritual involvement that help them experience sustained improvements in their drinking practices.

Recent research, for example, has focused on the utility of mindfulness- and acceptance-based interventions for the treatment of AUD, as these have been identified as elements of personal spiritual transformation. In particular, a growing area of research supports the use of mindfulness meditation for treating substance use disorder (Witkiewitz et al. 2014; Zgierska et al. 2009). Mindfulness-based relapse prevention (MBRP), an after-care intervention for substance use disorders that incorporates mindfulness practices with relapse prevention methods, has been shown to decrease substance use, heavy drinking, and substance-related problems significantly as compared with treatment as usual and standard relapse prevention in three randomized clinical trials (Bowen et al. 2009, 2014; Witkiewitz et al. 2014). Further, Garland and colleagues (2010) developed a program for AUD called mindfulness-oriented recovery enhancement involving using mindfulness meditation practices to reduce relapse. The group found significant effects of intervention in changing cognitive, affective, and physiological responses that often are predictive of alcohol relapse following treatment. Additional research has found that significant improvements in elements of spiritual growth such as acceptance and attentional awareness—defined as the ability to attend to what one deems relevant—as well as changes in the management of craving and negative affect, significantly mediate effects of mindfulness based interventions on substance use and related outcomes (Elwafi et al. 2013; Witkiewitz and Bowen 2010; Witkiewitz et al. 2013). Only a few studies have examined the association between mindfulness practices and spiritual gains (Amaro et al. 2010), so this is an area in need of future research.

Conclusion

References to the importance of spirituality in protecting individuals from excessive drunkenness date back to early religious texts and have been part of the research literature on harmful drinking and AUD since the early 1940s. Over the past 70 years, we have learned that religiosity and religious affiliation are not sufficient to protect against the development of AUD, but that spiritual experiences and spiritual practices, including prayer and mindfulness meditation, may be helpful in reducing hazardous drinking and in the treatment of AUD. Although AA affiliation and involvement has long been associated with the importance of spirituality in recovery, research on spirituality in AUD is not limited to AA. In recent years, increasing numbers of studies have used experimental designs to examine the effects of spiritual practices on alcohol use and AUD recovery, demonstrating that engaging in prayer may help reduce hazardous alcohol use (Lambert et al. 2010) and that engaging in mindfulness meditation practices reduces risk for relapse following treatment for AUD (Bowen et al. 2009, 2014; Witkiewitz et al. 2014). Future research should continue to examine methods of reducing hazardous alcohol use and improving outcomes in the treatment of AUD through spiritual practices.

Religious Affiliation and Spiritual Practices: An Examination of the Role of Spirituality in Alcohol Use and Alcohol Use Disorder *(continued)*

Financial Disclosure

The authors declare that they have no competing financial interests.

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Social and Cultural Contexts of Alcohol Use

Influences in a Social–Ecological Framework

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Alcohol use and misuse account for 3.3 million deaths every year, or 6 percent of all deaths worldwide. The harmful effects of alcohol misuse are far reaching and range from individual health risks, morbidity, and mortality to consequences for family, friends, and the larger society. This article reviews a few of the cultural and social influences on alcohol use and places individual alcohol use within the contexts and environments where people live and interact. It includes a discussion of macrolevel factors, such as advertising and marketing, immigration and discrimination factors, and how neighborhoods, families, and peers influence alcohol use. Specifically, the article describes how social and cultural contexts influence alcohol use/misuse and then explores future directions for alcohol research.

Keywords: Alcohol consumption; alcohol misuse; morbidity; mortality; risk factors; alcohol-related consequences; social factors; cultural factors; environmental factors

The alcohol research literature is overwhelmingly focused on risk factors, from the societal level down to the individual. Worldwide, 3.3 million deaths were attributed to alcohol misuse in 2012 (World Health Organization 2014). Excessive alcohol use is the third leading cause of death in the United States, accounting for 88,000 deaths per year (Centers for Disease Control and Prevention 2014). Globally, alcohol-attributable disease and injury are responsible for an estimated 4 percent of mortality and 4 to 5 percent of disability-adjusted life-years (DALYs) (Rehm et al. 2009). The harmful effects of alcohol misuse are far reaching and range from accidents and injuries to disease and death, as well as consequences for family, friends, and the larger society. Economic costs attributed to excessive alcohol consumption are considerable. In the United States alone, the costs of excessive alcohol use were estimated at $223.5 billion in 2006, or $746 per person (Bouchery et al. 2011). Much of these costs result from a loss in workplace productivity as well as health care expenses, criminal justice involvement, and motor vehicle crashes (Rehm et al. 2009).

This article reviews some of the cultural and social influences on alcohol use and places individual alcohol use within the contexts and environments where people live and interact. This is not an exhaustive review but aims to show the wide range of contexts that may shape alcohol use.

Disparities in and Influences on Alcohol Use: A Social–Ecological Framework

Alcohol consumption varies across gender and race/ethnicity. Across the world, men consume more alcohol than women, and women in more developed countries drink more than women in developing countries (Rehm et al. 2009). American men are much more likely than women to use alcohol (56.5 percent vs. 47.9 percent, respectively), to binge drink (30.4 percent vs. 16 percent, respectively), and to report heavy drinking (9.9 percent vs. 3.4 percent, respectively) (Substance Abuse and Mental Health Services Administration [SAMSHA] 2013). (Binge drinking is defined here as the number of instances in the past 12 months that women drank 4 or more drinks and men drank 5 or more drinks within a 2-hour period.) Among racial and ethnic groups, Whites report the highest overall alcohol use among persons age 12 and over (57.4 percent). American Indian/Alaska Natives report the highest levels of binge drinking (30.2 percent), followed by Whites (23.9 percent), Hispanic/Latinos

(23.2 percent), African Americans (20.6 percent), and Asians (12.7 percent) (SAMHSA 2013). Alarmingly, according to two nationally representative samples, trends in alcohol misuse increased among both men and women and African-American and Hispanic youth over the decade between 1991–1992 and 2001–2002. Rates of dependence also increased among men, young Black women, and Asian men during the same time period (Grant et al. 2004).

Given these trends, it is clear that a better understanding of the underlying social and cultural factors contributing to these disparities is needed. For example, socioeconomic status (SES) indicators (i.e., education, income, and occupation) usually are strong predictors of health behaviors and outcomes and tend to be positively associated with health. People with higher SES tend to drink more frequently than others (Huckle et al. 2010). Among drinkers, low-SES groups tend to drink larger quantities of alcohol (Huckle et al. 2010).

Like other health issues, alcohol use can be linked to a complex array of factors ranging from individual-level (i.e., genetics) to population-level (i.e., cultural and societal factors) characteristics (Berkman et al. 2000; Krieger 2001; Link and Phelan 1995). On a population level, emerging research has documented the relationship between social determinants and health (Berkman and Kawachi 2000; Berkman et al. 2000) and, specifically, the social epidemiology of alcohol use (Bernstein et al. 2007; Galea et al. 2004). Social capital theory suggests that social networks and connections influence health (Berkman et al. 2000). Individuals who have higher levels of social support and community cohesion generally are thought to be healthier because they have better links to basic health information, better access to health services, and greater financial support with medical costs. (Berkman and Kawachi 2000).

This article examines these population-level as well as individual influences through a social–ecological framework, which posits that human health and development occur across a spectrum—from the individual to the macro or societal level (Bronfenbrenner 1994). In the context of alcohol use, individuals are nested within their microsystem (their home, work, and school environments), which is nested itself within the larger community. Macrolevel factors, such as exposure to advertising, may influence family and peer network attitudes and norms, which ultimately affect individual attitudes and behaviors (see figure).

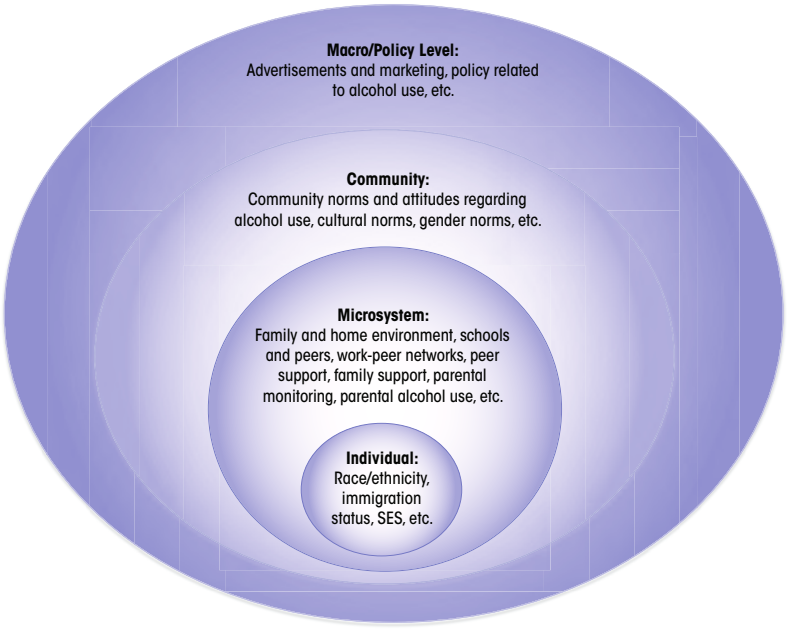

Figure A social–ecological framework for explaining influences on alcohol use. Individual-level factors that influence alcohol use are nested within home, work, and school environments, which are nested within the larger community. Macro-level factors, such as exposure to advertising, may influence family and peer network attitudes and norms, which ultimately affect individual attitudes and behaviors.

Societal Influences: Advertising, Marketing, and Social Media

Media exposure helps influence social norms about alcohol through advertising, product placements, and stories in a wide range of sources, including movies, television, social media, and other forms of entertainment. Although alcohol sales and marketing are highly regulated, people are exposed to a wide variety of alcohol and liquor advertisements, especially in the United States. Whether these advertisements directly result in an increase in consumption has been the topic of many public policy debates and much alcohol and consumer research. Recent studies have used robust methodological designs in order to assess the effects of advertisements on alcohol consumption (Grenard et al. 2013; Koordeman et al. 2012). Although longitudinal studies have found that alcohol commercials particularly affected younger adolescents' propensity to consume alcohol (Grenard et al. 2013), an experimental design randomly assigning college students to alcohol advertisements demonstrated no differences compared with the control group (Koordeman et al. 2012). It is likely that the effects of advertisement differ across age groups and races. The alcohol industry uses complex targeted marketing strategies that focus on African Americans, Latinos, and American Indians, among other demographic groups, such as youth and other ethnic minorities (Alaniz and Wilkes 1998; Moore et al. 2008). Empirical studies show that targeted alcohol marketing results in individuals developing positive beliefs about drinking, and creating and expanding environments where alcohol use is socially acceptable and encouraged (Alaniz and Wilkes 1998; Hastings et al. 2005; McKee et al. 2011). These factors can result in the onset of drinking and binge drinking, and in increased alcohol consumption (Tanski et al. 2015).

Since the introduction of flavored alcoholic beverages in the 1980s, the alcohol industry has engaged in targeted marketing efforts toward youth in general, and especially young women (Mosher and Johnsson 2005). Products with sweet fruity flavors, colorful appearance and packaging, as well as lower alcohol content are designed to appeal to young women. Fruity drinks mask the taste of traditional alcoholic beverages with the sugary flavors of soft drinks (Mosher and Johnsson 2005), making them more palatable for this consumer market. Although the alcohol industry claims that its marketing strategies target adults ages 21–29, products like flavored alcoholic beverages remain attractive to younger drinkers.

Research estimates that 38.5 percent of high school students have used alcohol in the past month, and 20.5 percent of teenagers started drinking before age 13 (Eaton et al. 2012). Approximately 75 percent of high school seniors and 64 percent of high school 10th graders report having experimented with alcohol (Kann et al. 2014). Youth under age 21 see and hear marketing for flavored alcoholic beverages disproportionally on a per capita basis compared with adults (Jernigan et al. 2005), and a disproportionate number of youth consume alcoholic beverages (Mosher and Johnsson 2005). Furthermore, youth exposed to alcohol advertisements tend to drink more on average than their peers who were exposed to less intensive alcohol-related marketing (Snyder et al. 2006). Specifically, the authors found that each additional advertisement viewed by youth increased the reported number of drinks consumed by 1 percent.

Alcohol marketing also can lead to youth and young adults developing alcohol brand preferences (Albers et al. 2014; Ross et al. 2015), which can influence their reports of alcohol consumption (Roberts et al. 2014). For example, youth reported on average 11 more drinks per month when responding to an online survey that used brand-specific measures compared with a survey using more general alcohol measures (Roberts et al. 2014). The relationship between alcohol brand receptivity and alcohol brand consumption also has been linked to whether and when adolescents begin to binge drink (Morgenstern et al. 2014).

Increased use of social media for alcohol marketing has paralleled changes in communication methods among adolescents and college-age youth (Hoffman et al. 2014). Marketing techniques for a wide range of products reflect studies that online platforms are likely to influence adolescent behaviors (Cook et al. 2013). Social media venues are most widely used by youth, with 92 percent of teens reporting being online daily and 24 percent online "almost constantly" (Lenhart 2015). Social-networking sites such as Twitter, Instagram, and Facebook feature alcohol-related marketing. One study found that by 2012, there were more than 1,000 alcohol-related sites on Facebook alone (Nhean et al. 2014). Alcohol use increases with the number of online peer ties and greater peer density, a measure of interconnectedness in the social network (Cook et al. 2013). Despite self-imposed regulations aimed at preventing underage youth from accessing alcohol advertisements on social media, more than two-thirds of advertisements on YouTube are accessible to youth under the legal drinking age (Barry et al. 2015).

Racial and ethnic minorities, especially those living in African-American communities, are likewise exposed to targeted alcohol beverage advertisements (Wilson and Till 2012). African Americans account for 13 percent of the U.S. population, but they purchase 67 percent of all malt liquor sold (Miller Brewing Company 2000). Malt liquor generally has higher alcohol content, is less expensive, and is sold in larger volumes than other beers and ales, and African Americans are exposed to more malt liquor advertisements than other groups. Billboards and other advertisements for malt liquor are disproportionately found in neighborhoods with higher percentages of African Americans, and rap music lyrics frequently mention malt

liquor (Herd 2013; McKee et al. 2011). When examining alcohol advertising in newspapers, Cohen and colleagues (2006) found that there were more alcohol-related ads in newspapers targeted to African-American readers compared with newspapers with a more general readership. Kwate and Meyer (2009) found a correlation between problem drinking among African-American women and exposure to alcohol advertisements, suggesting that as ad exposure increased, so did alcohol consumption.

These findings, however, must be interpreted with caution, as it is difficult to determine whether advertisements directly result in increased alcohol consumption. To begin with, a variety of marketing strategies including distribution, product development, pricing, and targeted marketing all may affect links between advertising and consumption (Alaniz and Wilkes 1998; Roberts et al. 2014). For example, Molloy (2015) found that after controlling for targeting, only moderate advertising effects are seen, despite the strong correlations between alcohol advertising and drinking among youth. It also is unclear which aspects of online social media advertisements are related to the observed correlations. Research shows that drinkers like advertising about alcohol more than nondrinkers do, respond neurologically to the advertising more intensively than nondrinkers do, and may recall the advertising more clearly (Snyder et al. 2006), making it harder to distinguish among the specific mechanisms behind the observed relationships. As a result, making causal statements about alcohol use and marketing is problematic because the temporal order between using alcohol and seeing advertisements is not frequently established (Snyder et al. 2006).

Despite these challenges, it is important to develop new strategies to systematically examine the impact of advertising and marketing on alcohol use among different populations. For example, researchers might continue to compare marketing and advertising strategies within specific neighborhoods to more fully understand targeted marketing's influence on alcohol use. Further research and evaluation studies also are needed that can help establish whether and how advertising and marketing can lead to alcohol use in vulnerable and disadvantaged populations.

Influences From Discrimination

A number of social and cultural factors predict increased alcohol use, including discrimination and its related stigma. The role of discrimination and stress in health-related risk behaviors, including alcohol use, is well established (Dawson et al. 2005; Hatzenbuehler 2009; Paradies 2006). The stress and coping framework frequently is applied to explain the influence of discrimination and stigma on health (Krieger 1999; Pascoe and Smart Richman 2009; Walters et al. 2002). This long-held theory posits that people consume alcohol to cope with the stress of their daily lives, including work-related stressors and racial and ethnic discrimination (Conger 1956).

Discrimination is seen as a key social stressor that elicits a physiological response, including elevated blood pressure and release of stress hormones (Williams and Mohammed 2009), which may have lifelong deleterious effects, including increased alcohol use (Pascoe and Smart Richman 2009). Self-reported unfair treatment and racial discrimination has been linked to higher alcohol use among Asian Americans (Chae et al. 2008; Gee et al. 2007; Yoo et al. 2010) and Latinos (Mulia et al. 2008).

The picture is less clear among African Americans. Although similar positive associations have been found between level of discrimination and alcohol use in this population (Boynton et al. 2014; Gibbons et al. 2004; Mulia et al. 2008), other recent studies (Kwate and Meyer 2009) among African-American adults have found no relationship between high levels of racial discrimination and heavy and episodic drinking. However, Borrell and colleagues (2007) did report an association between discrimination and past-year alcohol use. The mixed results among African Americans may relate more to SES than to discrimination. Past studies suggest that African Americans with higher levels of education were more likely to report experiencing discrimination, whereas the opposite was true among Whites (Borrell et al. 2007; Krieger et al. 1998). This may be because better educated African Americans find themselves in situations in which they may be exposed to discrimination, or they may be more acutely aware of how subtly it can be expressed. Whites of lower SES may be in the minority and therefore may be more likely to report experiencing discrimination. This may explain the mixed results found in this particular population segment, as socioeconomic position actually may mute the effects of discrimination on alcohol use. Further research is needed to examine these potential mechanisms and other underlying factors that interact with racial discrimination to influence and alcohol use and misuse among minorities.

Another group that may be at particular risk for alcohol problems stemming from their experiences with discrimination are those in the lesbian, gay, bisexual, and transgender (LGBT) community, who experience high levels of discrimination related to sexual orientation and gender identification (Krieger and Sidney 1997). One study found that more than two-thirds of LGBT adults experienced discrimination, and individuals who reported discrimination based on race, gender, and sexual orientation were almost four times more likely to use alcohol and other substances (McCabe et al. 2010). This suggests that future studies and public health interventions should focus not only on racial and gender discrimination, but also sexual orientation and gender identification.

Immigration-Related Influences

Societal influences can shape drinking behavior among immigrants to the United States. In 2010, nearly 40 million people, or 13 percent of the U.S. population, had been born in another country—the largest absolute number of U.S. immigrants ever and the highest proportion who are foreign born since the 1920s (Grieco et al. 2012). With wide diversity among immigrants in terms of national origin, language, religion, and social class, and with even more reasons for and processes of migration than ever before (Dubowitz et al. 2010), it is no surprise that the evidence on alcohol consumption among immigrants is similarly complex.

Immigration may influence alcohol consumption and its consequences in at least two ways. The first theory suggests that immigrants encounter difficulties and hardships as they transition into a new society and culture (Berry 1997). Hardships include the stress of experiencing new environments and cultures; living in poor neighborhoods; finding good, secure jobs in safe work environments; encountering few opportunities to enhance income or wealth; and engaging with fewer and smaller social networks that may otherwise offer instrumental and emotional support. It also is possible that immigrants may not become fully integrated into American society because of experiences with discrimination and obstacles in social mobility (Unger et al. 2014). Because these factors are associated with alcohol consumption and problems, immigrants may consume more alcohol (Unger et al. 2014). As they become settled in the new society, this consumption pattern decreases (Bui 2012). A second hypothesis posits that alcohol consumption increases the longer immigrants live in a new location (Lee et al. 2013). Over time, immigrants may learn the behaviors and adapt the lifestyles often associated with alcohol consumption in American society (i.e. experience acculturation) (Caetano 1987; Vaeth et al. 2012).

Strong evidence indicates that norms in countries of origin have long-term effects on the drinking patterns of immigrants (Cook et al. 2014). Recent immigrants generally have lower rates of alcohol consumption and excessive drinking than other U.S. residents (Brown et al. 2005; Szaflarski et al. 2011). Available reviews find that acculturation leads to more alcohol consumption among immigrants, including Latinos (Valencia and Johnson 2008; Zemore 2007). Higher acculturation is associated with higher odds of drinking and heavier drinking among Latino women (Zemore 2007). The findings for Latino men appear less clear cut, with high acculturation tied to greater likelihood of drinking but not a definitive pattern for problem drinking.

Studies are beginning to recognize the importance of premigration factors, including levels of alcohol use before migration as well as the cultural influences of countries of origin (Sanchez et al. 2014; Walsh et al. 2014). One study (Sanchez et al. 2014) among Latinos found that Latino men had higher levels of alcohol use before immigration, with steeper declines postmigration compared with Latino women. This finding suggests that future studies may need to focus on trajectories of alcohol use to address alcohol prevention efforts. Moreover, retaining culture of origin also has been shown to have protective influences for alcohol use (Schwartz et al. 2012), including protective family and traditional values.

Timing also may be critical in understanding how immigration is associated with alcohol consumption. Age at immigration can be seen as the developmental context of people's experiences when they first arrive in the United States. This context helps to shape language use, heterogeneity of social networks, and schooling. The social institutions that affect people's lives vary by age of immigration (Fuligni 2004; Rumbaut 2004). The number of social groups and institutions, such as schools, clubs, friendship networks, and family ties, geared toward supporting children to integrate into their new society is far greater than those available for adults (Takeuchi et al. 2007). These social groups, in turn, offer children greater access to the opportunity structures in a new culture. Conversely, immigrant children may have a larger set of social groups available to them than older immigrants. As a result, they also could experience a greater amount of negative stressors and influences that could lead to detrimental social and health outcomes as they mature. Immigrants who move to the United States at younger ages may be at risk for behaviors like alcohol use and misuse because they have the potential to be involved in social networks that may offer greater access and opportunity to engage in these behaviors, as well as lower levels of parental attachment (Hahm et al. 2003; Vaeth et al. 2012).

A recent study found that Mexican immigrants who come to the United States before age 14 have higher alcohol consumption rates than those who are older when they immigrate (Reingle et al. 2014). Immigrants who come at a younger age have alcohol consumption patterns similar to their U.S.-born counterparts. The study by Reingle and colleagues also shows that immigrants who arrive when they are younger than 14 and who live beyond the U.S.–Mexico border region have much higher rates of alcohol use than immigrants in the border region. This particular finding suggests that where immigrants live is another social context worth further investigation.

Community Influences

The literature on community influences on alcohol use focuses primarily on environmental aspects, such as neighborhood characteristics and opportunities for alcohol purchasing and consumption. For example, one study found that individuals who lived

in a neighborhood with a poorly built environment, characterized by inferior building conditions, housing, and water and sanitation indicators, were 150 percent more likely to report heavy drinking compared with those living in better built environments (Bernstein et al. 2007). Other studies have examined the spatial epidemiology of neighborhoods regarding alcohol availability, individual consumption, and community disorganization and violence (Cohen et al. 2006; LaVeist and Wallace 2000; Scribner et al. 2000; Shimotsu et al. 2013; Theall et al. 2011). Spatial relations between alcohol outlets and individual consumption also may be a key to explaining differential rates in alcohol use across racial/ethnic groups. A number of studies suggest that minority communities have higher concentrations of liquor stores than White communities (Alaniz and Wilkes 1998; LaVeist and Wallace 2000; Pollack et al. 2005; Romley et al. 2007; Treno et al. 2000), potentially increasing access to alcohol among minority populations (Freisthler et al. 2015; Scribner et al. 2000). Moreover, living in a disadvantaged neighborhood at an early age has long-term effects. Childhood exposure to violence leads to increased exposure to delinquent peers and alcohol use (Trucco et al. 2014). In another study, realizing how easy it is to get alcohol, witnessing neighborhood drug dealing, and seeing peers drink were all associated with increased alcohol use (Chung et al. 2014).

Relating neighborhood characteristics to alcohol use risk is useful for public health program planning because it allows policymakers and programmers to understand how changing structural-level factors of the built environment may affect health risk behaviors, including alcohol use. However, methodological challenges remain when analyzing the impact of complex community factors on individual behaviors. Such factors include social stratification (i.e., the probability of living in certain neighborhoods, which is higher for certain types of persons) and social selection (i.e., the probability that drinkers are more likely to move to certain types of neighborhoods). It remains unclear whether neighborhood disadvantage causes alcohol problems, and whether frequent drinkers are in fact usually more attracted to certain neighborhoods (i.e., self-selection). These challenges limit the interpretation of research on community-level effects. Some studies have attempted to address these issues using propensity matching and time-sensitive indicators (Ahern et al. 2008). Future studies should take these challenges into consideration and address subgroup differences in alcohol use norms across race/ethnicity and gender.

Cultural Norms

Cultural norms and beliefs are strong predictors of both current drinking and frequent heavy drinking (Brooks-Russell et al. 2013; Caetano and Clark 1999; LaBrie et al. 2012; O'Grady et al. 2011; Paschall et al. 2012). Across race and ethnicity, African Americans and Latinos report more conservative attitudes toward drinking compared with Whites (Caetano and Clark 1999; LaBrie et al. 2012). These more conservative norms may be associated with lower drinking rates among African Americans and Latinos compared with Whites (SAMHSA 2013). Few studies have examined diversity within racial and ethnic groups such as Latinos, Blacks, and Asians, limiting our ability to meet the needs of specific subpopulations. Some studies suggest that alcohol-related problems differ substantially across Latino subgroups, including higher rates of alcohol abuse and dependence among Mexican-American and Puerto Rican men compared with Cuban Americans and Central and South Americans (Caetano et al. 2008). These findings may best be explained by considerable differences in cultural norms, especially the cultural beliefs regarding appropriate alcohol use (Greenfield and Room 1997; LaBrie et al. 2012). For example, some scholars explain heavy-drinking patterns among Latino men through the concept of machismo, which has been a significant cultural influence for generations and remains integral to Latino male identity (Dolezal et al. 2000). Machismo suggests that Latino men attempt to appear strong and masculine because of cultural values, and drinking greater amounts of alcohol further exemplifies their masculinity. More recently, scholars have commented that concepts like machismo cannot account for the complexity of Latino drinking behavior (Caetano 1990).

Asians, on the other hand, generally are thought to have higher abstention rates compared with other racial and ethnic groups, especially when they are integrated within their ethnic cultures (Cook et al. 2012). One measure of the retention of ethnic values and cultural norms is generation status. That is, the longer immigrants have lived in the United States, the more likely they are to acculturate to the cultural norms of their destination community (Berry et al. 2006). Lower levels of ethnic identity may be one explanation for these differences across Asian subgroups. Japanese Americans, Filipino Americans, and Korean Americans often have been in the United States longer than other Asian subgroups, such as Cambodians, Thais, and Vietnamese, and also report higher levels of alcohol use compared with other Asian Americans and Asian immigrants (Iwamoto et al. 2012). Ethnic identity may promote stronger family values and traditional ties, leading to lower levels of alcohol use. Moreover, Asian-American adolescents who have a high attachment to family or who share their family's negative attitudes toward drinking are less likely to consume alcohol (Hahm et al. 2003).

Cultural norms also vary by context and place. Some alcohol researchers have used multilevel approaches to distinguish among the causal effects

of individual and neighborhood-level norms. For example, Ahern and colleagues (2008) found that neighborhood norms against drunkenness were a more robust and stronger predictor of binge drinking than permissive beliefs about it held either by the individual or family and friends. If an individual lived in a neighborhood that frowns on binge drinking, that individual was less likely to drink, even if he or she believed it acceptable to do so. This was particularly true for women, suggesting gender norms around alcohol use may be a factor.

Specifically, past studies found that gender differences in alcohol use may reflect the greater social stigma directed at women who drink. This seems to be more pronounced in certain cultures. Caetano and Clark (1999), for example, found stronger gender norms related to alcohol use in Latino cultures compared with the United States (Kulis et al. 2012). This results in greater gender differences in alcohol use among Latinos compared with other U.S. populations, with recent trends suggesting similar levels of binge drinking between men and women in Western cultures (Iwamoto et al. 2012). This may reflect changing beliefs about gender and social status. Although traditionally perceived as a "masculine" behavior, binge drinking is now more acceptable among women in certain cultures that foster more balanced gender roles (Lyons and Willott 2008).

Family and Peer Influences on Adolescent and Young Adult Drinking

Some of the strongest influences on adolescent drinking behavior come from the people that youth spend the most time with: family and friends. Studies have found that higher levels of alcohol use among parents and peers is associated with increased alcohol use among adolescents and young adults (Cruz et al. 2012; Dawson 2000; Mares et al. 2011; Osgood et al. 2013; Trucco et al. 2014; Varvil-Weld et al. 2014; Wallace et al. 1999; Walsh et al. 2014; Williams and Smith 1993). Developmentally, people's social contexts shift from the family unit during childhood to focus more on their peers and their schools during adolescence. Reflecting this, parental alcohol use seems to exert a greater influence before age 15 and diminishes over time (Dawson 2000).

Conversely, family support, bonding, and parental monitoring is associated with lower alcohol use (Bahr et al. 1995; White et al. 2006) and social networks and social support also have protective effects (Ramirez et al. 2012). For example, one study that assessed the effects of leaving home and attending college found that although the transition overall was associated with higher levels of alcohol use, young people with fewer friends who use alcohol reported higher levels of religiosity. Higher parental monitoring also protected against alcohol and marijuana use (White et al. 2006). Moreover, higher levels of familism (values that place family needs over individual needs) and being in a nuclear family served as protective factors among adolescents (Ewing et al. 2015).

Peer norms play an important role at this life stage (Jackson et al. 2014). By the late adolescent period, parental influences related to alcohol use are small compared with peer influences (Schwinn and Schinke 2014; Zehe and Colder 2014). Much of the focus on peer influences has highlighted the risk networks associated with alcohol use. Peer pressure (Studer et al. 2014), peer alcohol norms (Varvil-Weld et al. 2014), and socializing with substance-using peers (Patrick et al. 2013) were associated with alcohol misuse and binge drinking. Studies note that leaving the home environment, entering college, and joining Greek organizations increased alcohol use as a result of more socially permissive norms around drinking (Scott-Sheldon et al. 2008; White et al. 2006).

More recent studies have attempted to assess the synergistic influence of peers and families. Whereas the majority of studies on peers have focused on the negative consequences of social networks, research shows that greater parental support and monitoring can lead to prosocial peer affiliations (Williams et al. 2015). One study found that protective influences in parental domains can moderate the negative effects of negative peer influences among Latino college students (Varvil-Weld et al. 2014). In particular, maternal communication resulted in less alcohol use; conversely, maternal permissive norms and peer norms were associated with more alcohol use. Greater parental disapproval toward alcohol use is associated with lower involvement in peer networks that use alcohol, less peer influence to use, and greater self-efficacy and stronger negotiation skills to avoid alcohol (Nash et al. 2005). Interventions aimed at establishing and fostering conservative peer norms were found to be more effective than individual resistance training (Hansen and Graham 1991), whereas multilevel interventions incorporating peers, families, and communities are known to be effective among adolescents (Chapman et al. 2013; Perry et al. 2002; Toumbourou et al. 2013).

Existing successful interventions to reduce alcohol use include incorporating culturally sensitive delivery models, such as employing community health workers among Latino populations (Ornelas et al. 2014) and using Web-based interventions to change norms (Patrick et al. 2014). In a recent review, *Familias: Preparando la Nueva Generación,* a culturally grounded intervention for parents to support Mexican-heritage youth, showed reductions in parental drinking (Williams et al. 2015). Because past studies show that parents may potentially moderate negative peer influence, fostering synergistic solutions between multiple contexts should be a priority (Ewing et al. 2015).

Directions for Future Research

This article highlights examples of how societal factors, cultural norms, neighborhoods, and social contexts may be associated with alcohol misuse. Certain gaps in the literature clearly remain. Methodologically, these findings should be interpreted with caution, because it is difficult to distinguish between and among societal and community-level influences. Future studies should use advanced statistical methods such as multilevel modeling techniques, based on theoretical and conceptual approaches in population health. In addition, longitudinal data will help support causal hypotheses and relationships.

Risk and protective factors, prosocial peer affiliations, and synergistic relationships between social contexts are worth further research. Among immigrants, retaining the cultural values of the country of origin has shown to have protective influences on alcohol use, and this finding should be incorporated into future interventions for immigrant populations. Focusing on risk and protective factors will help inform future programs addressing alcohol initiation, specifically helping parents and communities understand how they may influence alcohol use among adolescents and young adults.

Alcohol research should also more actively acknowledge new social contexts among youth culture. A better understanding of the influence online social networking sites and new media have on alcohol use is particularly important among adolescent populations, and this should be explored more fully in future studies.

Developmentally appropriate strategies are needed to delay initiation of alcohol use, because the family environment may be less influential compared with the influence of peers, social norms, and media among older adolescents and young adults. Future interventions should focus on multiple levels of societal environments, from the community to the individual level.

Finally, given the changing demographic landscape of the United States, including a larger and more diverse immigrant population, interventions and treatment options should also reflect the growing needs of certain groups. However, studies have found that focusing only on changing social norms is insufficient, and that broader interventions that influence multiple levels of an individual's environment, such as family and schools, may have greater impact. Alcohol education programs need to also address individual intent and motivations while offering personalized feedback and protective behavioral strategies (Patrick et al. 2014). Public health and treatment programs need to be culturally sensitive, paying particular attention to cultural factors such as ethnic identification and orientation.

Financial Disclosure

The authors declare that they have no competing financial interests.

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Recent Developments in Alcohol Services Research on Access to Care

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In the United States, only about 10 percent of people with an alcohol or drug use disorder receive care for the condition, pointing to a large treatment gap. Several personal characteristics influence whether a person will receive treatment; additionally, many people with an alcohol use disorder do not perceive the need for treatment. The extent of the treatment gap differs somewhat across different population subgroups, such as those based on gender, age, or race and ethnicity. Recent health care reforms, such as implementation of the Patient Protection and Affordable Care Act of 2010, likely will improve access to substance abuse treatment. In addition, new treatment approaches, service delivery systems, and payment innovations may facilitate access to substance abuse services. Nevertheless, efforts to bridge the treatment gap will continue to be needed to ensure that all people who need alcohol and drug abuse treatment can actually receive it.

Key words: Alcohol use disorder; alcohol services research; health care disparities; health care financing; treatment; substance abuse treatment; treatment access; access to care; parity; socioeconomic disparity; special populations; gender; age; race; ethnicity; health care reform; Patient Protection and Affordable Care Act

Of the more than 18 million Americans who need treatment for alcohol use disorder (AUD), less than 10 percent actually receive care (Substance Abuse and Mental Health Services Administration [SAMHSA] 2013). This problem, often referred to as the substance abuse treatment gap, is a longstanding concern for alcohol services research. Studies suggest that many factors contribute to the treatment gap, ranging from inadequate treatment capacity to organization and financing policies, negative attitudes on the part of potential treatment seekers, and inequities in the distribution of care. However, today, the landscape of alcohol treatment is shifting with health care reform, the advent of new treatment modalities, and secular changes in the populations needing care. In light of these trends, the research and treatment communities are seeking new answers to old questions: What is the current scope and nature of the treatment gap? Which subpopulations are the most underserved? How are major policy changes affecting access to alcohol treatment? And how can the newest treatments become available to a wider segment of the population in need?

Understanding the Treatment Gap

Recent analyses of the U.S. population buttress claims that there exists a considerable unmet need for substance abuse treatment—enough to warrant serious, sustained attention by policymakers. It is safe to say that the substance abuse treatment gap in the United States is somewhere close to 90 percent. In other words, only about 10 percent of people with a current alcohol or drug use disorder receive care for the condition. This conclusion is based on a thorough national analysis that estimated the treatment gap using a wide range of possible metrics (Schmidt 2007*a*). The analysis found that even after using diverse measurement approaches, estimates of the treatment gap tended to cluster within a relatively narrow range of 8 percent to 12 percent. More recently, the 2014 National Survey on Drug Use and Health (NSDUH) found that approximately 18 percent of people needing treatment for alcohol and other drug use problems actually received any care in the previous year, and about 11 percent received specialty care (SAMHSA 2015). These estimates of the change in treatment gap pale in comparison to the magnitude of the problem they quantify.

The substantial gap between those who need treatment and those who actually get treatment has, in fact, been a longstanding issue in alcohol

services research. In the 1980s, researchers began trying to understand what distinguished people who receive treatment from those who do not (Weisner 1988). What began as an effort to simply describe the problem evolved into a wide-ranging research enterprise seeking to explain why so many Americans fail to obtain needed care. Further analyses demonstrated that a cluster of factors robustly predict the likelihood of receiving substance abuse treatment, including the client's age, gender, marital status, perceived need for treatment, and prior use of services (Weisner et al. 2002).

It also is clear that people who meet the criteria for an AUD often do not see a need for professional care. According to the 2014 NSDUH, only 6.3 percent of people diagnosed with substance use disorder or treated for substance use problems in a specialty treatment facility felt that they needed treatment (SAMHSA 2015), and the majority did not make an effort to seek care (SAMHSA 2015). Respondents cited several reasons for not seeking or receiving treatment, including not being ready to stop substance use, lack of health care coverage or means to afford treatment, fear of problems at work or stigmatization by others, and not knowing where to go for treatment. Others may question the efficacy of treatment (SAMHSA 2002). However, the reaction of family and friends to a person's drinking problem can motivate care seeking, even when the affected individual is hesitant, and social support also can influence responses to treatment (Worley et al. 2015).

Some investigators have examined the "thresholds of severity" at which individuals with a drinking problem will perceive a need for care (Schmidt 2007*a*). These studies found that a person who is experiencing symptoms of mental distress, in addition to having problems with substance use, is much more likely to see a need for treatment than is a person without those symptoms. Once again, perceptions by others in the problem drinker's life are critical factors in seeking care. Experiencing family, work, and legal problems also significantly increase the likelihood that people would see a need for care and eventually get there.

Who Lacks Care? Uneven Access Across Subpopulations

Not all subgroups in the U.S. population are equally affected by the treatment gap. To better understand the causes and extent of the treatment gap for people with AUD, it is useful to look separately at different subpopulations based on gender, age, race and ethnicity, and other variables.

Gender

During the 1980s, women were underrepresented in addiction treatment programs by a one-to-four ratio compared with men. Therefore, researchers prodigiously investigated the reasons contributing to this underrepresentation, finding that women largely sought care from other types of providers, such as mental health providers, to avoid the stigma of substance abuse treatment (Weisner and Schmidt 1992). Since then, the gender gap has substantially narrowed (Steingrímsson et al. 2012). Although almost twice as many men than women received any substance use treatment in 2014 (Center for Behavioral Health Statistics and Quality 2015), the prevalence of substance abuse and dependence similarly was about twice as high among men as it was among women.[1] The narrowing of this gender gap has led researchers to focus on other underserved populations.

Age

A significant concern today is the disproportionately low rate of treatment utilization, and particularly specialty treatment, among adolescents and young adults in the United States. According to the 2014 NSDUH, about 1.3 million adolescents ages 12–17, and 5.8 million young adults ages 18–25, needed treatment for substance use problems (SAMHSA 2015). However, only 8.5 percent of these adolescents and 8.0 percent of young adults received treatment at a specialty facility, compared with 13.2 percent of adults ages 26 and older who needed treatment (SAMHSA 2015). The need for treatment appears similar among male and female adolescents, as indicated by a similar prevalence of substance abuse and dependence, but females are more likely to receive care from professionals specially trained in substance abuse treatment (Center for Behavioral Health Statistics and Quality 2015).

Looking at the other end of the age spectrum, studies point to a treatment gap for elderly people with alcohol and illicit drug problems, albeit a narrower one. According to the 2014 NSDUH, more than 1.1 million people ages 65 and older needed treatment for a substance use disorder, but only about 234,000 people in this age group (or about 21 percent) received treatment (Center for Behavioral Health Statistics and Quality 2015). This treatment gap may, at least in part, result from difficulties with the identification and diagnosis of substance use problems in this population (Blow et al. 2002).

Race and Ethnicity

The debate about racial and ethnic disparities in health care access reached national prominence in 2002, with the publication of the watershed Institute of Medicine report *Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care* (Smedley et al. 2002). The report delivered a scathing view of gross inequities in access to, and the quality of, health care for America's racial and ethnic minority groups. Although it seemed almost inevitable that substance abuse researchers would uncover similar evidence of disparities, by and large,

[1] According to the 2014 NSDUH, the prevalence of abuse or dependence among men was 3.4 percent for illicit substances, 8.5 percent for alcohol, and 10.7 percent for illicit drugs or alcohol, compared with 1.9 percent, 4.4. percent, and 5.7 percent, respectively, among women (Center for Behavioral Health Statistics and Quality 2015).

those observed in the wider health care system appear far more pronounced.

Studies in the substance abuse field show more modest and subtle variations in treatment access by race and ethnicity (Schmidt et al. 2006). African Americans and Hispanics—the two groups most commonly studied—tend to experience more health and social consequences for a given level of drinking than their White counterparts. The higher incidence of negative social consequences among minorities could result from stress associated with discrimination or from differences in how various racial and ethnic communities respond to risky drinking and how the wider society responds to drinking within these communities (Mulia et al. 2009). With respect to treatment use, few differences exist between Whites, African Americans, and Hispanics, at least in those who experience alcohol problems on the less severe end of the spectrum. With increasing problem severity, however, African Americans and Hispanics have lower odds of entering treatment compared with Whites (Chartier and Caetano 2010; Schmidt et al. 2007*b*). In addition, when members of different ethnic groups do seek help for an alcohol problem, they tend to obtain different types of care. Hispanics receive less specialty care than do Whites (Schmidt et al. 2007*b*). Finally, although treatment retention is similar across ethnic groups, White patients receive more types of clinical services than Hispanics or African Americans, with the exception that African Americans receive more employment services (Niv et al. 2009).

One potential contributor to ethnic disparities in treatment access is geographic variation in the availability of treatment slots. In an interstate comparison of the alcohol treatment supply, McAuliffe and Dunn (2004) found that the Southern and Southwestern regions of the United States—regions with disproportionately large minority populations—are the most underserved. Surveys suggest that long wait times resulting from limited treatment capacities are a primary reason for unmet treatment need (Andrews et al. 2013). In national surveys, African Americans were disproportionately more likely to report lengthy wait times as a reason for not entering care (Schmidt et al. 2006). Individuals referred to treatment by the criminal justice system, who are more likely to belong to a minority group, also experience longer wait times (Andrews et al. 2013).

Who Pays? Health Care Reform, Parity, and Access to Care

Lack of or insufficient insurance coverage may be one of the barriers that prevents people with alcohol problems from entering treatment. Accordingly, recent health care reforms are expected to have a significant impact on access to substance abuse treatment. In the late 1990s and early 2000s, mental health and substance abuse spending was growing at a slower rate than the gross domestic product and shrinking as a share of all health care spending (Mark et al. 2011). Indications are that this could change dramatically under health care reform. Approximately 25 million individuals will become newly insured as a result of the Patient Protection and Affordable Care Act of 2010 (ACA), known colloquially as "Obamacare" (Mark et al. 2015). Even before that, reforms under the Mental Health Parity and Addiction Equity Act of 2008 (MHPAEA) required commercial health plans, as well as Medicaid managed-care plans, to cover substance abuse treatment services at comparable levels to medical and surgical services. The ACA expands access to health insurance through Medicaid, further promotes insurance parity, and encourages new models of payment and service delivery. Although the MHPAEA and the ACA do not guarantee parity coverage for all Medicaid recipients, they offer a variety of mechanisms by which States may do so at their discretion (Burns 2015). (For more information on the influence of these health care reforms on treatment access, see the sidebar "Parity, the Affordable Care Act, and Access to Treatment.")

It is notable, however, that empirical studies prior to these reforms did not identify insurance coverage as one of the most significant predictors of entering alcohol treatment (Schmidt and Weisner 2005). Because addiction treatment is heavily subsidized by a separate stream of federal block grant funding, uninsured individuals often appeared to have better access to alcohol treatment than some groups of insured people. The MHPAEA and ACA may be changing this by expanding access to health insurance, deepening mandates for parity, and offering unprecedented opportunities for service growth and delivery-system reform. Under the ACA, overall funding for substance abuse services is increasing (Buck 2011). Before the health care reforms, Medicaid was not a major funder of substance abuse treatment, but this now is changing (Andrews et al. 2015*b*).

The State of Massachusetts, which created the blueprint for the ACA, presents a window into the potential long-range impacts of the federal reforms. This State's experience paints a cautiously optimistic picture for the Nation. Since the State's health care reforms, treatment capacity in Massachusetts has expanded to accommodate a growing number of people seeking alcohol services. Treatment admissions increased by 17.1 percent, and daily censuses of patients in substance abuse treatment increased by 4.7 percent. However, the reforms in Massachusetts appear to be having somewhat mixed effects on the quality of care, and uninsured people continue to face challenges (Maclean and Saloner 2015).

In nationwide studies carried out since the passage of the ACA and the MHPAEA, having Medicaid or private insurance was associated with a higher likelihood of receiving substance abuse treatment among people

who perceived a need for it (Ali et al. 2015; Mechanic 2012). Moreover, national studies of health plans suggest that the 2008 MHPAEA parity law has met its goal of putting coverage for behavioral health care on par with coverage for medical and surgical care (Horgan et al. 2015). For people with commercial insurance, the MHPAEA has had modest effects on reducing out-of-pocket costs and increasing access to outpatient services (Haffajee et al. 2015). Federal parity also is associated with an increased probability of out-of-network visits and increased average spending on substance abuse treatment (McGinty 2015). Many predicted that, under parity laws, health plans would more aggressively manage utilization, for example, through more stringent requirements on prior authorization for services. However, a national survey of health plans found that only 5 percent of plans require prior authorization for outpatient substance abuse treatment (Merrick et al. 2015).

Although the evidence to date is promising, a variety of limitations in the implementation of the new laws suggest that it could take many years to realize the promise of federal parity and health care reform. Twenty States have completely opted out of the ACA's

Parity, the Affordable Care Act, and Access to Treatment

Although having insurance coverage is not the most important factor influencing access to substance abuse treatment, the ways in which insurance coverage works do affect treatment availability and influence people's decisions about seeking care. Recent health care reforms present both fresh opportunities and new barriers affecting treatment access.

The Mental Health Parity and Addiction Equity Act of 2008 requires group health plans offering mental health and addiction services to cover such services at the same levels that they cover other medical and surgical services. The law applies to Medicaid managed-care plans as well as to private plans, but exempts health plans with fewer than 50 employees. Parity technically means that all aspects of coverage are comparable to those covering medical and surgical care, including deductibles and copayments, limitations on the frequency of treatment, and methods of determining whether treatment is necessary. Coverage for alcohol treatment offered by insurance plans therefore becomes more generous under this reform. However, the law does not require that plans cover addiction treatment at all, nor does it require that all areas of addiction be covered. Because of this, there are concerns that companies previously offering some addiction treatment benefits may choose to drop coverage in response to the parity law (Stewart and Horgan 2011).

The Patient Protection and Affordable Care Act of 2010 (ACA) extends insurance coverage to more Americans by expanding Medicaid eligibility and requiring individuals to obtain insurance coverage. Because private insurance plans still are not required to furnish substance abuse coverage, the focus of discussions about access to alcohol and other substance treatment revolves primarily around the effects of the expanded Medicaid benefits. The ACA also includes ideas for health care delivery and payment reforms that are likely to help providers deliver a wider range of behavioral health services. It encourages the use of preventive services, continuity of care, and substance abuse education. It also allows providers treating mental illness to pay more attention to substance abuse problems and provides pathways for incorporating evidence-based treatments. As poor continuity and coordination of care accounted for part of the substance abuse treatment gap and problems with treatment access, the ACA may offer tools to address these issues (Mechanic 2012).

These two pieces of legislation seem to have an impact on the treatment gap. For example, insured people who heretofore ran into caps or limits on their substance abuse coverage may benefit from the parity requirement. In addition, some people who previously could not afford insurance will now be able to obtain coverage (Mark et al. 2011). However, although the ACA does not allow States to reduce Medicaid enrollment, they still can cut health care services funded through general State funds. Because substance abuse treatment relies heavily on non-Medicaid public funds through block grants, treatment and ancillary services remain especially vulnerable to funding cuts during State budget shortfalls (Mark et al. 2011).

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Medicaid expansion program, thus substantially limiting its national impact. There are further concerns that treatment systems may lack the capacity and manpower to treat the swelling numbers of newly covered individuals (Ghitza and Tai 2014; Weil 2015). One survey of State agencies found that fewer than half were helping providers to modernize care or had technical support to maximize insurance participation (Andrews et al. 2015*a*). Similarly, a study of public treatment programs in Los Angeles County found them ill prepared to align their programs with the new realities of health care reform (Guerrero et al. 2015).

Access to What? New Treatments and Service Delivery Systems

Services research has demonstrated that access to new treatment modalities and service-delivery forms is in flux under health care reform. Service delivery and payment innovations introduced by the ACA could facilitate access to services that have not previously been reimbursable, including comprehensive care management, care coordination, social support, transition care, collaborative care, and other evidence-based interventions. The ACA also has ushered in a trend toward integrating addiction and primary health care under the auspices of "patient-centered medical homes" (PCMH) and Medicaid "health homes" (Starfield and Shi 2004). Health homes target chronic-disease comorbidities prevalent in alcohol treatment populations, and almost all participating States include substance abuse in their qualifying conditions.

The PCMH model originated in private health plans as a strategy to lower costs while improving the quality and continuity of care. Under this model, substance abuse services are linked to primary care through strong referral networks using electronic medical records, or they may be "co-located" under one roof in efforts to more deeply integrate care (Rittenhouse and Shortell 2009). Early evaluations—mostly in large, integrated delivery systems—show that this model improves quality, with savings in total health care costs (Crabtree et al. 2011). To a more limited extent, PCMH applications have shown positive outcomes for accessibility and continuity of care in safety-net populations, where substance abuse treatment need is disproportionately high (Rittenhouse et al. 2012).

Health care reform further appears to be catalyzing a longstanding structural shift toward the use of screening and brief interventions (SBIs) delivered in mainstream medical care settings, most notably primary care and hospital settings (Babor and Higgins-Biddle 2000). SBIs may help close the treatment gap by expanding capacities within mainstream medical care settings. An SBI can be as brief as 5 to 10 minutes and can be particularly effective when performed by a primary care physician. It begins with an assessment of the patient's alcohol use; patients screening positive for an alcohol problem then are advised to cut down or abstain and may be referred for further professional help. Studies have long shown that SBI offers an evidence-based, cost-effective approach for reducing patients' drinking (Fleming and Barry 1991). Introducing SBI programs into settings such as Federally Qualified Health Centers,[2] schools, workplaces, and criminal justice settings could broaden their reach and also help more disadvantaged populations (Mulia et al. 2014). Health services researchers are developing and testing more streamlined Web-based approaches to training health care providers in SBI skills, which could increase the system's capacity to provide this form of care (Stoner et al. 2014). Electronic versions of SBI and "guided self-change" approaches also hold promise for allowing efficient self-treatment for people with moderately severe substance use disorders (Sinadinovic et al. 2014; Wagner et al. 2014). However, a 2010 national survey of health plans found that only 18 percent of insurance products required screening for alcohol- and drug-abuse problems in primary care (Garnick et al. 2014).

A related challenge is promoting the adoption of even newer evidence-based treatments, most notably pharmaceutical approaches. "Second-generation" medications, such as acamprosate and regular and extended-release naltrexone, are clinically efficacious during detoxification and recovery from alcohol abuse. A national survey of health plans found that 96 percent of insurance products included coverage for addiction medications (Horgan et al. 2014). However, for patients, difficulties in gaining health plan authorization and covering high copayments may be barriers to using addiction medications. Providers also face challenges ordering and obtaining licenses to administer certain medications.

Initiatives such as Advancing Recovery and the Medication Research Partnership have been effective in working with the public and private sectors to facilitate adoption of pharmacotherapies for AUD. These organizational-change initiatives bring payers and providers together into collaboratives that test organizational changes supporting the increased use of medications through brief, experimental "change cycles." Implementation strategies that work are quickly scaled up through sharing across members of the collaborative. Demonstrations suggest that supported partnerships such as these can achieve a wider adoption of evidence-based treatment practices more rapidly and effectively (Ford et al. 2015; Schmidt et al. 2012).

Bridging the Treatment Gap: A Continuing Agenda

As seen through the lens of health services research, problem drinkers face better prospects for treatment in

[2] Federally Qualified Health Centers are community-based organizations that offer comprehensive primary care and preventive care, including substance abuse services, to people of all ages, regardless of their ability to pay or health insurance status. They are therefore an important part of the health care safety net.

the current landscape, characterized by the expansion of insurance coverage under health care reform and parity laws, as well as rapid clinical innovations and service-delivery-system reforms. But it also is a landscape in which the need for care still far outstrips the supply of treatment—one in which waiting lists for care are long as the alcohol field looks to the wider health care system to build greater capacity. Above all, today's health services researchers describe a treatment system that is moving toward closer alignment with the wider health care system. This can be seen in the movement toward more integrated models of service delivery through the PCMH and Medicaid health homes. It also is evident in the push toward parity in insurance coverage, and in the scaling-up of SBI programs in primary care and other medical care settings. Finally, alignment with the greater health care system can be observed in the promotion of pharmaceutical therapies, most notably the new second-generation pharmaceuticals for treating addiction. Deepening collaboration between alcohol treatment and mainstream health care systems will likely lead to further—undoubtedly controversial—changes in services for people with alcohol problems. But this may very well be the field's best hope for solving what is arguably its greatest challenge: reaching a greater proportion of the population in need of care.

Acknowledgements

Work on this manuscript was supported by grants from the National Institute on Alcohol Abuse and Alcoholism (R01–AA–017197) and National Institute on Drug Abuse (R01–DA–29716). The author thanks Kathryn Ingle Calkins, Susanne Hiller-Sturmhöfel, and Juliana Fung for their assistance in the preparation of this article.

Financial Disclosure

The author declares that she has no competing financial interests.

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Focus On: Ethnicity and the Social and Health Harms From Drinking

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Alcohol consumption is differentially associated with social and health harms across U.S. ethnic groups. Native Americans, Hispanics, and Blacks are disadvantaged by alcohol-attributed harms compared with Whites and Asians. Ethnicities with higher rates of risky drinking experience higher rates of drinking harms. Other factors that could contribute to the different effects of alcohol by ethnicity are social disadvantage, acculturation, drink preferences, and alcohol metabolism. This article examines the relationship of ethnicity and drinking to (1) unintentional injuries, (2) intentional injuries, (3) fetal alcohol syndrome (FAS), (4) gastrointestinal diseases, (5) cardiovascular diseases, (6) cancers, (7) diabetes, and (8) infectious diseases. Reviewed evidence shows that Native Americans have a disproportionate risk for alcohol-related motor vehicle fatalities, suicides and violence, FAS, and liver disease mortality. Hispanics are at increased risk for alcohol-related motor vehicle fatalities, suicide, liver disease, and cirrhosis mortality; and Blacks have increased risk for alcohol-related relationship violence, FAS, heart disease, and some cancers. However, the scientific evidence is incomplete for each of these harms. More research is needed on the relationship of alcohol consumption to cancers, diabetes, and HIV/AIDS across ethnic groups. Studies also are needed to delineate the mechanisms that give rise to and sustain these disparities in order to inform prevention strategies. **KEY WORDS: Alcohol consumption; alcohol-attributable fractions; alcohol burden; harmful drinking; alcohol and other drug–induced risk; risk factors; ethnicity; ethnic groups; racial groups; cultural patterns of drinking; Native Americans; Hispanics; Blacks; African Americans; Asian Americans; Whites; Caucasians; injury; intentional injury; unintentional injury; fetal alcohol syndrome; gastrointestinal diseases; cardiovascular diseases; cancers; diabetes; infectious diseases**

Research has shown differential social and health effects from alcohol use across U.S. ethnic groups, including Whites, Blacks, Hispanics, Asians, and Native Americans. The relationship of ethnicity to alcohol-related social and health harms partially is attributed to the different rates and patterns of drinking across ethnicities. Some ethnic groups have higher rates of alcohol consumption, putting them at greater risk of drinking harms. However, other ethnic minorities experience health harms from drinking that are disproportionate to their consumption. Differences in social and socioeconomic factors and biological differences related to alcohol metabolism also could contribute to alcohol's varying effects across populations. This article reviews current research examining the harms of drinking for U.S. ethnic groups. It examines such social harms as driving under the influence and alcohol-attributed violence but primarily focuses on health harms like fetal alcohol syndrome (FAS), liver diseases, and cancers.

The research reviewed focuses on Whites, Blacks, Hispanics, Asians, and Native Americans (i.e., American Indians and Alaska Natives) in the United States as general ethnic groups, although significant subgroup differences within populations also are evident. There are limitations to using these general categories because ethnicity encompasses a combination of characteristics such as tribe, ancestry, national group, birthplace, and language, which could have distinct relationships to patterns of drinking and alcohol-related harms (Caetano 1986; Cheung 1993; Heath 1990–1991). People with multiethnic backgrounds also are not well represented by these general groups. Nevertheless, studies that examine ethnicity and alcohol-attributed harms provide important information about public health and serve to identify high-risk groups in the population. This article shows that Native Americans, Hispanics, and Blacks are disproportionately affected by the adverse social and health harms from alcohol consumption.

Drinking Patterns and Other Determinants of Risk for Alcohol-Related Harms

Heavy drinking and binge drinking contribute to a variety of alcohol-attributed social and health harms (Naimi et al. 2003; Rehm et al. 2010). Heavy alcohol use, as defined by the National Institute on Alcohol Abuse and Alcoholism's (NIAAA's) *Helping Patients Who Drink Too Much: A Clinician's Guide* (NIAAA 2005), is defined as consuming more than 4 standard drinks per day (or more than 14 per week) for men and more than 3 per day (or more than 7 per week) for women. One standard drink is equivalent to 12 ounces of

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beer, 5 ounces of wine, or 1.5 ounces of 80-proof spirits. Binge drinking is defined as consuming five or more drinks in approximately 2 hours for men and four or more drinks for women (NIAAA 2004).

Other than these patterns of consumption, the volume of alcohol intake, defined as the total alcohol consumed over a time period, is linked to social and health harms. Most diseases (e.g., injury, some cancers, and liver cirrhosis) have a detrimental dose-response relationship with alcohol as risk increases with higher-volume alcohol consumption, whereas coronary heart disease and diabetes display a J- or U-shaped relationship (Howard et al. 2004; Rehm et al. 2010; Roerecke and Rehm 2012). The J and U shapes are characterized by both detrimental and beneficial (e.g., increased high-density lipoprotein "good cholesterol") (Goldberg and Soleas 2001) effects of alcohol use, with higher risks for abstainers and heavy drinkers compared with light or moderate drinkers. However, this relationship is complex and varies by age, gender, and ethnicity (Roerecke and Rehm 2012). Drinking levels that may be protective of cardiovascular health among men also may increase the risk for other harms such as injury, violence, gastrointestinal disease, and some cancers.

Epidemiological studies show that these high-risk patterns of drinking and drinking volume vary by U.S. ethnic group. Ethnicities with greater drinking volume and higher rates of daily and weekly heavy drinking could be at greater risk for experiencing alcohol-attributed harms. Among adult drinkers in the United States, based on the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) (Chen et al. 2006), Native Americans and Hispanics have greater alcohol consumption than other ethnic minority groups. Rates of daily heavy drinking were higher among Hispanics (33.9 percent), Native Americans (28.4 percent), and Whites (27.3 percent) compared with Blacks (22.5 percent) and Asians (19.2 percent). Weekly heavy drinking was highest among Native Americans (21.9 percent), followed by Blacks (16.4 percent), Whites (16.3 percent), Hispanics (11.8 percent), and Asians (9.8 percent). Based on the 2001–2002 NESARC data, Caetano and colleagues (2010) reported that White men consumed a higher volume of alcohol (22.3 drinks per month) than Black men (18.9 drinks per month) and Hispanic men (17.8 drinks per month) and that White women consumed more (6.2 drinks per month) compared with Black women (4.9 drinks per month) and Hispanic women (3.9 drinks per month). The sample for these estimates of drinking volume was the U.S. population of Whites, Blacks, and Hispanics and included abstainers. However, a study by Mulia and colleagues (2009) of current drinkers in the United States showed that Whites consumed less alcohol than Hispanics and more than Blacks. The differences between these two studies could reflect a higher rate of abstinence from alcohol among Hispanics (25.7 percent) compared with Whites (13.4 percent) in the U.S. population (Chen et al. 2006). The study that included abstainers (Caetano et al. 2010), who by definition consume zero drinks, showed higher drinking volume for Whites, whereas the study excluding abstainers (Mulia et al. 2009) reported higher volume for Hispanics. Other ethnic minority groups with higher abstinence rates include Blacks (24.7 percent) and Asians (39.1 percent). Native Americans (17.14 percent) have lower rates of abstinence than other minority groups.

Alternatively, the negative effects from drinking could be explained by factors other than alcohol consumption. Mulia and colleagues (2009) showed that Black and Hispanic adult drinkers were more likely than White drinkers to report alcohol dependence symptoms and social problems from drinking at the no/low level of heavy drinking. Blacks also experience negative health effects from alcohol use despite showing a later onset of use and levels of use often comparable with, if not lower than, Whites (Chartier et al. 2011; Chen et al. 2006; Russo et al. 2004). Other factors associated with ethnic disparities in alcohol-related harms include social disadvantage, characterized by lower socioeconomic status, neighborhood poverty, greater neighborhood alcohol availability, reduced alcohol treatment utilization, and unfair treatment or discrimination (Chae et al. 2008; Chartier and Caetano 2011; Cunradi et al. 2000; Mulia et al. 2008; Nielsen et al. 2005; Zemore et al. 2011). Some ethnic subgroups are more likely to consume high-alcohol-content beverages (e.g., malt liquor), which could result in greater social and health harms (Vilamovska et al. 2009). Preference for such beverages seems to be more common in lower-income ethnic minority communities (Bluthenthal et al. 2005). Some ethnic minority groups also face stressors related to the acculturation process. Higher acculturation, U.S.-born nativity, and longer residence in the United States are risk factors associated with alcohol use disorders and alcohol-related social problems among Hispanics, particularly women (Alegria et al. 2007, 2008; Caetano et al. 2009, 2012; Zemore 2007). Another potential contributor is ethnic differences in the alcohol content of poured drinks. Kerr and colleagues (2009) showed that Black men had drink sizes with larger average alcohol content compared with other groups, which partially could explain the higher risks for alcohol-related harms. Genes responsible for alcohol metabolism also vary across ethnic groups and could be associated with susceptibility for alcohol-related diseases. Among Whites, Blacks, and Asians, alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) genotypes have been linked in combination with drinking to alcohol-related cancers, birth defects, and pancreatitis (Yin and Agarwal 2001).

Ethnicity and Alcohol-Attributed Harms

Alcohol-attributed harms can be both acute and chronic conditions that are wholly caused (e.g., alcoholic liver cirrhosis) or associated with alcohol use via intoxication, alcohol dependence, and the toxic effects of alcohol (Rehm et al. 2010). The major injury and disease categories linked to alcohol consumption include (1) unintentional injuries, (2) intentional injuries, (3) FAS, (4) gastrointestinal diseases, (5) cardiovascular diseases, (6) cancers, (7) diabetes, and (8) infectious diseases (World Health Organization [WHO] 2011). Evidence

is incomplete on the relationship between ethnicity, drinking, and each of these categories. Below, those alcohol-related harms are described that have available findings by ethnic group in addition to important gaps in this scientific literature. Alcohol use disorders are causally linked to drinking and vary by ethnicity (i.e., more likely in Native Americans and Whites) (Hasin et al. 2007), but this disease category is not described here.

Unintentional Injuries

Unintentional injuries associated with alcohol use include falls, drowning, and poisoning (WHO 2011). However, most available research on ethnicity, alcohol use, and injuries is focused on motor vehicle crashes. Alcohol-impaired driving and crash fatalities vary by ethnicity, with Native Americans and Hispanics being at higher risk than other ethnic minority groups. Past-year driving under the influence (DUI) estimates based on the 2007 National Survey on Drug Use and Health were highest for Whites (15.6 percent) and Native Americans (13.3 percent) relative to Blacks (10.0 percent), Hispanics (9.3 percent), and Asians (7.0 percent) (Substance Abuse and Mental Health Services Administration [SAMHSA] 2008). National surveys generally show lower DUI rates for Hispanics than Whites, but studies based on arrest data identify Hispanics as another high-risk group for DUI involvement (Caetano and McGrath 2005; SAMHSA 2005). The DUI arrest rate for Native Americans in 2001, according to the U.S. Department of Justice (Perry 2004), was 479 arrestees per 100,000 residents compared with 332 for all other U.S. ethnic groups.

Based on a 1999–2004 report from the National Highway Traffic Safety Administration (Hilton 2006), rates of intoxication (i.e., blood alcohol concentration [BAC] more than or equal to 0.08 percent) for drivers who were fatally injured in a motor vehicle crash were highest for Native Americans (57 percent) and Hispanics (47 percent) and lowest for Asians (approximately 20 percent), with Whites and Blacks falling in between. Across ethnic groups, most drinking drivers killed were male, although the proportion of female drivers who were intoxicated among fatally injured drivers was highest (i.e., more than 40 percent) for Native Americans. Centers for Disease Control and Prevention (CDC) (2009*b*) statistics on alcohol-related motor vehicle crash deaths also point to an important subgroup difference for Asians. In 2006, the overall death rate among Asians (1.8 per 100,000 people) obscured the death rate among Native Hawaiians and other Pacific Islanders (5.9), which was less than the rate for Native Americans but similar to that for Hispanics (14.5 and 5.2, respectively).

Intentional Injuries

Suicide

Native Americans are overrepresented in national estimates of alcohol-involved suicides. A CDC report (2009*a*) based on 2005–2006 data from the National Violent Death Reporting System presented findings on alcohol and suicide across ethnic groups. Recent alcohol use was reported among suicides in 46 percent of Native Americans, 30 percent of Hispanics, 26 percent of Whites, 16 percent of Blacks, and 15 percent of Asians. Among those tested for alcohol, the rates of intoxication (BAC higher than or equal to 0.08) were highest for Native Americans (37 percent), followed by Hispanics (29 percent), Whites (24 percent), Blacks (14 percent), and Asians (12 percent). Age-groups identified as being at high risk for alcohol-involved suicide included Native Americans ages 30 to 39 (54 percent of suicide victims had BACs higher than or equal to 0.08), Native Americans and Hispanics ages 20 to 29 (50 percent and 37 percent, respectively), and Asians ages 10 to 19 (29 percent). Males were at higher risk than female drinkers in all ethnic groups except Native Americans; the percentages of alcohol intoxication among Native American suicides were equal for males and females (37 percent).

Violence

Ethnic groups are differentially affected by alcohol-attributed violence, including intimate-partner violence (IPV). Alcohol plays an important role in IPV and other types of relationship conflicts (Field and Caetano 2004; Leonard and Eiden 2007). Based on data from the National Study of Couples, general rates of male-to-female partner violence (MFPV) and female-to-male partner violence (FMPV), are highest among Black couples (23 percent and 30 percent, respectively), followed by Hispanic (17 percent and 21 percent) and White (12 percent and 16 percent) couples (Caetano et al. 2000). The National Study of Couples provides general population data on IPV, which includes mostly moderate violence and may differ from other studies of severe violence. In this study, regardless of ethnicity, men were more likely than women to report drinking during partner violence. Drinking during a violent episode by the male or the female partner, respectively, was more frequent among Blacks (MFPV: 41.4 percent and 23.6 percent; FMPV: 33.7 percent and 22.4 percent) than among Whites (MFPV: 29.4 percent and 11.4 percent; FMPV: 27.1 percent and 14.7 percent) and Hispanics (MFPV: 29.1 percent and 5.4 percent; FMPV: 28.4 percent and 3.8 percent). Longitudinal findings, using 5-year National Study of Couples data, identified female-partner alcohol problems (i.e., alcohol dependence symptoms and social problems) in Black couples and male- and female-partner alcohol consumption in White couples as risk factors for IPV (Field and Caetano 2003). Some evidence also suggests that interethnic couples, involving White, Black, and Hispanic partners of different ethnic backgrounds, are a high-risk group for relationship violence. Relative to intraethnic couples, these interethnic couples had higher prevalence rates of IPV, which was associated with binge drinking and alcohol problems among male partners (Chartier and Caetano 2012).

Alcohol also contributes to violence victimization among Native Americans (Yuan et al. 2006). Several studies

indicate that Native Americans are at greater risk for alcohol-related trauma (e.g., IPV, rape, and assault) compared with other U.S. ethnic groups (Oetzel and Duran 2004; Wahab and Olson 2004). Based on 1992–2001 National Crime Victimization Survey data, the U.S. Department of Justice (Perry 2004) reported that 42 percent of all violent crimes (i.e., rape, sexual assault, robbery, aggravated assault, and simple assault) were committed by an offender who was under the influence of alcohol. In particular, Native American violent crime victims were more likely (62 percent) than other violent crime victims to report alcohol use by their offender, including Whites (43 percent), Blacks (35 percent), and Asians (33 percent).

Fetal Alcohol Syndrome

Using data from the 2001–2002 NESARC, Caetano and colleagues (2006) examined alcohol consumption, binge drinking, and alcohol abuse and dependence among women who were pregnant during the past year. Most women (88 percent) who reported being pregnant and also a drinker at any point in the past 12 months indicated that they did not drink during pregnancy. Rates of past-year alcohol abuse (0.8 percent to 2.3 percent) and dependence (1.2 percent to 2.8 percent) were similar and low in White, Black, Hispanic, and Asian pregnant women. Binge drinking and alcohol consumption without binge drinking among pregnant women were highest in Whites (21.1 percent and 45.0 percent, respectively) compared with other ethnic groups (0 percent to 10.7 percent and 21.0 percent to 37.3 percent). White women in this study were at greater risk for an alcohol-exposed pregnancy. However, other studies found that Black, Hispanic, and Asian women were less likely to reduce or quit heavy drinking after becoming pregnant (Morris et al. 2008; Tenkku et al. 2009). Blacks and Native Americans are at greater risk than Whites for FAS and fetal alcohol spectrum disorders (Russo et al. 2004). From 1995 to 1997, FAS rates averaged 0.4 per 1,000 live births across data-collection sites for the Fetal Alcohol Syndrome Surveillance Network and were highest for Black (1.1 percent) and Native American (3.2 percent) populations (CDC 2002).

Gastrointestinal Diseases

Liver disease is an often-cited example of the disproportionate effect of alcohol on health across ethnic groups. Native Americans have higher mortality rates for alcoholic liver disease than other U.S. ethnic groups (see figure). According to the National Vital Statistical Reports (Miniño et al. 2011) on 2008 U.S. deaths, age-adjusted death rates attributed to alcoholic liver disease for Native American men and women were 20.4 and 15.3 per 100,000 people, respectively, compared with 6.9 and 2.4 per 100,000 for men and women in the general population.

Blacks and Hispanics have greater risk for developing liver disease compared with Whites (Flores et al. 2008), and

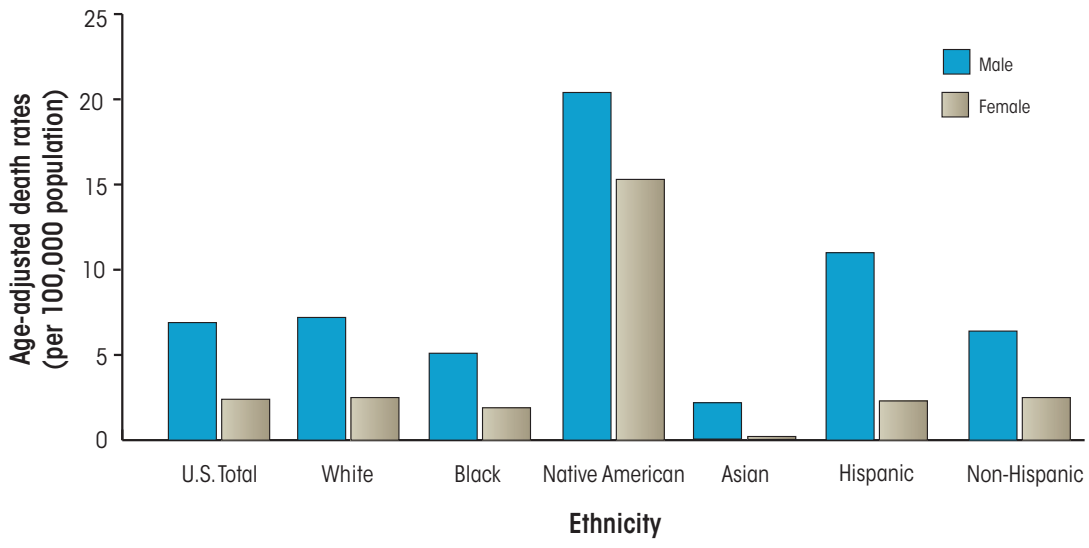

Figure In 2008, age-adjusted death rates attributed to alcoholic liver disease for Native American men and women were 20.4 and 15.3 per 100,000 people, respectively, compared with 6.9 and 2.4 for men and women in the general population.

SOURCE: Miniño, A.M. et al., Deaths: Final data for 2008. *National Vital Statistics Reports* 59(10):1–52, 2011.

death rates attributed to alcohol-related cirrhosis across populations of Whites, Blacks, and Hispanics are highest for White Hispanic men (Yoon and Yi 2008). Blacks show a greater susceptibility than Whites to alcohol-related liver damage, with risk differences amplified at higher levels of consumption (Stranges et al. 2004). Based on data from the National Center for Health Statistics, 1991–1997, mortality rates for cirrhosis with mention of alcohol were higher in White Hispanics and Black non-Hispanics compared with White non-Hispanics (Stinson et al. 2001). Male mortality rates for alcohol-related cirrhosis in White Hispanics and non-Hispanic Blacks were 114 percent and 24 percent higher, respectively, than the overall male rate (5.9 deaths per 100,000 people); female rates in White Hispanics and non-Hispanic Blacks were 16 percent and 47 percent higher than the overall female rate (1.9 deaths per 100,000 people). In contrast, death rates for White non-Hispanic and Black Hispanic males and females were lower than overall rates for each gender. In addition, there is considerable variation in deaths from liver cirrhosis across Hispanic subgroups, with mortality rates highest in Puerto Ricans and Mexicans and lowest in Cubans (Yoon and Yi 2008).

Cardiovascular Diseases

Although moderate alcohol consumption has been associated with a reduced risk for coronary heart disease (CHD) (Goldberg and Soleas 2001), there is some evidence that ethnic groups differ in terms of this protective effect, particularly for Blacks compared with Whites. Sempos and colleagues (2003) found no protective health effect for moderate drinking in Blacks for all-cause mortality, as previously reported in Whites. Kerr and colleagues (2011) reported the absence of this protective effect for all-cause mortality in Blacks and Hispanics. Similar findings have been described for hypertension and CHD risks in Black men compared with White men and women (Fuchs et al. 2001, 2004) and for mortality among Black women without hypertension (Freiberg et al. 2009). Mukamal and colleagues (2010) also showed that the protective effects of light and moderate drinking in cardiovascular mortality were stronger among Whites than non-Whites. Pletcher and colleagues (2005) found evidence that the dose-response relationship between alcohol consumption and increased coronary calcification, a marker for CHD, was strongest among Black men.

Cancers

In 1988, the WHOInternational Agency for Research on Cancer (IARC) reviewed the epidemiologic evidence on the association between alcohol consumption and cancer and found a consistent association between alcohol consumption and increased risk for cancers of the oral cavity, pharynx, larynx, esophagus, and liver (IARC 1988). Regardless of ethnicity, the risk of developing these cancers is significantly higher among men than women (National Cancer Institute 2011*c*, *d*, *e*). The incidence and mortality rates for these cancers also vary across ethnic groups. Regarding cancers of the oral cavity and pharynx, incidence rates among White and Black men are comparable (16.1 and 15.6 per 100,000, respectively); however, mortality rates are higher among Black men (6.0 versus 3.7 per 100,000 for White men) (National Cancer Institute 2011*e*). For cancer of the larynx, both incidence and mortality rates are higher among Black men than among White men (incidence, 9.8 and 6.0; mortality, 4.4 and 2.0) (National Cancer Institute 2011*c*). Although these differences may be explained by differential use of alcohol and tobacco in relation to gender and ethnicity, there is some evidence that even after controlling for alcohol and tobacco use, Blacks continue to be at increased risk for squamous cell esophageal cancer and cancers of the oral cavity and pharynx (Brown et al. 1994; Day et al. 1993).

The majority (approximately 90 percent) of all primary liver cancers are hepatocellular carcinomas (HCC) (Altekruse et al. 2009). Alcohol-related and non–alcohol-related liver cirrhosis usually precede HCC and are the two most common risk factors (Altekruse et al. 2009; El-Serag 2011; Pelucchi et al. 2006). The relative risk for developing this cancer increases with increased levels of alcohol consumption (Pelucchi et al. 2006). By ethnic group, 2003–2005 age-adjusted incidence rates for HCC per 100,000 persons were highest among Asians (11.7), followed by Hispanics (8.0), Blacks (7.0), Native Americans (6.6), and Whites (3.9) (Altekruse et al. 2009). Death rates for HCC per 100,000 people also are higher among minority groups (i.e., 8.9, 6.7, 5.8, 4.9, and 3.5 for Asians, Hispanics, Blacks, Native Americans, and Whites, respectively).

In 2007, the IARC reconvened and added breast and colorectal cancers to the list of cancers related to alcohol use (Baan et al. 2007). Research has demonstrated consistent, albeit weak, dose-response relationships between alcohol consumption and these cancers (Cho et al. 2004; Collaborative Group on Hormonal Factors in Breast Cancer 2002; Moskal et al. 2007; Singletary and Gapstur 2001). Alcohol consumption also contributes to the stage at which breast cancer is diagnosed (Hebert et al. 1998; Trentham-Dietz et al. 2000; Vaeth and Satariano 1998; Weiss et al. 1996). This could be because of the timing of disease detection, since heavy drinking has been associated with a lack of mammography utilization (Cryer et al. 1999). Alcohol consumption also may contribute to more rapid tumor proliferation (Singletary and Gapstur 2001; Weiss et al. 1996). Data from the Surveillance, Epidemiology, and End Results (SEER) Program indicate that White women, relative to women from ethnic minority groups, have higher incidence rates of breast cancer (i.e., Whites, 127.3; Blacks, 119.9; Asians, 93.7; Native Americans, 92.1; and Hispanics, 77.9 per 100,000 people) (National Cancer Institute 2011*a*). Black women, however, are more likely to be diagnosed with advanced disease (Chlebowski et al. 2005) and have significantly higher mortality rates than White women (i.e., 32.0

per 100,000 versus 22.8 per 100,000 people) (Chlebowski et al. 2005; National Cancer Institute 2011*a*). Regarding colorectal cancer, Blacks have higher incidence (67.7) and mortality (51.2) rates than all ethnic groups combined (55.0 and 41.0, respectively) (National Cancer Institute 2011*b*). Unfortunately, little is known about how drinking differentially affects ethnic differences in breast and colorectal cancers.

Diabetes

In 2010, the prevalence of diabetes was 7.1 percent, 12.6 percent, 11.8 percent, and 8.4 percent among Whites, Blacks, Hispanics, and Asians, respectively (National Institute of Diabetes and Digestive and Kidney Diseases 2011). Age-adjusted mortality rates in 2007 were 20.5, 42.8, 28.9, and 16.2 per 100,000 people among Whites, Blacks, Hispanics, and Asians (National Center for Health Statistics 2011). Data on mortality rates for diabetes among Hispanics may be underreported as a result of inconsistencies in the reporting of Hispanic origin on death certificates (Heron et al. 2009). Despite higher risks for the development of and death from diabetes in Hispanics and Blacks compared with Whites, little evidence is available to delineate the relationship of alcohol to diabetes across ethnic groups. Studies among both diabetics and nondiabetics demonstrate a J- or U-shaped curve between alcohol consumption and insulin sensitivity (Bell et al. 2000; Davies et al. 2002; Greenfield et al. 2003; Kroenke et al. 2003). Likewise, two large epidemiologic studies among diabetic subjects show that moderate alcohol consumption is associated with better glycemic control (Ahmed et al. 2008; Mackenzie et al. 2006). An important limitation of these studies, however, is that few included ethnic minority groups or failed to emphasize possible differences in relation to ethnicity in their analyses.

Infectious Diseases

Among the infectious diseases attributable to alcohol (e.g., pneumonia, tuberculosis) (WHO 2011), human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) are most relevant to U.S. ethnic health disparities. In 2009, Blacks represented 44 percent of new HIV infections and Hispanics represented 20 percent. Infection rates by gender for Blacks were 15 times (for men) and 6.5 times (for women) those of Whites, and rates for Hispanics were 4.5 times for men and 2.5 times for women, compared with rates for Whites (CDC 2011). In addition, alcohol consumption has been associated with increased HIV infection risk (Bryant et al. 2010). Caetano and Hines (1995) showed that heavy drinking predicted high-risk sexual behaviors in White, Black, and Hispanic men and women, with more Blacks than Whites and Hispanics reporting risky sexual behaviors. Among HIV-infected patients, there also is evidence that increased alcohol consumption negatively affects adherence to antiretroviral medication regimens (Chander et al. 2006; Cook et al. 2001; Samet et al. 2004) and HIV disease progression (Conigliaro et al. 2003; Samet et al. 2003). Despite these strong individual associations between ethnicity and HIV/AIDS and alcohol and HIV/AIDS, there is limited research across ethnicities on alcohol use and HIV infection or disease progression.

Conclusions

This article identifies U.S. ethnic-group differences in alcohol-attributed social and health-related harms. Three minority ethnicities are particularly disadvantaged by alcohol-related harms. Native Americans, relative to other ethnic groups, have higher rates of alcohol-related motor vehicle fatalities, suicide, violence, FAS, and liver disease mortality. Unlike other ethnic groups, in which men are primarily at risk for alcohol-related harms, both Native American men and women are high-risk groups. Hispanics have higher rates of alcohol-related motor vehicle fatalities, suicide, and cirrhosis mortality. Blacks have higher rates of FAS, intimate partner violence, and some head and neck cancers, and there is limited empirical support in Blacks for a protective health effect from moderate drinking. These patterns of findings provide recognition of the health disparities in alcohol-attributed harms across U.S. ethnicities. However, further research is needed to identify the mechanisms that give rise to and sustain these disparities in order to develop prevention strategies. The contributing factors include the higher rates of consumption found in Native Americans and Hispanics, but more broadly range from biological factors to the social environment. More research on the relationship of alcohol to some cancers, diabetes, and HIV/AIDs across ethnic groups is also needed. There is limited evidence for how drinking differentially affects ethnic differences in breast and colorectal cancers and in diabetes and HIV/AIDS onset and care, and few findings for how alcohol-attributed harms vary across ethnic subgroups. ■

Acknowledgements

The authors thank Kierste Miller for her help in preparing this paper. This work was supported by NIAAA grant R01–AA–016319.

Financial Disclosure

The authors declare that they have no competing financial interests.

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Genetic and Environmental Determinants of Stress Responding

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The risk for alcohol dependence throughout development is determined by both genetic and environmental factors. Genetic factors that are thought to modulate this risk act on neurobiological pathways regulating reward, impulsivity, and stress responses. For example, genetic variations in pathways using the brain signaling molecule (i.e., neurotransmitter) dopamine, which likely mediate alcohol's rewarding effects, and in two hormonal systems involved in the stress response (i.e., the hypothalamic–pituitary–adrenal axis and the corticotropin-releasing factor system) affect alcoholism risk. This liability is modified further by exposure to environmental risk factors, such as environmental stress and alcohol use itself, and the effects of these factors may be enhanced in genetically vulnerable individuals. The transition from alcohol use to dependence is the result of complex interactions of genes, environment, and neurobiology, which fluctuate throughout development. Therefore, the relevant genetic and environmental risk factors may differ during the different stages of alcohol initiation, abuse, and dependence. The complex interaction of these factors is yet to be fully elucidated, and translational studies, ranging from animal studies to research in humans, and well-characterized longitudinal studies are necessary to further understand the development of alcohol dependence. **KEY WORDS: Alcohol dependence; alcoholism; alcohol use and abuse; alcohol and other drug use initiation; risk factors; genetic factors; environmental factors; stress; stress response; neurobiology; biological development; brain; hypothalamic–pituitary–adrenal axis; corticotropin-releasing factor system; animal studies; human studies; literature review**

The development of alcohol dependence is a complex process influenced by both genetic and environmental risk factors (Prescott and Kendler 1999). The relative contributions of genetic and environmental influences fluctuate across development. During adolescence the initiation of alcohol use is strongly influenced by environmental factors (Dick et al. 2007; Heath et al. 1997; Karvonen 1995; Latendresse et al. 2008; McGue et al. 2000), whereas the genetic contribution to alcohol use at this stage is nonspecific and increases the risk for general externalizing behavior (Moffitt 1993; Moffitt et al. 2002). Specific genetic factors increasingly become relevant, however, as patterns of alcohol use are established (Hopfer et al. 2003; Pagan et al. 2006), particularly in mid-adulthood when dependence tends to emerge (Kendler et al. 2010; Schuckit et al. 1995). Gene–environment interactions also play a role because the influence of certain genetic factors seems to increase when a person is exposed to relevant environmental risk factors (Uhart and Wand 2009). Therefore, the development of dependence can be conceptualized within a temporal framework of genes, environment, and behavior.

The purpose of this review is to explore, within this framework, the contribution of some of the neurobiological systems that are important for the development of alcohol dependence. One of these is the mesolimbic dopaminergic system, which is involved in inducing the rewarding effects of alcohol and plays a central role in early alcohol use. Another pathway that also has been implicated in alcohol abuse, and particularly in the transition to alcohol dependence, involves two stress-response systems, the hypothalamic–pituitary–adrenal (HPA) axis and the extrahypothalamic corticotropin-releasing factor (CRF) stress response system, which mediate the interaction of psychosocial stress and early alcohol use. Both of these systems exemplify how the effects of genes and environment may be augmented during critical periods of alcohol use and dependence across the lifespan. For example, the dopaminergic system undergoes developmental transformations during adolescence that are associated with increased reward sensitivity and risk taking (Spear 2000), which presents a window of vulnerability for exposure to alcohol and stress. Then, as alcohol use continues through life, chronic exposure to alcohol can enhance the activity of (i.e., upregulate) the HPA and CRF systems. This dysregulation of the stress response systems

becomes a pathological feature of alcohol dependence, perpetuating chronic alcohol drinking based on an allostatic shift[1] of the CRF system (Koob 2010). Moreover, the HPA, CRF, and dopaminergic systems can influence early alcohol drinking as a result of gene–environment interactions. This article will summarize the literature that has explored how genetic variation within the dopaminergic and stress response systems can influence the risk of alcohol dependence and how the exposure to relevant environmental risk factors and their interaction with genetic variants may influence alcoholism pathology. The effects of genes and environment on alcohol dependence will be discussed in a developmental framework from early childhood to adolescence as well as in the context of the development of dependence, when drinking behavior shifts from recreational use to dependence.

Role of Dopaminergic and Stress Response Systems in Alcohol Initiation and Early Alcohol Use

Environmental Factors and the Dopaminergic System

Several environmental factors have been shown to influence the initiation of alcohol consumption and its use during adolescence, including the level and quality of parental monitoring, peer-group influences, alcohol availability, and socioregional effects (Dick et al. 2007; Heath et al. 1997; Karvonen 1995; Latendresse et al. 2008; McGue et al. 2000). Thus, maternal and paternal alcohol use has been positively correlated with adolescent alcohol use at ages 14 and 17 (Latendresse et al. 2008). Moreover, the level of urbanization was found to correlate with alcohol use in Finnish adolescents at ages 16 and 18 (Karvonen 1995), and peer-group drinking behavior was one of the strongest predictors of problematic drinking in a cohort of Spanish adolescents (Ariza Cardenal and Nebot Adell 2000).

Once alcohol use has been initiated, neuronal networks are activated that engage the brain circuits mediating the rewarding effects of alcohol use (i.e., the reward neurocircuitry). This activation attributes salience to alcohol and serves as an incentive for alcohol use to continue (Robinson and Berridge 1993). Neuronal networks that are known to mediate these effects include those using the signaling molecules (i.e., neurotransmitters) glutamate and γ-aminobutyric acid (GABA) as well as the endogenous opioids (Gass and Olive 2008; Malcolm 2003; Oswald and Wand 2004). In addition, signal transmission involving the neurotransmitter dopamine in the mesolimbic system (Di Chiara and Imperato 1988) is particularly important for the establishment of regular alcohol consumption because alcohol-induced dopamine release is believed to contribute to the rewarding effects of alcohol (for reviews see, Soderpalm et al. 2009; Tupala and Tiihonen 2004). The mesolimbic system is a set of interconnected brain structures including the ventral tegmental area (VTA), nucleus accumbens (NAc), and components of the limbic system (e.g., the amygdala). Studies in rats found that alcohol consumption can increase dopamine signaling in the NAc (Weiss et al. 1996). Conversely, dopaminergic neurotransmission is decreased during withdrawal in the NAc and VTA of rats treated chronically with ethanol (Diana et al. 1993).

Environmental risk factors during early life and adolescence may interact with the dopaminergic system to influence alcohol intake. Two such factors are exposure to environmental stress and alcohol consumption itself. The developing adolescent brain undergoes substantial changes in the strength with which signals are transmitted between neurons (i.e., in synaptic plasticity) (Bava and Tapert 2010; Giedd 2003). These changes include increased dopaminergic inputs to the prefrontal cortex that peak during adolescence and decrease later in life (Kalsbeek et al. 1988; Rosenberg and Lewis 1994). Furthermore, dopamine levels in the NAc also peak during adolescence, before decreasing during subsequent brain maturation (Philpot and Kirstein 2004). These neuronal alterations are believed to promote sensation-seeking and risk-taking behavior during adolescence, which in turn increase the propensity for alcohol initiation and alcohol use (Spear 2000). Exposure to alcohol and/or stress during early life (i.e., from the prenatal period through adolescence) has been shown to have lasting consequences on the dopamine system that have a significant impact on the risk for alcohol abuse.

The Effects of Early Alcohol Use on the Dopaminergic System

Studies in rats found that exposure to alcohol during the prenatal period decreases the levels of two important enzymes involved in regulating dopamine activity—the dopamine transporter and the dopamine hydroxylase enzyme—in the VTA (Szot et al. 1999). Moreover, rats chronically treated with ethanol during adolescence displayed persistently elevated baseline dopamine levels in the NAc during adulthood, even after a period of 15 days abstinence (Badanich et al. 2007). Finally, repeated ethanol injections in preadolescent and adolescent rats increased subsequent dopamine activity in the NAc, with the largest increases observed in preadolescence. Early ethanol exposure in these rats decreased the ability of subsequent ethanol injections to elicit dopamine release from the NAc (Philpot and Kirstein 2004). These findings suggest that ethanol exposure in early life may influence the response to alcohol in later life. Indeed, additional studies have confirmed that both pre- and postnatal exposure to alcohol increase the sensitivity of rats to the locomotor effects of alcohol and to an agent that mimics dopamine's effects (i.e., a dopamine agonist), apomorphine

[1] The term allostasis refers to the process through which various biological processes attempt to restore the body's internal balance (i.e., homeostasis) when an organism is threatened by various types of stress in the internal or external environment. Allostatic responses can involve alterations in HPA axis function, the nervous system, various signaling molecules in the body, or other systems.

(Barbier et al. 2009). Therefore, at least in rodents, early alcohol exposure seems to confer lasting effects on neuronal dopamine activity that can alter behavioral responses to subsequent alcohol exposure. Indeed, rats chronically treated with ethanol both prenatally and during adolescence also show an increased preference for alcohol and increased alcohol intake as adults (Barbier et al. 2009; Pascual et al. 2009). Furthermore, stress-induced alcohol consumption was associated with an earlier age of drinking onset in Wistar rats (Fullgrabe et al. 2007; Siegmund et al. 2005).

Studies in humans have confirmed the potential long-lasting impact of early alcohol exposure, demonstrating that an early initiation of alcohol use is associated with an increased risk of later problems with alcohol. For example, Hawkins and colleagues (1997) noted that the earlier drinking is initi-

The Extrahypothalamic Corticotropin-Releasing Factor System and the Transition to Alcohol Dependence

As described in the main article, corticotropin-releasing factor (CRF) is a key component of one of the body's main stress response systems, the hypothalamic–pituitary–adrenal (HPA) axis. Moreover, activation of the HPA axis in response to stressful situations as well as alcohol ingestion plays an important role in the development of alcohol dependence. However, studies in rodents and macaques have shown that enhanced activity (i.e., upregulation) of the CRF system in response to chronic alcohol exposure in several brain regions not immediately related to the HPA system (e.g., the amygdala) also is a key characteristic of alcohol dependence. CRF is an anxiety-inducing peptide, and rodent models of motivation have demonstrated that CRF, administered either directly into the brain or under the skin, induces conditioned place aversion (Cador et al. 1992). In addition, studies in mice found that transient elevation of CRF levels in the forebrain during early development increased anxiety in later life compared with control animals (Kolber et al. 2010).

Studies of a rat strain bred for high alcohol preference (i.e., the mSP rats) found that the animals display an increased behavioral sensitivity to stress and a lowered threshold for stress-induced reinstatement of alcohol-seeking behavior (Hansson et al. 2006). Gene expression analyses across different brain regions of the mSP strain revealed a significantly enhanced expression of a gene, *CRF1,* which encodes one of the CRF receptors. Additional gene sequence analyses of the mSP rats identified a DNA variation (i.e., polymorphism) in a regulatory region (i.e., the promoter) of the *CRF1* gene that is unique to the mSP rats, suggesting that segregation of this polymorphism may have occurred during selection for the alcohol preference trait. However, alcohol consumption reduced CRF1 levels in the amygdala and the nucleus accumbens (NAc) in mSP rats, indicating that the animals may consume alcohol to reduce CRF activity in these regions (Hansson et al. 2007).

Studies in *Rhesus* macaques also have confirmed the link between the CRF system, stress, and alcohol because a polymorphism (–248C/T) in the promoter of the CRF gene was associated with differential behavioral and hormonal responses to stress. Animals that carried the T allele DNA variant at this site displayed greater HPA axis responses to separation stress and increased alcohol intake if they were exposed to early-life adversity in the form of peer rearing (Barr et al. 2009). These findings demonstrate that genetic variation in the CRF system associated with increased sensitivity to stressors also is correlated with increased alcohol consumption in both rats and primates. Because alcohol consumption is known to reduce the activity of the HPA axis, hyperactivity of this system in animals carrying risk variants of the CRF gene likely is a motivating factor for alcohol consumption in these animals, and this effect is enhanced when the animals are exposed to stressors.

Animal studies also have demonstrated that agents that block the activity of the CRF1 receptor (i.e., CRF1 antagonists) may be suitable for treatment of alcohol dependence (Gehlert et al. 2007). Although animals do not exhibit all aspects of alcohol dependence found in humans, certain components of the disorder can be modeled in rodents. Thus, researchers induced a "postdependent state" in rats by first subjecting the animals to involuntary intermittent exposure to alcohol vapor and then allowing them 3 weeks of recovery from the exposure (Sommer et al. 2008). After this recovery period, the animals displayed increased CRF1 levels in the amygdala, comparable to those observed in mSP rats at baseline. In addition, the postdependent animals exhibited increased fear suppression of behavior that persisted for 3 months after cessation of alcohol exposure, as well as increased voluntary alcohol consumption. This postdependent phenotype could be reversed by a CRF1 antagonist, 3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethylpropyl)-2,6-dimethyl-

ated in adolescence, the greater the levels of alcohol misuse at ages 17 to 18. Furthermore, people who begin drinking at age 14 or younger are more likely to become alcohol dependent later in life (Grant and Dawson 1997). Few studies have been conducted to determine the precise mechanism by which early alcohol exposure affects the risk for subsequent alcohol abuse and dependence. However, Pascual and colleagues (2009) demonstrated that in adolescent rats chronically treated with ethanol, two neurotransmitter receptors—dopamine receptor 2 (DRD2) and glutamate receptor (NMDAR2B)—show lower levels of a chemical modification (i.e., phosphorylation) in the prefrontal cortex compared with adults chronically treated with ethanol. This finding suggests that alcohol use during adolescence causes neurobiological changes to the dopamine system that are not observed in adult animals.

imidazo[1,2-b]pyridazine (MTIP) (Funk et al. 2006; Sommer et al. 2008), confirming the role of increased CRF activity during alcohol dependence. Other studies also demonstrated that selective CRF1 antagonists reduced alcohol self-administration in alcohol-dependent animals but had no effect in alcohol-naïve animals (Funk et al. 2006, 2007). The exposure to stress, which often triggers relapse in abstaining alcoholics, also reinstates alcohol-seeking behavior in postdependent animals. CRF1 antagonists can suppress this behavior in animals (Le et al. 2000; Liu and Weiss 2002; Marinelli et al. 2007), further confirming their relevance as a potential pharmacotherapy for alcohol dependence. Finally, CRF1 antagonists can block the anxiety-like responses exhibited during withdrawal from alcohol in animals (Breese et al. 2005).

The potential of CRF1 antagonists in the treatment of alcohol dependence now also is being considered in humans. CRF1 antagonists previously have been assessed in the treatment of depression and anxiety (Zobel et al. 2000) and Phase II/Phase III clinical trials with these agents currently are underway for the treatment of alcohol use disorders (www.clinicaltrials.gov; Zorrilla and Koob 2010). The results of these trials may pave the way for the clinical consideration of CRF1 antagonists for addictive disorders. If such compounds are efficacious in humans, pharmacogenetic studies may identify those patients who are most amenable to CRF1 antagonist treatment, especially among those who are exposed to high levels of lifetime stress.

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The Effects of Environmental Stress on the Dopaminergic System

Environmental stress is one of the most pertinent risk factors for alcohol dependence. The exposure to early-life stress sensitizes animals to drugs of abuse (Fahlke et al. 1994; Piazza et al. 1991; Shaham and Stewart 1994) and also increases alcohol consumption in later life (Fahlke et al. 2000). Alterations in the dopaminergic mesolimbic system that persist into adulthood are believed to explain, at least in part, these behavioral adaptations (for review, see Rodrigues et al. 2011). For example, studies in rats found that chronic exposure to cold stress in adolescence altered both basal and stress-evoked release of dopamine and another neurotransmitter, norepinephrine,[2] in the medial prefrontal cortex, NAc, and striatum compared with stress-naïve rats (Gresch et al. 1994). Other studies in Sprague-Dawley rats demonstrated that stress caused by separation from the mother during the first 2 weeks of life blunted the animals' dopamine response to restraint stress in adulthood (Jahng et al. 2010). Although no human studies analyzing the effect of early-life stress and alcohol sensitization exist, imaging studies using functional magnetic resonance imaging (fMRI) to analyze reward anticipation have found that childhood adversity is associated with blunted subjective responses to reward-predicting cues as well as with impaired reward-related learning and motivation (Dillon et al. 2009). Such findings demonstrate that early environmental experiences can alter the impact of a reward and that similar effects can be observed across species.

Other studies have evaluated the effects of early-life stress on alcohol consumption or alcohol dependence. Such studies found that even exposure to prenatal stress can have an impact on later alcohol-related behaviors because the offspring of mice that repeatedly were restrained during the last 7 days of gestation subsequently demonstrated enhanced alcohol consumption—an effect that has been linked to persistently elevated dopaminergic and glutamatergic neurotransmission in the forebrain (Campbell et al. 2009). In humans, retrospective studies examining early-life experiences and alcohol consumption found that childhood stressors were associated with alcohol dependence during adulthood (Ducci et al. 2009; Pilowsky et al. 2009). In a study of the adult American population (i.e., the National Epidemiologic Survey on Alcohol and Related Conditions [NESARC]), two or more stressful life events in childhood significantly increased the risk for alcohol dependence in adulthood (Pilowsky et al. 2009). Furthermore, early initiation of alcohol use in human adolescents is associated with exposure to traumatic life events and symptoms of posttraumatic stress disorder (Wu et al. 2010).

Thus, exposure to stress and/or alcohol consumption during early life may influence dopaminergic neurotransmission, with lasting adaptations into adulthood and notable consequences for subsequent alcohol use. However, the impact on different individuals varies, and a portion of this variability can be attributed to genetic factors. Indeed, studies of rats have shown that exposure to chronic unpredictable stress increases the levels of a dopamine-metabolizing enzyme, tyrosine hydroxylase (TH), in the VTA but that the extent of this increase differs drastically between different rat strains (Ortiz et al. 1996). Additional research in *Rhesus macaques* identified a variation (i.e., polymorphism) in the gene encoding dopamine receptor 1 (DRD1)[3] that was associated with increased alcohol consumption in animals exposed to peer-rearing conditions compared with maternally reared animals that carried the same polymorphism (Newman et al. 2009).

Studies in humans also have shown that genetic factors mediate the effects of stress and alcohol on the risk for alcohol dependence. Schmid and colleagues (2009) analyzed 291 young adults in the Mannheim Study of Children at Risk for two polymorphisms in the gene encoding the dopamine transporter. The investigators found that the age of first alcohol use and of intensive alcohol consumption mediated the association between these polymorphisms and early alcohol abuse and dependence. Genetic variation in another gene, *KCNJ6*, which is expressed in the brain, mediates the effects of early-life stress on alcohol abuse in adolescence. It induces inhibition of neuronal signaling at the level of the signal-receiving (i.e., postsynaptic) dopaminergic neurons (Kuzhikandathil et al. 1998). Furthermore, the protein encoded by the *KCNJ6* gene, the membrane potasium channel GIRK2, is co-expressed in TH-positive cells of mice (Schein et al. 1998). Individuals who carry a certain *KCNJ6* variant and are exposed to high levels of psychosocial stress in early life display increased risky drinking behavior in adolescence; moreover, the same polymorphism is associated with alcohol dependence in adults (Clarke et al. 2011).

Genes in other neurobiological systems also mediate the effects of early-life stress on alcohol consumption, including genes encoding the serotonin receptor (Laucht et al. 2009) and the GABA receptor subunit α-2 (*GABRA2*) (Enoch et al. 2010). Another important gene is that encoding the μ-opioid receptor (*OPRM1)*. It also moderates the effects of stress and alcohol with implications not only for alcohol use but also for recovery from alcohol dependence. Alcohol activates the μ-opioid receptor in the VTA, which causes inhibition of GABAergic neurons; this in turn results in disinhibition of dopaminergic neurons and, thus, increased dopamine release in the ventral striatum (Spanagel 2009). In macaques, a certain polymorphism in the *OPRM1* gene (i.e., the C77G polymorphism) predicts the degree of distress upon exposure to maternal separation (Barr et al. 2008). In humans, the equivalent polymorphism (i.e., the A118G polymorphism) is associated

[2] Norepinephrine also is known as noradrenaline.

[3] The variation was located at the beginning of the gene, in a DNA region that did not encode a part of the final protein (i.e., in the 5′ untranslated region of the gene).

with the quality of parent–child interactions under conditions of poor parenting (Copeland et al. 2011). Finally, in both macaques and humans the same polymorphisms are associated with subjective/behavioral responses to alcohol (Barr et al. 2007, 2008; Ramchandani et al. 2010). The role of this polymorphism further has been demonstrated in studies using a μ-opioid receptor antagonist, naltrexone, that commonly is used to treat alcohol dependence. In heavy drinkers, the A118G polymorphism mediates the effects of naltrexone on positive mood, craving, and enjoyment from alcohol (Ray and Hutchison 2004). Furthermore, the presence or absence of the A118G polymorphism can help predict which individuals will benefit from naltrexone treatment for alcohol dependence (Oslin et al. 2003).

Taken together, the findings described here indicate that early exposure to alcohol and stress can increase the subsequent risk for alcohol dependence, at least in part because they induce changes in the dopamine system. However, these effects are moderated by genetic factors in the dopamine pathways and other neurobiological systems.

Brain Stress Response Systems and the Development of Alcohol Dependence

As indicated by the observations discussed in the preceding section, the dopamine system is an important neurobiological system mediating early alcohol use. In addition, stress response systems in the brain have been implicated in alcohol initiation and in the escalation of alcohol use from episodic use to abuse and, ultimately, dependence. Stress responses are crucial for survival by allowing the organism to coordinate appropriate behavioral adaptations to adverse stimuli and are essential homeostatic processes. Central components of the stress response include activation of the HPA axis, increases in norepinephrine turnover in a brain region, the locus coeruleus, and activation of CRF systems (Habib et al. 2001). CRF acts through two pathways. First, it acts as a signaling hormone inside the HPA axis, where it is released from the paraventricular nucleus of the

The IMAGEN Study

The IMAGEN study (www.imagen-europe.com) is the first study aimed at identifying the genetic and neurobiological basis of individual variability in impulsivity, reinforcer sensitivity, and emotional reactivity, as well as determining their predictive value for the development of common psychiatric disorders. The data collection of IMAGEN began in 2007. Since then, the study has collected comprehensive behavioral and neuropsychological data, as well as functional/structural neuroimaging data for 2,000 14-year-old adolescents. These data are complemented by genome-wide association (GWA) data on the study participants. These genetic analyses target approximately 600,000 DNA markers distributed across the genome, using the Illumina Quad 660 chip.

Data from the first wave of IMAGEN became available in 2010 in an extensive database (Schumann et al. 2010), and since then several articles have been published on the dataset, contributing toward a greater understanding of the adolescent brain. For example, Peters and colleagues (2010) showed that adolescent smokers display lower activation of the ventral striatum during reward anticipation compared to their nonsmoking peers. Other studies identified gender-dependent amygdala lateralization during face processing and created probabilistic maps of the face network in the adolescent brain (Schneider et al. 2010; Tahmasebi et al. 2010).

The sample will be followed up at age 16 to investigate the predictive value of genetic factors and intermediate phenotypes for the development of mental disorders, such as alcohol dependence. The full dataset from the follow-up will be completed in 2012. A second follow-up is planned to be completed when the participants reach age 18.

In conclusion, IMAGEN integrates technological and methodological advances in the field of cognitive neuroscience as well as in the fields of human and molecular genetics. This comprehensive approach, together with the large sample sizes, will provide new insights into the interplay between genes and environments that results in individual variability in brain structure, function, and psychological traits. The complex phenotypic and genotypic profiling provided by IMAGEN will be vital in identifying biomarkers that aid in earlier diagnosis and in the developments of treatments for psychiatric disorders, including alcohol dependence.

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hypothalamus. It then is transported to the anterior pituitary, where it binds to CRF receptors (CRF1 and CRF2), thereby eliciting the release of adrenocorticotrophic hormone (ACTH). ACTH production ultimately results in the release of stress hormones (i.e., glucocorticoids) from the adrenal glands. The main glucocorticoid in humans is cortisol. Second, CRF acts outside of the hypothalamus (i.e., extrahypothalamically) because immunological tests have detected its presence in the extended amygdala and the brainstem (Swanson et al. 1983).

Studies have demonstrated that exaggerated HPA axis responses to stress can precede the onset of alcoholism. Nondependent sons of alcoholic fathers (who are at increased risk of alcoholism) displayed increased cortisol and ACTH responses to psychosocial stress compared with people with no family history of alcoholism (Uhart et al. 2006; Zimmermann et al. 2004*a*, *b*). Furthermore, alcohol had a greater attenuating effect on ACTH and a related hormone (i.e., arginine vasopressin [AVP]) in people with alcoholic fathers, suggesting that alcohol may be more rewarding for such individuals (Zimmermann et al. 2004*b*). These findings also indicate that interindividual differences in HPA axis activity may underlie some of the variation observed in the vulnerability to alcohol dependence.

As alcohol dependence develops, the stress response systems are upregulated, and this hyperactivity may in fact be a pathological component of dependence (Koob 2008). It has been hypothesized that as dependence develops, the motivation for alcohol use shifts from positive reinforcement, whereby alcohol is consumed for its pleasurable effects, to negative reinforcement—that is, the drinker consumes alcohol to alleviate the negative emotional effects encountered during withdrawal and into protracted abstinence (Koob and Le Moal 2008). The development of negative emotional states has been proposed to include the recruitment and subsequent deregulation of various brain stress system, including the HPA axis, extrahypothalamic CRF, and various others[4] (George et al. 2008; Koob 2008). Genetic variation in genes encoding components of these stress response systems therefore may be relevant for the risk for alcohol dependence.

Genetic Influences on Stress Responding and Their Role in Alcohol Dependence

The variability between individuals in stress responding results at least partially from inherited factors (Armbruster et al. 2009; Linkowski et al. 1993; Meikle et al. 1988) that also may influence the risk of alcohol dependence. For example, polymorphisms that affect only a single DNA building block (i.e., single nucleotide polymorphisms [SNPs]) in the gene encoding CRF1 were associated with alcohol consumption and a lifetime prevalence of drunkenness in two independent samples (Treutlein et al. 2006). One of those polymorphisms, known as rs1876831, was found to moderate the effects of stress on drinking. Thus, adolescents at age 15 who had experienced negative life events in

[4] Additional brain stress response systems involve the signaling molecules norepinephrine, neuropeptide Y, tachykinins, and dynorphins.

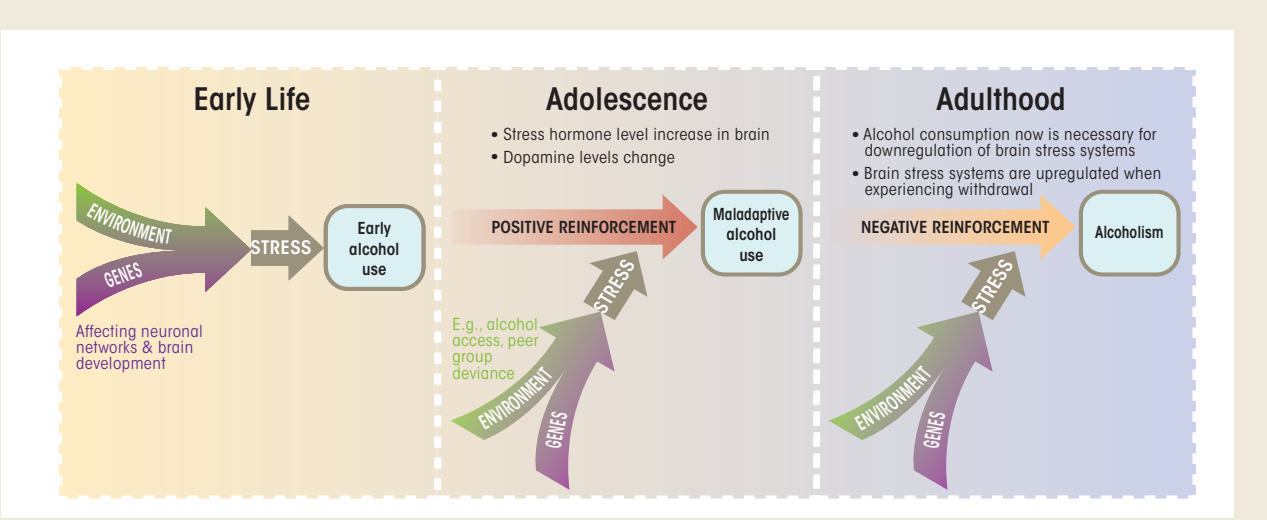

Figure Schematic depiction of the typical progression from alcohol use to alcohol dependence. Both genetic and environmental factors influence each stage of disease progression. Early-life experiences, including prenatal environments and early-life stressors, may affect the onset of alcohol use. In adolescence, heightened sensation seeking, resulting from an increase in cortical dopamine neurons, often results in experimentation with alcohol. In adulthood, alcohol use may occur to downregulate brain stress systems in individuals suffering from alcohol dependence. Thus, early alcohol use is motivated by positive reinforcement, whereas later stages are driven by negative reinforcement, when alcohol is consumed to alleviate negative emotional states.

the past 3 years and who carried the variant (i.e., allele) of rs1876831 that was associated with increased risk of drinking displayed increased alcohol consumption per drinking occasion and greater lifetime rates of heavy drinking (Blomeyer et al. 2008). A similar effect also was observed at age 19, when the risk allele was associated with earlier age of onset of alcohol use and higher alcohol consumption in individuals exposed to stressful life events (Schmid et al. 2010). Furthermore, a gene–environment interaction was detected with a combination of several gene variants (i.e., a haplotype) in the *CRF1* gene (which also contains rs1876831) and childhood sexual abuse in a large cohort of Australians recruited for the Nicotine Genetics Project (Saccone et al. 2007). Individuals who had experienced childhood abuse but carried a protective polymorphism of the *CRF1* gene had lower lifetime alcohol consumption scores and rates of alcohol dependence (Nelson et al. 2009).

Further genetic factors mediating the association between the stress response and alcohol consumption are found in genes encoding the receptors to which cortisol binds after it is released from the adrenal gland when the HPA becomes activated (Bjorntorp 2001). Cortisol binds to glucocorticoid receptors (GRs) that are made up of two identical subunits (i.e., form homodimers). These receptors interact with certain DNA sequences, glucocorticoid response elements (GREs), in the target genes, thereby activating those genes as part of the stress response (Gower 1993; Simons et al. 1992). The GRs are encoded by a family of genes known as nuclear member subfamily 3 (*NR3C*) genes.

Researchers have identified functional polymorphisms in the genes encoding two receptors, NR3C1 and NR3C2, which are associated with differential responses to stress (Wust et al. 2004). For example, a SNP, N363S that results in an altered receptor, protein (i.e., a non-synonymous SNP) in *NR3C1* is associated with increased glucocorticoid sensitivity (Huizenga et al. 1998) as well as elevated levels of cortisol in the saliva of healthy people in response to psychosocial stress (Wust et al. 2004). Moreover, a haplotype that includes three SNPs and is located in a noncoding region of the *NR3C1* gene also is associated with enhanced sensitivity to glucocorticoids (Stevens et al. 2004). Because chronic alcohol consumption can increase HPA axis activity in animals and humans (Rivier 1996; Rivier and Lee 1996; Waltman et al. 1994), polymorphisms in genes encoding components of the HPA axis may increase the risk for alcohol abuse. Indeed, a recent study of 26 SNPs across the *NR3C1* gene in 4,534 adolescents identified several variants that were associated with onset of drinking and drunkenness by age 14, suggesting that genetic variation in *NR3C1* can influence the risk of alcohol abuse in adolescence (Desrivieres 2010). Likewise, variants in the gene encoding the ACTH precursor, promelanocortin *(POMC)*, have been associated with substance abuse, including alcohol abuse (Zhang et al. 2009).

Genes encoding components of the norepinephrine stress response system also have been linked to variability in the response to stress. Thus, polymorphisms in the *ADRA2A* gene, which encodes adrenergic receptors that inhibit norepinephrine release from the neuron, are associated with certain aspects of the stress response as determined by measuring blood pressure and heart rate (Finley et al. 2004). In addition, variants in the *ADRA2A* gene are associated with alcohol abuse phenotypes in humans. For example, in a study analyzing 23 SNPs in *ADRA2A* as well as in a gene *SLC6A2* (which encodes the norepinephrine transporter, NET1) in association with adult alcohol dependence identified two SNPs in *ADRA2A* associated with a positive family history of alcoholism and four SNPs in *SLC6A2* associated with adult alcohol dependence (Clarke et al. 2010).

All of these studies demonstrate that genes that regulate stress responding also influence the risk for alcohol dependence. Thus, people who display increased sensitivity to stress may consume alcohol to dampen the exaggerated stress responses and therefore may find alcohol more rewarding. These people also may more readily experience the negative emotional states associated with withdrawal after chronic alcohol exposure, which may accelerate the transition to dependence. However, the precise relationship between genes, stress, and alcohol use is complex, and gene–environment interactions are notoriously difficult to elucidate (Flint and Munafo 2008). Therefore, translational studies analyzing the effects of genetic factors and stress and their interactions under tightly controlled experimental conditions using animal models are warranted (Barr and Goldman 2006). Indeed, the study of the extrahypothalamic CRF system in animals has helped to clearly delineate the role of brain stress systems in the pathology of alcoholism, and this system is now a plausible target for future alcoholism pharmacotherapies. (For more information on these studies, see the sidebar "The Extrahypothalamic CRF System and the Transition to Alcohol Dependence.")

Another confounding issue for the study of gene–environment interactions is that many studies are conducted retrospectively, and the participants' recall of environmental risk factors may not be accurate. Therefore, prospective longitudinal studies are of great importance to advance the field of gene–environment interactions in alcohol dependence. One study that illustrates how such methodological issues can be addressed is the IMAGEN study, a longitudinal initiative funded by the Framework 6 program of the European Commission and the Medical Research Council that tracks the interplay between genetic polymorphisms and environmental stressors from early adolescence onward. The study collects neuropsychological, behavioral, and functional/structural neuroimaging data and also conducts genetic analyses on a sample of 2,000 adolescents from age 14 onward. (For more information

on this study, see the sidebar "The IMAGEN Study.")

Conclusion and Future Perspectives

Dopaminergic and stress response pathways jointly are engaged upon the commencement of alcohol consumption. Genetic polymorphisms within these pathways may affect the risk of developing alcohol dependence. The effects of exposure to environmental stressors that increase the risk of developing alcohol dependence may be augmented in genetically vulnerable individuals. In some cases, these genetic variants may vary the impact that a particular stressor has within a specific time window (see the figure). To elucidate the role of alcohol usage as a consequence of environmental stressors, and as an environmental stressor in itself, longitudinal studies of the interplay between genes and environments are needed.

The IMAGEN study is an ongoing longitudinal study that attempts to address the role of genes and the environment in alcohol use. The extensive phenotypic database available from this study will allow researchers to test the hypothesis that overactivity of the brain's stress systems, resulting from childhood maltreatment and neglect, may affect brain development and ultimately behaviors such as alcohol use. Alcohol use patterns of the IMAGEN participants are recorded to investigate the long-term effects of early intoxication on cognitive development and behavior. Finally, genetic analyses investigating the association of genetic markers distributed across the genome with specific traits or behaviors (i.e., genomewide association data) are available for each participant and may demonstrate the relationship between genes of the stress response system and intermediate phenotypes (Schumann et al. 2010).

Longitudinal gene–neuroimaging studies, such as the IMAGEN study, aim to clarify the role of the HPA axis and supplementary stress systems in the development and maintenance of alcohol dependence. Such studies will elucidate how alcohol use fluctuates throughout development under the influence of genetic and environmental factors. A better understanding of these factors will promote novel therapies for alcohol dependence as well as approaches to prevent the disorder. ■

Financial Disclosure

The authors declare that they have no competing financial interests.

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The Impact of Gene–Environment Interaction on Alcohol Use Disorders

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This article describes three types of gene–environment interactions and the challenges inherent in interpreting these interactions. It also reports on what is known about gene–environment interactions in the field of alcohol use disorders (AUDs). Twin studies of the interaction of genetic and environmental influences on AUDs have resulted in relatively consistent findings and have suggested general mechanisms for interaction effects. These studies generally find that environments that exert more social control (e.g., higher parental monitoring, less migratory neighborhoods, etc.) tend to reduce genetic influences, whereas other environments allow greater opportunity to express genetic predispositions, such as those characterized by more deviant peers and greater alcohol availability. Conversely, the gene–environment literature that has been developed surrounding specific genes has focused largely on the role of stress as a moderator of genetic effects. KEY WORDS: Alcohol use disorders (AUDs); genetic factors; environmental factors; genetic and environment interactions; twin studies; statistical models; stress; literature review

This article explores interactions between genetic and environmental effects on alcohol use disorders (AUDs). Two contrasting ideas define what it means to have genes and environment interact. The first approach—the one that this article will focus on—is a statistical perspective. This approach is based on statistical models in which genetic and environmental factors are sometimes measured indirectly (i.e., latent variable modeling—often in twin studies) and sometimes directly via molecular methods (examples of both kinds of interactions are provided below). The statistical approach does not consider the underlying biological process. Rather, it is based on observing processes from afar and modeling them.

The second approach is based on a biological or molecular perspective. The early work by Jacob and Monod on the operon model of gene regulation established that environmental effects can profoundly influence gene expression (Morange 1998). For example, by switching the source of food for bacteria (e.g., from glucose to lactose), researchers can activate a new set of genes that metabolize the lactose molecule. This is another way of thinking about how genes and environment "interact" but one that differs rather dramatically from the statistical viewpoint. From this perspective, the term interact refers to a biological process, measuring environmental exposures in biologically meaningful ways and looking at processes such as gene expression.

Statistical interactions do not equal biological interactions. In fact, any neurobiological system involves multiple gene products interacting with each other, such as components of signaling cascades, neurotransmitters and their receptors, or degradative enzymes. The world of biology seems like nothing but interactions of one molecule with another. Some biologists take this to mean that when we look at the effect of genetic variation, we should see interactions everywhere and that most gene effects involve such interactions. However, this is not true. A large corpus of work in statistical genetics in tractable organisms consistently has shown that most genetic effects look additive (Mather and Jinks 1982). Further explanation of this is beyond the scope of this article. In general use, the term interact sometimes only means "to act together." This is consistent with the technical concept of an additive model in which the main effects of genes and environment interact. In this article, the term interact will refer to its technical statistical meaning.

Examining gene–environment interactions from a statistical perspective is exemplified by the work of the statistician Ronald Fisher and best expressed in the development of the analysis of variance. In this highly influential statistical technique, as explained in any standard statistical textbook, Fisher posited an approach that first took into account main effects. For example, by studying the height of a particular plant 10 weeks after planting, one could examine the effect of the two different plant strains (reflecting genes) and the two different fertilizers (reflecting the environment). This would produce a main effect for each variable. Beyond

this, one would look for a gene–environment (or more technically a "strain by fertilizer") interaction. This interaction would reflect any explanatory power left over after accounting for the main effects. In many such cases, as noted above, no significant interaction is detected. That is, research shows the effects of genes on the phenotype and the effects of environment on the phenotype and no significant interaction. This is what statisticians will call an additive model—one in which the effects of genes and environment just add together.

If research does detect a significant gene-by-environment interaction, the effects of genes and environment on the phenotype (e.g., plant height) are not independent of one another. The impact of genes depends on environmental exposure and the impact of the environment depends on the effect of genes. Note that these two statements are conceptually equivalent. Expressed in yet another way, the central concept of genotype-by-environment interaction is that of conditionality. That is, it is not possible to understand how genes are acting without taking the environment into account, and vice versa.

Types of Gene–Environment Interactions and Challenges With Their Interpretation

This section will review three examples of gene–environment effects, which are illustrated in figure 1. Figure 1 shows five groups differing in level of genetic liability for a particular trait Y (e.g., symptoms of an alcohol use disorder [AUD]), from low to high. The diamonds represent the group with the lowest liability; the asterisks represent the highest-liability group. The x-axis shows the effect of the environment in five increasing categories. Level 1 reflects a very benign environment that conveys no increase at all on trait Y. As the environment becomes more pathogenic—from levels 2 to 5—it has a progressively greater and greater impact on trait Y.

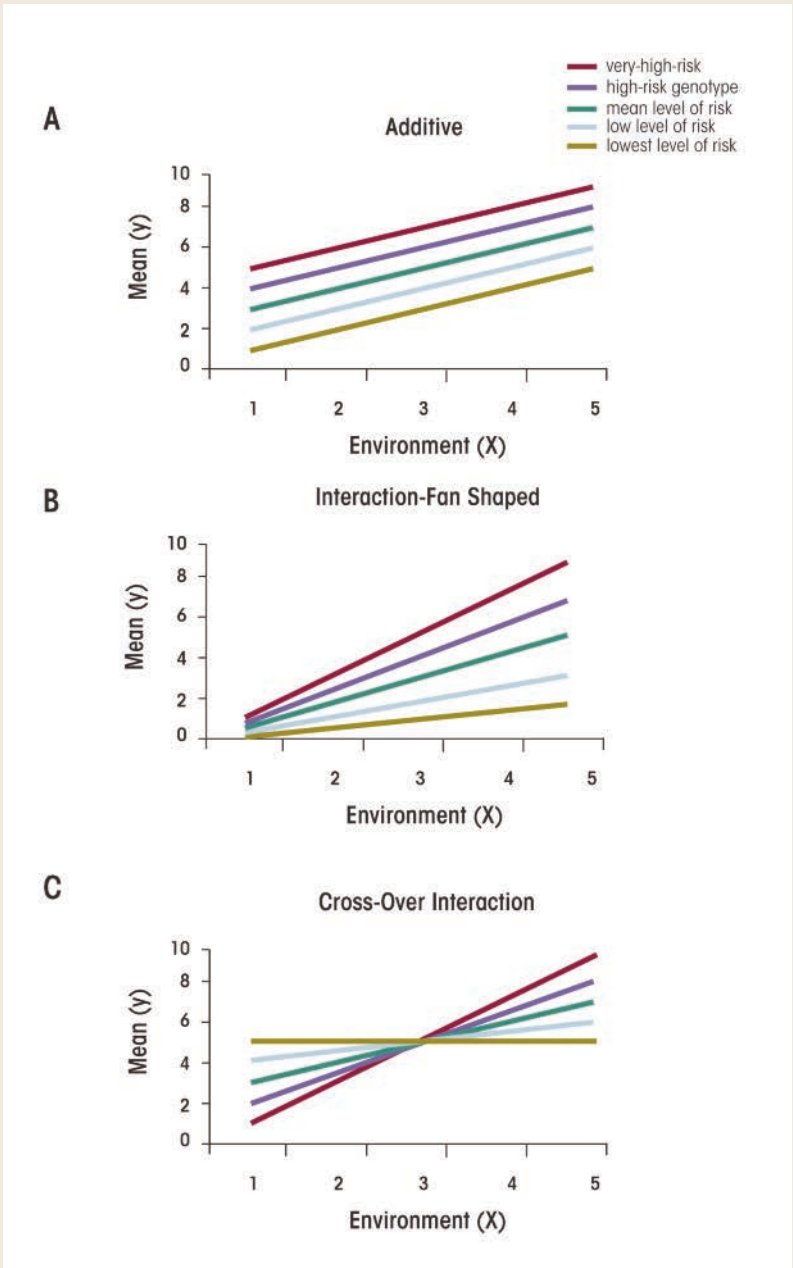

Figure **A–C)** The effect of genes and environment are used to predict the mean level of a quantitative trait Y. The lines depict five different genotypes with varying levels of liability to trait Y (e.g., symptoms of alcohol dependence). The environmental level of risk is depicted on the X-axis and ranges from level 1 (very low risk) to 5 (very high risk). **A)** An additive model of genetic and environmental effects. The key feature of this model is that the lines are all parallel—that is, the increase in the level of trait Y associated with a more adverse environment is the same for all genotypes. **B)** A fan-shaped interaction of genetic and environmental effects on trait Y. **C)** A cross-over interaction of genetic and environmental effects on trait Y.

Panel A in the figure depicts an additive model. The lines all are parallel with one another. Increasing from low- to high-risk environments (i.e., from environments 1 to 5), the increase in the level of Y is the same across all five genotypes. Genes and environment act independently of one another.

Panel B in the figure depicts what is known as a "fan-shaped" interaction. Note that the impact of genes is dependent on the environment, and vice versa. The key characteristic of a fan-shaped interaction is that, in benign environments, the difference in the level of the outcome variable (i.e., Y) as a function of the level of genetic liability is quite modest. That is, genes are not doing that much in a protective environment. However, with increasingly severe environmental exposures, the difference between genotypes increases. (In theory, of course, it does not have to be the case that the genetic differences are more pronounced in adverse environments than in benign environments. It could be that under very adverse conditions the environment becomes all important, but under more normative environmental conditions there is opportunity to see genetic differences.) Genes have a much more potent impact on the phenotype in a stressful environment. Another useful way to conceptualize such fan-shaped interactions is to see that genes in this context do two different things. First, they set the mean level of genetic liability. Second, they affect an individual's sensitivity to the impact of the environment.

Figure 3 depicts a crossover interaction, in which the order of genetic effects changes as a function of the environment. Those at lowest risk in environment 1 are at highest risk in environment 5. One would expect the environment, on average, to have an impact on the phenotype because the average level of risk for individuals in environment 5 (the highest risk environment) will be substantially greater than the average level of risk in the most benign environment (environment 1). However, in general, the main effect on the genotype is limited in this situation, because of a balance between the risk-decreasing effects in benign environments and the risk-increasing effects in malignant environments.

The literature surrounding plant and animal genetics indicates that fan-shaped interactions generally are more common than crossover interactions (Lynch and Walsh 1998; Mather and Jinks 1982). They are more difficult to interpret, however, because a statistical transformation of the scale of measurement can make many fan-shaped interactions disappear. That is, by examining the raw scale scores for a particular trait, it is possible to find significant evidence for a fan-shaped interaction. However, applying statistical analysis (i.e., logarithm or square-root transformation) of the scale scores often causes the interaction to disappear (Lynch and Walsh 1998; Mather and Jinks 1982).

Determining whether the interaction is indeed legitimate is a complicated question. Part of the answer has to do with the degree of "grounding" of the particular scale of measurement that one is examining. In studies of AUD risk, the particular measures are relatively arbitrary and might reflect the number of endorsed *Diagnostic and Statistical Manual, Fourth Edition* (DSM–IV) criteria. In this case, it is difficult to strongly argue that the number of DSM criteria is inherently more real than the square root of those numbers. This adds an extra interpretational difficulty to many analyses of genotype–environment interaction that do not carefully explore the degree to which transformations of the scale of measurement can make the interactions disappear.

A related problem is the common use of logistic regression in the analyses of genotype–environment interaction. Logistic regression is a convenient statistical tool when the dependent measure is dichotomous—such as whether an individual does or does not have a particular disorder. However, logistic regression involves a logarithmic transformation of the probability of being affected. This profoundly changes the nature of relationships between variables, because two variables that multiply as regular numbers will add together when logarithms are applied. The interpretation of interactions that relies solely on logistic regression therefore is rendered relatively treacherous. The interpretation of these results depends in part on a long argument in the epidemiological literature about whether the additive or the multiplicative model of risk is most appropriate.

Eaves (2006) simulated the effect of candidate genes and specific environmental factors in predicting a normally distributed continuous variable using a purely additive model (as in panel A of the figure). The resulting continuous results were dichotomized at a particular threshold value, and the dichotomized data were analyzed by logistic regression. Depending on the nature of the simulation, genotype–environment interaction was detected (spuriously) in 70 to 100 percent of the simulations. These results indicate that genotype–environment studies that detect interactions using logistic regression for dichotomous dependent measures should be interpreted with caution. It is quite challenging in such studies to determine whether the result is valid or an artifact of the statistical measures used. Kendler and Gardner (2010) have further explored this puzzling question of the interpretation of interactions.

Gene–Environment Interaction in the Field of AUDs

Examples of Latent Gene–Environment Interaction

Alcohol research is an area where one might imagine gene–environment interaction effects to be particularly important in etiological models because, by definition, exposure to alcohol is a necessary condition for the eventual development of alcohol-related problems. For example, one of the most widely replicated genetic associations with alcohol dependence is the protective role of a genetic variant responsible for the enzyme aldehyde dehydrogenase (i.e., *ALDH2*).[1] The enzyme produced

by a genetic variant in *ALDH2* is comparatively inactive, interfering with the metabolism of alcohol, which leads to facial flushing and other aversive physiological symptoms when alcohol is consumed (Shen et al. 1997). Accordingly, the association between this gene and risk for alcohol dependence necessarily operates through alcohol exposure. Environments that modify the extent of exposure to alcohol therefore would be predicted to moderate the degree to which genetic variability is important. In the extreme, this becomes obvious. If there is no alcohol in the environment, then genetic risk factors for AUDs cannot, by definition, express themselves.

A growing twin literature provides evidence that a variety of different environmental domains that influence access to alcohol and opportunity to engage in alcohol use moderate the importance of genetic influences. One of the earliest illustrations of gene–environment interaction in the area of substance use research demonstrated that genetic influences on alcohol use were greater among unmarried women, whereas having a marriage-like relationship reduced the impact of genetic influences on drinking (Heath et al. 1989). Religiosity also has been shown to moderate genetic influences on alcohol use among female subjects, with genetic factors playing a larger role among individuals without a religious upbringing (Koopmans et al. 1999).

Adolescent alcohol use also seems to be particularly influenced by gene–environment interactions, as might be expected because most adolescents are moving through a developmental period when adult guardians still exert a fair degree of control over their environment. Genetic influences on adolescent substance use are enhanced in environments with lower parental monitoring (Dick et al. 2007*b*), and easy availability of alcohol (Kendler et al. 2010), as well as in the presence of substance-using friends (Dick et al. 2007*a*; Harden et al. 2008; Kendler et al. 2010). Socioregional or neighborhood-level influences also have been shown to moderate the importance of genetic influences on substance use. Genetic influences for late-adolescent alcohol use (and early-adolescent behavior problems, which are genetically correlated) are enhanced in urban environments, communities characterized by greater migration, and neighborhoods with higher percentages of slightly older adolescents/young adults (Dick et al. 2001, 2009*a*; Rose et al. 2001). These community-based moderation effects presumably reflect differences in the availability of alcohol, role models, neighborhood stability, and community-level monitoring across different areas.

It is likely that many of the important moderating effects of the environment associated with alcohol use and related externalizing behavior reflect differences in social control and/or opportunity, resulting in differential expression of individual predispositions (Shanahan and Hofer 2005). Accordingly, the relevant environments are likely to vary across developmental stage. There is some indication of this in the Finnish twin data, where parental monitoring showed significant moderating effects on substance use starting earlier in adolescence (age 14), whereas the moderating role of peer substance use was not apparent until later in adolescence (age 17). More research in this area is necessary to delineate the developmental periods during which specific environments are critical because alcohol use patterns (and their etiological influences) are dynamic across the transition from adolescence to young adulthood. This also is likely to be true across stages of adulthood, although comparatively little research has been dedicated to this area.

Examples of Gene–Environment Interaction Involving Molecular Variants

As explained above, gene–environment interaction can be detected through the study of genetic influences that are inferred via comparisons of different types of relatives (such as twins) (i.e., latent genetic influences), or through the study of specific measured genes by molecular techniques. Gene–environment interactions modeled latently have the advantage of providing information about the overall genetic effect averaged across the entire genome but tell nothing about the specific underlying biology. Studies of specific genes have the advantage of providing information about the underlying biology, but they are (at this point) largely limited to studying single genes in a system in which there are likely to be hundreds of genes involved.

The literature surrounding specific gene–environment interactions in the area of alcohol use has developed largely independently of the latent gene–environment interaction literature reviewed above. Much of the literature examining measured gene–environment interactions with alcohol use outcomes has focused on stress, which was measured in a variety of ways, a moderator of specific genetic influences. The relationship between stress and alcohol use is complex, with human experimental studies, animal studies, and epidemiological studies all yielding equivocal evidence as to whether stress induces alcohol use (Schwandt et al. 2010; Veenstra et al. 2006). However, the gene–environment interaction literature presupposes that one of the reasons for these disparate findings may be that stress is more likely to induce alcohol use and problems in people who are genetically vulnerable, similar to the literature surrounding the experience of stressful life events and the onset of depression (Kendler et al. 1995).

A number of studies have tested for interactions between alcohol-related outcomes and various measures of stress with the genetic variation for length of the promoter region of the serotonin transporter gene (*5-HTTLPR*) (i.e., whether the genetic variant [allele] for long or short promoter region is associated with stress and alcohol use). Two studies found enhanced risk

[1] By convention, gene names in animals are written in uppercase and lowercase and italicized. Gene names in humans are written in all caps and are italicized, whereas the acronyms for the encoded proteins are all caps but not italicized.

associated with the short allele in the presence of a stressful environment. Covault and colleagues (2007) found that the short allele was associated with more frequent drinking and heavy drinking as well as drug use in college students if they had experienced multiple negative life events in the past year. Kaufman and colleagues (2006) found that the short allele conferred vulnerability to early alcohol use, and that this effect was stronger among maltreated children. Conversely, in the Mannheim Study of Children at Risk, the long allele was associated with more hazardous drinking in males among those exposed to high psychosocial adversity, as defined by early psychosocial stress and/or current life events (Laucht et al. 2009). In a study of Swedish adolescents, having two different alleles (i.e., being heterozygous) at the long/short polymorphism was associated with a higher intoxication frequency in the presence of neutral or bad family relations, which is biologically unlikely (Nilsson et al. 2005). Accordingly, the genetic model associated with the interaction has been inconsistent across studies, and the primary outcomes and measures of the experience of stress have varied considerably.

A more consistent picture has emerged from studies using experimental manipulations of the environment. In a unique prevention study testing for gene–environment interaction associated with the serotonin transporter gene, Brody and colleagues (2009*b*) found that youth carrying the short allele were more likely to initiate high-risk behavior (including alcohol and marijuana use, as well as sexual behavior) over time if they were in the control condition rather than the prevention condition. Similarly, short allele carriers showed increases in substance use over time, but this association was reduced when youth received high levels of involved-supportive parenting (Brody et al. 2009*a*, *b*). Related studies in monkeys indicate that the short allele is associated with higher baseline alcohol consumption (Barr et al. 2004) and increased aggression (Suomi 2006) under conditions of peer rearing (a stressful environment) compared with mother rearing. These studies suggest that experimental manipulation of the environment may be more likely to yield replicable interaction effects than observational designs, as previously has been argued from a statistical perspective (McClelland and Judd 1993). Interaction effects associated with experimental manipulations of the environment also may be more robust because interventions often operate across a variety of environmental domains (e.g., by influencing parenting processes, peer interactions, and equipping individuals with personal tools that are applicable across a variety of settings). Thus, any interaction effects that are detected may be more likely to be replicated for reasons similar to why twin studies, which examine aggregate genetic effects, are more likely to be replicated (discussed further below).

A few studies have evaluated gene–environment interactions with a variant of the gene for the dopamine type 2 receptor (i.e., the *DRD2* Taq1A polymorphism, which actually is located in the neighboring gene *ANKK1*). These studies have suggested that DRD2 A1 carriers show higher alcohol-related problems in the presence of stress (Bau et al. 2000; Madrid et al. 2001) and have higher novelty seeking when their child-rearing environment was assessed as punitive (Keltikangas-Jarvinen et al. 2009). Similarly, there is a small literature surrounding a genetic variant for the enzyme monoamine oxidase (MAO) (i.e., the MAOA polymorphism), adversity, and alcohol-related outcomes. MAO degrades serotonin, dopamine, and norepinephrine, which are all involved in the stress response. One study found a main effect of the MAOA promoter polymorphism on the risk for substance use disorders and an interaction with parenting (Vanyukov et al. 2007). In another study, the MAOA low-activity allele was associated with alcoholism, and particularly with antisocial alcoholism, but only among women experiencing childhood sexual abuse (Ducci et al. 2008). In yet another small study of female adolescents, the long variant increased risk for alcohol-related problems in the presence of an unfavorable environment (as defined by poor family relations or maltreatment/abuse). However, this effect was opposite that reported in the other studies (Nilsson et al. 2008). Accordingly, the association between this genotype and alcohol-related outcomes remains equivocal.

A few notable efforts have been made to extend the measured genotype–environment interaction literature in the field of alcohol-related outcomes in new directions. One such effort tested for moderation effects associated with brain gene expression in rodent models. Evidence in alcohol-preferring rats suggested that variation in the corticotrophin-releasing hormone releasing receptor 1 (*crhr1*) gene was associated with increased sensitivity to relapse into alcohol seeking induced by environmental stress (Bjork et al. 2010). The Mannheim Study of Children at Risk found an association between variants in *crhr1* and higher rates of heavy drinking and more drinking per occasion among 15-year-olds if they had experienced a greater number of negative life events over the previous 3 years (Blomeyer et al. 2008). An extension of this study followed up the adolescents at age 19 and also found that this gene interacted with stressful life events to predict both drinking initiation in adolescence and progression to heavy alcohol use in young adulthood (Schmid et al. 2010).

In addition, Dick and colleagues have attempted to bridge the gap between the latent gene–environment interaction literature and specific measured gene–environment interactions by developing hypotheses about the risk associated with genes. On the basis of twin studies suggesting that genetic influences on adolescent substance use are moderated by parental monitoring (Dick et al. 2007*b*) and peer substance use (Dick et al. 2007*a*), the researchers tested for moderation of the association of two genes associated with adult alcohol dependence in the Collaborative

Studies on Genetics of Alcoholism project. The two genes were for the γ-aminobutyric acid receptor (GABAR) subunit α-2 (*GABRA2*) (Edenberg et al. 2004) and the cholinergic muscarinic 2 receptor (*CHRM2*) (Wang et al. 2004). The researchers found evidence for gene-by-interaction effects in the direction predicted by the twin studies, namely genetic effects were enhanced under conditions of lower parental monitoring (Dick et al. 2009*b*) and higher peer-group antisocial behavior (Latendresse et al. 2011).

Conclusions

Although there is a burgeoning literature surrounding gene–environment interactions in the field of alcohol use and related disorders, far more remains to be understood. In general, the findings from gene-by-environment twin studies have been relatively consistent and have suggested general mechanisms for interaction effects. The common theme that emerges across findings of gene–environment interactions from the twin literature is that environments that exert more social control (e.g., higher parental monitoring, less migratory neighborhoods, etc.) tend to reduce genetic influences, whereas other environments allow greater opportunity to express genetic predispositions, such as those characterized by more deviant peers and greater alcohol availability. Conversely, the gene–environment literature that has been developed surrounding specific genes has focused largely on the role of stress as a moderator of genetic effects. Clearly, there is a disconnect between these literatures. In addition, it is likely that there are other important mechanisms of gene–environment interaction effects in relation to alcohol use and the development of problems. Many other variables, both individual and psychosocial, are known to affect drinking behavior, such as beliefs about alcohol, self-esteem, school attitudes, parental expectancies and messages surrounding alcohol use, and family disruption (Donovan and Molina 2011). It will be important to integrate these literatures, and the broader basis of etiological findings and associated environmental factors, into theoretical models of how gene–environment interaction effects operate with respect to alcohol use.

Another important area for future research is an expansion of the molecular studies of gene–environment interaction beyond a small number of polymorphisms from a handful of genes that are widely studied in the psychological literature (i.e., *5-HTT, MAOA,* and *DRD2*). The existent studies have been based on small samples, and results have been inconsistent. Although a focus on single genes may help advance theoretical models about particular biological pathways of risk, they face the same challenge (and currently have been met with the same fate) as studies of main effects of individual genes. That is, they have been notoriously difficult to replicate consistently. This is in contrast to the generally robust gene–environment interaction effects that have emerged from studies of latent genetic influences and, previous to that, the robustness of heritability estimates. This likely reflects the difference between studying overall genetic effects, versus specific genes in a complex polygenic system. The field of genetics has moved toward creating polygene scores that aggregate across many genes and show predictive power in cases where individual genes cannot be detected (Purcell et al. 2009). Moving studies of measured gene–environment interaction in this direction, to encompass aggregate genetic risk, may be one way to improve replicability of effects and to enhance cross-fertilization between quantitative and molecular genetic research.

This approach has the potential to advance our understanding of gene–environment effects. Similar to the way that evidence for heritability from twin studies for a given outcome was originally used to justify searching for specific genes involved in that outcome, evidence for gene–environment interactions from twin studies also can be used to develop hypotheses to test for gene–environment interactions associated with specific, identified genes. Change in the overall heritability across environmental contexts does not necessarily dictate that any one specific susceptibility gene will operate in a parallel manner. However, a change in heritability suggests that at least a good portion of the involved genes (assuming many genes of approximately equal and small effect) must be operating in that manner for a difference in heritability by environment to be detected. In this sense, one is "loading the dice" when testing for specific candidate gene-by-environment interaction effects with an environment that already has been shown to moderate the overall importance of genetic influences on that outcome. As additional research begins to clarify how specific genetic variants contribute to risk for AUDs, greater cross-talk between the twin literature, gene-identification studies, and studies testing for measured genotype-by-environment interactions will be critical to producing a more systematic research program aimed at understanding gene-by-environment effects for this critical and socially important condition. ■

Acknowledgments

This manuscript was prepared with support from grants AA–15416 and K02–AA–018755 (to Danielle M. Dick) and R37–AA–011408 and P20–AA–017828 (to Kenneth S. Kendler) from the National Institute on Alcohol Abuse and Alcoholism.

Financial Disclosure

The authors declare that they have no competing financial interests.

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