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THE JOURNAL OF THE NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

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Compiled June 2024

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Alcohol Res. 2022;42(1):02 | https://doi.org/10.35946/arcr.v42.1.02 Published: 13 January 2022

NIAAA 50th ANNIVERSARY FESTSCHRIFT

Age, Period, and Cohort Effects in Alcohol Use in the United States in the 20th and 21st Centuries

Implications for the Coming Decades

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Acknowledgments
Dr. Keyes would like to thank Dr. Deborah Hasin for insightful feedback and edits on this paper. This article was supported by National Institutes of Health grant R01AA026861.

Disclosures
The author declares no competing financial or nonfinancial interests.

Publisher's Note
This article was based on a presentation by Dr. Keyes at the NIAAA 50th Anniversary Science Symposium, "Alcohol Across the Lifespan: 50 Years of Evidence-Based Diagnosis, Prevention, and Treatment Research," held on November 30–December 1, 2020. Links to the videocast are available on the NIAAA 50th Anniversary Science Symposium agenda webpage.
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This article is part of a Festschrift commemorating the 50th anniversary of the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Established in 1970, first as part of the National Institute of Mental Health and later as an independent institute of the National Institutes of Health, NIAAA today is the world's largest funding agency for alcohol research. In addition to its own intramural research program, NIAAA supports the entire spectrum of innovative basic, translational, and clinical research to advance the diagnosis, prevention, and treatment of alcohol use disorder and alcohol-related problems. To celebrate the anniversary, NIAAA hosted a 2-day symposium, "Alcohol Across the Lifespan: 50 Years of Evidence-Based Diagnosis, Prevention, and Treatment Research," devoted to key topics within the field of alcohol research. This article is based on Dr. Keyes' presentation at the event. NIAAA Director George F. Koob, Ph.D., serves as editor of the Festschrift.

KEYWORDS: alcohol; age-period-cohort; cohort effects; gender; socioeconomic status

Alcohol consumption, including any alcohol use; patterns of high-risk use, including binge drinking; and alcohol use disorder (AUD) incidence and prevalence, differs substantially over time and by life stage. Variation also occurs across demographic groups, and such differences themselves vary across time and place. In the first quarter of the 21st century, changes in incidence and prevalence of alcohol use and alcohol-related health consequences have been accelerating. Understanding the magnitude and direction of these changes informs hypotheses regarding the reasons underlying alcohol consumption changes across time and development, including both long-term historical changes as well as abrupt shifts. It also permits determining the optimal focus of research and targets of services. Such surveillance is informed by science and statistical considerations of variation by age, period, and cohort effects.

Age-, period-, and cohort-effect estimation has proved to be an extraordinarily useful framework for organizing and interpreting data, uncovering patterns, and identifying causes of trends in incidence and prevalence of many health conditions and mortality over time. This article provides an overview of the conceptual basis of such effects as related to alcohol consumption, and reviews recent studies of age-period-cohort variation, especially regarding gender, social class, and specific beverage and drinking patterns.

Age, Period, and Cohort Effects and Their Importance

Age Effects

Age effects refer to the effects of a person's age on their health. They may be caused by the accumulation of exposure or social experiences; critical and sensitive developmental windows; or immunological periods of vulnerability, such as infancy and end of life. Extensive evidence documents that alcohol use is most likely to begin during adolescence or young adulthood, peak during the transition to adulthood, and generally decrease thereafter.[1,2] However, these age patterns are not static; in the United States, for example, the onset and peak of alcohol use has been shifting in recent decades to a later point in development.[3] Because onset and persistence of alcohol use are in part social phenomena and are amenable to policy interventions (e.g., changes in minimum legal drinking age laws),[4] the specific structure and magnitude of age effects are historically variable. However, the general patterns of onset early in adult maturation, and desistence during adulthood, have been largely stable over historical time.

Period Effects

Period effects refer to changes in outcome that affect all individuals alive in a particular period—that is, a year or set of years. Reasons for period effects include changing environmental or social factors that affect incidence and persistence of certain behaviors or disorders, policy or law changes, or other environmental conditions that affect health. For alcohol use, numerous factors have been associated with substantial changes in consumption patterns, including major policy initiatives to restrict access to alcohol, such as U.S. Prohibition from 1920 to 1933, and broad economic factors, such as booms and recessions that affect spending on nonessential goods. The general social climate for heavy drinking has also changed over time as advocacy movements placed the dangers of heavy consumption into stark focus, followed by policies to increase criminal sanctions on impaired driving.[5] However, as detailed below, such policy changes are not simply period effects because they often impact age groups differently; therefore, their effects may manifest as cohort effects.

Cohort Effects

Against the backdrop of age and period effects, cohort effects have also proven to be powerfully predictive of a range of health behavior, including alcohol use. Cohort effects can perhaps be most efficiently conceptualized as age-by-period interactions.[6] For example, a cohort effect would be apparent if historical change across time in a health behavior such as alcohol consumption resulted in increasing overall prevalence (i.e., a period effect), but the increase in prevalence is faster or slower for people in different age groups (i.e., an age by period interaction). Cohort effects can also be conceptualized as a unique rate of an outcome for individuals depending on birth year.[7]

Before reviewing the current literature on cohort effects in alcohol use, it is important to understand that cohort effects are powerfully predictive of many health outcomes, and critical to consider when evaluating trends. There are numerous historical examples of particular birth cohorts with increased rates of disease outcomes and mortality in the United States, including all-cause mortality,[8,9] tuberculosis,[10] peptic ulcer,[11] lung cancer,[12] and other diseases. More recently, the strong influence of generational cohort effects is apparent in the leading U.S. contributors to premature mortality, including obesity, hepatitis C, drug overdose, and suicide.[13–16] Similarly, numerous studies in recent decades have found that alcohol use and health outcomes related to heavy consumption cluster by birth cohort, as well as have exhibited age and period effects at various points in history. Cohort effects have long been documented in substance use,[17,18] including alcohol use and alcohol-related harms,[19] as described in more detail below.

Recent Alcohol Use Time Trends in the United States

Time trends in alcohol use and alcohol-related harms have been dynamic in the United States, especially over the last 2 decades. Among adolescents, the prevalence of alcohol use has declined. Data from two major nationally representative surveys—Monitoring the Future and the National Survey on Drug Use and Health—converge in demonstrating these reductions. Although the specific prevalence of any alcohol use and binge drinking differs between the two surveys, both document substantial, sustained reductions in adolescent drinking over the last 20 years.[20,21] The most recently published data from the Monitoring the Future Study, depicted in Figure 1, show the trend in past 2-week binge drinking among 12th grade adolescents through 2019; as the figure shows, binge drinking declined from a peak in approximately 1982 to less than 20% for both boys and girls in 2019.[22]

In contrast, adult alcohol use and binge drinking has been increasing. A meta-analysis of six national surveys of alcohol use found (Figure 2) that from 2000 to 2016, the overall prevalence of binge drinking increased approximately 7.5% per decade across the 2 decades analyzed.[23] Importantly, however, these increases were primarily concentrated among women, as discussed further below.

The observation that changes over time in alcohol consumption differed by age immediately raises the possibility of cohort effects. Indeed, many studies using different data sources and analytical approaches have documented cohort effects for numerous alcohol-related outcomes. Generally, post-World War II U.S. birth cohorts had higher rates of consumption than earlier cohorts,[19,24,25] driving much of the increase in consumption in the 1970s and 1980s. For many of these studies, however, reliance on retrospective recall is a common limitation. Avoiding this limitation, Kerr et al.[24,26] used the National Alcohol Surveys, which reports current consumption patterns that are less subject to recall issues. These analyses documented that several birth cohorts had higher risks of alcohol consumption and binge drinking throughout the life course, especially men born in the late 1970s and women born in the early 1980s. In contrast, among cohorts born in the 1990s and later, alcohol use has consistently been declining during adolescence and early adulthood. However, those same cohorts have exhibited accelerating drinking after transition to adulthood.[27]

In sum, the cohorts of today's adults who are now in their 30s and 40s were part of the historical shift toward declining alcohol consumption in adolescence. This decline is explained in part by shifts in the minimum legal drinking age across states, especially in the 1980s,[27] yet declines continued thereafter, potentially aided by focused prevention efforts on reducing underage drinking. However, because drinking then accelerated during the transition to adulthood, adult rates of drinking did not benefit from these prevention efforts. Indeed, Patrick et al. (2019) have documented an overarching historical shift in the age effect on binge drinking among recently born cohorts; thus, the peak age of binge drinking in 1996 to 2004 was 2 years later than it was in 1976 to 1985.[3]

In addition to these overall age, period, and cohort effects, additional variation across other levels of dynamic change have implications for prevention, policy, and causal etiology assessments. Three areas of variation that have received substantial attention are gender, socioeconomic status, and beverage type.

Effects of Gender

Men consume more alcohol and are more likely to have AUD compared with women,[1] but the gender gap has been closing for decades in the United States and elsewhere.[19,25] However, the manner in which the gender gap is closing differs by birth cohort. Among today's birth cohorts of adolescents (i.e., those born in and around the same year), the gender gap is closing because for more than 30 years, alcohol consumption and binge drinking have declined among both boys and girls, but the decline is faster for boys than girls (see Figure 1).[28] Conversely, in adults, alcohol consumption and binge drinking have increased, especially in the past 10 years, and those increases have been greater for women than for men (see Figure 2).[23] The recent increases in drinking among women reflect the high-risk cohorts identified by Kerr et al.[26] as they age into middle-adulthood. Interestingly, compared to earlier generations, these cohorts of women progressed through adolescence with lower alcohol use and binge drinking, yet had a faster acceleration of their drinking during the transition to adulthood, resulting in high levels of alcohol use and strong cohort effects in adulthood.[27]

Additional analyses have indicated that the increases in alcohol consumption and binge drinking among women in midlife are concentrated among those with high levels of education,[29] occupational prestige,[30] and income,[29] suggesting that traditional gender norms sanctioning alcohol consumption are shifting among women now occupying traditionally male statuses and spaces. The human costs of these increases in consumption are reflected in alcohol-related mortality rates. These rates have doubled between 1999 and 2016,[31] with the largest increases observed among women and adults emerging into midlife, consistent with alcohol consumption trends.

Effects of Socioeconomic Status

Historically, the role of socioeconomic status has been a critical axis for examining trends over time in alcohol consumption, as exemplified by the higher consumption rates in adult women, who are increasingly occupying high socioeconomic positions. Overall, individuals with a higher socioeconomic status are less likely to fully abstain from alcohol compared to those with a

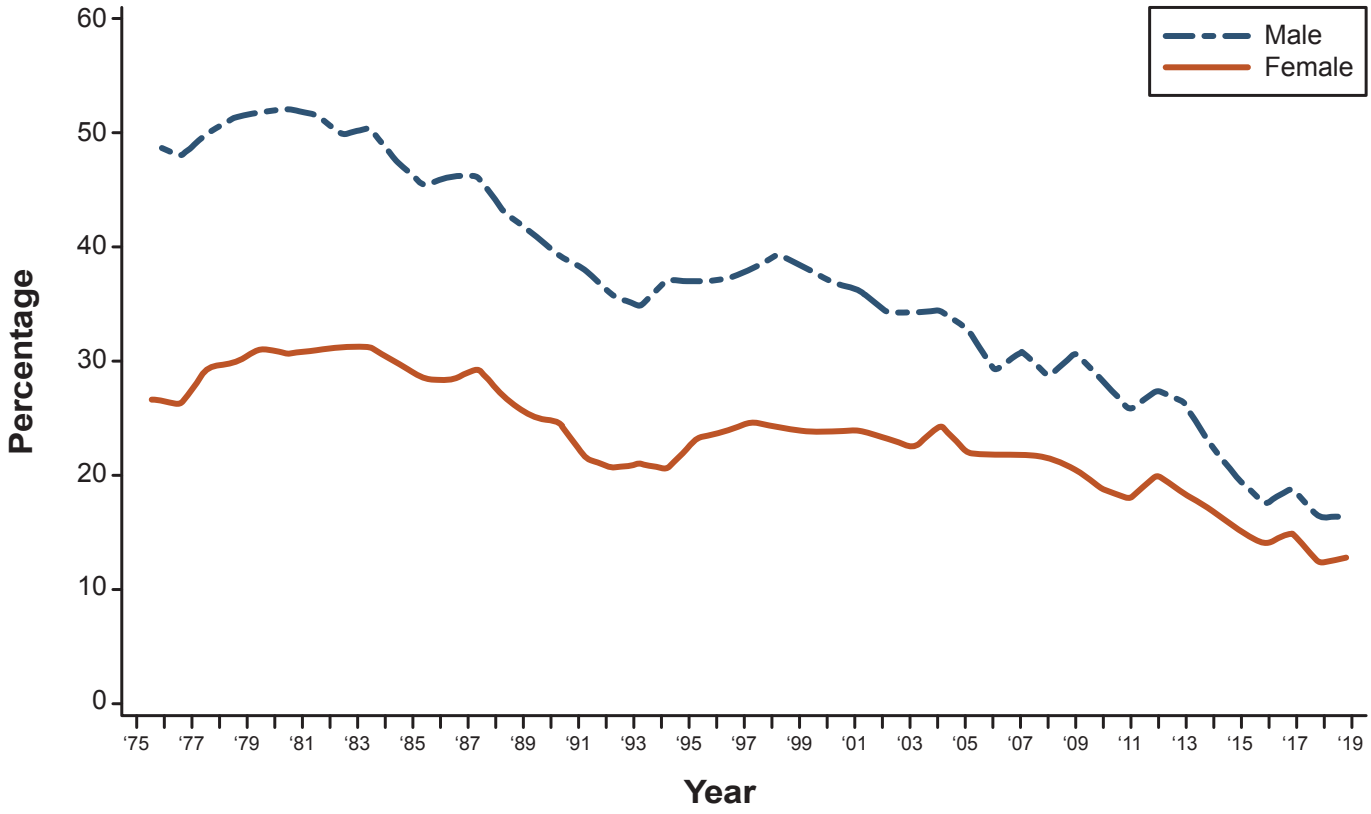

Figure 1. Trends in 2-week prevalence of binge drinking (≥ 5 or more drinks in about 2 hours), by gender. *Source:* Adapted with permission from Johnston et al. (2019).[22]

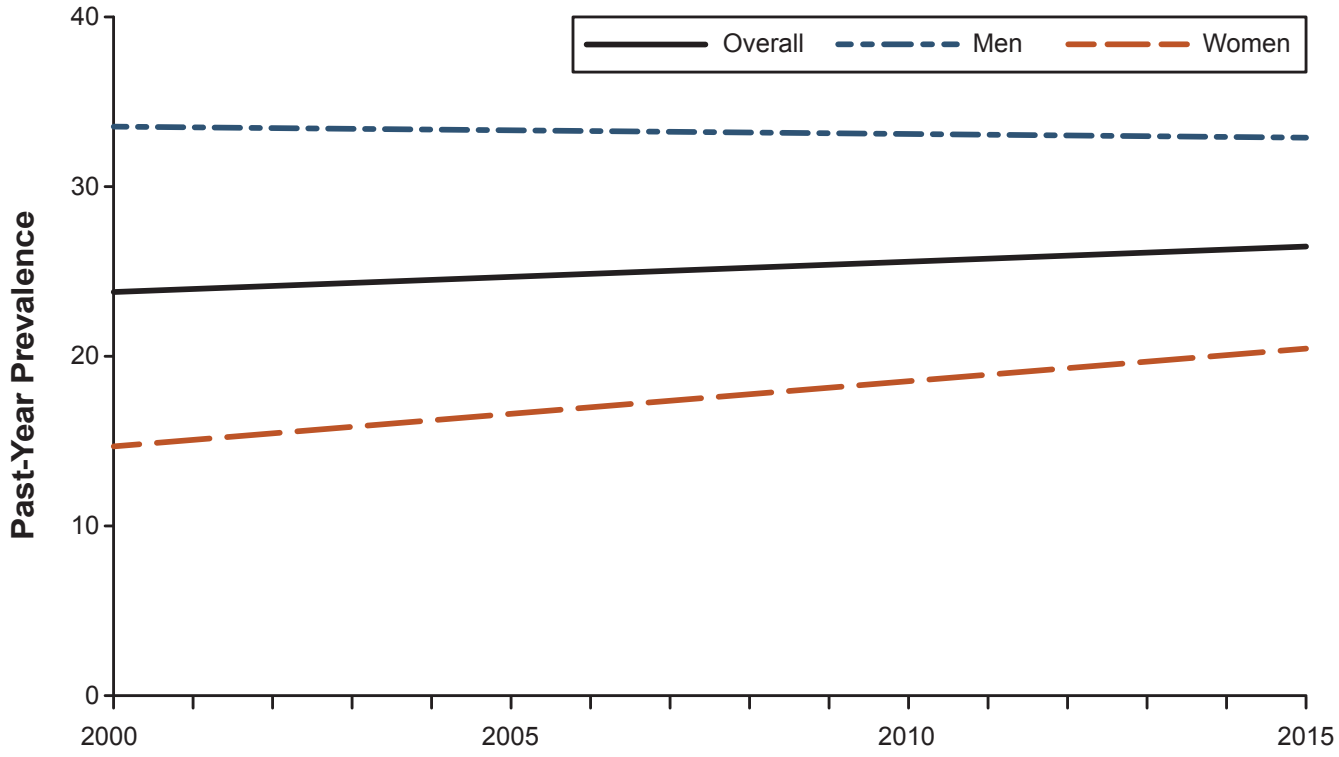

Figure 2. Simulated trend lines for past-year binge drinking prevalence overall and by gender. Results are based on trend estimates from meta-analysis and use of 2002 NSDUH data to establish baseline prevalence. *Source:* Adapted with permission from Grucza et al.[23]

lower status.[32] The relationship between socioeconomic status and binge drinking or AUD, however, is more mixed and depends on the socioeconomic indicator, population, and time period analyzed.[33–35] Further, population distributions of socioeconomic status are an outcome of economic conditions (i.e., income and wealth are functions of times of economic expansions and recessions); therefore, trends in socioeconomic status, and who achieves and maintains high status positions, are important potential drivers of population trends.

Renewed attention to theories of the relationship between social class and health has been prompted by evidence that recent increases in U.S. mortality, including alcohol-related and other substance-related mortality, are concentrated among men with less than a high school education.[36] However, these findings run counter to available data on heavy drinking birth cohorts. The birth cohorts identified by Case and Deaton[36] are different than the birth cohorts emerging into adulthood in the 1970s and 1980s or those of college age in 2002 to 2012, suggesting that the dynamics of alcohol-related harm are likely to substantially change in the decades to come. Indeed, National Alcohol Survey data show that cohort trends in U.S. alcohol consumption are primarily driven by changes in education.[37] As more recent cohorts have entered college at higher rates, drinking and binge drinking have become concentrated in these college-attending young adults. The alcohol consumption cohort effect of those born in the late 1970s and early 1980s is attributable largely to their high rates of college attendance. Conversely, however, there may be signs of emerging socioeconomic differences when considered across gender (more on gendered trends in alcohol consumption below). For example, from 2002 to 2012, binge drinking was largely stable among college-attending young adults, but slightly increased among non-college enrolled women (from 29% to 33%) while decreasing among non-college-enrolled men.[38] Continued surveillance of the role of socioeconomic status within trends in alcohol consumption, and beyond education into other indicators, is warranted.

Effects of Beverage Type

Another important area for research is variation in alcohol consumption dynamics by type of alcoholic beverage. Although all alcoholic beverages are carcinogenic, beverage types vary in ethanol concentration and potential for harm, as well as in their prevalence and popularity across demographic groups. A growing literature indicates that the types of alcoholic beverages that individuals in the United States are consuming are dynamic and may depend on cohort. Kerr et al. (2004)[39] found that pre-1940s cohorts preferred spirits throughout the life course compared with later cohorts. In contrast, cohorts born in the 1940s through 1970s, especially men, tended to prefer beer, and wine has been gaining dominance in beverage preferences among younger cohorts. These changes may be related at least in part to marketing and sales efforts by the alcohol industry to increase profits. For example, the increase in wine consumption, which has been observed in alcohol sales surveillance,[40] is commensurate with the increases in income and education in the United States, as wine is marketed as a prestige product and is often sold at high price points. Additional analyses have found that the alcohol content of beverages is increasing in the United States,[41,42] portending potential further harm and greater rates of AUD.

The dynamics of cohort effects on beverage preferences are particularly salient for the role of alcohol policy and reduction of alcohol-related harms. Sales restrictions and alcohol taxes have a substantial, demonstrable overall impact on population-level consumption and alcohol-related harms,[43] although this varies to some extent by age of consumer, level of consumption, and beverage type.[44] For example, tax variations by beverage type can influence trends in the consumption of particular beverages. Spirit and wine consumption is typically most sensitive to price and tax policy changes,[45] and although consumption of spirits has been increasing in the United States in recent years, there has been little change in tax and price regulations. This suggests that one driver of the increase in spirits consumption is that they are becoming effectively less expensive over time. Beer and wine are also regulated differently in many states; thus, changing dynamics in the popularity of each beverage have implications for how effective beverage-specific alcohol taxes are in reducing sales and, consequently, harm. Regulations related to alcohol sales and consumption that can respond to market changes in beverage preferences (e.g., increased taxes on wine and spirits that reflect their growing share of the alcohol market) may be an important lever for promoting public health in the coming decades.

Differences in Drinking Patterns Among Cohorts

Taken together, the literature on age, period, and cohort effects in alcohol research indicates that different cohorts have different drinking patterns and that socioeconomic and demographic factors are critical to contextualizing the observed trends. Although it is possible to document time and cohort trends with the available data, understanding why alcohol consumption patterns are changing is more challenging.

Certainly, alcohol policies play a fundamental role in determining population-level patterns of consumption, and the way that policies target particular demographic groups (intentionally or unintentionally) creates opportunities for cohort effects to emerge. For example, the adoption of a minimum legal drinking age of 21 across states throughout the 1980s mediates a portion of the decline in alcohol consumption among U.S. adolescents since then.[27] However, consumption

has continued to decline for decades after the increase in drinking age, suggesting that additional factors, such as the public health investment in underage drinking prevention, provided further benefits. Numerous other policies have shifted and impacted population-level alcohol consumption since the U.S. Prohibition, including restrictions on where and when alcohol can be sold, state monopolies on sales, criminal penalties for hazardous use, and others.[46,47] These policies likely have affected different age groups in different ways, depending on their developmental stage when exposed to newly restrictive or permissive alcohol policies.

Of course, alcohol policies are not the only determinant of alcohol consumption and, consequently, of age, period, and cohort effects. Substantial research has evaluated the impact of social norms and social roles, as well as community and societal norms and values on changes in alcohol use over time.[48,49] Social values have an inherent role in the use of alcohol, and the acceptability of drinking and drunkenness within and across social groups at different times and different life stages is potentially a powerful factor influencing population-level consumption. For example, heavy consumption on college campuses, especially within social institutions such as Greek life,[50] is often normative and expected, but norms and values around alcohol use swiftly change as young adults encounter the social norms of early adulthood.[51] Moreover, these normative trajectories and patterns become variable as societal roles and values themselves change. For example, religious attendance and the importance of religion have long been a robust predictor of decreased alcohol consumption.[52] However, the centrality of religion to U.S. adolescents and adults has been declining for more than a decade,[53] and this decline explains a portion of the cohort effects in binge drinking among today's adults.[54] Monitoring these and other broader societal changes is critical to determining the influences that mediate shifts in alcohol consumption over time.

For example, the coming years will be critical to determining the effects of health knowledge regarding alcohol-related risks on population consumption. For decades, low levels of alcohol consumption were considered protective, especially for cardiovascular health.[55] The evidence supporting this hypothesis, however, was subject to substantial confounding,[56] and dissemination of the message of alcohol's protective effects was well-funded by the alcohol industry, which had a clear financial incentive.[55] Recently, studies using large administrative databases and quasi-experimental designs, such as Mendelian randomization, have called into question and refuted the idea that a moderate level of alcohol consumption benefits health.[57,58] The extent to which public health messages shift to reflect this change in scientific consensus may be important in reducing population-level alcohol-related harms. These changes may further manifest as cohort effects, as the dissemination and implementation of health information and guidelines are likely to affect age groups differently as they progress through the life course.

Conclusions

Alcohol consumption continues to be a leading contributor to morbidity and mortality, both in the United States and worldwide. Although significant progress in reducing adolescent and young adult alcohol use has been achieved and sustained for decades, it is offset by increases in drinking during the transition to adulthood. The cohorts currently at midlife, especially women, are increasing alcohol consumption and binge drinking at greater levels than other cohorts, portending health consequences that may persist for decades. Understanding the motivations for consumption, destigmatizing the use of services to reduce consumption, and increasing the availability and accessibility of such services are necessary to improve population health. Moreover, age, period, and cohort effect estimations are critical surveillance tools for epidemiology and population health research. Such assessments have already answered critical questions and uncovered patterns in the data that specifically identify high-risk groups requiring prevention and intervention efforts.

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ALCOHOL RESEARCH
Current Reviews

Alcohol Res. 2020;40(3):02 ● https://doi.org/10.35946/arcr.v40.3.02

Published: 12 November 2020

Epidemiology of Recovery From Alcohol Use Disorder

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Almost one-third of the U.S. population meets alcohol use disorder (AUD) criteria on a lifetime basis. This review provides an overview of recent research on the prevalence and patterns of alcohol-related improvement and selectively reviews nationally representative surveys and studies that followed risk groups longitudinally with a goal of informing patients with AUD and AUD researchers, clinicians, and policy-makers about patterns of improvement in the population. Based on the research, alcohol use increases during adolescence and early adulthood and then decreases beginning in the mid-20s across the adult life span. Approximately 70% of persons with AUD and alcohol problems improve without interventions (natural recovery), and fewer than 25% utilize alcohol-focused services. Low-risk drinking is a more common outcome in untreated samples, in part because seeking treatment is associated with higher problem severity. Sex differences are more apparent in help-seeking than recovery patterns, and women have lower help-seeking rates than men. Whites are proportionately more likely to utilize services than are Blacks and Hispanics. Improving recovery rates will likely require offering interventions outside of the health care sector to affected communities and utilizing social networks and public health tools to close the longstanding gap between need and utilization of AUD-focused services.

KEY WORDS: alcohol; alcohol use disorder; recovery; remission; natural recovery; epidemiology; alcohol treatment utilization; low-risk drinking

INTRODUCTION

Substance use disorder (SUD) is among the most prevalent mental health disorders in the United States and in general clinical practice, with 7% of the U.S. population age 12 and older (19.7 million people) having an SUD of some kind in 2018.[1] Alcohol use disorder (AUD) is the most prevalent SUD, with 5% of persons age 12 and older reporting AUD in 2018.[1] Of persons with an SUD in 2018, and excluding those with a tobacco use disorder, 60% had AUD, 27% had an illicit drug use disorder, and 13% had disorders

involving alcohol and illicit drugs.[1] On a lifetime basis, almost one-third of persons in the United States meet criteria for AUD.[2] In addition to the high AUD prevalence, many more individuals engage in risky drinking or experience alcohol-related negative consequences that fall short of meeting clinical diagnostic criteria for AUD.[3] Thus, harmful alcohol use is a major public health problem, costing the United States approximately $250 billion per year, and it is the third leading cause of preventable death.[4]

Most individuals who develop an AUD or have subclinical alcohol-related problems will reduce or resolve their problem on their own or with assistance from professional alcohol treatment or mutual help groups.[5-9] The epidemiology of this robust phenomenon is the focus of this article. After initial consideration of complexities involved in defining improvement in alcohol-related problems, which is discussed in depth by Witkiewitz et al.,[10] this article describes the prevalence and heterogeneity of pathways to recovery and examines relationships between patterns of seeking help for and improvements in alcohol-related problems. Then, the topic is examined from a life span developmental perspective, which is less well-researched and involves relationships among age-related rates of problem onset, reduction, and persistence. The final section discusses differences in the overall patterns previously discussed as a function of gender and race/ethnicity. Emphasis is placed on illustrative recent findings. Earlier work is covered in prior literature.[11,12]

DEFINING IMPROVEMENT IN ALCOHOL-RELATED PROBLEMS

As discussed by Witkiewitz et al.,[10] the conceptualization and measurement of improvements among persons with AUD and the constellation of improvements that define "recovery" have been debated for decades and continue to evolve. Clinical diagnostic criteria for AUD are offered by the American Psychiatric Association's fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5)[3] and the World Health Organization,[13] with the former predominating in the United States. Numerous reputable organizations offer definitions of low- and high-risk drinking practices[4,14] as well as AUD recovery or remission.[15] These various criteria have been revised over time as research evidence has accumulated, generally in the direction of recognizing that alcohol consumption and AUD occur on severity continua. Furthermore, most individuals who engage in harmful alcohol use either do not meet AUD criteria or meet criteria for a mild disorder characterized by lower levels of symptomology.[16]

Characterizations of improvement in alcohol-related problems have correspondingly become more nuanced over time in recognition of the heterogeneity of pathways, processes, and outcomes relevant to understanding how people reduce or resolve alcohol-related problems.[10] The term "recovery" is generally reserved for broad-based, sustained improvements in drinking practices and other areas of functioning adversely affected by drinking. Therefore, this article uses the term "recovery" to refer to a broadly conceived process resulting in sustained improvements in multiple domains, and uses the term "remission" to refer to more limited improvements in specific symptoms or problem behaviors (e.g., drinking practices). This is in line with the National Institute on Alcohol Abuse and Alcoholism's (NIAAA) recent definition of recovery from AUD as distinct from remission from AUD, defined symptomatically based on DSM-5 criteria, or cessation of heavy drinking without characterizing the presence or absence of other symptoms or improvements. It also is consistent with other recovery definitions, including those from the recovery community or patient perspectives, that encompass improved well-being and functioning

and are not limited to attainment of abstinence or stable low-risk drinking.[8,17]

It is also important to acknowledge the association of the term "recovery" with Alcoholics Anonymous (AA) and other mutual support groups. Even though the term is widely used in the clinical literature, many persons attempting to resolve their alcohol problems do not identify with being in recovery[8] and reject clinical labels indicative of AUD, especially those individuals attempting to resolve a drinking problem on their own.[9] Moreover, salutary improvements can occur in circumscribed areas of alcohol-related dysfunction, and reductions in drinking can contribute to improved health and well-being even if ongoing drinking falls short of traditional definitions of recovery that emphasize abstinence as a required element.[18]

As discussed by Witkiewitz and Tucker,[16] a core issue debated for decades is the extent to which drinking practices should be central to defining improvement or recovery. Early writings regarded sustained abstinence as the hallmark of recovery among persons with severe alcohol problems who had repeatedly been unable to limit their drinking or abstain.[19] Newer clinical diagnostic systems such as DSM-5 emphasize development of tolerance and physical dependence and drinking in harmful ways and under conditions that increase risk for adverse consequences.[3] Drinking practices are not a criterion in accepted diagnostic systems for AUD, including DSM-5, and most schemes define recovery based on symptom reduction, improved functioning, and well-being and are not heavily focused on drinking practices per se. Yet, the large treatment outcome literature concerned with promoting recovery has relied heavily on drinking practices as the major outcome metric, typically by using quantity-frequency criteria considered indicative of higher-risk drinking practices (any occasions of more than 14 drinks weekly or more than five drinks daily for men; more than seven drinks weekly or more than four drinks daily for women in the past year).[4,14]

Recent work, however, has shown that such consumption-based thresholds lack sensitivity and specificity for predicting problems related to drinking and do not differentiate individuals based on measures of health, functioning, and well-being.[20,21] Improvements in functioning and life circumstances are considered central features of recovery in many models, including AA, but assessment of these domains is a relatively recent development, primarily evident in clinical research.[18,21] It is generally lacking in survey research that has provided the bulk of epidemiological data on population patterns of alcohol-related improvement, so this body of work only partially addresses the multiple domains considered important for investigating recovery, broadly defined.

A second core issue is that improvement in alcohol-related problems, including recovery from AUD, is a dynamic process of behavior change. Thus, longitudinal studies provide superior information to cross-sectional studies with retrospective assessments of drinking status, although the latter are common in the literature. Cross-sectional surveys have utility if they employ sound retrospective measures of past drinking status, but this is another qualification of the current epidemiological database on alcohol-related improvement and recovery. Longitudinal research has become more common in recent years. However, the intervals over which repeated measures are obtained rarely exceed 3 to 5 years, although there are notable exceptions with follow-ups of 8 to 10 years or more.[22-24] Following large nationally representative samples for decades would be ideal, but the inevitable limitations on research resources have resulted in a collective body of work that generally comprises large representative studies that are cross-sectional or have short-term (e.g., 1 year) follow-ups. Studies with longer-term follow-ups tend to employ smaller, less representative samples. These core issues should be kept in mind when considering the epidemiology of improvements in alcohol-

related problems, including recovery from AUD, as discussed next.

RECOVERY PATHWAYS AND RELATIONSHIPS BETWEEN HELP-SEEKING AND DRINKING-RELATED OUTCOMES

Population-based survey research conducted over many decades has consistently revealed the following patterns with respect to improvements in alcohol-related problems:

- The majority of individuals who develop AUD reduce or resolve their problem over time.[7,8,25] Rates of improvement vary widely depending on features of the research, such as the intervals over which drinking status was assessed (e.g., lifetime basis, shorter-term assessment based on a year or more); demographic characteristics, problem severity, and help-seeking status of respondents; and how improvement or recovery/remission was measured. But improvement over time is a reliable pattern and one that argues against a view of AUD as an inevitably progressive disease process.
- Seeking help for drinking problems from professional treatment or community and peer resources such as mutual help groups is uncommon,[1,26] and a large gap persists between population need and service utilization. Most surveys indicate that less than 25% of persons in need utilize alcohol-focused helping resources.
- The great majority of persons who resolve their drinking problems do so without interventions, and such "natural recoveries" are the dominant pathway to problem resolution. Survey research has typically found that more than 70% of problem resolutions occur outside the context of treatment.[7,9]
- Stable low-risk drinking (moderation) is a relatively more common outcome in untreated samples, in part because seeking treatment is associated with higher problem severity,[7,12] and most treatment programs emphasize abstinence.

For example, Fan and colleagues[7] reported on the past-year prevalence of AUD recovery in the United States by using data from the NIAAA-funded 2012–2013 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC-III)[2] and DSM-5 diagnostic criteria.[3] Survey respondents who met AUD criteria prior to the past year (n = 7,785) were assessed with respect to their current (past-year) AUD and risk drinking status. Drinking status was determined based on quantity-frequency criteria considered indicative of higher-risk drinking practices and DSM-5 AUD symptom counts. Measures of functioning and well-being were not collected.

Only 34% of respondents had persistent AUD, and most respondents had some degree of problem reduction; 16% achieved abstinence without symptoms, and 18% achieved low-risk drinking without symptoms. In addition, only 23% of the Fan et al. sample reported having ever received alcohol treatment, and those who did tended to fall into the persistent AUD (26%) or abstinent without symptoms (43%) outcome groups that generally are associated with higher problem severity.[7] In contrast, among the subset of respondents who reported abstinence or low-risk drinking without symptoms, 87% of those who reported low-risk drinking without symptoms were never treated, and only 12% were treated. An additional 15% of the sample reported low-risk drinking with symptoms, and 15% reported high-risk drinking without symptoms.[7] This is a refinement in outcome measurement compared to earlier surveys and illustrates the heterogeneity of recovery-relevant outcomes even in the absence of assessment of functioning and well-being.

This illustrative representative sample survey, among others,[8,9] reveals a more optimistic and variable view of recovery pathways and outcomes than suggested by early research using treatment samples, which emphasized the chronic, relapsing nature of alcohol problems and the difficulty of maintaining remission. Population data indicate that, even though alcohol problems are prevalent, most affected individuals have less serious problems than the minority who seek treatment,

and many improve on their own, including achieving stable abstinence or low-risk drinking without problems.

In contrast to these encouraging findings concerning rates of improvement, population research on the prevalence and patterns of help-seeking for alcohol-related problems indicates that the gap between need and service utilization is large and chronic. This is the case even though alcohol-related services have improved and expanded considerably over the past several decades[27,28] and reliably yield benefits for a majority of recipients. Among the 25% or fewer who seek care, sources of care span the professional, community, and peer-helping sectors. Within the professional sector, care is diffused through mental health, medical, and community services systems, and only a minority receive alcohol-focused services from qualified programs or professionals.[8,27]

Prevalence estimates for utilization of different types of alcohol services are not reliably available for several reasons. For example, specialty treatment programs are often addiction-oriented and not alcohol-specific, most include mutual help group participation as a program requirement, and the anonymity principle of mutual help groups deters determination of utilization rates apart from treatment. Nevertheless, membership estimates for AA (2.1 million members worldwide, including 1.3 million U.S. residents; https://www.aa.org) suggest that AA participation is relatively widespread. Comparable membership data are not available for other mutual help groups such as Self-Management and Recovery Training (SMART Recovery), which holds more than 3,000 meetings per week worldwide (https://www.smartrecovery.org/), and LifeRing Secular Recovery, which offers more than 140 face-to-face meetings in the United States as well as online meetings and other electronic supports (https://www.lifering.org/). Regarding professional treatment, the 2016 National Survey on Drug Use and Health estimated that about 3.8 million U.S. residents age 12 and older received any type of substance use treatment in the past year,[27] but these numbers are not specific to alcohol treatment. Also missing are data on relative remission rates as a function of type of care-seeking.

Higher problem severity predicts help-seeking, with higher severity reflected in greater alcohol dependence levels and alcohol-related impairment in areas of life functioning such as intimate, family, and social relationships; employment and finances; and legal affairs.[29] Perceived need also predicts help-seeking; however, even among those who perceive a need, only 15% to 30% receive help,[30] and problem recognition often precedes seeking care by a decade.[28] Thus, although most individuals who develop AUD will eventually resolve their problem, treatment utilization remains less used as a pathway to recovery. This pattern has persisted for decades despite recent expansion in the spectrum of services beyond clinical treatment to offer less costly and less intensive services that often can be accessed outside of the health care system and are suitable for those with less severe problems.[28] In addition, provisions of the Patient Protection and Affordable Care Act expanded access to and coverage of services for SUD.

RECOVERY ACROSS THE LIFE SPAN

Studies that followed risk groups and people with drinking problems longitudinally—typically using smaller samples than survey research—provide information on patterns of improvement and recovery across the life span. Some studies assessed functioning and life circumstances, in addition to drinking practices, and revealed the following age-related patterns with respect to the onset of and improvements in alcohol-related problems:

- Drinking to intoxication, binge drinking, and alcohol-related problems increase during adolescence and early adulthood, generally peaking between ages 18 and 22. Prevalence of past-year binge drinking (45%) and AUD (19%) is highest in the early 20s[31] and then decreases beginning in the mid-20s and continuing well

after early adulthood. This nonlinear trajectory for the majority of adolescents and young adults, often termed "maturing out," has been found in cross-sectional and longitudinal research using large national samples[2,32,33] and by the annual cross-sectional National Survey on Drug Use and Health.[1]

- Adult role transitions (e.g., employment, marriage, parenthood) and personal maturation (e.g., decreased impulsivity) are associated with remission or recovery in early adulthood.[31,34-36] As is the case for the general adult population with AUD, only about a quarter of adolescents and young adults in need of treatment receive it.[1]
- A subset of young adults who engage in harmful alcohol use and develop AUD in early adulthood show persistent or escalating problems in later life. Alcohol use before age 21 predicts persistence and severity of harmful use throughout the life span;[37] however, reductions in problem drinking in early adulthood are more likely to occur among individuals who had the most severe problems at earlier ages.[34]
- Development of AUD is less common after age 25, and reductions in problem drinking, including recovery from AUD, continue past early adulthood and across the adult life span, including through late middle and old age (ages 60 to 80 and older).[22,34] Reductions in problem drinking at older ages are predicted by relatively heavier alcohol use in early old age that prompted complaints from concerned others.[22]

These trends favoring increased remission rates over the life span are generally representative of the population, but can mask important nuances about age-related associations between problem onset, remission, and recurrence rates.[31,34-36] For example, Vergés and colleagues[35,36] used NESARC data from Waves 1 and 2 (from 2001–2002 to 2004–2005) to "deconstruct" age-related patterns of three different dynamic changes that contributed to overall age-related trends in the prevalence of DSM-IV alcohol dependence at each wave. Although rates of new alcohol problem onset and recurrence of or relapse to earlier problems declined with age, rates of persistence of alcohol problems over time were relatively stable across ages 18 to 50 and older. These different processes that contributed to the overall trend of decreased alcohol-related problems with increasing age suggest that "maturing out"—as young people assume adult roles—is not a sufficiently complete account of remission rates across the life span.

In related research that also used NESARC data from Waves 1 and 2, Lee and colleagues examined how rates of remission, which they termed "desistance," from mild, moderate, or severe levels of AUD varied across age groups ranging between ages 20 to 24 and 48 to 55.[34] Using Markov models to characterize patterns of longitudinal transitions in drinking status, they found differences in rates of AUD desistance from young adulthood to middle age as a function of AUD severity levels. Desistance rates from severe AUD, defined as six or more DSM-IV symptoms, were considerably higher in earlier age groups (ages 25 to 29 and 30 to 34) relative to older age groups (ages 35 to 39, 40 to 47, and 48 to 55) as compared to rates found in surveys that aggregated data across AUD severity levels. Desistance rates from moderate AUD showed a similar, but less dramatic pattern across age groups, whereas desistance rates from mild AUD were relatively stable across age groups. When considered with the work of Vergés and colleagues,[35,36] these studies (1) show that resolution of severe AUD contributes heavily and distinctively to early adulthood remission prevalence, and (2) highlight the importance of deconstructing overall AUD prevalence curves by taking into account onset, remission, and recurrence of different levels of AUD severity over the life span.

Finally, a few studies observed increased binge drinking among middle-aged and older adults,[33] suggesting dynamic changes may occur in binge drinking in midlife; these changes are not well researched. Similarly, most natural recovery research comprises samples showing that midlife recovery from AUD is normative.[9,38] Middle age is also when treatment entry tends to occur.[5] Recovery in midlife and later ages is

associated with an accumulation of alcohol-related problems coupled with life contexts that support and reinforce maintenance of drinking reductions and involve post-resolution improvements in functioning and well-being.[38,39]

ROLE OF GENDER AND RACE/ETHNICITY

Remission

In addition to age, rates of recovery or remission of AUD symptoms vary by gender and race/ethnicity. Using NESARC Wave 1 data, Dawson et al. found that older age and female gender predicted abstinence, but not low-risk drinking, in both treated and untreated respondents who had alcohol dependence prior to the past year.[5] Compared to non-Hispanic Whites, non-Hispanic Blacks had proportionately higher rates of abstinence than low-risk drinking. In the Fan et al.[7] replication of Dawson et al.[5] using NESARC-III data, female gender predicted both abstinence and low-risk drinking.

Also using NESARC-III data, Vasilenko et al. examined AUD prevalence by age and race/ethnicity (White, Black, Hispanic).[40] Although AUD prevalence generally peaked in the 20s and declined steadily with age, prevalence was higher for Whites at younger ages and higher for Blacks at older ages. This cross-over pattern typically occurred around age 60. In midlife, prevalence was similar for Blacks and Whites. Also, Whites reported higher AUD rates than Hispanic respondents at all ages, and men reported higher AUD rates than women until older age, when women were more likely than men to report AUD in their 70s. However, the number of participants older than age 70 was very small.

The study by Lee et al. that investigated age-related patterns of AUD desistance as a function of AUD severity also found gender and race/ethnicity differences.[34] Desistance patterns for males were generally consistent with the full sample findings—namely, elevated desistance rates for severe AUD in early adulthood and relatively stable rates for mild and moderate AUD. In contrast, females showed markedly higher rates of desistance from moderate AUD in early adulthood compared to older ages and attenuated rates of desistance from severe AUD compared to males during ages 30 to 34 only. With respect to race/ethnicity, results for Whites were generally consistent with the full sample, but findings differed for Hispanics and Blacks. For Hispanics, the early adulthood spike in rates of desistance from severe AUD was more time-limited, occurring only during ages 30 to 34 with much lower rates during ages 25 to 29. For Blacks, desistance rates for mild AUD also were relatively stable but were elevated for both moderate AUD (ages 25 to 29 and 30 to 34) and severe AUD (ages 25 to 29). For severe AUD, desistance rates among Blacks were very low during ages 30 to 34.

Patrick and colleagues analyzed age and gender relations with binge drinking using data from 27 cohorts of the annual Monitoring the Future surveys (1976 to 2004).[41] Participants were followed from 12th grade (modal age 18) through modal age 29/30. Across cohorts, the age of peak binge drinking prevalence increased from age 20 in 1976–1985 to age 22 in 1996–2004 for women, and from age 21 in 1976–1985 to age 23 in 1996–2004 for men. Similar to the typical population life span trajectory for AUD remission, for men the high prevalence of binge drinking persisted through ages 25 to 26, followed by reductions during the late 20s. For women ages 21 to 30, more recent cohorts reported significantly higher binge drinking prevalence than in earlier cohorts, with risk remaining high throughout the 20s. These shifts toward older age of peak binge drinking prevalence indicate an extension of risks associated with harmful alcohol consumption in young adulthood, especially for women.

Taken together, these studies on rates of improvement by gender and race/ethnicity suggest that many of the differences observed involve variations in the timing and extent of reductions in binge drinking and AUD during either young adulthood or older age, even though all groups tended to show overall patterns similar to the

population as a whole. Differences during midlife were less extensive, although this developmental period has not been the focus of much research.

Help-Seeking

Help-seeking patterns and preferences also vary by gender and race/ethnicity. The gap between need and receipt of treatment is larger for women than for men, even after controlling for the higher prevalence of AUD and greater problem severity among men.[42,43] For example, using NESARC data from Waves 1 and 2, Gilbert et al. found that women identified as having DSM-IV alcohol abuse or dependence at Wave 1 had significantly lower odds than men at Wave 2 of having used any alcohol service, specialty treatment, or mutual help groups.[42] These utilization differences occurred even though women and men reported similar low perceived need for help and similar numbers of treatment barriers. Women were more likely to report expecting that their problem would improve without intervention, whereas men were more likely to report prior help-seeking that was unhelpful. No differences in service utilization or perceived need were found for race/ethnicity among White, Black, and Hispanic respondents. Consistent with the larger literature, greater alcohol problem severity was associated with higher odds of service utilization.

Studies using pooled data from multiple waves of the national probability samples collected in the National Alcohol Surveys found differences in service utilization as a function of gender and race/ethnicity.[44,45] Zemore et al. used pooled data from three waves (1995–2005) to investigate lifetime alcohol treatment utilization and perceived barriers among Latinx respondents ($N = 4,204$).[44] Among respondents, 3.4%, 2.7%, and 2.1% reported any lifetime treatment, AA participation, and institutional treatment, respectively. Men were significantly more likely than women to report receipt of any treatment services (5.6% vs. 1.1%), AA (4.7% vs. 0.6%), or institutional treatment (3.2% vs. 1.0%). Completion of the study interview in English (4.3%) versus Spanish (2.3%) also predicted higher utilization. These patterns were similar among the subsample of respondents who reported lifetime alcohol dependence, among whom rates of service utilization were much higher (20.4% for men and 15.3% for women). The authors suggested that underutilization of treatment by women and Spanish speakers may be due to cultural stigma against women with an alcohol problem, concerns about racial/ethnic stereotyping or stigmatization when seeking treatment, and additional barriers faced by individuals who are uncomfortable speaking English.

A later study using pooled data from the 2000–2010 National Alcohol Surveys included Whites, Blacks, and Latinx participants and found lower service utilization among Latinx, Blacks (vs. Whites), and women (vs. men).[45] Racial/ethnic differences in utilization were moderated by gender. Among women, only 2.5% of Latinas and 3.4% of Blacks with lifetime AUD used specialty treatment compared to 6.7% of Whites; among men, the corresponding figures were 6.8% for Latinos, 12.2% for Blacks, and 10.1% for Whites.[45] Higher utilization among Whites than among Blacks and Hispanics also was found using the 2014 cohort from the National Survey on Drug Use and Health.[46]

Overall, research on race/ethnicity and help-seeking is not extensive, and groups other than Whites, Blacks, and Hispanics/Latinx have not been well studied.[47] Available research suggests that the gap between need and service utilization common among those with an alcohol problem is accentuated among ethnic and racial minority groups; however, research is in its infancy on why this is the case and how to address it.

DISCUSSION

Research on the epidemiology of recovery from AUD is somewhat uneven in scope and methods, and gaps remain in the knowledge base. Nonetheless, the bulk of evidence converges in showing that (1) improvements in alcohol-related problems, including recovery from AUD, are commonplace; (2) natural recovery is the

dominant pathway; (3) greater problem severity is associated with treatment utilization; and (4) low-risk drinking outcomes are more common among untreated samples. Problem prevalence and rates of remission of AUD symptoms in the U.S. population peak during the 20s and are followed by a slow, steady decline over the adult life span. The specific ages when these characteristic dynamics in the temporal patterning of harmful alcohol use and remission of symptoms occur vary somewhat as a function of gender and race/ethnicity, but the overall general pattern is well established.

These findings provide a rich foundation concerning population patterns and dynamics of recovery, remission, and help-seeking. Future research aimed at disaggregating these complex associations at the population level should be a priority and can inform approaches to promoting remission and recovery in two general ways.[48] First, longitudinal studies of the onset of and improvements in alcohol-related problems[31,34-36] exemplify how epidemiological risk factors are reliably associated with the course of alcohol problem development and improvement and can be used to target at-risk individuals for preventive interventions. Second, "upstream" population-level interventions can be applied to prevent or reduce the determinants of risk (e.g., through changes in policy, taxation, and health and community infrastructure). The latter approach, although less common, takes advantage of the well-established prevention paradox—small reductions in harmful alcohol use by risky drinkers with less serious problems result in far greater health improvements at the population level than do changes in harmful alcohol use by the minority of persons with AUD.

This body of research qualifies the usual characterization of AUD as a chronic, relapsing/remitting disorder for which intensive intervention is essential for recovery. That characterization may be representative for a small minority of persons with more severe AUD, but it is inaccurate for the large majority of persons with mild to moderate problems, many of whom resolve their problems the first time they attempt to quit and often without interventions.[9,49] Whether this qualification applies to SUD other than AUD is not established.

The recovery literature is characterized by a mix of cross-sectional population surveys with short-term retrospective assessments (1 year is typical) and prospective follow-ups of smaller-sized samples of risk groups that, with some notable exceptions,[22-24] also had relatively short follow-ups. Use of data from the multiple waves of the NESARC dominates this research literature. Although the NESARC obtained data from a very large nationally representative sample of the U.S. population age 18 and older (e.g., $N = 36{,}309$ in NESARC-III), it shares limitations inherent to most survey research—namely, assessments must be relatively brief, meaning that the domains of inquiry must be limited and selected carefully and cannot be probed to obtain the detail typically useful in clinical applications.

These design characteristics have contributed to gaps in the literature due to overreliance on drinking practices as the major outcome metric and less common measurement of functioning, well-being, and life circumstances, which are central features of recovery and can occur with or without reductions in drinking. Correlates of remission rates are being reported with increasing frequency in survey research, but tend to be limited to demographic characteristics, problem severity variables related to drinking practices, help-seeking history, and, in some cases, psychiatric comorbidity. Other than the seminal research program of Moos and colleagues,[22,39] assessment of functioning, context, and well-being surrounding drinking behavior change is a relatively recent development, primarily evident in clinical research[18,21] and process-oriented research on natural recovery.[38] Connecting these research literatures in meaningful ways in future investigations is essential for broadening scientific knowledge about how affected individuals reduce and resolve their alcohol-related problems and for guiding improvements in alcohol services that are responsive to heterogeneity in recovery-related outcomes and pathways.

Another issue in need of further research involves deconstruction of separable processes that contribute to overall problem prevalence and remission rates across the life span. As highlighted in the research of Vergés, Lee, Sher, and colleagues,[31,34-36] overall population rates are influenced by age-related associations between problem onset, remission, and recurrence rates, which raises questions about whether remission patterns reflect a simple "maturing out" of harmful alcohol use that began in early adulthood. Based on the available data, Lee and Sher[31] concluded: "[T]he continual declines in AUD rates observed throughout the life span . . . appear mainly attributable to reductions in new onsets . . . whereas potential for desistance from an existing AUD may peak in young adulthood . . . [especially] for those with a severe AUD" (p. 37).

The timing and targeting of prevention and treatment programs could be refined to enhance intervention effectiveness if these age-related associations between problem onset, remission, and recurrence rates were firmly established and used to guide intervention delivery. Conducting this kind of research is challenging because it requires collecting data on all three processes over the life span, and there are additional complexities in studying the tails of the age distribution. For example, clinical diagnostic systems may overdiagnose AUD in adolescence, which would inflate estimates of remission rates in early adulthood.[50] Attrition biases are of concern with advancing age as poor health and death may remove proportionately more older adults with AUD from population samples, thereby inflating estimates of remission rates in old age particularly from severe AUD.[5,34]

A final generalization from this research concerns the limited contribution of alcohol treatment or other alcohol-focused services to recovery prevalence in the population. Low rates of service utilization have persisted despite improvements in AUD treatment and lower threshold options[28] and the expansion of access and coverage of services for SUD provided by the Affordable Care Act. The enduring gap between population need and service utilization despite these advances strongly suggests that alternative avenues are needed to increase intervention diffusion and uptake. It has proven insufficient to offer improved treatment predominately through the health care sector, and priority needs to be given to reaching broader segments of the at-risk population of drinkers who contribute most of the alcohol-related harm and cost. Nevertheless, a sizable subset of individuals with AUD improve or recover without interventions, and recent evidence suggests that individuals with more severe AUD exercise some degree of appropriate self-selection into treatment.[29] Empirical questions warranting further investigation are how to distinguish among individuals or risk groups for whom natural recovery is a high probability outcome and how to segment the market so that treatment services are targeted and available for those in need who are not likely to achieve recovery without treatment.

Further improvements in reducing the prevalence of AUD and increasing the prevalence of recovery likely depend on dissolving the silos that have long existed between clinical and epidemiological research and applications[11] and finding novel ways to disseminate evidence-based services to the large underserved at-risk population of drinkers who will not use professional services, at least in their present form. It is also important to consider a broader public health approach to dispel long-held beliefs that alcohol is a problem only for those with severe AUD and that those with AUD can resolve their problem only through abstinence. Perpetuation of these myths over many decades has stigmatized the disorder and deterred help-seeking among the millions of people who would benefit from drinking reductions.

In conclusion, recovery from AUD and alcohol-related problems is the most common outcome among those with problem alcohol use, and recovery without abstinence is possible, even among those with severe AUD. Changing

the narrative to highlight the high likelihood of recovery could help engage more individuals in alcohol-related services and may encourage individuals to reduce their drinking in the absence of formal treatment.

Acknowledgments

Portions of the research reported were supported in part by National Institutes of Health, National Institute on Alcohol Abuse and Alcoholism grant R01 AA022328.

Financial Disclosure

The authors have no competing financial interests to disclose.

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

Published: 29 October 2020

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

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

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

INTRODUCTION

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

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

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

NARROWING GENDER GAPS

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

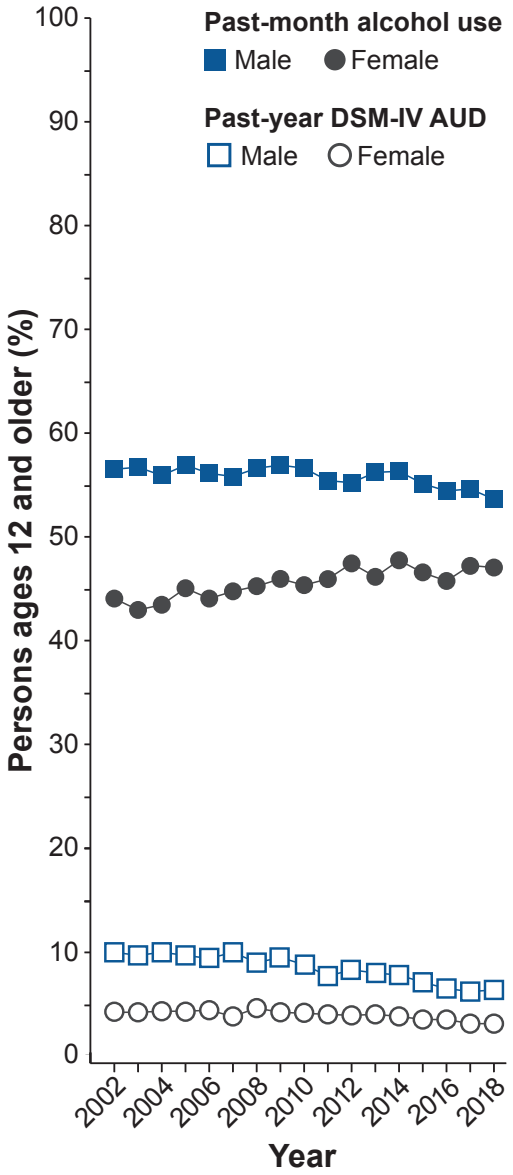

Figure 1 Narrowing gender gaps in the prevalence of past-month alcohol use and past-year DSM-IV AUD between females and males age 12 and older using data from NSDUH 2002–2012. Gender gaps narrowed for both measures, primarily due to increases in alcohol use among females and smaller declines in AUD among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

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

Drinking patterns

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

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

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

Overall deaths

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

Cirrhosis deaths

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

Driving under the influence

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

Gender gaps are narrowing

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

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

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

ADOLESCENTS

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

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

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

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

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

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

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

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

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

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

EMERGING ADULTS

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

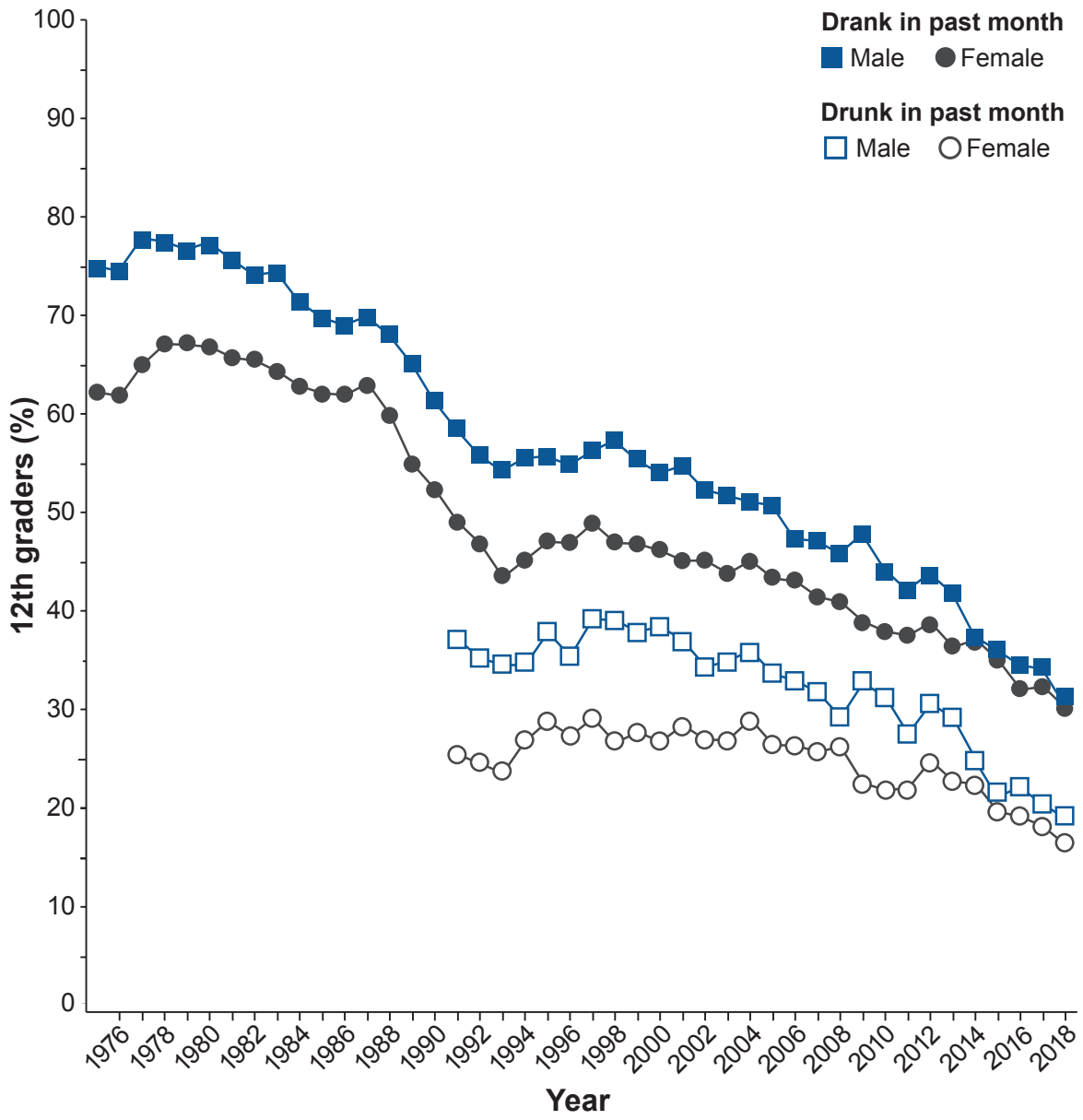

Figure 2 Past-month alcohol use from 1975 to 2018 and past-month drunkenness from 1991 to 2018 among 12th graders. Alcohol use and drunkenness declined more for young males than for young females, leading to disappearing gender gaps in 12th grade. *Source:* Adapted from Johnston, 2019.[22]

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

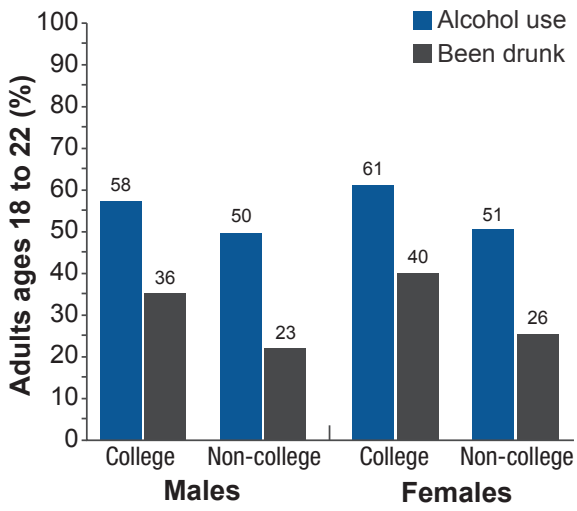

Figure 3 Past-month alcohol use and drunkenness among emerging adults (ages 18 to 22) based on college status. Both measures are declining more for emerging adult males than for emerging adult females, leading to disappearing gender gaps. *Source:* Adapted from Schulenberg et al., 2019.[21]

ADULTS

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

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

SEXUAL ORIENTATION

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

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

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

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

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

PREGNANCY

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

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

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

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

HEALTH EFFECTS

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

MEDICAL EMERGENCIES AND DEATHS

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

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

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

DRIVING UNDER THE INFLUENCE

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

HARMS TO OTHERS

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

SUMMARY

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

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

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

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

Financial Disclosure
The author declares no competing financial interests.

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The Epidemiology of Post-Traumatic Stress Disorder and Alcohol Use Disorder

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For more than 40 years, research has shown that individuals with post-traumatic stress disorder (PTSD) use alcohol and experience alcohol use disorder (AUD) to a greater degree than those with no PTSD. AUD and PTSD have shown a durable comorbidity that has extended through decades and through changes in disorder definitions. Some research shows that veterans who have experienced PTSD have a high likelihood of developing AUD, perhaps reflecting the self-medication hypothesis. Other research shows that people with substance use disorder are likely to be exposed to traumatic situations and develop PTSD. These two areas of research could represent two separate relationships between PTSD and AUD. Finally, there is still no clear determination of which cluster of PTSD symptoms is most closely associated with AUD.

KEY WORDS: alcohol use disorder; epidemiology; NESARC; post-traumatic stress disorder; veterans

Introduction

The harmful use of alcohol has been of interest to doctors for centuries, and minimizing the harm caused by alcohol use disorder (AUD) has been a priority of psychiatrists in the United States since at least 1917.[1] However, although traumatic experiences are ubiquitous throughout human history, it was only after the Vietnam War that psychiatrists codified the harms caused by traumatic stress into a distinct diagnosis.[2] For more than 40 years, it has been known that individuals with post-traumatic stress disorder (PTSD) use alcohol and experience AUD more than those with no PTSD. This link between PTSD and AUD subsequently has been broadened beyond Vietnam veterans to include veterans of other wars and anyone exposed to trauma. The considerable psychological distress caused by AUD and PTSD, both separately and together, affects the lives of millions of men and women, including

underrepresented populations, such as people with other mental health conditions.

Disorder Definitions

This section provides an overview of commonly used definitions and how they have changed over time.

AUD

In 1952, the first edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) included "alcoholism" as one of two disorders under the category of "addiction."[3] The pithy, two-sentence definition instructed that an alcoholism diagnosis be used in cases of "well-established addiction to alcohol." Since then, the definition of what is now called AUD has been significantly expanded and refined for each edition of the DSM.[2,4-7]

The third edition of the DSM (DSM-III) was published in 1980. In this edition, the disorders were called "alcohol abuse" and "alcohol dependence."[2] A diagnosis of alcohol abuse required:

- A "pattern of pathological alcohol use," which was defined by features such as the need for daily alcohol consumption to function, the inability to reduce or stop drinking, remaining intoxicated for at least 2 days, or blackouts
- "Impairment in social or occupational functioning due to alcohol use," which could include violent behavior, absences from work, or losing a job
- "Duration of disturbance of at least 1 month"

A diagnosis of alcohol dependence required the first two criteria of alcohol abuse, along with indications of tolerance (the need to increase the amount of alcohol to achieve the desired effect) or withdrawal (the development of physical symptoms after reducing or discontinuing alcohol consumption).

The 1987 revision of the third edition, the DSM-III-R, introduced major diagnostic changes for alcohol-related disorders. In the DSM-III-R, an "alcohol dependence" diagnosis required three out of nine possible criteria, and an "alcohol abuse" diagnosis required only two.[5] The diagnosis of alcohol abuse was to be used only for individuals who had alcohol-related problems but did not meet the requirements for alcohol dependence. The DSM-IV diagnoses were substantially similar to those in the DSM-III-R.[6]

In the DSM-5, the terms "alcohol dependence" and "alcohol abuse" were removed, and the two separate diagnoses were replaced with one diagnosis—AUD.[7] The DSM-5 lists 11 symptoms for the disorder, and an AUD diagnosis now has levels of severity based on the number of symptoms presented. The presence of two to three symptoms indicates mild AUD, four to five symptoms indicate moderate AUD, and six or more symptoms indicate severe AUD.

PTSD

Unlike AUD, PTSD has only been included in the DSM since the third edition. In one of the first published articles on the occurrence of PTSD in the general population, Helzer and colleagues described the inclusion of PTSD in the DSM-III as a "compromise" for veterans' groups and mental health personnel advocating for recognition of what was commonly called "post-Vietnam syndrome."[8] Adding PTSD as a possible diagnosis for anyone who had experienced a trauma was a middle ground between those who hypothesized that the disorder was unique to Vietnam veterans and those who believed it might not exist at all.

In the DSM-III-R and DSM-IV, a PTSD diagnosis was defined by experiencing a qualifying traumatic event (Criterion A) and three other clusters of symptoms: re-experiencing the event (Criterion B), emotional numbing and avoidance of cues and reminders of the event (Criterion C), and hyperarousal (Criterion D).[5,6] King and colleagues conducted a factor analysis on the Clinician-Administered PTSD Scale, a measurement tool based on the DSM-IV diagnostic criteria, and found that these four clusters of symptoms best defined the disorder.[9] This four-cluster model subsequently has been used in many examinations of the connections between PTSD symptoms and alcohol use.

The definition of PTSD was updated significantly for the DSM-5.[7] The major changes included:

- Reclassification of PTSD as a trauma- and stressor-related disorder instead of an anxiety disorder
- Elimination of the criterion that the person's response to the traumatic event must involve intense fear, helplessness, or horror

- Addition of the requirement that the symptoms cannot be attributed to the physiological effects of substance misuse, a medication, or another medical condition

Conditional disorders

Both PTSD and AUD are conditional disorders; that is, both disorders can be diagnosed only if certain prerequisite conditions are met—specifically, a traumatic event or alcohol use. In the DSM-III, the prerequisite condition for PTSD was "existence of a recognizable stressor that would evoke significant symptoms of distress in almost everyone."[2] In the same edition, the section on substance use disorder (SUD) referred to "the maladaptive behavior associated with more or less regular use of the substances."

Importantly, analyses can be conducted on the risk for the exposure to an event among the entire population, and then among those who experienced an event. Social determinants of health for the diagnoses may vary considerably based on likelihood of being exposed to an event or exposure to a substance. Conversely, risk for who later develops a diagnosis, given exposure, may be different as well. For this reason, it is important to evaluate both risk for exposure as well as risk for a disorder among those exposed.

Prevalence Surveys in the United States

Since the late 1970s, several U.S. surveys have collected information on mental health conditions, including AUD, SUD, and PTSD. These surveys include the Epidemiological Catchment Area (ECA) program, the National Comorbidity Survey (NCS), and the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC).

ECA

In 1978, the President's Commission on Mental Health concluded that the existing body of research could not answer these fundamental questions: What is the prevalence of mental health conditions in the United States, and are people with mental health conditions receiving adequate treatment?[10] The ECA was designed to answer these questions.[11] Although the ECA study did not include a nationwide sample, sites were chosen to be representative of the U.S. population and included Baltimore, Maryland; Durham, North Carolina; Los Angeles, California; New Haven, Connecticut; and St. Louis, Missouri. The ECA program used the National Institute of Mental Health (NIMH) Diagnostic Interview Schedule (DIS) to conduct face-to-face interviews with more than 20,000 people.[12,13] The NIMH DIS questions were based on DSM-III diagnostic criteria. At all five sites, information on alcohol use was collected, and the St. Louis location also assessed traumatic event experiences and PTSD.[8]

The ECA program reported that the lifetime prevalence of DSM-III alcohol abuse and dependence was almost 14%.[14] Prevalence varied by location, from about 11% in New Haven and Durham to about 16% in St. Louis. Individuals who had problems with alcohol were almost three times as likely to have a co-occurring mental disorder as those with no alcohol problem. Antisocial personality disorder and SUD were the most common co-occurring disorders.

The information collected at the St. Louis location provided one of the first estimates of the prevalence of PTSD in the general population. Of the 2,493 participants, about 16% were exposed to at least one qualifying traumatic event.[8] Of this group, about 8.4% developed PTSD.[15] Also, individuals who met criteria for PTSD were more likely to report alcohol-related problems than those who did not meet PTSD criteria.

NCS

The Survey Research Center at the University of Michigan's Institute for Social Research conducted a national study of comorbidity between 1990 and 1992.[16] Trained interviewers administered a modified version of the World Health Organization's Composite International Diagnostic Interview (CIDI), which was based on the DIS, to 8,098 individuals representing the contiguous 48 states. The NCS used the DSM-III-R definitions to assess alcohol dependence, alcohol abuse, and PTSD.

In the NCS sample, qualifying PTSD traumatic events were reported by 61% of men and 51% of women.[16] Although more men reported experiencing traumatic events than women, women who

experienced trauma were more than twice as likely than men to develop PTSD (20% vs. 8%). About 14% of the sample met criteria for lifetime alcohol dependence.[17] Also, respondents who met criteria for PTSD were more than twice as likely to report co-occurring alcohol abuse or dependence, and they were almost three times as likely to report drug abuse or dependence.[16]

NESARC Waves 1 and 2

The NESARC studies conducted in 2001 to 2002 (Wave 1) and 2004 to 2005 (Wave 2) collected nationally representative data on AUD and other mental disorders using the Alcohol Use Disorder and Associated Disabilities Interview Schedule (AUDADIS), which was designed by the National Institute on Alcohol Abuse and Alcoholism (NIAAA). The AUDADIS interview questions, heavily based on the CIDI, used DSM-IV criteria. NESARC Wave 2 consisted of 34,653 face-to-face interviews with individuals previously interviewed in Wave 1.[18] According to data from Wave 2, the lifetime prevalence of alcohol abuse was found to be about 27% for men and 13% for women, and the lifetime prevalence of alcohol dependence was about 21% for men and 10% for women.[19]

The survey data showed that 77% of the respondents had experienced a qualifying traumatic event, as defined by the DSM-IV.[18] The most commonly reported stressful life events were indirect experience of 9/11, serious illness or injury to someone close, and unexpected death of someone close. Of those who had experienced a trauma, about 8% developed PTSD. Individuals with PTSD were more likely to report mood disorders, anxiety disorders, SUD, and suicidal behavior than respondents without PTSD. Also, respondents with PTSD were more likely than those without PTSD to have co-occurring AUD, after controlling for sociodemographic factors such as age and race. However, this association was no longer significant when the analysis controlled for other co-occurring mental health conditions in addition to the sociodemographic characteristics.

NESARC-III

The most recent NESARC interviews, conducted between 2012 and 2013, included a representative sample of 36,309 adults in the United States, and DSM-5 criteria were used.[20] According to data from the NESARC-III, lifetime prevalence of AUD was 29%, and past 12-month prevalence was about 14%.[21] Prevalences were higher among men, Whites, Native Americans, younger adults, and those who were previously married or never married. The lifetime prevalence of severe AUD was about 14%, and the past 12-month prevalence was more than 3%. Less than 20% of respondents who experienced AUD in their lifetime ever sought treatment for the condition.

In the NESARC-III sample, about 69% of respondents had experienced a qualifying traumatic event.[22] Of this group, almost 9% met lifetime criteria for PTSD, and almost 7% met the criteria in the previous 12 months. Rates were higher among younger adults, Whites, Native Americans, and those with less education and lower incomes. PTSD was significantly associated with other psychiatric conditions, such as SUD, mood disorders, anxiety disorders, and personality disorders. Specifically, respondents who had PTSD, versus those who did not, were 1.5 times as likely to meet criteria for SUD and 1.2 times as likely to meet criteria for AUD in their lifetime, even after adjusting for other psychiatric disorders.

Prevalence Surveys Outside the United States

Through many decades, despite numerous definition changes for each, AUD and PTSD consistently co-occur. This durable comorbidity has been found in large, small, representative, and targeted samples. U.S. surveys, such as the St. Louis sample of the ECA,[8] the NCS,[16] and the NESARC,[23] have consistently found relationships between alcohol problems and PTSD.

Co-occurrence of AUD and PTSD has also been found in Europe, where rates of trauma exposure and PTSD vary greatly from country to country.[24] In a 2004 analysis of a survey of the general population of six European countries, the European Study of the Epidemiology of Mental Disorders, which used the DSM-IV criteria for disorders, researchers reported that individuals with PTSD were twice as likely than those without PTSD to have co-occurring

alcohol abuse and were three times as likely to have co-occurring alcohol dependence.[25] An examination of the 1997 National Survey of Mental Health and Wellbeing, an Australian survey of more than 10,000 individuals, reported that about 1 in 4 individuals with PTSD also had AUD.[26]

Co-Occurring Disorders

Some populations, such as military veterans and people with SUD, are at high risk for comorbidities, including co-occurring AUD and PTSD. For example, in one study of a sample of individuals seeking treatment for SUD, alcohol misuse was associated with meeting the criteria for a PTSD diagnosis.[27] In another notable case, 141 Australian firefighters who had been exposed to a trauma and screened positively for potential PTSD were followed for several years.[28,29] After 42 months, 42% of the participants had AUD, and 54% had experienced PTSD.

PTSD before AUD

The consistent association between PTSD and AUD has led to debate about which condition develops first. One theory is that individuals with PTSD use alcohol and other substances to numb their symptoms and later develop AUD or SUD. This self-medication hypothesis was proposed by Khantzian to explain behavior exhibited by individuals with AUD and SUD who were being treated in a clinical setting.[30] This theory has been supported by the demonstration of a mechanism that may encourage alcohol cravings. In laboratory settings, individuals with both AUD and PTSD reported increased cravings for alcohol after being presented with a trauma stimulus, as compared to a neutral stimulus.[31] Other epidemiologic research has shown that a diagnosis of PTSD using the DSM-III-R criteria was predictive of later development of SUD.[32,33] Trauma exposure alone, in the absence of a PTSD diagnosis, did not predict SUD.

Alternatively, some evidence shows that people exposed to trauma might be less likely to develop AUD after a traumatic experience. In a study of survivors of the Oklahoma City bombing in 1995, North and colleagues found that no new cases of AUD were reported after the bombing.[34] This finding mirrors a previous study of individuals who experienced a mass shooting in 1991.[35] In that study, three new cases of AUD were reported, but overall incidence of alcohol misuse significantly decreased in both men and women. These findings may indicate that some traumatic experiences bestow a type of survivor resilience that is protective against later development of AUD. Further research is needed to understand this phenomenon.

AUD before PTSD

An alternative to the self-medication hypothesis was proposed in 1992. Using the St. Louis ECA, Cottler and colleagues hypothesized that individuals who had SUD may have been exposed to more circumstances that cause traumatic events.[15] This heightened exposure may lead to experiencing more traumatic events and, ultimately, increase the likelihood of developing PTSD; although other explanations, such as AUD increasing sensitivity for developing PTSD, may also contribute. In the St. Louis ECA example, Cottler and colleagues confirmed their hypothesis, and they suggested that the use of substances such as opiates or cocaine led to even greater risk of exposure to traumatic events and an increased likelihood of developing PTSD.[15]

Several years later, this hypothesis was tested again in a sample of 464 drug users.[36] In this study, the onset of drug use preceded exposure to traumatic events for men, but for women there was no difference in the timing of the events. A similar pattern of substance misuse leading to dangerous and traumatic experiences was found among African American women at risk for HIV.[37] In a study that examined African Americans with SUD who were not receiving treatment, alcohol and substance misuse, with the exception of crack cocaine use, preceded the traumatic events.[38] Finally, a longitudinal study of adults in Michigan found that PTSD predicted increased likelihood of SUD at a 5-year follow-up, but preexisting SUD did not predict later exposure to trauma or PTSD.[33]

Prevalence in veterans

Drinking alcohol has been associated with the military for centuries. Military personnel use alcohol to cope with fear and other strong emotions

experienced during and after combat.[39] Combat is the traumatic event most strongly associated with PTSD, and the ECA found that about 20% of veterans who were wounded in the Vietnam War developed PTSD.[8] More recently, veterans of the Iraq and Afghanistan wars who had PTSD were twice as likely to report alcohol misuse as those with no PTSD.[40] More than 28% of veterans screened positive for alcohol misuse, and 37% screened positive for PTSD. Of those who met criteria for PTSD, 76% had co-occurring depression, which was more than twice the rate of depression among veterans who did not have PTSD. Similarly, a prospective study of service members in the United Kingdom found that those who had experienced combat increased their drinking more than those who had not been deployed.[41] This finding was particularly strong for respondents who thought they might be killed or for those who experienced hostility from civilians while deployed.

Soldiers with PTSD who experienced at least one symptom of AUD may be disinhibited in a way that leads them to make risky decisions, including the potential for aggression or violence. One study conducted with veterans of the wars in Iraq and Afghanistan demonstrated a link between PTSD and AUD symptoms and nonphysical aggression.[42] Veterans with milder PTSD symptoms who misused alcohol were more likely to perpetrate nonphysical aggression than veterans who did not misuse alcohol. However, this relationship was not demonstrated with significance among veterans who had more severe PTSD symptoms.

Prevalence in women

Researchers continue to find more traumatic events and PTSD in women than in men. For example, in the NESARC Wave 2, lifetime prevalence of PTSD among women who experienced trauma was twice as high as the prevalence among similar men.[18] A review of community samples reported that the prevalence of co-occurring SUD and PTSD among women is higher than the prevalence among men,[43] and women who experienced abuse or neglect were significantly more likely to have AUD than controls.[44] Higher prevalence in women compared to men has also been found in women who use illicit substances.[36]

Women who have experienced sexual assault or childhood sexual abuse appear to have particularly high rates of psychiatric disorders, including PTSD and AUD. In one notable study, women who self-reported childhood sexual abuse had an increased likelihood of having psychiatric disorders or SUD.[45]

AUD and PTSD Symptom Clusters

Several studies have examined how the four clusters of PTSD symptoms (re-experiencing, effortful avoidance, emotional numbing, and hyperarousal) may affect how individuals develop and recover from PTSD and AUD. If some symptom clusters are closely associated with AUD, that information may be useful when screening people with PTSD for potential AUD. In an early study, hyperarousal symptoms were associated with AUD, whereas other clusters were not.[46] However, later research found mixed results, with one study finding no relationship between any symptom cluster and AUD,[47] and another study finding that the re-experiencing cluster was most strongly associated with alcohol problems.[48] A study of veterans of the Iraq and Afghanistan wars found that the emotional numbing cluster, compared to the other symptom clusters, was significantly associated with alcohol misuse, even when controlling for other variables associated with AUD, such as depression and direct combat exposure.[40] Finally, in a different study, a reduction of PTSD symptoms in each cluster was associated with less severe drinking overall, and a reduction in hyperarousal symptoms preceded positive changes in alcohol use.[49]

Conclusion

The association between AUD and PTSD has been elucidated due to the development of standardized assessments for the ECA using the DSM-III DIS. Assessments that followed have used the foundational structure and question format of the DIS to interview participants. They include the CIDI, AUDADIS, and, recently, the Psychiatric Research Interview for Substance and Mental Disorders. In fact, the DIS has continued to be revised based on the DSM and the International

Classification of Diseases, making it one of the most durable standardized diagnostic assessments in the field.

AUD and PTSD have shown a consistent comorbidity over many decades and in diverse populations. The strong relationship is present in representative surveys of the United States, throughout Europe, and in Australia. The relationship persists in studies of population subgroups at risk, such as veterans of the wars in Vietnam, Iraq, and Afghanistan; firefighters; women; and people with SUD. Although men have a higher prevalence of AUD than women, and women have a higher prevalence of PTSD than men, any individual with either disorder is more likely to have the other.

The evidence suggests that there is no distinct pattern of development for the two disorders. Some evidence shows that veterans who have experienced PTSD tend to develop AUD, perhaps reflecting the self-medication hypothesis. However, other research shows that people with AUD or SUD have an increased likelihood of being exposed to traumatic situations, and they have an increased likelihood of developing PTSD. It is possible that these two bodies of evidence represent two separate relationships between PTSD and AUD. Additionally, the conditional nature of the disorders, based on the exposure to an event or a substance, makes this a complex relationship for analysis, interpretation, and intervention for treatment.

Currently, there are several questions that remain unanswered. How different are the outcomes of the disorders when one or the other develops first? Are any of the PTSD symptom clusters more likely to lead to AUD? Are there particular traumatic experiences that provide some resilience against developing AUD? Are there significant differences in the occurrence and trajectory of PTSD and AUD among racial and ethnic minorities? These questions, and others, should be addressed by further research to ultimately minimize the harm experienced by the millions of individuals who experience AUD and PTSD.

Acknowledgments

This article was supported by the National Institute on Drug Abuse grant DA035167, University of Florida Substance Abuse Training Center in Public Health and National Center for Research Resources grant 5KL2RR029888, and the University of Florida Clinical and Translational Science Award.

Financial Disclosure

The authors declare that they have no competing financial interests.

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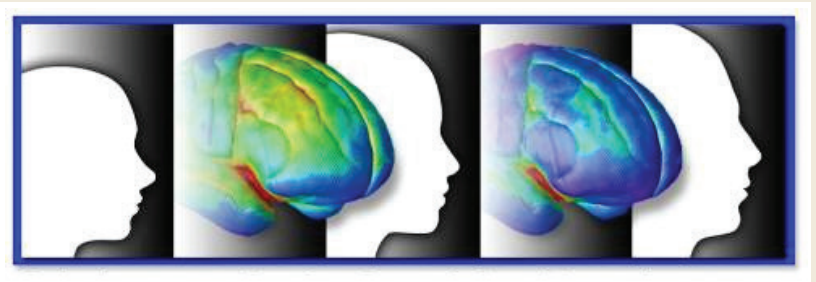
NIH's Adolescent Brain Cognitive Development (ABCD) Study

Alcohol Research: Current Reviews Editorial Staff

Adolescence is the stage of life during which most people begin using alcohol, and it is also a time of considerable social, psychological, and physiological change. The brain, particularly the frontal cortex, continues to develop throughout adolescence and does not fully mature until early adulthood. Adolescent alcohol exposure can impair brain development, compromise short- and long-term cognitive functioning, and increase the likelihood of developing alcohol-related problems during adolescence and later in life. Furthering our understanding of the developing brain—as well as how differences in brain structure and function that exist prior to alcohol and other substance use contribute to substance use disorders—is a high priority for the National Institutes of Health (NIH).

In September 2015, NIH launched the Adolescent Brain Cognitive Development (ABCD) Study, the largest long-term study of brain development and child and adolescent health in the United States. The ABCD Study will recruit more than 11,000 9- to 10-year-olds to capture data before children begin using alcohol or other addictive substances. It will integrate structural and functional brain imaging; genetic testing; and neuropsychological, behavioral, and other health assessments of study participants conducted over a 10-year period, yielding a substantial amount of information about healthy adolescent brain development. Data gathered from participants will allow the creation of



baseline standards for typical brain development (similar to those that currently exist for height, weight, and other physical characteristics). These data are expected to illuminate how brain development is affected by substance use and other childhood experiences, such as patterns of sleep, use of social media, and engagement in sports and with video games. It may also reveal neurobiological, cognitive, and behavioral precursors of substance misuse and other risk behaviors, and ultimately inform preventive and treatment interventions.

The ABCD Consortium consists of a Coordinating Center, a Data Analysis and Informatics Center, and 21 research sites across the country. Recruitment, which began in September 2016, is expected to span 2 years. ABCD workgroups have established standardized and harmonized assessments of neurocognition, physical and mental health, social and emotional functions, and culture and environment. They also have established multimodal structural and functional brain imaging and bioassays. Brain imaging and biospecimen collection for genetic and epigenetic analyses will be done every other year, and the remaining assessments will be conducted semiannually or annually.

One important goal of the ABCD Study is to create a unique data resource for the entire scientific community by embracing an open science model. Curated, anonymized data will be released annually to the research community, along with the computational workflows used to produce the data, beginning 1 year after data collection begins.

ABCD is supported by the National Institute on Alcohol Abuse and Alcoholism, the National Institute on Drug Abuse, the National Cancer Institute, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the National Institute of Mental Health, the National Institute on Minority Health and Health Disparities, the National Institute of Neurological Disorders and Stroke, the NIH Office of Behavioral and Social Sciences Research, and the Division of Adolescent and School Health at the Centers for Disease Control and Prevention.

For more information, visit http://abcdstudy.org/index.html.

The Epidemiology of Binge Drinking Among College-Age Individuals in the United States

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Rates of alcohol consumption continue to be a concern, particularly for individuals who are college age. Drinking patterns have changed over time, with the frequency of binge drinking (consuming four/five or more drinks for women/men) remaining high (30% to 40%). Young adults in the college age range are developmentally and socially at higher risk for drinking at binge levels. Changes in autonomy, parental control, norms, and attitudes affect binge drinking behaviors. This article reviews those changes, as well as the individual and environmental factors that increase or decrease the risk of participating in binge drinking behaviors. Risk factors include risky drinking events (e.g., 21st birthdays), other substance use, and drinking to cope, while protective factors include religious beliefs, low normative perceptions of drinking, and use of protective behavioral strategies. Additionally, this article discusses the physical, social, emotional, and cognitive consequences of consuming alcohol at binge levels. Alcohol policies and prevention and intervention techniques need to incorporate these factors to reduce experiences of alcohol-related problems. Targeting policy changes and prevention and intervention efforts toward young adults may increase effectiveness and prevent both short- and long-term consequences of binge drinking.

Key words: Alcohol consumption; binge drinking; consequences; risk and protective factors; young adults

Binge drinking, particularly among college-age individuals, has been a significant topic of research for more than 20 years because of associations between greater quantity and frequency of alcohol consumption and alcohol-related consequences. To identify factors associated with binge drinking over time, several large-scale studies have assessed trends in binge drinking among young adults. This article aims to summarize those trends and the developmental and social factors that impact the likelihood of, the risk and protective factors related to, and the negative alcohol-related consequences of binge drinking behaviors. Some studies examined young adults who are not in college, but the majority of the literature regarding binge drinking focuses specifically on college students. Further, there is variability in the definition of college students. Some studies sampled only full-time students from four-year institutions, whereas other studies included part-time and community college students.

The term "binge drinking" has a somewhat controversial history. The term was originally defined by Wechsler and colleagues as five or more drinks for men, or four or more drinks for women (5/4+), on a single occasion.[1] Criticisms of this conceptualization of binge drinking were based largely on the substantial variability in blood alcohol concentrations (BACs) due to differences in weight and duration of consumption. When individuals who met these binge drinking criteria had consumed the alcohol over a long period of time, they did not reach BACs higher than .08%.[2,3]

In 2004, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) provided a revised definition of binge drinking, acknowledging that consuming 5/4+ drinks in a 2-hour time period would result in a BAC of at least .08% for most individuals. Although subsequent questions continue to be raised regarding the validity of defining binge drinking at 5+ or 5/4+ on one occasion, these are still the most commonly used definitions in the literature. Research covered in this review includes studies on binge

drinking that use the 5/4+ criteria or a BAC of at least .08%.

Trends in Young Adult Binge Drinking Rates

Binge drinking among young adults has concerned researchers and educators for decades, prompting multiple national initiatives to track patterns in binge drinking. The longest continuous running national survey of drug and alcohol use among adolescents and young adults is the Monitoring the Future (MTF) study, which is funded by the National Institute on Drug Abuse and conducted by the University of Michigan's Institute for Social Research.[4] Approximately 15,000 high school seniors in 133 schools are surveyed each year, and, since 1976, a subset of about 2,400 have been followed biennially by mail. Survey results indicate that the rate of self-reported college student binge drinking in the previous 2 weeks dropped from 1980 (44%) to 1993 (40%) and continued to decrease through 2014 (35%). Estimates for college student engagement in extreme binge drinking, defined as consuming 10 or more drinks on one occasion in the previous 2 weeks, varied from 14% in 2005 to 20% in 2014.

Another national survey assessing college student binge drinking is the Substance Abuse and Mental Health Services Administration's (SAMHSA) National Survey on Drug Use and Health (NSDUH), which includes yearly assessments of 60,000 to 70,000 individuals ages 12 and older. Results indicate that for young adults ages 18 to 25, rates of binge drinking in the previous 30 days decreased slightly from 44.6% in 1988 to 37.7% in 2014.[5]

The Core Alcohol and Drug Survey sampled more than 140,000 students and found a slight decline in the percentage of students who binge drank in the previous 2 weeks, from 45.9% in 2006 to 43.9% in 2013.[6,7] The College Alcohol Survey (CAS) also attempted to assess student drinking rates. At 120 colleges, the CAS measured alcohol use among college students at four time points between 1993 and 2001.[8] The survey included more than 14,000 students and provided the first gender-specific measure of binge drinking (i.e., 5/4+ drinks for males/females). Contrary to findings from the MTF study and the Core Alcohol and Drug Survey, the CAS found little change between 1993 (43.2%) and 2001 (44.5%) in the number of students reporting binge drinking in the previous 2 weeks.[9]

The most recently initiated nationwide survey of college student alcohol use is the National Epidemiologic Survey on Alcohol and Related Conditions. This survey began the first of three waves of data collection in 2001, which included data from approximately 43,000 individuals.[10] Prevalence rates, only reported for 2001, indicate that 57% of 18- to 24-year-olds binge drank in the previous year, and 40% binge drank 12 or more times in the previous year.

College attendance, gender, and ethnic variations in binge drinking have been identified. A number of studies have examined differences in alcohol use between college and same-age noncollege peers, consistently finding higher rates of heavy drinking and alcohol-related problems among college students than among noncollege peers.[11] The annual prevalence of alcohol use reported in the MTF study suggested small differences between male and female drinking rates and modest decreases over time.[4] However, a declining gender gap exists for binge drinking rates, with female binge drinking (i.e., 4+) decreasing from 31% in 1988 to 26% in 2014, and male binge drinking (i.e., 5+) decreasing more substantially, from 52% to 43%.

Currently, the MTF study does not report racial or ethnic differences in binge drinking among college students. However, the U.S. Centers for Disease Control and Prevention reported that more White college students engaged in binge drinking in the previous 30 days (31.6% of females and 49.4% of males) than Hispanic students (22.6% of females and 39.9% of males).[12] Also, African American students (6.1% of males) were less likely to report binge drinking than White students (22.8% of males), although this difference was less pronounced among females.

Rates of binge drinking have also been assessed in military samples. Starting in 1980, the U.S. Department of Defense issued several large-scale, anonymous health surveys (most recently called the Health Related Behaviors Survey) to active-duty military personnel, with the first assessment of binge drinking appearing in 1998. Rates of binge drinking for military personnel overall increased from 35% in 1998 to 47% in 2008.[13] The 2008 survey sampled more than 28,000 service members and found that young adult military personnel (ages 18 to 25) had the highest rates of frequent binge drinking (once a week or more) at 26%.[14] This is significantly higher than the rate for same-age civilians (16%), as reported in the 2007 NSDUH.[15] Rates of binge drinking also differ by military branch.[14]

Developmental and Social Factors

Developmental and social factors are important contributors to binge drinking among college-age adults. The college-age years (approximately ages 18 to 24) correspond with the developmental stage widely referred to as "emerging adulthood."[16,17] Dramatic cultural changes in the United States and other countries with similar socioeconomic structures have occurred over time. Arnett notes that post–high school education rose from 14% in 1940 to more than 60% in the mid-1990s.[16] College attendance has resulted in the delay of traditional adult responsibilities. Consequently, in recent decades this developmental period has become a time when individuals

explore new freedoms and experiment with behaviors that were previously less accessible, including alcohol consumption.[18,19]

In their seminal paper, "Getting Drunk and Growing Up: Trajectories of Frequent Binge Drinking During the Transition to Young Adulthood," Schulenberg and colleagues identified five distinct trajectories of binge drinking that occur in young adults ages 18 to 24.[20] This analysis was one of the first to use a national sample to identify distinct patterns of changes in binge drinking over time. The national sample included four consecutive waves of data from the MTF study. More than 90% of the sample was categorized as engaging in no binge drinking during any wave (35.9%). Or, they were categorized as one of five binge drinking trajectories:

1. Rare (16.7%): binge drinking during at least one wave but no frequent binge drinking, defined as two or more binge episodes in the past 2 weeks.
2. Decreasing (11.7%): frequent binge drinking during Wave 1 and decreasing or no frequent binge drinking by Wave 4.
3. Fling (9.9%): frequent binge drinking during Wave 2 or Wave 3 but no binge drinking in Wave 1 or Wave 4.
4. Increasing (9.5%): no frequent binge drinking during Wave 1 increasing to frequent binge drinking by Wave 4.
5. Chronic (6.7%): frequent binge drinking throughout Waves 1, 2, 3, and 4.

Most young adults reported binge drinking during at least one of the four assessment waves, but less than half of the sample drank at rates that could be considered problematic.[20] Young adults in the Increasing and Chronic categories were identified as having the most difficulty navigating the transition to adulthood. Identified trajectories were associated with stability and changes in alcohol problems, attitudes regarding heavy drinking, and heavy drinking or drug-using peers.

Interrelated factors associated with increased heavy drinking and alcohol-related problems include moving out of the parent home, going to college, and decreased parental involvement, each of which has a unique contribution. Moving out of the parent home contributed to the risk of increased drinking, but additional risk was found for students who lived on campus.[21] White and colleagues found that living in a college environment contributed to increases in heavy drinking more than all the other developmental factors they examined.[22] Further, although peer influences are paramount among college students, one study found that parental involvement played a protective role in reducing the likelihood of problem drinking.[23]

For young adults ages 18 to 24, many of the factors attributed to high rates of binge drinking are social in nature. Perceptions and overestimations of the prevalence and approval of heavy drinking among one's peers have been consistently documented and associated with heavier drinking. Reducing normative misperceptions has been the most consistently supported brief intervention strategy for reducing heavy drinking among young adults. Most studies that successfully used such interventions to reduce perceived norms also demonstrated reductions in drinking.[24-28]

The vast majority of research on the influence of social norms on heavy drinking has been done using college samples. Similar results have been found in the general adult population, with heavy drinkers more likely to view heavy drinking as normative and to overestimate drinking norms.[29] In a large general population study of adults who drank alcohol at least monthly (N = 14,009), age was negatively associated with normative misperceptions of drinking.[30] However, the magnitude of the correlation was only .07, suggesting that age is not a strong predictor of normative perceptions of drinking.

The MTF study collected data (for ages 18 to 30) on perceived close-friend disapproval of respondents' binge drinking once or twice per weekend. Respondents ages 19 to 22 and 23 to 26 reported less disapproval from their friends (54.5% and 52.3%, respectively) relative to respondents ages 18 (65.6%) and ages 27 to 30 (57.1%).[4] Few studies have directly examined perceived norms and their influence on college versus noncollege young adult binge drinking, but the available evidence suggests perceived norms have less influence on noncollege young adults.[31]

Related to social norms, membership in specific groups has been associated with higher rates of binge drinking. Foremost among these are college fraternity or sorority affiliation,[32-34] participation in collegiate athletics,[35,36] and being in the military, especially the U.S. Army or U.S. Marines.[14,37,38]

Risk and Protective Factors

Person-level risk factors. Demographic factors such as age, sex, and race have been linked to binge drinking rates among college students. Individuals who began drinking before age 16 were found to be more likely to binge drink in college.[39] An examination of MTF data found that, among recent cohorts, individuals entering the 18 to 26 age range reported less binge drinking than previous cohorts, and individuals leaving the 18 to 26 age range reported more binge drinking than previous cohorts.[40] Several longitudinal studies found that male college students were more likely than female students to binge drink.[41,42] Also, studies have shown that White college students were more likely to engage in binge drinking than non-White students.[39,43]

Personality traits and individual difference variables have also been identified as risk factors for binge drinking. A longitudinal investigation

using MTF data from 18- to 24-year-olds found that individuals lower in self-efficacy had a greater likelihood of engaging in binge drinking over time.[42] Similarly, another longitudinal study among adults ages 18 to 31 found that, across time points, problem drinkers scored higher on disinhibition.[41]

Binge drinking also has been positively correlated with neuroticism-anxiety and impulsive sensation-seeking. In particular, one study found that women who engaged in binge drinking tended to score higher on neuroticism-anxiety, and men who engaged in binge drinking were more likely to score highly on impulsivity and sensation-seeking.[44] Another study found that binge drinkers tended to be less conscientious and more thrill-seeking than those who did not engage in binge drinking.[45] Also, individuals who scored higher on measures of antisocial personality disorder were more likely to engage in binge drinking.[46]

Other studies report that motivations for drinking and attitudes toward drinking can influence the likelihood of binge drinking. Drinking to cope with negative affect and drinking to fit in with peers have both been associated with binge drinking.[45] Sex-seeking as a motivation for drinking has been associated with binge drinking among college men.[45] Individuals who reported drinking alcohol for the purpose of getting drunk were also more likely to engage in binge drinking.[42] Positive attitudes toward drinking have also been associated with an increased likelihood of binge drinking among college students.[39]

Problem behaviors and other substance use also have been associated with binge drinking. For example, one longitudinal study found that, across ages 18 to 31, heavy drinkers were more likely to exhibit problem behavior.[41] A longitudinal examination of trajectories of binge drinking found that adolescents who reported using drugs and scored low on measures of depression were more likely to engage in binge drinking at an earlier age during young adulthood.[46]

In conclusion, several consistent risk factors for binge drinking have been identified, including early onset of alcohol use, being male, identifying as White, having low self-efficacy, scoring high on disinhibition, scoring high on neuroticism-anxiety (for women), being impulsive and sensation-seeking (especially for men), having higher scores on antisocial personality disorder measures, using alcohol to cope or fit in with others, using alcohol for sex-seeking purposes, drinking to get drunk, exhibiting problem behavior, scoring low on depression, and engaging in other substance use.

Risky contexts and events. Specific events and contexts that promote heavy drinking are additional factors that contribute to high rates of binge drinking. Such events include New Year's Eve, St. Patrick's Day, and Halloween.[47,48] Some high-risk drinking events tend to be more prevalent in young adulthood. For example, homecoming, athletic events, weddings, and graduations are all relatively common events for people in this age range and have been associated with heavy drinking.[49,50] In addition, 21st birthdays,[51] spring break,[48] football tailgating,[52] pregame partying,[53-55] and drinking games[56,57] have all been associated with excessive drinking among college students. For undergraduates, weekends and the beginning of a semester have been associated with higher levels of drinking.[47,49]

Social influences, often from close relationships, can contribute to increased risk of binge drinking among college students. For example, having parents who are alcoholics, having friends who drink, and participating in Greek life have all been associated with a greater likelihood of binge drinking.[46,58-60] Also, peer drinking and use of cigarettes and marijuana have been associated with an increased likelihood of binge drinking.[61]

Person-level protective factors. Several protective factors associated with a lower likelihood of engaging in binge drinking have been identified. Gender is one of these factors. Females tend to drink less than males.[62] Also, females and individuals with higher grade point averages tend to use more protective behavioral strategies, such as alternating drinking alcohol and water.[63] Protective behavioral strategies have been shown to reduce the likelihood of experiencing negative alcohol-related consequences.[62,64]

Protective contexts and events. Certain cultural climates that promote a normative perception of disapproval toward excessive drinking can protect their adherents against binge drinking. For example, parental disapproval of alcohol use protects against binge drinking.[39,61] Many religions disapprove of drinking heavily and promote drinking only in moderation or ban drinking among members altogether. As such, religion can exert a protective influence on college student binge drinking.[61,65] Neighborhood norms against heavy drinking have also been found to protect against binge drinking.[66]

College environments tend to encourage heavy drinking; however, some contextual factors surrounding students can protect against binge drinking and negative alcohol-related consequences. Drinking in college is often a social activity among friends. Close friends who encourage safe drinking can help protect against the negative consequences of excessive drinking.[67] College drinking that occurs in locations that provide food and water or that accompanies a meal has been shown to reduce negative alcohol consequences.[68] Additionally, drinking that occurs in bars is somewhat regulated, because bartenders can stop serving individuals who appear drunk.[69] These specific college drinking contexts allow for use of protective behavioral strategies, such as eating food, drinking water, limiting the number of drinks consumed, and drinking with close friends.[62]

Other factors specific to certain colleges have been associated with lower rates of binge drinking. For instance,

college students who attended schools with higher social capital (defined as the average time students spent volunteering) were less likely to engage in binge drinking.[70] Furthermore, research has suggested that attending commuter schools, all-female colleges, and Protestant religious colleges is associated with lower rates of binge drinking.[39]

Certain social roles and their inherent responsibilities can lead to lower likelihood of binge drinking. For example, studies have found that cohabitation, getting married, and having children all protect against heavy drinking.[71-75]

Alcohol-related laws and policies and their connections to the likelihood of binge drinking have been examined. Plunk, Cavazos-Rehg, Bierut, and Grucza found that more permissive laws regarding the minimum legal drinking age were associated with more binge drinking.[76] Using MTF data collected from 1976 to 2011 from high school seniors who were followed up to age 26, Jager, Keyes, and Schulenberg found that laws dictating the minimum legal drinking age were associated with decreases in binge drinking for 18-year-olds, but those laws were associated with increases in binge drinking rates across all male participants ages 18 to 22.[40] Another study found that lower age requirements for purchasing and consuming alcohol were associated with more hazardous and problematic drinking. These findings have clear implications for alcohol policy.[76]

Another study investigated whether personal endorsement of alcohol policies was associated with college student drinking. The authors found that college students who personally endorsed the alcohol laws and policies were significantly less likely to binge drink.[77] Thus, laws that set a minimum drinking age or a low BAC level for drivers, and personal endorsements of college alcohol policies, can serve as protective contextual factors against college student binge drinking.

Consequences of Binge Drinking

Overall, binge drinking and frequent binge drinking have been consistently, significantly, and positively associated with alcohol-related problems.[78,79] These problems impact multiple aspects of life for young adults and the people around them and include physical, legal, emotional, social, and cognitive consequences, as well as an increased likelihood of having an alcohol use disorder.

Physical and legal outcomes. Binge drinking is associated with significant increased risk for experiencing consequences, including physical harm, legal problems, and failure to meet role obligations (e.g., work responsibilities). Active-duty military personnel who binge drink are about five times as likely to report drinking and driving or riding with someone who has been drinking.[38] College students who binge drank in the previous year were more than twice as likely to be taken advantage of sexually or have unplanned sex, and they were four times as likely to be physically injured.[80] Additionally, individuals who engaged in frequent binge drinking reported experiencing more sick days and having poorer overall physical and mental health than non–binge drinkers.[81] Binge drinkers also reported having greater sleep problems, including having more trouble falling asleep and staying asleep than those who did not binge drink.[82] Binge drinking also increases an individual's likelihood of driving after drinking.[80,83]

Emotional and social outcomes. Binge drinking has been associated with a variety of negative emotional and social outcomes. For example, binge drinkers tended to score higher on measures of depression and anxiety[84-86] and reported lower positive mood than nondrinkers.[86,87] Furthermore, students who binge drank in the previous year were more than twice as likely to report having serious thoughts of suicide.[80] Another study reported that feelings of remorse after drinking were more common following a binge drinking episode than a nonbinge episode.[1] Few longitudinal studies have examined associations between emotions and binge drinking; however, frequent binge drinking in young adulthood has been found to increase risk for depression 5 years later.[88]

Social outcomes related to binge drinking often involve negative interpersonal interactions and failure to meet relational obligations. When compared to infrequent and non–binge drinkers, frequent binge drinkers are twice as likely to experience interpersonal consequences, including arguing with friends,[1] experiencing strain on relationships,[89] and getting into physical fights.[38] Binge drinkers in college were two to three times as likely to miss class and twice as likely to perform poorly or get behind on schoolwork.[1,80] Among active-duty military personnel, frequent binge drinking was associated with failure to be promoted and substandard work performance.[38]

Cognitive outcomes. Binge drinking results in high concentrations of alcohol entering the bloodstream quickly, which can affect cognitive processing. One of the most prevalent cognitive effects of binge drinking is blacking out, a failure to encode memories. Frequent binge drinkers are twice as likely as infrequent binge drinkers to experience blackouts.[1] Several studies reported that the consumption of alcohol at binge levels was associated with poor performance on cognitive tasks, such as recall, spatial recognition, search, and planning tasks.[86,90-92] Also, gender differences in cognitive function have been noted, with women being more susceptible to the negative cognitive effects of binge drinking.[87,93]

Research suggests that binge drinking affects the amygdala and prefrontal cortex, and that repeated binge drinking can damage these brain structures.[94] One study reported that extreme binge drinkers (those who consumed 10 or more drinks per occasion) displayed electroencephalography

(EEG) spectral patterns similar to the patterns displayed in individuals with alcohol use disorder, suggesting that extreme binge drinking can alter the brain negatively and permanently.[95] Examination of the effects of binge drinking on cognitive structures and on performance in young adults continues to expand as more psychological research incorporates cognitive and neurological testing.

Alcohol use and abuse disorders. In addition to the negative consequences of binge drinking, frequent binge drinking is associated with increased likelihood of consuming alcohol at twice (8+/10+ drinks for women/men) or even three (12+/15+ drinks for women/men) times binge drinking levels.[96] These high-intensity levels of drinking likely intensify the risk of experiencing negative alcohol-related consequences.

Young adults who binge drink have alcohol use disorder scores that are double the scores of those who do not meet binge drinking criteria.[97] Also, binge drinkers report consuming twice the alcohol per week and spending a third more time drinking than non–binge drinkers.[97] Both occasional and frequent binge drinking are associated with a significantly greater risk of abusing alcohol and becoming dependent than non–binge drinkers or abstainers.[80,85,98] Rates of alcohol abuse and dependence in college student binge drinkers have been reported to be between 14% and 24%.[99] Furthermore, alcohol withdrawal symptoms have been reported by 15% to 29% of students.[99]

Conclusion

Research on binge drinking in college-age samples suggests that binge drinking rates have decreased over time. Despite this trend, rates still remain high, with 30% to 40% of young adults reporting binge drinking at least once in the previous month. Developmentally and socially, this age range is at higher risk for consuming alcohol at binge levels. This review summarized individual and environmental factors associated with increased or decreased risk for binge drinking. Understanding these factors is important in guiding future prevention and intervention efforts and in shaping alcohol policies. Targeting prevention and intervention efforts toward young adults during their college years may increase the effectiveness of those efforts, reducing the negative consequences of alcohol use and averting problematic trajectories.

Financial Disclosure

The authors declare that they have no competing financial interests.

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Surveys That Include Information Relevant to Binge Drinking

Alcohol Research: Current Reviews Editorial Staff

This table provides a brief overview of selected surveys administered in the United States and internationally that collect information that can be used to study binge drinking. This list reflects relevant surveys referenced in this issue of *Alcohol Research: Current Reviews*. It is not a comprehensive compilation of all of the surveys relevant to this topic.

Select U.S. Surveys

Survey Name and Frequency	Population Surveyed	Binge Drinking Measure* and Definition of a Drink	Notes
• Behavioral Risk Factor Surveillance System (BRFSS) • Every year since 1984	Civilian noninstitutionalized adults ages 18 and older	• Binge drinking is measured as 5+ drinks for males or 4+ drinks for females on an occasion in the past 30 days. • One drink is equivalent to a 12-ounce beer, a 5-ounce glass of wine, or a drink with one shot of liquor.	The survey was first administered in 15 states. It became a nationwide surveillance system in 1993 and is now administered in all 50 states, the District of Columbia, and 5 U.S. territories. Since 2011, this survey has included adult students living in college housing. https://www.cdc.gov/brfss
• Core Alcohol and Drug Survey • Every year from 2006 to 2013	College students	• Binge drinking is measured for males and females as 5+ drinks in one sitting in the past 2 weeks. • A drink is defined as a bottle of beer, a glass of wine, a wine cooler, a shot glass of liquor, or a mixed drink.	http://core.siu.edu/results/index.php
• Harvard School of Public Health College Alcohol Study • Conducted four times (1993, 1997, 1999, and 2001)	4-year college students	• Binge drinking is measured as 5+ drinks for males or 4+ drinks for females once in the past 2 weeks. • A drink is defined as a 12-ounce beer, a 4-ounce glass of wine, a 12-ounce wine cooler, or a shot of liquor taken straight or in a mixed drink.	http://archive.sph.harvard.edu/cas/About
• Health Related Behaviors Survey of Active Duty Military Personnel • About every 3 years since 1980	Active-duty service and U.S. Coast Guard members	• Binge drinking is measured as 5+ drinks for males or 4+ drinks for females on the same occasion in the past 30 days. • A drink is defined as a can or bottle of beer, a glass of wine or a wine cooler, a shot of liquor, or a mixed drink with liquor in it.	Most recent report available: https://www.documentcloud.org/documents/694942-2011-final-department-of-defense-survey-of.html

*Surveys may not explicitly use the term binge drinking.

Surveys That Include Information Relevant to Binge Drinking *(continued)*

Select U.S. Surveys

Survey Name and Frequency	Population Surveyed	Binge Drinking Measure* and Definition of a Drink	Notes
• Monitoring the Future (MTF) study • Every year since 1975	8th, 10th, and 12th graders in public and private schools, college students, and young adults	• Binge drinking is measured for males and females as 5+ drinks in a row in the past 2 weeks. • The definition of a drink varies slightly among survey forms, although a drink is generally defined as a bottle of beer, a glass of wine, a wine cooler, a shot glass of liquor, a mixed drink, etc.	This survey began with 12th graders in 1975. Since 1991, surveys of 8th and 10th graders have been conducted annually. Beginning with the class of 1976, a randomly selected sample from each senior class has received biennial follow-up surveys. http://www.monitoringthefuture.org
• National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) • Three surveys conducted since 2001 to 2002	Civilian noninstitutionalized adults ages 18 and older	• NESARC does not explicitly measure binge drinking, although respondents are asked about drinking at or above levels commonly used to assess binge drinking. For males ages 65 and younger, the level is 5+ drinks in a single day or in 2 hours or less. For males ages 65 and older and women, the levels are 4+ drinks in 2 hours or less, 4+ drinks in a single day, and 5+ drinks in a single day. • One standard drink is defined as 0.6 ounces of ethanol.	Three NESARC waves have been conducted. Wave 1 was from 2001 to 2002, Wave 2 was from 2004 to 2005, and NESARC-III was from 2012 to 2013. https://www.niaaa.nih.gov/research/nesarc-iii
• National Survey on Drug Use and Health (NSDUH) • 1979, 1982, 1985, 1988, 1990, and every year thereafter	Civilian noninstitutionalized population ages 12 and older	• Binge drinking is measured as 5+ drinks for males or 4+ drinks for females on the same occasion on at least 1 day in the past 30 days. NSDUH defined binge drinking as 5+ drinks for males and females until 2015. • A drink is defined as a can or bottle of beer, a glass of wine or a wine cooler, a shot of liquor, or a mixed drink with liquor in it.	Called the National Household Survey on Drug Abuse (NHSDA) from 1979 to 2001, called NSDUH since 2002. https://www.samhsa.gov/data/population-data-nsduh
• Youth Risk Behavior Surveillance System (YRBSS) • Every 2 years since 1993	9th through 12th graders in public and private schools in the United States	• Binge drinking is measured as 5+ drinks for males or 4+ drinks for females on a single occasion in the past 30 days. Before 2017, YRBSS surveys defined binge drinking for males and females as 5+ drinks. • A drink includes beer, wine, wine coolers, and liquor such as rum, gin, vodka, or whiskey.	The YRBSS includes national surveys conducted by the Centers for Disease Control and Prevention. It also includes state, territorial, tribal government, and local surveys conducted by departments of health and education, which provide data representative of mostly public high school students in each jurisdiction. https://www.cdc.gov/healthyYouth/data/yrbs/index.htm

Surveys That Include Information Relevant to Binge Drinking *(continued)*

Select International Surveys†

Survey Name and Frequency	Population Surveyed	Binge Drinking Measure* and Definition of a Drink	Notes
• Australian School Students Alcohol and Drug (ASSAD) survey • Every 3 years since 1984	Students ages 12 to 17 who are in school years 7 to 12 and are from government, Catholic, and independent schools in the state of Western Australia	• Risky drinking is defined as drinking 4+ standard drinks on any 1 day, if alcohol was consumed in the previous week. • A standard drink is defined as any drink containing 10 grams of alcohol.	https://www.mhc.wa.gov.au/reports-and-resources/reports/australian-school-students-national-alcohol-and-drug-survey
• European School Survey Project on Alcohol and Other Drugs (ESPAD) • Every 4 years since 1995	European students ages 15 to 16	• Heavy episodic drinking is defined as drinking 5+ alcoholic beverages on one occasion at least once in the past 30 days. • Nationally relevant examples of a drink are included in the surveys.	The ESPAD survey notes that its measure of heavy episodic drinking corresponds to a cutoff of approximately 9 centiliters of pure alcohol. http://www.espad.org
• Healthy Ireland • 1998, 2002, and 2007	Adults ages 18 and older from private households in the Republic of Ireland	• Binge drinking is defined as 6+ standard drinks on one occasion in the past 12 months. • A standard drink is defined as a half pint or a glass of beer, lager, or cider; a single measure of spirits; a single glass of wine, sherry, or port; or a bottle of alcopop (long neck).	Healthy Ireland is the successor to the Survey of Lifestyle, Attitudes and Nutrition in Ireland. http://www.healthyireland.ie/accessibility/healthy-ireland-survey

†For a list of additional international surveys relevant to binge drinking, see **Gender Differences in Binge Drinking: Prevalence, Predictors, and Consequences** in this issue.

Alcohol Misuse and Kidney Injury: Epidemiological Evidence and Potential Mechanisms

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Chronic alcohol consumption is a well-known risk factor for tissue injury. The link between alcohol use disorder (AUD) and kidney injury is intriguing but controversial, and the molecular mechanisms by which alcohol may damage the kidneys are poorly understood. Epidemiological studies attempting to link AUD and kidney disease are, to date, inconclusive, and there is little experimental evidence directly linking alcohol consumption to kidney injury. However, studies conducted primarily in other organs and tissues suggest several possible mechanisms by which alcohol may promote kidney dysfunction. One possible mechanism is oxidative stress resulting from increased production of reactive oxygen species, which leads to an excessive amount of free radicals, which in turn trigger tissue injury and increase inflammation. In addition, AUD's effect on other major organs (liver, heart, intestines, and skeletal muscle) appears to promote unfavorable pathological processes that are harmful to the kidneys. Notably, these mechanisms have not yet been validated experimentally in the kidney. Additional research is needed to clarify if alcohol does indeed promote kidney injury and the mechanisms by which alcohol-induced kidney injury may occur.

Key words: Alcoholic nephropathy; nephrotoxicity; acetaldehyde; proteinuria; glomerular filtration rate (GFR); glomerulonephritis; alcohol use disorder (AUD); kidney injury

Alcohol use disorder (AUD) is a substantial public health problem, affecting 15.7 million people age 12 and older in the United States (Center for Behavioral Health Statistics and Quality 2016). In 2012, 5.9 percent of all global deaths were attributable to alcohol—7.6 percent for men and 4.0 percent for women. Moreover, alcohol-attributable deaths have increased worldwide, making alcohol the fifth leading risk factor for premature death and disability in 2010 and the first among people ages 15 to 49 (World Health Organization 2014).

Among the major consequences of chronic AUD that contribute to alcohol-related morbidity and mortality are liver cirrhosis, liver cancer, pancreatitis, and cardiovascular complications. To date, the epidemiological evidence connecting AUD and an increased incidence of chronic kidney disease is controversial. However, several preclinical studies suggest that alcohol consumption has a profound effect on the kidney and imply that there may be an independent pathologic entity, which we refer to here as "alcoholic kidney injury."

Studies conducted primarily in other organs and tissues suggest several possible mechanisms by which alcohol may promote kidney dysfunction. In particular, alcoholic kidney injury may be associated with a complex interaction of ethanol-induced oxidative stress and pro-inflammatory alterations. This may be complicated by the interplay between the kidneys and other organs, including the liver, intestines, skeletal muscle, and cardiovascular system. This brief synopsis reviews the evidence in support of these hypotheses.

Kidney Diseases and AUD: Lessons From Epidemiology

It is well established that cardiovascular diseases (including hypertension and ischemic heart disease) and diabetic microvascular complications are major risk factors for the development of chronic kidney diseases (Briasoulis et al. 2012; Carlsson et al. 2005; Reynolds et al. 2003; Ronksley et al. 2011). In turn, heavy alcohol consumption is implicated in the development of these cardiac diseases, with chronic, heavy drinkers at higher risk than those who consume small to moderate amounts of alcohol.

That said, epidemiological data have yet to confirm a relationship between alcohol consumption and chronic kidney disease. A recent meta-analysis (Cheungpasitporn et al. 2015) found little support for such a relationship. The researchers performed an extensive literature search using online databases (MEDLINE, EMBASE and Cochrane Databases) to identify studies investigating the association between high alcohol consumption and chronic kidney disease, end-stage renal disease, or proteinuria (i.e., excess protein in the urine that indicates kidney damage). Their analysis included 20 studies representing a total of 292,431 patients. The researchers reported that the pooled risk ratios of chronic kidney disease, proteinuria, and end-stage renal disease in patients with high alcohol consumption were 0.83, 0.85, and 1.00, respectively, indicating decreased risk or no risk of kidney disease in heavy alcohol consumers (Cheungpasitporn et al. 2015).

Other studies report similar findings, showing that the incidence of kidney disease is comparable or even lower in heavier drinkers (more than 210 g/week alcohol consumption) than in those who drink moderately (70–210 g/week alcohol consumption) (Buja et al. 2011; Knight et al. 2003; Koning et al. 2015; Reynolds et al. 2008; Sato et al. 2014; Yamagata et al. 2007). In contrast, some studies find that heavy alcohol consumption may predict poorer outcome in patients with chronic kidney diseases (Kronborg et al. 2008; Shankar et al. 2006; White et al. 2009). For example, White and colleagues (2009) reported that heavier drinkers (those consuming more than 30 g of alcohol/week) were at higher risk of incident albuminuria, which is typically a symptom of kidney disease. Japanese (Yamagata et al. 2007) and Italian (Buja et al. 2011) cohort studies revealed a U-shaped association between alcohol consumption and incidence of proteinuria. It is possible that the contradictory findings are the result of varying effects of different types of alcoholic beverages on the kidney, or the result of different alcohol consumption patterns in different countries. In addition, the self-reporting nature of drinking behaviors and the amount of alcohol consumed may bias some of the conclusions as shown, for example, by Parekh and Klag (2001), who found that people who drink heavily underreport their alcohol consumption.

Potential Mechanisms of Alcoholic Kidney Injury: Lessons From Experimental Studies

If alcohol consumption does in fact influence kidney disease, the question remains: How? There is direct and indirect evidence for several possible mechanisms. These changes are caused either by alcohol itself or by excessive amounts of the products formed when cells break down (or metabolize) alcohol, including acetaldehyde, NADH, and free radicals. These alcohol-related pathophysiologic changes in cells have been linked to damage in many organs and may play a role in kidney damage. In addition, complex interactions between organs may further complicate and accentuate the development of kidney pathology in people with AUD (see figure).

Oxidative Stress

Free radicals (also called reactive oxygen species [ROS]) are one of the by-products of alcohol metabolism and are known to cause cellular damage, unless the body can use antioxidants to clean them up. Oxidative stress occurs when the body cannot detoxify free radicals as fast as they are being produced, and it is pivotal in triggering alcohol-related tissue injury. Studies suggest that several mechanisms produce ROS in alcohol-damaged organs, including the liver (Cederbaum et al. 2009), heart (Tan et al. 2012; Varga et al. 2015), and kidney (Latchoumycandane et al. 2015). The mechanisms producing ROS in organs include nonenzymatic mechanisms such as mitochondrial electron transport chain malfunction (Gyamfi et al. 2012; Mantena et al. 2008) and enzymatic mechanisms that involve enzymes such as NADPH oxidases (Kono et al. 2000) and the enzyme CYP2E1 (Lu and Cederbaum 2008). CYP2E1 is of particular interest when thinking about potential mechanisms for alcohol-related kidney damage. The body mainly metabolizes alcohol using the enzyme alcohol dehydrogenase, which is expressed primarily in the liver. However, during chronic ethanol consumption, the body also uses CYP2E1 in the liver as well as the kidneys. Interestingly, studies find that CYP2E1 induction is much more robust in the kidneys compared with the liver (Roberts et al. 1994; Zerilli et al. 1995). This massive induction of CYP2E1 in the kidneys results in oxidative stress that modifies phospholipids in cell membranes. Such modified phospholipids may in turn activate immune cells called neutrophil granulocytes, which further aggravates oxidative stress, promoting a vicious cycle (Latchoumycandane et al. 2015).

Studies suggest that ethanol consumption may increase renal expression of other potential sources of free radicals involving a family of enzymes called nitric oxide synthases (Tirapelli et al. 2012). Nitric oxide synthase stimulates the production of nitric oxide, which, if produced excessively, can react with other molecules and create free radicals that trigger tissue damage in the kidneys (Pacher et al. 2007; Szalay et al. 2015). Tirapelli and colleagues (2012) showed that ethanol consumption increased the expression of two nitric oxide synthases. However, it is still unclear exactly how ethanol upregulates nitric oxide synthases, or whether it does so directly or indirectly. It may be that toxins released from the intestines into blood circulation because of ethanol's effects on the digestive system activate the expression of nitric oxide synthase. Another theory suggests that both enzymes may undergo the process of uncoupling due to oxidation or lack of critical coenzymes (e.g.,

tetrahydrobiopterin). Uncoupling eventually leads to generation of damaging ROS like superoxide anion, instead of the vasorelaxant nitric oxide that maintains normal blood flow in the kidney.

Alcohol-Metabolism Derived Intermediaries

Along with oxidative stress, increasing evidence suggests that some nonoxidative mechanisms also factor into alcohol-related organ damage. Specifically, ethanol metabolism produces fatty acid ethyl esters in various organs (Laposata and Lange 1986), which can cause ethanol-induced organ damage. Calabrese and Rizza (1999) found that ethanol induced a significant increase in the levels of fatty acid ethyl esters. They measured the highest levels in the heart, followed by kidney, brain, and liver.

Due to the metabolism of ethanol, significant amounts of acetate are produced and subsequently incorporated into acetyl-coenzyme-A, a molecule that participates in metabolism of proteins, lipids, and carbohydrates. This leads to the reprogramming of systemic metabolism. Protein acetylation—adding an acetyl group to a protein—is integral to regulating processes controlled by mitochondria, including fatty acid metabolism and antioxidant defense (Choudhary et al. 2014). Our current understanding is that the balance of lysine acetylation and deacetylation (the removal of an acetyl group) of key proteins (e.g., of the master regulator of mitochondrial biogenesis, PGC-1 alpha) serves, at least in part, to trigger a switch in metabolic status in conditions of overnutrition or undernutrition (Bai et al. 2015; Ghanta et al. 2013; Jeninga et al. 2010). A recent study demonstrated that ethanol induces mitochondrial protein hyperacetylation (excessive modification by acetylation of the lysine residues of a protein) in the kidney, which might interfere with the function of some mitochondrial proteins involved in alcohol metabolism or defense against oxidative stress (e.g., superoxide dismutase 2, aldehyde dehydrogenase 2, gluthatione peroxidase). This could also be a significant factor contributing to ethanol-induced mitochondrial dysfunction in the kidneys (Harris et al. 2015).

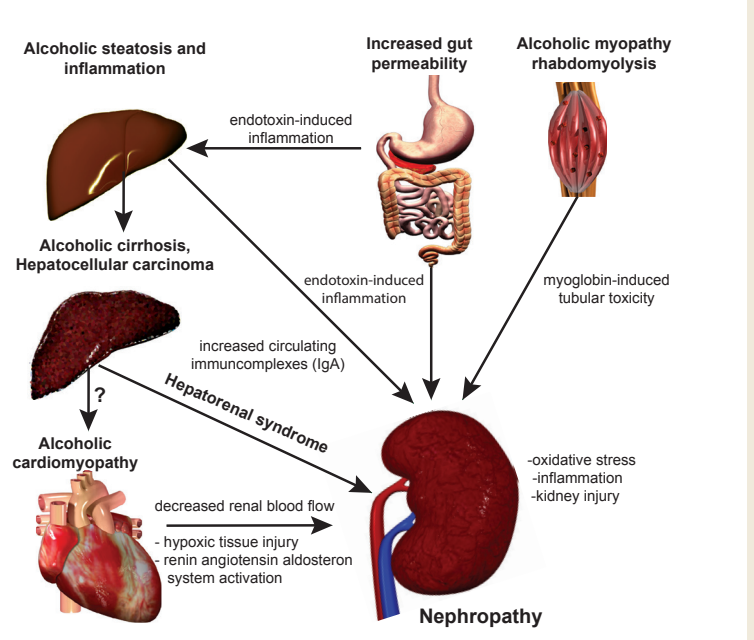

Figure Possible mechanism for alcohol-induced kidney injury. Chronic alcohol consumption induces profound injury in several organs that may affect and aggravate the deleterious effect of ethanol on the kidney. Ethanol itself markedly induces the expression of the microsomal ethanol oxidation system (CYP2E1), producing reactive oxygen species as a byproduct. Increased gastrointestinal permeability and endotoxin load may lead to alcoholic steatohepatitis resulting in excessive immunoglobulin A (IgA) load (due to increased intestinal production and decreased hepatic IgA clearance). IgA deposits may accumulate in the kidney, leading to glomerulopathy. Renal microcirculatory alterations in advanced liver cirrhosis leads to hepatorenal syndrome. Alcohol-induced skeletal muscle damage leads to excessive amounts of circulating myoglobin, causing renal tubular injury as a result of increased oxidative stress. Due to the development of alcoholic cardiomyopathy, chronic renal hypoxia develops, activating the renin–angiotensin–aldosterone system (RAAS), which in turn leads to further free radical production and to the propagation of fibrotic pathways.

Alcohol-Induced Intestinal Damage

Alcohol-induced intestinal damage and increased mucosal translocation of bacterial endotoxin are crucial in the initiation and progression of alcoholic liver injury and in the pathogenesis of other alcohol-related diseases (Bala et al. 2014; Purohit et al. 2008). (For an in-depth discussion of alcohol and the digestive tract, see the article by Keshavarzian in this issue.) The direct role of alcohol-related endotoxin release in alcoholic kidney injury has not yet been studied. However, it is possible that activation of the innate immune system due to endotoxins released by a leaky gut plays a central role in the development of renal

damage, as it does for liver damage (Zhang et al. 2008).

Substantial experimental and clinical evidence suggests that increased intestinal permeability and endotoxin release caused by excessive alcohol consumption leads to higher levels of circulating immunoglobulin A (IgA), an antibody critical to the immune response of mucous membranes. The kidney is particularly sensitive to an increased IgA load. In fact, IgA glomerulonephritis—acute inflammation of the kidney caused by an IgA immune response—is one of the most common types of primary glomerulonephritis worldwide (D'Amico 1987). This IgA-related kidney disease leads to clinical symptoms of renal injury and eventually progresses into renal failure (Amore et al. 1994; Bene et al. 1988; Pouria and Feehally 1999). Experimental studies suggest that heavy alcohol consumption induces IgA kidney disease (Smith et al. 1990). In addition, rats given intragastric infusions of a commercial whiskey (1.5 ml/100 gm body weight) 3 times a week along with a nutrient-deficient diet develop a more severe form of IgA nephropathy (Amore et al. 1994).

Evidence also exists that alcohol-related damage to the liver, in particular advanced liver cirrhosis, leads to hepatorenal syndrome (HRS)—a deterioration in renal function related to impaired circulation. The underlying mechanisms involved in the development and progression of HRS are incompletely understood, although it is plausible that the altered balance between vasoconstrictor and vasodilator factors plays a significant role (Lenz 2005).

Alcoholic Skeletal Myopathy: A Potential Indirect Mechanism

Severe AUD is frequently associated with various acute or chronic muscle symptoms, including difficulties with gait, muscle cramps, pain, and overall reduced muscle mass. In fact, biochemical lesions in the muscles and the resulting myopathy develop independently of any peripheral neuropathy, macro- and micronutrient malnutrition, and overt liver disease in people with AUD. In chronic alcoholic myopathy, a person's entire muscle mass may be reduced by up to one-third. It is the most common skeletal muscle disorder in the industrialized world, present at varying severity in approximately half of alcohol misusers (Preedy et al. 2001). To date, studies have not examined whether there is a direct link between acute alcoholic myopathy and kidney injury. However, several lines of research suggest there might be a connection.

Although the mechanism of alcoholic myopathy is not fully understood, it is likely that disruption of mitochondria-related energy homeostasis is important in promoting muscle cell (myocyte) injury (Eisner et al. 2014). In rare cases in malnourished chronic alcoholics, acute alcoholic myopathy, also termed acute alcoholic necrotizing myopathy or alcoholic rhabdomyolysis, also may occur, which may lead to reversible or irreversible acute kidney injury (Haller and Knochel 1984; Hewitt and Winter 1995; Muthukumar et al. 1999; Sofat et al. 1999).

A few studies have linked rhabdomyolysis and myoglobin toxicity with acute kidney injury, supporting a possible association among alcohol use, alcohol-related acute myopathy, and kidney damage. For example, Belliere and colleagues (2015) showed a link between rhabdomyolysis and excessive macrophage infiltration in the kidney, which in turn led to pro-inflammatory marker expression and consequent tissue injury (Belliere et al. 2015). Another study by Plotnikov and colleagues (2009) showed that mitochondria isolated from rat kidneys were damaged by oxidative stress when incubated with myoglobin. This finding suggests that rhabdomyolysis and myoglobin toxicity may trigger oxidative stress in the kidney via mitochondrial injury.

Alcoholic Cardiomyopathy: Another Potential Confounder

Several epidemiological studies have shown that mild alcohol consumption benefits cardiovascular health (Coate 1993; Kannel and Ellison 1996) by reducing the risk of coronary heart disease (Mukamal et al. 2006). In contrast, heavy drinking leads to the development of nonischemic dilated cardiomyopathy (Klatsky 2007) and significantly increases the risk of sudden cardiac death (Hookana et al. 2011).

Chronic or acute heart failure can lead to chronic or acute dysfunction in the kidneys, known as cardiorenal syndrome (Cleland et al. 2012). The complex renal pathophysiological response leads to fluid buildup in tissues, ischemic injury, peripheral vasoconstriction, and activation of the hormone system that helps regulate blood flow (called the renin–angiotensin–aldosterone system, or RAAS) (Palazzuoli and Ronco 2011). The overactivation of RAAS further aggravates oxidative stress in chronic alcoholism (Ungvari et al. 2004). As a consequence, oxidative stress not only propagates kidney failure, but it also contributes to the progression of chronic heart failure (Pacher et al. 2005) and leads to a vicious cycle in alcohol-induced cardiovascular complications.

Conclusions

As noted above, there is much to learn about alcoholic kidney disease and the complex interplay among multiple organs affected by alcohol consumption. Although research suggests several potential mechanisms by which alcohol may directly or indirectly affect the kidneys, they have not yet been validated experimentally. Future research will hopefully explore these hypotheses to provide a better understanding of alcoholic kidney injury. This article highlights the effects of other organs on kidney and renal function; however, it should be noted that alcoholic kidney injury itself may have negative metabolic consequences. One such

complication is impaired vitamin D metabolism (Shankar et al. 2008), which may influence the function of several other organs, creating a vicious cycle.

The treatment of alcoholic kidney injury is still largely symptomatic, despite accumulating knowledge about underlying mechanisms. Both preclinical and human studies highlight the central role of oxidative stress and inflammation in triggering and driving the pathological processes associated with alcoholic kidney injury. Early diagnosis of this condition and rigorous abstinence from alcohol are very important for slowing down the progression of the disease and allowing the kidneys to regenerate.

Acknowledgments

The authors are indebted to Dr. George Kunos, NIAAA Scientific Director, for his ongoing support and critical reading of the manuscript. Dr. Varga was supported by a grant from the Rosztoczy Foundation. Dr. Matyas was supported by a scholarship from the Hungarian-American Enterprise Scholarship Fund/Council on International Educational Exchange.

Financial Disclosure

The authors declare that they have no competing financial interests.

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Uniting Epidemiology and Experimental Disease Models for Alcohol-Related Pancreatic Disease

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Findings from epidemiologic studies and research with experimental animal models provide insights into alcohol-related disease pathogeneses. Epidemiologic data indicate that heavy drinking and smoking are associated with high rates of pancreatic disease. Less clear is the association between lower levels of drinking and pancreatitis. Intriguingly, a very low percentage of drinkers develop clinical pancreatitis. Experimental models demonstrate that alcohol administration alone does not initiate pancreatitis but does sensitize the pancreas to disease. Understanding the effects of alcohol use on the pancreas may prove beneficial in the prevention of both pancreatitis and pancreatic cancer.

Key words: Alcohol-related disease; alcohol-related pancreatic disease; pancreas; pancreatitis; pancreatic cancer; epidemiology; smoking; animal models; experimental disease models

Inflammation of the pancreas, or pancreatitis, can occur suddenly (i.e., acute pancreatitis) or after a long period of damage (i.e., chronic pancreatitis). Chronic pancreatitis is characterized by inflammation that does not improve, and becomes worse over time. Gallstones are a common cause of acute pancreatitis, which is usually resolved with adequate treatments in a few days. Heavy alcohol use over many years is the most common cause of chronic pancreatitis (Yadav and Lowenfels 2013), but cystic fibrosis, tobacco smoking, autoimmune conditions, high levels of calcium or fat in the blood, and certain medications can also cause chronic pancreatitis (National Institute on Diabetes and Digestive and Kidney Diseases 2016). Chronic pancreatitis can lead to diabetes and pancreatic cancer (Yadav and Lowenfels 2013). Since there are no current methods for treating pancreatitis or preventing recurrent episodes of nongallstone-related pancreatitis,understanding the risk factors for this condition is critical to prevention.

Following a review of the epidemiology of both acute and chronic pancreatitis, and pancreatic cancer and the influence of alcohol use and other risk factors, this article examines current experimental models that explore alcohol's role in pancreatic disease and the cellular mechanisms at work. It focuses on the currently accepted view of alcohol-related pancreatic disease, which holds that alcohol mediates the progression from acute to chronic disease through a number of mechanisms. Following recurrent acute attacks, alcohol may trigger changes leading to chronic pancreatitis and pancreatic cancer. This can happen through alterations in cell signaling pathways; the toxic effects of

alcohol's metabolites on pancreatic cells; oxidative stress; and by promoting activation of pancreatic stellate cells (PSCs), which play an important role in the development of scarring (i.e., fibrosis), inflammation, and tissue damage.

The Burden of Pancreatic Diseases

Acute pancreatitis is among the most common gastrointestinal causes of inpatient admission to U.S. hospitals. The annual incidence of acute pancreatitis ranges from 13 to 45 per 100,000 people, and chronic pancreatitis from 2 to 14 per 100,000 (Machicado et al. 2016; Yadav and Lowenfels 2013). The incidence of chronic pancreatitis in European countries varies from 1.8 cases per 100,000 people in the Netherlands (Spanier et al. 2013) to 13.4 cases per 100,000 in Finland (Jaakkola and Nordback 1993). A population-based U.S. study noted little change in the incidence of chronic pancreatitis between two time periods (from 3.3 in 1940–1969 to 4.0 per 100,000 in 1977–2006). In Japan, however, a progressive increase in incidence from 5.4 in 1994 to 11.9 in 2007 and 14.0 in 2014 has been noted (Machicado et al. 2016).

Prevalence estimates for chronic pancreatitis are limited to only a few countries (Machicado et al. 2016). Although these rates vary widely, from 13.5 per 100,000 in China to 126 per 100,000 in India, estimates show less variability in the United States, France, Spain, and Japan, ranging from 25 to 50 per 100,000. Similar to incidence, prevalence estimates from Japan increased from 28.5 per 100,000 people in 1994 to 52.4 per 100,000 people in 2014 (Machicado et al. 2016). A 10-year study of patients at 22 hospitals in China also found an increasing prevalence (from 3.08 cases per 100,000 people in 1996 to 13.52 per 100,000 in 2003) (Wang et al. 2009). Although acute pancreatitis affects men and women equally, chronic pancreatitis, especially alcohol-related cases, is more common among men (Yadav and Lowenfels 2013).

Pancreatic cancer accounts for about 3 percent of all cancers in the United States and about 7 percent of cancer deaths (American Cancer Society 2016). Worldwide, the annual incidence rate for pancreatic cancer is about 8 per 100,000 people (Yadav and Lowenfels 2013). Both pancreatitis and pancreatic cancer affect Blacks more than Caucasians, although the reasons for this racial disparity are unclear (Wilcox et al. 2016; Yadav and Lowenfels 2013).

Progression from Acute to Chronic Pancreatitis

The risk of progression from acute to chronic pancreatitis is higher among alcoholics and smokers, and higher in men than in women. A meta-analysis of 14 studies on this progression concluded that 10 percent of patients with a first episode of acute pancreatitis and 36 percent of patients with recurrent acute pancreatitis develop chronic pancreatitis (Sankaran et al. 2015). Other research found that, following an episode of alcohol-related acute pancreatitis, the risk of progression to chronic pancreatitis was approximately 14 percent with complete abstinence or only occasional drinking, 23 percent with decreased but daily drinking, and 41 percent with drinking at the same level as before the acute episode (Takeyama 2009).

Morphological Changes in the Pancreas from Acute to Chronic Pancreatitis

Nikkola and colleagues (2014) used imaging technology (secretin-stimulated magnetic resonance cholangiopancreatography) to examine the morphological changes induced by an initial episode of alcoholic pancreatitis. The researchers followed 44 patients after their first episode of alcohol-associated pancreatitis for up to 9 years. They found that whereas a single episode of acute pancreatitis could induce chronic changes, morphological progression (i.e., pancreatic cysts, parenchymal changes, and atrophy) was more frequent in patients with moderate or severe first attacks and in those who had recurrent attacks of pancreatitis.

Risk Factors for Alcohol-Related Pancreatic Disease

A meta-analysis of 51 international population-based studies concluded that heavy alcohol use was an important risk factor for pancreatic disease (Alsamarrai et al. 2014). Overall, the studies demonstrated an estimated 40 percent increased risk of pancreatic disease in heavy drinkers (i.e., those reporting more than 20 drinks per week). The prevalence of pancreatitis is approximately four times higher among people with a history of alcoholism (Yadav et al. 2007). Historically, an estimated 60 to 90 percent of chronic pancreatitis cases were attributed to alcohol use (Coté et al. 2011). However, more recent research suggests a lower prevalence of heavy drinking among chronic pancreatitis patients than previously estimated (Frulloni et al. 2009; Yadav et al. 2009). One recent study estimating the prevalence of alcohol-related pancreatitis used data from 539 patients and 695 unaffected study participants enrolled in a study of pancreatic disease at U.S. treatment centers (Coté et al. 2011). An estimated 44.5 percent of chronic pancreatitis cases were classified as alcohol related, based on physician assessment. The authors acknowledge that the lower-than-expected rate of alcohol-related disease may be due to the specialized nature of the treatment centers, the fact that alcohol users may be less likely to seek care, or because physicians who attribute a patient's disease to alcohol use would be less likely to refer them to a specialist's care. In Japan, a questionnaire to assess alcohol use among patients with alcoholic pancreatitis

found that women developed pancreatitis at a younger age, with shorter duration of alcohol use, and after smaller cumulative amounts of alcohol consumption compared with male patients (Masamune et al. 2013). In this study, continued drinking led to the recurrence of pancreatitis.

Some studies have suggested a threshold of alcohol use above which there is an increased risk for pancreatitis. Yadav and colleagues (2009) found the threshold to be 5 drinks per day for chronic pancreatitis. The relationship between lower levels of alcohol consumption and pancreas disorders is less well defined. In one recent meta-analysis of seven published studies, researchers noted a dose-dependent relationship between alcohol use and chronic pancreatitis in both sexes and for acute pancreatitis among men (Samokhvalov et al. 2015). Interestingly, a J-shaped relationship for the association with acute pancreatitis was noted among women, with a protective effect at less than 40 grams of ethanol per day (2 to 3 drinks) (Samokhvalov et al. 2015). Another recent study across a large diverse population not included in the meta-analysis observed a protective effect of moderate drinking on recurrent acute or chronic pancreatitis in men, and for all pancreatitis in women (Setiawan et al. 2016). Suggested explanations for this observation are a decreased risk of gallstone formation with moderate drinking, characteristics of the study population (older cohort), difficulty in assessing accurate exposure information, and possible contamination of the control group with former drinkers (Yadav 2016). Biological plausibility for how moderate drinking may have a protective effect is discussed later in this review. Data on the role of type and pattern of alcohol consumption and risk of pancreatitis are too limited to make definitive conclusions.

For pancreatic cancer, results from meta-analyses estimate a 20-percent increased risk from consuming 3 drinks per day (Maisonneuve and Lowenfels 2015; Tramacere et al. 2010). Another meta-analysis of individual participant data for more than 800,000 people found 22 percent increased risk of pancreatic cancer among people who consumed more than 3 drinks per day, although the association was only significant in women (Genkinger et al. 2009). A meta-analysis of alcohol's impact on risk for 23 types of cancer that included 572 studies found that heavy drinkers had a significantly higher risk of pancreatic cancer (relative risk of 1.19) compared with nondrinkers and occasional drinkers (Bagnardi et al. 2015).

Alcohol and Smoking Interactions

Cigarette smoking and heavy alcohol use, commonly co-occurring behaviors, increase risk for pancreatitis and pancreatic cancer (Yadav and Whitcomb 2010). A study of 108 smokers with alcohol-related chronic pancreatitis examined disease outcomes in relation to tobacco dose. The researchers concluded that smoking accelerates the course of pancreatic disease in a dose-dependent fashion, separate from the level of alcohol consumption (Rebours et al. 2012). A meta-analysis of 12 studies reported that while smoking increases the risk of chronic pancreatitis independently from alcohol, the effects of smoking are stronger for alcohol-related pancreatitis (Andriulli et al. 2010). In a recent study, Setiawan and colleagues (2016) found that smoking was significantly associated with nongallstone acute and chronic pancreatitis. The risk associated with current smoking was highest among men who consumed more than 4 drinks per day. For pancreatic cancer, among current smokers, heavy alcohol consumption was associated with a significantly increased pancreatic cancer risk. Risk was increased insignificantly among light and moderate drinkers who were smokers (Rahman et al. 2015).

Research comparing pancreatic duct-cell function in current and former smokers with never-smokers found that smoking was an independent predictor of cell dysfunction, after controlling for age, gender, and alcohol intake. The study also found no interaction between smoking status and alcohol consumption in predicting duct-cell dysfunction (Kadiyala et al. 2013).

Alcohol and Genetic Interactions

Although alcohol abuse and smoking are major environmental risk factors for pancreatic disease, only a small percentage of drinkers and smokers develop pancreatic disease (Yadav and Lowenfels 2013). This has led to a search for a role of genetic differences that could explain the susceptibility of some individuals to the effects of alcohol on the pancreas. Whitcomb and colleagues (2012) identified an association between genetic variants of Claudin-2 (*CLDN2*) and the risk of alcoholic pancreatitis. *CLDN2* is an X-linked gene involved in tight junction permeability and is expressed by pancreatic acinar cells. Alterations in the function of tight junctions in the pancreas or possibly in the intestinal epithelium could inappropriately expose the pancreas to toxins that could interact with the direct effects of alcohol in the pancreas. A recent study (Koziel et al. 2015) concluded that genetic mutations in SPINK1, a protein that inhibits activation of trypsinogens within the pancreas, may predispose individuals to severe acute pancreatitis, especially in patients that abuse alcohol.

As described in these epidemiologic studies (Yadav and Lowenfels 2013), pancreatic disease appears to be triggered by repeated acute attacks in combination with heavy alcohol use and other factors such as smoking and genetic factors.

Molecular Mechanisms of Alcohol-Related Acute and Chronic Pancreatitis

The general concepts that have been followed in developing animal models for alcohol research are based on observations originally described by Comfort and colleagues (1946). They found histological changes consistent with acute pancreatitis in patients with chronic pancreatitis. When followed longitudinally, these patients had greater amounts of necrosis indicative of acute pancreatitis early in the disease course and fibrosis in later stages, suggesting that chronic pancreatitis developed from repeated attacks of acute pancreatitis.

Studies using animal models of pancreatitis have supported the idea that alcohol-related exocrine pancreatic disease is induced by the combination of ethanol and other factors. For example, cholecystokinin (CCK) analogues cause pancreatitis in rodents in the absence of alcohol treatments only at doses much greater than those needed to activate known physiologic responses such as pancreatic enzyme secretion and gallbladder contraction (Lam et al. 2007). However, in ethanol-fed animals, CCK causes acute pancreatitis when given at more physiologic doses (Pandol et al. 1999). In other examples, ethanol feeding exacerbates pancreatitis due to hyperlipidemia and pancreatic-duct obstruction (Grauvogel et al. 2010). Ethanol-feeding models have also been used to show that alcohol impedes recovery from acute pancreatitis, resulting in promotion of chronic-pancreatitis features of chronic inflammation and fibrosis (Gukovsky et al. 2008).

Other animal models are based on previous observation of the increased susceptibility of people with compromised immunity (a common consequence of alcohol abuse) to viral pancreatitis. Using a mouse model, Jerrells and colleagues (2007) found that ethanol consumption alone does not produce pancreatic damage but causes viral pancreatitis to be more severe and prolonged. Similarly, others have shown that alcohol feeding and lipopolysaccharide (LPS) administration, to mimic the effects of alcohol on increased circulating LPS in humans, promotes pathologic features of chronic pancreatitis (Fortunato et al. 2006; Nakayama et al. 2014; Vonlaufen et al. 2007, 2011). Importantly, Vonlaufen and colleagues (2011) showed in the LPS-alcohol model that alcohol withdrawal causes regression of the features of chronic pancreatitis, indicating the importance of alcohol in promoting disease progression as originally described in humans (Comfort et al. 1946).

To emphasize, alcohol feeding alone had minimal pathologic effects in these models. Furthermore, the initiating agents for causing pancreatitis (i.e., CCK, LPS, duct obstruction, or viral infection) at the doses used in the corresponding models have minimal effects on pancreatitis responses in the absence of alcohol treatments.

Role of Pancreatic Acinar Cells and Ductal Cells

Research into the molecular mechanisms of alcohol-related pancreatitis has largely focused on the pancreatic acinar cell, the component of the pancreas devoted to synthesis, storage, and secretion of digestive enzymes. These studies suggest that alcohol does not directly damage acinar cells but may make cells susceptible to other factors that trigger cell damage. For example, in vitro and in vivo studies that focus on the effects of CCK on the transcription factor NF-κB, an intracellular signaling pathway involved in the inflammatory response of pancreatitis, show that alcohol treatments augment CCK-induced NF-κB activation (Pandol et al. 1999). Another study suggested that alcohol activates a specific isoform of the signaling molecule known as protein kinase C (i.e., protein kinase C epsilon, PKCε), which, in turn, is involved in NF-κB activation and the initiation of pancreatitis (Satoh et al. 2006). Further research using experimental models of acute pancreatitis examined the mechanisms through which PKCε regulates cell death. The researchers found that PKCε knockout mice (in which PKCε is genetically deleted) had decreased inflammation and necrosis and less severe acute pancreatitis in response to high doses of CCK analogues (Liu et al. 2014). In addition, alcohol has been found to promote secretion of digestive enzymes from the basolateral aspect of the acinar cell via mechanisms involving protein kinase C (Cosen-Binker 2007). Basolateral enzyme secretion would inject the digestive enzymes into the tissue of the pancreas where they can cause injury to the pancreas and pancreatitis.

More recently, studies have turned to determining effects of alcohol on the pancreatic duct cell, which is important for producing fluid secretion and carrying digestive enzymes secreted by the acinar cell into the gut lumen, where they are needed for meal digestion. These studies show that excessive alcohol drinking can cause inhibition of the function of the same transporter that is inhibited by mutation in cystic fibrosis (Maléth et al. 2015). These findings, and the fact that the acinar cells and duct cells must both perform their functions in a coordinated fashion to prevent disease (Hegyi et al. 2011), suggest that alcohol can promote pancreatitis via its actions on one or both of the key cellular components of the pancreas.

Role of Pancreatic Stellate Cells

Alcohol-related pancreatitis has been linked to the activation of pancreatic stellate cells (PaSC) (Apte et al. 1999, 2000; Vonlaufen et al. 2007, 2011). PaSC are normal resident cells in the exocrine pancreas. They are present in the periacinar space and have long cytoplasmic processes that surround the acinar structures and ducts of the exocrine pancreas (Omary et al. 2007).

In their normal state, often referred to as "quiescent," PaSC provide basement membrane and organization of the pancreatic epithelium. However, in pathologic states such as alcohol-induced pancreatitis, PaSC participate in disease pathogenesis after transforming into an "activated" state (also known as a "myofibroblastic" state) (Omary et al. 2007). These cells target an injured area and play a role in tissue repair (Apte et al. 1999). However, when they develop into a sustained activated state inappropriately, PaSC play a major role in alcohol-related pancreatitis. They mediate both the fibrosis and chronic inflammatory response of chronic alcoholic pancreatitis as well as pancreatic cancer (Apte et al. 2013). Regarding chronic pancreatitis, research suggests that this activation is mediated by alcohol, its toxic metabolite (i.e., acetaldehyde), or oxidative stress. Researchers have sought to identify the intracellular signaling pathways mediating PaSC responses. The goal of such research would be to develop strategies to target specific signaling molecules and interrupt PaSC activation, inhibiting abnormal fibrogenesis.

Recent studies suggest that the mitogen-activated protein kinase (MAPK) pathway, a major intracellular signaling pathway, plays a role in regulating the effects of alcohol and its metabolite acetaldehyde on PaSC (Apte et al. 2007). In addition, alcohol has been shown to activate the membrane-bound enzyme complex nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system, contributing to PaSC proliferation (Hu et al. 2007).

To address the epidemiologic observations of combined effects of alcohol and smoking, Lee and colleagues (2015) showed that cigarette smoking extract as well as nicotine and one of its major metabolites caused activation of PaSC. This activation was mediated via nicotinic acetylcholine receptors they found on the PaSC, and alcohol added to the effects of the smoking molecules.

The following sections summarize other potential co-factors that might trigger alcohol-related pancreatitis, including the participation of ethanol metabolites in alcohol-induced pancreas pathology.

Ethanol Metabolism in the Exocrine Pancreas

Metabolism of ethanol by the exocrine pancreas occurs by both oxidative and nonoxidative routes (Gukovskaya et al. 2002; Haber et al. 2004). The oxidative pathway is the predominant pathway for ethanol elimination in the body, occurring mostly in the liver. In the oxidative pathway, ethanol is converted to acetaldehyde by alcohol dehydrogenases (ADH), and then acetaldehyde is converted to acetate by mitochondrial aldehyde dehydrogenases (ALDH). Both enzymes are functional and present in the exocrine pancreas. The nonoxidative route of ethanol metabolism involves covalent coupling of ethanol with fatty acids to yield lipophilic fatty acid ethyl esters (FAEEs). This pathway provides the transient storage of ethanol while it awaits oxidative metabolism for removal from the body. The importance of the nonoxidative pathway comes from observations that humans dying from alcohol intoxication have high levels of FAEEs in the pancreas (Laposata and Lange 1986) and the finding that the FAEEs are formed using the enzyme carboxylester lipase, a highly expressed digestive enzyme made in the pancreas and secreted during lipid digestion (Huang et al. 2014).

There has been increasing evidence that the nonoxidative pathway plays an important role in alcohol pathogenesis in the acinar cell. For example, FAEEs were found to cause necrosis in pancreatic acinar cells by inducing sustained increases in free concentrations of Ca^{2+} in the cytoplasm from released intracellular stores, leading to toxicity of mitochondria and failure to produce ATP (Criddle et al. 2004, 2006). In addition, FAEE administration to experimental animals causes pancreas pathology (Lugea et al. 2003). Moreover, studies using pharmacologic and genetic inhibition of ADH caused pancreatitis responses in animal models, while pharmacologic inhibition of carboxylester lipase inhibited pancreatitis responses (Huang et al. 2014; Kaphalia et al. 2010).

Several genetic polymorphisms in the enzymes metabolizing ethanol have been described in humans in the last decade. A recent review by Aghdassi and colleagues (2015) summarizes these polymorphisms and their potential for conferring high susceptibility to alcohol-related pancreatic disorders. The most common polymorphism, an inactive ALDH2 gene, affects 40 to 50 percent of East Asians who exhibit high levels of acetaldehyde in blood after alcohol consumption, and higher susceptibility to acetaldehyde toxicity and certain forms of cancer (Chao et al. 2000; Yokoyama et al. 2010).

However, studies on the relevance of specific genetic polymorphisms of ethanol-metabolizing enzymes on pancreatic disorders have been limited, and the resulting data equivocal. Future studies will help to clarify whether these polymorphisms alone or in combination alter the susceptibility to alcohol-related chronic pancreatitis and pancreatic cancer.

Alcohol and the Cholinergic System

The neurotransmitter acetylcholine may play a role in alcohol-induced pancreatic damage. Lugea and colleagues (2010) found that atropine dramatically reduced cerulein-induced pancreatitis in alcohol-fed rats, indicating that alcohol-ensitizing effects are mediated at least in part through activation of cholinergic pathways. This effect is independent of the effects of smoking on nicotinic receptors present on the PaSC, described below.

Alcohol and Mitochondrial Dysfunction

Mitochondrial membrane permeabilization (MMP) triggers mitochondrial dysfunction and cell death and leads to tissue damage. The mitochondrial permeability transition pore (MPTP) plays a critical role in MMP. Research with pancreatic cells from mice found that oxidative metabolism of ethanol sensitizes mitochondria to activate MPTP, making them more sensitive to the toxicity by low concentrations of Ca^{2+} in the cell. This leads to mitochondrial failure and ATP depletion, making the pancreas susceptible to pancreatitis (Huang et al. 2014; Shalbueva et al. 2013).

Alcohol, Autophagy, and Lysosomes

Autophagy is a natural and regulated process for the cell to disassemble unnecessary or dysfunctional components. This disassembly allows for an orderly recycling of cellular components. The process of autophagy involves isolating targeted cellular constituents within a double-membrane vesicle known as the autophagosome. The autophagosome eventually fuses with the cell's lysosomes to form a compartment where lysosomal enzymes carry out the disassembly. Recent studies have shown the importance of normal autophagy and lysosomal function in the mechanism of pancreatitis (Gukovskaya et al. 2016). That is, animal models created with genetic inhibition of key autophagic mediators (i.e., autophagy protein 5, Atg5, or Atg7) or the glycoprotein required for lysosomal integrity (i.e., lysosomal-associated membrane protein-2, LAMP2) lack normal autophagic processing, resulting in inappropriate processing of digestive enzymes in the acinar cells and spontaneous pancreatitis. Further, in nonalcoholic models of pancreatitis, findings of disordered fusion and function of the lysosomal-autophagic system have been described (Gukovskaya et al. 2016).

Several studies have demonstrated the effects of alcohol on lysosomal and autophagy function. For example, Wilson and colleagues (Haber et al. 1993; Wilson et al. 1990, 1992) demonstrated that an alcohol diet or treatment of isolated lysosomes with FAEEs or cholesteryl esters caused lysosomal fragility and leakage of lysosomal enzymes into the acinar cell cytosol. Furthermore, more recent studies show that alcohol feeding and LPS treatment decrease the expression of LAMP2 in the pancreas of animals (Fortunato et al. 2009; Mareninova et al. 2015). In sum, these studies show that alcohol feeding, FAEE, and LPS cause lysosomal and autophagy dysfunction, which may result in pancreatitis responses.

Dietary Factors

Thiamine Deficiency. Thiamine (vitamin B1) is essential for pancreatic acinar-cell function. Cells obtain thiamine from their surroundings and enzymatically convert it into thiamine pyrophosphate (TPP), which is transported to mitochondria by the mitochondrial TPP transporter (MTPPT). Srinivasan and colleagues (2015) found that, in mice, chronic alcohol exposure significantly inhibited TPP uptake, which was associated with decreased expression of MTPPT protein and activity of the gene for MTPPT in pancreatic acinar cells. The authors suggest that this effect of alcohol could have a negative effect on physiologic function of the mitochondria in the acinar cell and make them susceptible to pathologic responses with stress.

Folate Deficiency. Dietary folate is critical for pancreatic health. A study in rats receiving a chronic alcohol diet found a significant decrease in folate uptake by isolated pancreatic cells compared with rats not receiving alcohol. The alcohol-fed rats also had decreased activity in both of the major folate uptake systems (i.e., reduced folate carrier and proton-coupled folate transporter) (Said et al. 2010).

Fiber. A population-based prospective analysis of dietary factors for pancreatitis in the United States found that the majority of dietary factors were mainly associated with the risk of gallstone-related pancreatitis, with the notable exception of dietary fiber (Setiawan et al. 2017). The investigators found dietary fiber to be inversely associated with both gallstone- and nongallstone-related acute pancreatitis but not suspected chronic pancreatitis. Fiber has been associated with changes in gut microbiota, improvements in gut epithelial tightness, and prevention of endotoxin transit into the system (Blaut 2015; Ghanim et al. 2009). Importantly, experimental animal models of pancreatitis show that endotoxin can promote the development and severity of pancreatitis (Fortunato et al. 2006; Vonlaufen et al. 2007). Insoluble fiber may also have a protective effect by reducing the development of gallstones (Tsai et al. 2004), a major cause of acute pancreatitis. Dietary fiber has also been associated with reduced pancreatic cancer risk (Wang et al. 2015).

Vitamin D. Vitamin D deficiency is associated with several disorders. However, epidemiological data linking vitamin D deficiency to an increased risk for alcoholic and nonalcoholic chronic pancreatitis or pancreatic cancer are scarce and inconsistent (Hoogenboom et al. 2016; Waterhouse et al. 2016).

In experimental settings, a recent study found that a vitamin D agonist decreases features of chronic pancreatitis, including fibrosis and inflammation (Sherman et al. 2014), supporting the participation of vitamin D signaling in the development of pancreas scarring. Further research should clarify the clinical relevance of the experimental data.

Alcohol-Induced Adaptive Systems and Pancreatitis

Despite the increased risk for pancreatic damage among heavy drinkers, the

incidence of clinical pancreatitis in heavy drinkers is low (~5 percent) (Yadav et al. 2007). One potential explanation for the low rate of pancreatitis among heavy drinkers is that alcohol induces adaptive systems that serve to protect the pancreas from the damaging effects of alcohol. This theory holds that disease progresses when the damaging effects are stronger than the protective effects, or when the protective systems are impaired. Thus, the combination of alcohol use and another risk factor could represent an overwhelming burden and therefore lead to disease progression.

Research using animal models has examined the role of a cellular stress response (i.e., the unfolded protein response, UPR) as an adaptive response to heavy alcohol use that may protect the pancreas from alcohol's damaging effects (Lugea et al. 2015; Pandol et al. 2011). The UPR is critical for efficient functioning of the endoplasmic reticulum (ER) in the pancreatic acinar cell, because the ER provides for the synthesis of cellular components necessary for transporting digestive enzymes manufactured in ER to zymogen granules for storage and for secretion.

Lugea and colleagues (2011) examined this protective effect in mice with and without the gene for the X-box binding protein 1 (XBP1), a transcription factor that promotes synthesis of cellular components for protein transport and secretion. XBP1 is a key regulator of the adaptive UPR in the pancreas. The researchers found that ethanol feeding in control mice causes a marked increase in the activated form of XBP1 associated with minor pancreatic damage. But in mice with an inability to increase activated XBP1, ethanol feeding results in pancreatic damage. This protective response stimulated by alcohol may be one reason why so few alcoholics develop pancreatic disease. The results of the experiments suggest that enhancing the protective responses may provide opportunities for prevention and treatment of pancreatic diseases.

Molecular Mechanisms of Alcohol-Related Pancreatic Cancer

Most genetically engineered mouse models of pancreatic cancer are based on genetic mutations in the *Kras* gene. Mice expressing mutant *Kras* develop early and advanced forms of the most common pancreatic cancers in humans. However, *Kras* mutations alone are not sufficient to induce progression to the invasive stage of pancreatic cancer. Rather, different transgenes have been used to create models that progress to invasive cancer. For example, one common model based on *Kras* mutations is the PDX1-Cre;LSL-$Kras^{G12D}$ model. Xu and colleagues (2015) reported using this model in mice exposed to alcohol and given injections of cerulein. The mice developed fibrosis and had an increased level of cancerous lesions. The authors concluded that alcohol independently increased pancreatic-cancer risk associated with fibrosis. Another animal model induces pancreatic cancer through the implantation of dimethylbenzanthracene (DMBA) in the pancreas. Research using this method in mice resulted in the development of both precursor lesions and invasive tumors. There was a higher relative frequency of tumors in mice receiving alcohol compared with the control group (Wendt et al. 2007).

The precise molecular mechanisms by which alcohol use may promote the development and/or progression of pancreatic cancer are not well defined. Although not evaluated in experimental models of pancreatic cancer, the oxidative ethanol metabolite acetaldehyde can act as a carcinogen by forming DNA adducts (Yu et al. 2010). In addition, alcohol might favor cancer development by causing oxidative stress and lipid peroxidation. Alcohol abuse may also accelerate tumor progression by promoting pancreatic inflammation. In this respect, studies using mouse models of pancreatic cancer demonstrated that recurrent pancreatic inflammation is required for the transformation of premalignant lesions into pancreatic cancer (Guerra et al. 2007), and epidemiologic studies indicate that chronic pancreatitis is a major risk factor for pancreatic cancer in humans (Duell et al. 2012). Finally, recent studies have shown that alcohol use may induce epigenetic changes, mainly histone acetylation and DNA methylation, which affect expression of many genes. However, the full involvement of epigenetic mechanisms in alcohol-related chronic pancreatitis or pancreatic cancer has yet to be investigated.

Conclusions

The combination of epidemiologic and experimental animal-model observations continues to reveal insights into both disease pathogenesis and potential adaptive protective mechanisms of alcohol use. The relationship between heavy alcohol consumption and acute and chronic pancreatitis is well established (Yadav 2016). The highest rates of nongallstone-related pancreatitis are observed in those who drink the greatest amount of alcohol. A recent epidemiological observation of a potential protective effect of moderate alcohol use should be considered preliminary, encourage further research to confirm and determine generalizability of these findings, and elucidate the potential mechanism. Further, smoking is associated with significant risk for nongallstone-related pancreatitis and may add to the risk of pancreatitis with heavy drinking. A very low percentage of drinkers develop pancreatitis. Experimental models demonstrate that alcohol administration alone may not initiate pancreatitis, but it sensitizes the pancreas to pancreatitis by other insults.

Work in these models also reveals that the pancreas adapts to alcohol administration using the endoplasmic reticulum-based UPR to prevent injury. There is increasing interest in the role of carboxyester lipase, a pancreatic digestive enzyme, in forming fatty acid ethyl esters, which exert toxic

effects through sustained increases in intracellular Ca^{2+} concentrations. These in turn cause mitochondrial failure and decreased ATP production necessary to prevent cellular necrosis. The effects of alcohol use on pancreatic-cancer risk are largely through its promotion of repeated episodes of acute inflammatory pancreatitis and chronic pancreatitis. Understanding and preventing the injurious effects of alcohol use on the pancreas resulting in pancreatitis will likely also have a large benefit on prevention of pancreatic cancer. The figure presents a summary of epidemiologic and mechanistic findings in an attempt to provide an impetus for further developments in the field.

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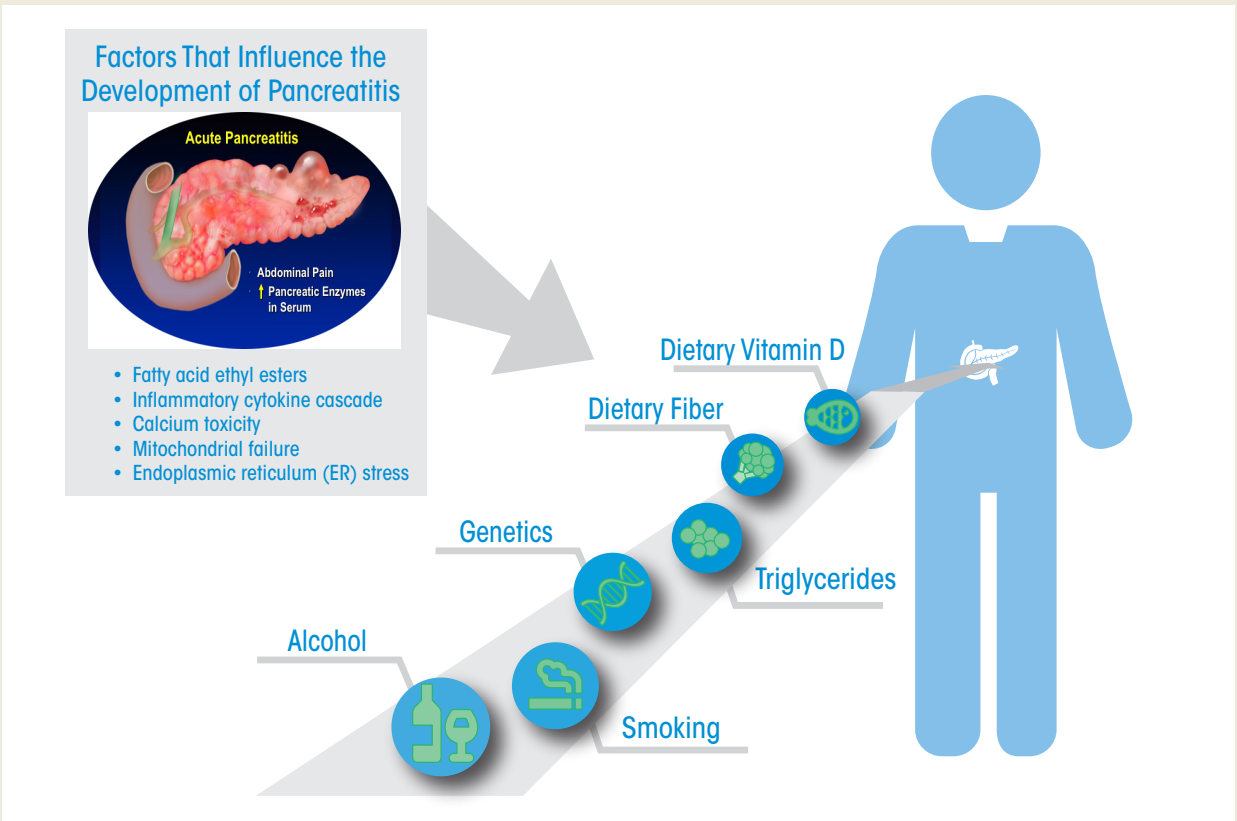

Figure The figure emphasizes the association of alcohol abuse, smoking, high triglycerides, and specific genetic mutations in promoting pancreatic disease. Dietary fiber and vitamin D are associated with protection from pancreatitis. The insert in the upper-left aspect of the figure shows the factors in the pancreatic tissue that are involved in the mechanisms of pancreatitis development.

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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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Alcohol Consumption in Demographic Subpopulations

An Epidemiologic Overview

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Alcohol consumption is common across subpopulations in the United States. However, the health burden associated with alcohol consumption varies across groups, including those defined by demographic characteristics such as age, race/ethnicity, and gender. Large national surveys, such as the National Epidemiologic Survey on Alcohol and Related Conditions and the National Survey on Drug Use and Health, found that young adults ages 18–25 were at particularly high risk of alcohol use disorder and unintentional injury caused by drinking. These surveys furthermore identified significant variability in alcohol consumption and its consequences among racial/ethnic groups. White respondents reported the highest prevalence of current alcohol consumption, whereas alcohol abuse and dependence were most prevalent among Native Americans. Native Americans and Blacks also were most vulnerable to alcohol-related health consequences. Even within ethnic groups, there was variability between and among different subpopulations. With respect to gender, men reported more alcohol consumption and binge drinking than women, especially in older cohorts. Men also were at greater risk of alcohol abuse and dependence, liver cirrhosis, homicide after alcohol consumption, and drinking and driving. Systematic identification and measurement of the variability across demographics will guide prevention and intervention efforts, as well as future research.

Key words: Alcohol consumption; alcohol abuse and dependence; alcohol use disorder; health consequences; burden of health; injury; demographics; epidemiology; age; race; ethnicity; gender; surveys; National Epidemiologic Survey on Alcohol and Related Conditions; National Survey on Drug Use and Health

Alcohol consumption is common across diverse populations in the United States; however, the level of consumption and its consequences vary considerably across major demographic subgroups. This review presents findings on the distribution and determinants of alcohol use and its aspects (i.e., age of onset, abstention vs. any drinking, binge drinking, and heavy drinking), alcohol abuse and dependence as defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM–IV) (American Psychiatric Association 1994),[1] and related health consequences. The health consequences considered include a selection of those often linked to alcohol consumption, such as unintentional and intentional injuries as well as liver disease (World Health Organization 2011). The article aims to summarize recent research and provide a comprehensive depiction of alcohol consumption and alcohol-related group differences across age, race/ethnicity, and gender. The growing emphasis on these group differences in alcohol epidemiologic research can expand our understanding of the etiology of alcohol use disorder (AUD), including the contribution of social contextual risk factors, and the receipt of prevention and treatment services.

The information presented in this article is based primarily on self-reported alcohol use as ascertained in two large surveys of the U.S. general population—

[1] *Alcohol Research: Current Reviews* generally uses the term alcohol use disorder (AUD) to denote the full range of disorders, from abuse to dependence, associated with heavy drinking, as specified in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (American Psychiatric Association 2013). Exceptions to this policy may be made when referring to studies using other diagnostic criteria. For more detail on the specific criteria used to diagnose the disorders mentioned in this article, readers should consult the original studies cited in the text.

the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) and the National Survey on Drug Use and Health (NSDUH). The NESARC, funded by the National Institute on Alcohol Abuse and Alcoholism, with supplemental funding from the National Institute on Drug Abuse, is a two-wave, longitudinal study of adults ages 18 and older that provides rich information on the epidemiology of alcohol and drug use disorders, psychiatric disorders, other health-related conditions and characteristics, and risk and protective factors (Grant et al. 2004). To ascertain these conditions, the survey used the interviewer-administered Alcohol Use Disorder and Associated Disabilities Interview Schedule—DSM–IV Version (AUDADIS–IV) (Grant 1997). Wave 1 was conducted in 2001–2002 and Wave 2 in 2004–2005. The NSDUH, funded by the Substance Abuse and Mental Health Services Administration (SAMHSA), is a national cross-sectional survey conducted annually of people ages 12 and older that is designed to track trends in substance use and other variables and collects data on substance use through self-administered computerized interviews (SAMHSA 2014).

The estimates presented throughout this article were derived across both waves of the NESARC as well as across several years of the NSDUH. Use of both of these datasets gives readers a comprehensive overview of findings from large-scale U.S. surveys on the epidemiology of alcohol consumption. In addition, the NESARC and NSDUH complement one another in several ways:

- Both surveys include adults age 18 and older. In addition, the NSDUH assesses alcohol and other drug use among adolescents (i.e., ages 12–17). Therefore, incorporating information from both surveys presents a picture of alcohol consumption across the life course.

- Test–retest reliability coefficients for AUDADIS–IV alcohol consumption and AUD diagnoses have been shown to be good to excellent (kappa ≥ 0.60) in a wide range of studies in the United States (Canino et al. 1999; Grant et al. 1995, 2003; Hasin et al. 1997) and elsewhere (Chatterji et al. 1997; Vrasti et al. 1998). AUDADIS–IV alcohol dependence also demonstrated fair to very good concordance with a clinician-administered interview (Cottler et al. 1997) and psychiatrist re-interviews (Canino et al. 1999).

Alcohol consumption from an early age can have long-term effects on the trajectory of drinking and health consequences across the life course.

The alcohol-dependence factor structure was significantly associated with external criterion variables (Grant et al. 2007), offering further support for the validity of the diagnosis. Less reliability and validity information is available on the NSDUH measure of AUD.

- The NSDUH data have been collected annually on a cross-section of the population, thus supplying a different type of information (i.e., yearly trends) that is not captured in the two waves of the NESARC.

- The two waves of interviews of the NESARC respondents 3 years apart constitute a longitudinal study following a large national cohort of people over time. This allows for causal inference, specifically regarding temporality, as well as for estimates of incidence, persistence, and offset when considering determinates of alcohol use and AUD. In contrast, discerning temporal ordering of variables is more difficult in cross-sectional designs, such as that of the NSDUH.

In addition to the NESARC and NSDUH, this article includes other recently published data from peer-reviewed journals to present the most current information and additional relevant research to supplement findings from these surveys.

Alcohol-Use Epidemiology

In the NESARC Wave 1 sample, approximately 65 percent of respondents reported any past-year consumption and 51 percent reported consuming at least 12 drinks in the past year (Dawson et al. 2004). Further, 17.8 percent and 4.7 percent, respectively, reported symptoms and criteria indicating a diagnosis of lifetime and past-year alcohol abuse, and 12.5 and 3.8 percent, respectively, reported symptoms and criteria indicating a diagnosis of lifetime and past-year alcohol dependence (Grant et al. 2004; Hasin et al. 2007). Similar results were obtained in secondary analyses with the 2002 NSDUH sample, the survey for which data are available that corresponds most closely to the NESARC Wave 1 sample. In the 2002 NSDUH, approximately 88 percent of respondents reported any alcohol consumption in their lifetime and around 70 percent reported past-year consumption (Grucza et al. 2007). Thus, the differences in estimates are slight.

The two-wave study design of the NESARC enabled researchers to make accurate estimates of the incidence and persistence of alcohol abuse and dependence over a 3-year period. Incident cases are those respondents who developed a disorder for the first time in their lives during the specified period (Grant et al. 2009). In the NESARC, 1-year incidence of alcohol abuse was 1.02 percent and 1-year

incidence of alcohol dependence was 1.70 percent (Grant et al. 2009). Persistent cases are respondents who met the criteria for a current disorder at Wave 1 and continued to meet these criteria throughout the 3-year period. An analysis of the persistence of alcohol dependence between Waves 1 and 2 of the NESARC indicated that the disorder persisted in 30.1 percent of respondents with alcohol dependence at baseline (Hasin et al. 2011).

The following sections examine alcohol use and its consequences in specific subgroups of the general U.S. population based on age, race/ethnicity, and gender.

Alcohol Use and Its Consequences in Different Age Groups

In data analyses by age, the NESARC and NSDUH samples frequently have been collapsed into different age groups. NESARC results commonly are presented in four age groups: 18–29 years, 30–44 years, 45–64 years, and 65 years and older. NSDUH results commonly are divided into five age groups: 12–17 years, 18–25 years, 26–35 years, 36–49 years, and 50 years and older. For clarity, the specific age groups analyzed are clearly identified below when presenting published findings.

More generally, the population can be subdivided into adolescents, young adults, middle-aged adults, and older adults; accurate information on drinking behaviors and related consequences is important for each of these groups. Among adolescents and young adults, alcohol consumption from an early age can have long-term effects on the trajectory of drinking and health consequences across the life course (Patrick et al. 2013); moreover, these two age groups represent the peak age of onset for AUD (Hasin et al. 2007). Middle-aged adults are important to study because many people whose AUD began in young adulthood "mature out" of such a disorder in this age group (Dawson et al. 2005, 2006; Lee et al. 2013; Watson and Sher 1998); further, the mean age of individuals with AUD is 42.2 years (Cohen et al. 2007). Finally, it is essential to examine alcohol use in older adults, because alcohol consumption in this age group can exacerbate many pre-existing vulnerabilities to physical and mental health problems (Sacco et al. 2009).

Abstention Versus Drinking and Binge Drinking

Despite the fact that alcohol sales to individuals under age 21 are illegal in the United States, many initiate drinking between the ages of 12 and 14, and the prevalence of alcohol use and binge alcohol use increases sharply as adolescents transition into early adulthood (i.e., ages 18–21) (Faden 2006). Consistent with previous studies (Grant 1997; Grant et al. 2001), early drinking initiation in NESARC participants predicted frequency of binge drinking between Waves 1 and 2 (Hingson and Zha 2009). In the NESARC Wave 2 sample, the risk for binge drinking in the 12 months before Wave 2 was approximately twice as high among respondents with drinking onset at age 16 or younger compared with respondents whose drinking began at age 21 or older (Hingson and Zha 2009). In fact, drinking onset across all adolescent age groups (i.e., age 14 or younger, age 15–16, age 17–18, and age 19–20) was associated with significantly higher odds of binge drinking compared with drinking onset at age 21 (i.e., the minimum legal drinking age) (Grant et al. 2001).

The prevalence of any alcohol consumption peaks among young adults. Thus, 73.1 percent of NESARC Wave 1 respondents ages 18–29 reported drinking in the past year. Further, 21.1 percent of young adults reported drinking heavily (5 or more drinks for men or 4 or more drinks for women) more than once a month, and 11 percent reported drinking heavily more than once a week (Dawson et al. 2004). Among young adults, those enrolled in college drink heavily more frequently than their nonstudent counterparts (Dawson et al. 2004).

After age 30, the incidence and prevalence of alcohol consumption generally decreases gradually with age, particularly after age 65 (Chan et al. 2007). In the 2002 NESARC, respondents ages 30–44 had a 25 percent lower prevalence of any past-year drinking compared with respondents ages 18–29. Respondents ages 45–64 and age 65 and older had a 50 percent and 68 percent, respectively, lower prevalence of any past-year drinking compared with the youngest group (Dawson et al. 2004). In the 2002 NSDUH, lifetime and past-year alcohol-use prevalence among adults age 65 and older was 78 percent and 50 percent, respectively (Moore et al. 2009). In the NESARC Wave 1 sample, the odds of past-year alcohol use were particularly low among respondents age 85 or older (odds ratio [OR] = 0.64) and ages 75–84 (OR = 0.64), compared with a reference group of 65- to 74-year-olds (Moore et al. 2009). More recently, in the 2007 NSDUH sample, 43 percent of adults age 65 and older reported past-year alcohol use (Blazer and Wu 2011). The mean number of drinks per drinking occasion also declines with age. Thus, adults ages 18–34 on average consume more than 2 drinks per drinking occasion, adults ages 35–64 between 1 and 2 drinks per occasion, and adults age 65 and older less than 1 drink per occasion (Chan et al. 2007).

DSM-IV–Defined Alcohol Dependence and Abuse

In the NESARC, prevalence of current and lifetime alcohol abuse and dependence generally decreased with age (Hasin et al. 2007). A similar pattern was evident for incident AUD (Grant et al. 2009). Age of drinking onset also was a predictor of alcohol dependence and abuse in both the NSDUH and NESARC. Among NSDUH respondents age 21 or older

at the time of the interview who had started drinking before age 14, about 15 percent reported an AUD after age 21. Among those who had begun to drink at ages 15–17, ages 18–20, or age 21 and older, in contrast, only 9 percent, 5 percent, and 2 percent, respectively, reported an AUD after age 21 (SAMHSA 2014). In the NESARC, respondents with drinking onset before age 16 had approximately twice the odds of developing alcohol dependence/abuse between Waves 1 and 2 compared with respondents whose drinking began at age 21 or later (Hingson and Zha 2009).

In addition, compared with the oldest age group (i.e., age 50 and older), the odds of incident alcohol abuse and dependence after controlling for NESARC Wave 1 demographic and clinical characteristics were significantly higher among people ages 20–29, with ORs of 11.6 for alcohol abuse and 8.7 for alcohol dependence. The risk also was higher among respondents ages 30–54 compared with people age 55 and older (OR = 4.3 for alcohol abuse and OR = 3.5 for alcohol dependence) (Grant et al. 2009). Overall, in the NESARC, 1.2 percent of women and 4.8 percent of men age 50 and older were classified as having either current alcohol dependence or current alcohol abuse (Balsa et al. 2008). Similarly, in the 2005–2007 NSDUH, 1.9 percent and 2.3 percent of adults ages 50–64 endorsed dependence and abuse, respectively, as did 0.6 percent and 0.9 percent, respectively, of adults ages 65 and older (Blazer and Wu 2011).

People in older age groups not only have lower prevalence of alcohol abuse or dependence but also have fewer alcohol-related role-function problems (e.g., problems at work or school). Thus, in the NSDUH, adults ages 26–34 had higher odds of such problems compared with adults ages 65 and older, followed by young adults ages 18–25 and adults ages 35–49, respectively (Alameida et al. 2010).

The finding that younger cohorts were at a higher risk of AUD in both surveys could indicate a true age effect or could be the result of underrepresentation among older cohorts as a result of differential mortality or poor recall of remote events. Birth cohort effects, or historical effects, also may contribute to the observed findings, but prospective population-based investigation is required to adequately address this issue.

Alcohol-Related Health Consequences

The health burden associated with alcohol use stretches across the lifespan, beginning in utero, with prenatal alcohol exposure resulting in a variety of adverse birth effects, including fetal alcohol syndrome as the most severe consequence (Warren et al. 2011). Over the life course, alcohol use contributes to a variety of health conditions and risk behaviors. Among adolescents, heavy alcohol use is correlated with other risky health behaviors, including tobacco use, violence, suicide, and driving under the influence (Windle 2003). In the NESARC Wave 1 sample, young adults ages 20–29 were most likely to engage in risk behavior after drinking (age 20–24 versus 50 or older, OR = 6.5; age 25–29 versus 50 or older, OR = 4.2) compared with older adults (age 50 or older). The oldest age group (age 50 or older) in the sample was the least likely to drive under the influence of alcohol (Hingson and Zha 2009). Overall, the proportion of alcohol-related deaths was highest among young adults ages 18–24 and decreased with age (Rehm et al. 2014).

Alcohol Use and Its Consequences in Different Racial/Ethnic Groups

In analyses of NESARC data, alcohol consumption and AUD most commonly have been investigated in five U.S. Census–defined racial/ethnic groups: Whites, Blacks, Native Americans, Asians, and Hispanics. The NSDUH uses the same racial/ethnic categories, with the addition of respondents reporting two or more races, because over time, individuals are increasingly endorsing more than one race, indicating a growing population of people identifying as biracial or multiracial (Hirschman et al. 2000; Jones and Bullock 2012).

Abstention Versus Drinking and Binge Drinking

In the 2007 NSDUH, current (i.e., past 30 days) alcohol consumption was most prevalent among Whites (59.8 percent) and least prevalent among Asian Americans (38.0 percent). Native Americans/Alaskan Natives (47.8 percent), Hispanics (46.3 percent), and Blacks (43.8 percent) reported similar prevalence of any alcohol consumption (Chartier and Caetano 2010). In the NESARC Wave 1, the prevalence of current alcohol consumption was highest among Whites (63.5 percent), followed by Hispanics (60.3 percent) and Blacks (52.5 percent) (Caetano et al. 2010). However, the prevalence of weekly drinking (i.e., once per week or more) was higher among Hispanics (14.1 percent) than among Whites (13.6 percent) and Blacks (11.4 percent) in the same sample (Caetano et al. 2010).

An analysis of Asian-American adults from the NESARC Wave 2 sample showed that Asians reported the least amount of drinking compared with other groups. However, heterogeneity in alcohol consumption existed within this group, with Korean, Japanese, Taiwanese, and Chinese subpopulations reporting the highest per-capita annual alcohol consumption and Vietnamese, Malaysian, Indian/Afghan/Pakistani, and Indonesian groups reporting the lowest consumption (Cook et al. 2012). The level of acculturation, measured by the use of the subject's native Asian language, also influenced patterns of alcohol consumption. Among Asian Americans from countries of origin with low per-capita annual alcohol consumption, the probability of being a current

drinker was highest among those who reported low use of Asian languages. Among Asian Americans from countries of origin with higher per-capita annual alcohol consumption, the probability of being a current drinker was similar regardless of Asian-language use (Cook et al. 2012).

Hispanic subgroups also display heterogeneity in alcohol consumption. In the 2003–2005 NSDUH, the prevalence of current alcohol use was highest among Cubans, followed by Puerto Ricans, Mexicans, and people of Central/South American descent (Lipsky and Caetano 2009). These patterns differed for binge and heavy drinking, which had the highest prevalence among Puerto Ricans, followed by Mexicans, Cubans, and Central/South Americans. Varying degrees of acculturation may help to explain these subgroup differences among Hispanics; however, the impact of acculturation on drinking also may vary by gender and age (Lipsky and Caetano 2009).

Racial/ethnic differences also exist with respect to binge drinking and heavy drinking during pregnancy. Pregnant White women reported more binge drinking during pregnancy than other racial/ethnic groups (Caetano et al. 2006). However, another study using the Pregnancy Risk Assessment Monitoring System (2001–2005) found that among those who binge drank in the last month, Black, Hispanic, and Asian women were less likely to reduce heavy drinking during pregnancy compared with White women (Tenkku et al. 2009). More research on alcohol consumption patterns among pregnant women by ethnic group is needed to better elucidate racial disparities in the risk for fetal alcohol syndrome (Tenkku et al. 2009).

DSM-IV–Defined Alcohol Dependence and Abuse

Both alcohol abuse and alcohol dependence are most prevalent among Native Americans and least prevalent among Blacks and Asians. For example, among Native Americans in the NESARC Wave 1 sample, 5.8 percent met criteria for past-year alcohol abuse and 6.4 percent met criteria for past-year alcohol dependence, whereas among Asians, 2.1 percent met criteria for past-year alcohol abuse and 2.4 percent met criteria for past-year alcohol dependence (Hasin et al. 2007). Among Blacks, the prevalence for past-year alcohol abuse and dependence was 3.3 percent and 3.6 percent, respectively, and among Hispanics it was 4.0 percent for both past-year abuse and dependence (Hasin et al. 2007). Among drinkers, Blacks and Hispanics reported more symptoms of past-year alcohol dependence than did Whites (Mulia et al. 2009).

One-year incident rates of alcohol abuse and dependence in the NESARC Wave 2 sample varied little by race (Grant et al. 2009). However, this analysis did not include Native Americans or Asians because of small sample sizes. The only significant difference by race was that Blacks had significantly lower odds than Whites to report incident alcohol abuse (OR = 0.6) at Wave 2 of the NESARC, controlling for Wave 1 demographic characteristics and psychiatric disorders. No significant differences existed between Hispanics and Whites (OR = 0.8) (Grant et al. 2009).

A more recent analysis of Asians within the NESARC Wave 1 sample demonstrated some variations in the lifetime prevalence of AUD among Asian-American ethnic subgroups. For example, 5.4 percent of East Asians (i.e., whose countries of origin were the People's Republic of China, Japan, Korea, or the Republic of China [Taiwan]), 4.3 percent of Southeast Asians (i.e., whose countries of origin were Indonesia, Malaysia, Vietnam, Thailand, Laos, Cambodia, Myanmar, or a Pacific Island nation), and 3.6 percent of South Asians (i.e., whose countries of origin were India, Afghanistan, Pakistan, or Iran) met criteria for a DSM–IV AUD (Lee et al. 2015).

Among Hispanic subgroups, the prevalence of alcohol abuse and dependence was highest in Mexicans, followed by Puerto Ricans, and was lowest among Cubans (Lipsky and Caetano 2009). Some Hispanic subgroups exhibited a protective effect of foreign-born nativity on risk for alcohol abuse or dependence. For example, in NESARC Wave 1, 4.8 percent of foreign-born Cuban Americans reported a lifetime DSM–IV AUD, compared with 28.1 percent of U.S.-born Cuban Americans. A similar, albeit less extreme, pattern was found among Puerto Ricans, with 14.5 percent of island-born Puerto Ricans but 21.4 percent of U.S.-born Puerto Ricans reporting a lifetime AUD (Alegria et al. 2006).

Alcohol-Related Health Consequences

The burden of alcohol consumption and AUD on physical health varies by racial/ethnic group. Hispanic White males have higher age-adjusted death rates from liver cirrhosis than non-Hispanic White males, Hispanic Black males, non-Hispanic Black males, and females (i.e., Hispanic White females, non-Hispanic White females, Hispanic Black females, and non-Hispanic Black females) (Yoon and Yi 2012). Within the Hispanic subgroup, Puerto Ricans and Mexicans have the highest mortality rates attributable to liver cirrhosis. Conversely, Asians had the lowest death rates attributable to alcoholic liver disease of all racial/ethnic groups (Hoyert and Xu 2012).

Genetic factors may contribute to racial/ethnic differences in alcohol-related health consequences. For example, in Asian populations, including Asian Americans (Cook et al. 2005; Duranceaux et al. 2008), the prevalence of certain genetic variants encoding the alcohol-metabolizing enzymes alcohol dehydrogenase (ADH) and acetaldehyde dehydrogenase 2 (ALDH2) is higher than in other U.S. racial/ethnic groups. One genetic variant encoding an inactive

ALDH2 enzyme that is found primarily in Asian populations is associated with an elevated risk of cancer and digestive disease from alcohol consumption (Oze et al. 2011). This association may apply to Asian Americans as well, a topic warranting further research.

The prevalence of accidents and injuries associated with alcohol consumption, especially with heavy drinking and AUD, also often varies across racial/ethnic groups. For example, the National Violent Death Reporting System provides toxicological information on suicide victims based on coroner/medical examiner reports, death certificates, and toxicological laboratory findings. Analyses of these data have shown that fewer non-Hispanic Blacks (25.6 percent) had positive blood alcohol concentrations at the time of suicide compared with Hispanics (40.3 percent) and non-Hispanic Whites (34.3 percent) (Karch et al. 2006).

Alcohol consumption also is associated with violent crimes. In one study, the offender was under the influence of alcohol in 42 percent of violent crimes studied. However, this percentage differed substantially among racial/ethnic groups and was greatest among Native Americans (62 percent), followed by Whites (43 percent), Blacks (35 percent), and Asians (33 percent) (Chartier et al. 2013). Furthermore, although Blacks in the United States have lower prevalence of alcohol consumption, binge drinking, and AUD compared with non-Hispanic Whites, they still had higher prevalence of alcohol-related homicide (Stahre and Simon 2010). Likewise, Blacks reported drinking during an episode of interpersonal violence more often (i.e., in 41.4 percent of cases) compared with Whites (29.4 percent) and Hispanics (29.1 percent) (Chartier et al. 2013).

Racial/ethnic differences also exist in the prevalence of alcohol use in traffic crashes. According to the National Highway Traffic Safety Administration, the prevalence of intoxication among drivers who are fatally injured in car crashes is highest among Native Americans and Hispanics, followed by Whites, Blacks, and Asians (Chartier et al. 2013). Moreover, Native Americans (4.1 percent) and Whites (3.3 percent) report drinking and driving significantly more often than do Asians (1.4 percent), Hispanics (2.1 percent), and Blacks (1.5 percent) (Chou et al. 2006). However, significant heterogeneity regarding alcohol use and traffic crashes exists within Asians subgroups, with Pacific Islanders and Native Hawaiians reporting prevalence of alcohol-related motor vehicle crashes similar to that of Hispanics (Chartier et al. 2013).

In summary, ethnic minorities make up more than one-fifth of the U.S. population (U.S. Census Bureau 2013). Their risk for drinking, AUD, and other alcohol-related consequences differs markedly. Studies consistently find that Native Americans are at particularly high risk for alcohol-related health consequences. However, despite these negative consequences for Native Americans, their impact on alcohol-related health consequences in the U.S. population overall is less pronounced because Native Americans are a relatively small racial group compared with others. Future research is needed on various ethnic and racial groups to better inform the allocation of prevention and intervention efforts.

Gender-Differences in Alcohol Use and Its Consequences

Abstention Versus Drinking and Binge Drinking

Among NESARC Wave I participants, 40 percent of women were abstinent in the past year, compared with 32 percent of men. In addition, men reported more drinks per drinking occasion than women (Chan et al. 2007). Likewise, in the 2011 NSDUH, 57.4 percent of men were past-month drinkers compared with only 46.5 percent of women (Wilsnack et al. 2013). Although epidemiologic findings consistently support that men are at increased risk for alcohol consumption, current drinking, and heavy drinking compared with women, this gap is closing in younger cohorts (Keyes et al. 2008, 2010; SAMHSA 2014). As Western social norms continue to shift away from "traditional" gender roles that see women only as homemakers and mothers, women report greater lifetime largest number of drinks consumed in one sitting and greater frequency of binge drinking than they did in earlier surveys, leading to a closing of the gender gap not only in consumption but also in alcohol-related consequences (Keyes et al. 2008, 2010).

Of particular concern regarding drinking among women is alcohol consumption during pregnancy. Any alcohol drinking during pregnancy can be unsafe (Vall et al. 2015). In particular, binge drinking and heavy drinking during pregnancy are harmful to the fetus and have been related to increased risk for fetal alcohol syndrome (Caetano et al. 2006; Vall et al. 2015). In the NESARC Wave 1 sample, about one-third of pregnant women reported drinking during the last year (Caetano et al. 2006). In the combined NSDUH data from 2012 and 2013, the percentage of pregnant women who reported binge drinking and heavy drinking was 2.3 percent and 0.4 percent, respectively (SAMHSA 2014).

DSM-IV–Defined Alcohol Dependence and Abuse

In the NESARC Wave 1, the prevalence of current (i.e., in the last 12 months) alcohol abuse and alcohol dependence was 6.9 percent and 5.4 percent, respectively, among men and 2.6 percent and 2.3 percent, respectively, among women (Hasin et al. 2007). Also, between NESARC Wave 1 and Wave 2, men had significantly higher odds than women to develop incidents of alcohol abuse (OR = 2.3) and dependence (OR = 2.4), controlling for Wave 1 demographic characteristics

and psychiatric disorders (Grant et al. 2009).

Clinicians often consider AUD among women as "telescoped," with a later onset of alcohol use but shorter times from initiation to dependence and treatment (Keyes et al. 2008). However, in a recent analysis, Keyes and colleagues (2008) found little evidence for a telescoping effect among women in the general population. Further, sex differences in the prevalence of AUD seem to have decreased over time. As a result, younger women may require more targeted prevention and intervention efforts (Keyes et al. 2008, 2011). Current (Brown et al. 2012) and lifetime (Cavanaugh and Latimer 2010) alcohol abuse or dependence were prevalent among pregnant women (Vesga-Lopez et al. 2008), emphasizing the need for targeted interventions among this population (Mitchell et al. 2008). Women who had been pregnant in the past year also were 1.7 times more likely than non-pregnant women to seek treatment for alcohol abuse or dependence in the previous year (Vesga-Lopez et al. 2008).

Alcohol-Related Health Consequences

Mortality associated with AUD is higher among men than among women (Rehm et al. 2014). For example, with the exception of Native Americans, mortality rates from alcoholic liver disease were at least twice as high among men compared with women (Hoyert and Xu 2012). Gender differences also existed with respect to alcohol-related morbidity. Thus, although alcohol overall contributed to 32 percent of liver cirrhosis cases, the rates differed significantly between men (39 percent of cases) and women (18 percent of cases) (Room et al. 2005).

With regard to alcohol-related accidents and injuries, males were more likely than females to drive after drinking too much in most age and racial/ethnic groups (Chou et al. 2006). Alcohol also contributed to 7 percent of falls, 10 percent of drowning incidents, and 18 percent of poisonings each year, mostly among men, as well as to a greater proportion of self-inflicted injuries among males (15 percent) than among females (5 percent) (Room et al. 2005). Moreover, male gender was a significant risk factor for alcohol-related suicide in all racial/ethnic groups except Native Americans, where alcohol was involved in similar proportions of male and female suicides (Chartier et al. 2013). Overall, the groups reporting the highest rates of alcohol use among suicide victims were Native Americans ages 30–39, Native Americans and Hispanics ages 20–29, and Asians ages 10–19 (Chartier et al. 2013). Finally, alcohol contributed to 24 percent of homicides, with the proportion of alcohol-related homicides higher among males (26 percent) than among females (16 percent) (Room et al. 2005).

Methodological Issues

Despite the usefulness of using data from two nationally representative surveys to obtain an accurate picture of alcohol use and its consequences in the U.S. population, methodological differences between the two surveys may have contributed to some differences in population estimates (Grucza et al. 2007). For example, the private, self-administered questions in the NSDUH may have elicited some higher prevalence estimates of use than the face-to-face interviews used in the NESARC. However, the NESARC indicates a higher prevalence of AUD, perhaps resulting from the greater number of items that allowed for more in-depth probing of DSM–IV abuse and dependence criteria. Other factors, including response rates, questionnaire structures, and question text also could contribute to different estimates. Although any of these factors may have contributed to differences between the two surveys (Grucza et al. 2007), the largely common findings across the surveys attest to the robustness of the findings to methodological variation.

Conclusions

In the United States, AUD accounts for a high and potentially preventable proportion of overall disability and mortality. However, the burden of disease related to alcohol use and its consequences differs significantly between population subgroups. The myriad of genetic, social, and environmental risk factors for AUD and their impact in various subpopulations remain to be elucidated. Future epidemiologic studies will include information necessary to prevent and treat alcohol and drug use disorders by identifying factors that increase the risk of these disorders and their persistence in the general population as well as in specific subgroups.

Population-level surveys, such as the NSDUH and the NESARC, are valuable tools to describe the epidemiology of alcohol consumption and AUD in the United States. Although varying methodology may limit comparability and interpretation of estimates between these epidemiologic studies, both surveys were conducted in nationally representative samples with methodological rigor. Consequently, both surveys present a valid depiction of alcohol consumption and related disorders and can offer important information needed to develop evidence-based measures to prevent the onset of AUD and comorbidity, as well as to identify factors that increase the risk of alcohol problems.

A better understanding of the age, race/ethnicity, and gender-based differences in the various alcohol variables discussed in this review would be gained by considering the social, political, and economic context of alcohol use in various populations. These factors are discussed further in other articles in this issue.

Acknowledgments

This research was supported by grants from the National Institutes of Health (U01–AA–018111, to Hasin;

T32–DA–031099, to Brown [PI] and Hasin), and the New York State Psychiatric Institute (to Hasin).

Financial Disclosure

The authors declare that they have no competing financial interests.

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Measuring the Burden—Current and Future Research Trends

Results From the NIAAA Expert Panel on Alcohol and Chronic Disease Epidemiology

Rosalind A. Breslow, Ph.D., M.P.H., R.D., and Kenneth J. Mukamal, M.D.

Alcohol has a significant impact on health and well-being, from the beneficial aspects of moderate drinking to the detrimental effects of alcoholism. The broad implications of alcohol use on public health have been addressed through a wide range of epidemiological and clinical studies, many of which are described in this issue of *Alcohol Research: Current Reviews.* Where chronic disease is involved, alcohol use can be a risk factor that not only affects the onset of various chronic diseases but also exacerbates the ongoing extent and severity of those diseases. Lifestyle choices and genetic influences also contribute to, or help to alleviate, that risk. **KEY WORDS: NIAAA Expert Panel on Alcohol and Chronic Disease Epidemiology; alcohol consumption; alcohol burden; chronic disease; risk factors; epidemiology; research; diabetes; cardiovascular disease; cancer; stroke; liver disease; genetic factors; eating behaviors; clinical trials**

Research is continuing to investigate how alcohol impacts chronic disease. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) hosted a 2-day Expert Panel on Alcohol and Chronic Disease Epidemiology in August 2011 to review the state of the field on alcohol and chronic disease. The panel was chaired by Kenneth J. Mukamal, M.D., and Rosalind A. Breslow, Ph.D., M.P.H., R.D., and was convened by NIAAA's Division of Epidemiology and Prevention Research.

Panel members (see textbox) represented a wide range of backgrounds and expertise, ranging from alcohol-related chronic diseases and risk factors to methods and technology. Among the chronic diseases addressed were diabetes, cardiovascular disease, cancer, stroke, and liver disease. The broader aspects of the design and implementation of clinical trials and the implication of technological advances for research also were considered. Other topics included the links between genetics and other lifestyle factors, such as eating behavior, and the relationship between drinking and various chronic diseases. Taken together, these summaries provide unique insight into the current state of research on alcohol's role in chronic disease and the direction these investigations may take in the future. (For more information on the epidemiological challenges of elucidating the effects of alcohol consumption and drinking as they relate to the initiation/ exacerbation and treatment of chronic diseases, see the article by Shield and colleagues [pp. 155–173]). Panel members also were asked what research they would most strongly support if funds were unlimited and how they might scale back that research if funding were limited (see Future Ideas textbox). Highlights from this panel are presented below and specific recommendations are listed in the accompanying sidebar.

Clinical Trials

Clinical studies include clinical nutrition studies, controlled feeding studies, and metabolic studies. This type of research has numerous strengths for studying alcohol and chronic disease, including the ability to control alcohol dose and diet, collect abundant biologic samples from a variety of tissues, assess cause and effect, and examine mechanisms—all with a relatively small number of participants enrolled for a short period of time.

Clinical study end points typically are surrogate markers for chronic diseases because the disease itself may take years or even decades to develop. For example, lipoproteins and markers of inflammation have been used as surrogates for cardiovascular disease, insulin sensitivity for diabetes, and DNA damage for cancer.

According to Dr. David J. Baer, considerable need for controlled clinical studies on alcohol and chronic disease still exists. There have been few clinical studies, even on cardiovascular disease (Brien et al. 2011), which is the focus of most alcohol-related chronic disease research. He also noted the relatively few controlled clinical studies of alcohol and obesity (Sayon-Orea et al. 2011) that were advocated by the

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Report of the Dietary Guidelines Advisory Committee on the Dietary Guidelines for Americans (U.S. Department of Agriculture 2010).

Dr. Baer suggested the following future opportunities for alcohol and chronic disease research:

- Drinking patterns;
- Effects on metabolism and disease risk;
- Non-ethanol components of alcoholic beverages;
- Possible effects on cardiovascular disease, diabetes (insulin sensitivity), cancer, and bone metabolism;
- Gender and age differences (pre- and postmenopausal women, men);
- Genetic basis for response of chronic disease surrogate markers to alcohol;
- Energy metabolism, body weight regulation, and insulin sensitivity;
- Interaction of alcohol with lower-fat or higher-protein diets; and
- Bone metabolism.

Cardiovascular Disease

Studies on alcohol and cardiovascular disease have yielded important findings with regard to public health. For example, we now know that the association of alcohol use within recommended limits with lower risk of heart disease depends more on the frequency with which alcohol is consumed and not on the type (Cleophas 1999). Wine, beer, and spirits all have been associated with reduced risk of myocardial infarction. Modest differences in the effects of those different types of alcohol are thought to be more a result of lifestyle differences among drinkers rather than a direct link to a specific type of alcohol. How often people drink alcohol has a larger impact on cardiovascular disease. Among men, drinking more frequently seems to have a greater impact than the actual amount consumed (Mukamal et al. 2003); effects are less clear among women. The beneficial effects of alcohol also have been shown to be similar for people with existing cardiovascular disease or diabetes (Costanzo et al. 2010; Koppes et al. 2006) and those in the general population. In addition to its beneficial effects on coronary heart disease, moderate drinking has been found to reduce the risk of ischemic stroke but at a lesser magnitude and with lower levels of consumption (Klatsky et al. 2001).

Although the exact mechanisms involved in these cardioprotective effects still are under investigation, the putative benefits on cardiovascular disease likely are the result of alcohol's effects on lipids and insulin sensitivity (Dijousse et al. 2009).

In his presentation, Dr. Kenneth J. Mukamal noted that standard epidemiologic studies of alcohol consumption and coronary heart disease incidence or mortality are no longer useful, as virtually all prospective studies performed since 1980 have shown that moderate drinking reduces risk (Corrao et al. 2000; Mukamal et al. 2010; Ronksley et al. 2011). Recent analytic strategies have resulted in more precise statistical estimates, but the conclusion is unchanged. In essence, he stated, "We've been doing the same epidemiology since 1992."

Dr. Mukamal suggested the following future opportunities for alcohol and cardiovascular disease research:

- Effects of heavy and binge drinking;
- Effects of changes in alcohol consumption over time;
- Differences in effect of gender-specific drinking patterns;
- Genetic interactions;
- Studies of new mechanisms directly related to alcohol's effects (for example, cholesterol efflux capacity) (Khera et al. 2011);
- Pooling projects for questions that require large samples; and
- Use of case crossover designs to account for both triggering events and chronic use (Mostofsky 2011).

Cancer

Alcohol consumption increases the risk for several cancers, including breast, colon, liver, and upper aero-digestive cancers (oral, pharynx, larynx, and esophagus) (Schutze et al. 2011; World Cancer Research Fund 2007). The potential mechanisms underlying alcohol's effects include the carcinogenicity of acetaldehyde (for colorectal cancer and upper aero-digestive tract cancers), which is an intermediate product of alcohol metabolism; impairment of the one-carbon nutrient metabolism (for colorectal cancer); alteration of hormone levels (for breast cancer); and oxidative stress resulting from alcohol metabolism.

Dr. Edward Giovannucci noted the paucity of research on drinking patterns and cancer. He acknowledged too that studies can yield disparate findings, describing a study that initially showed no relationship between average alcohol consumption and prostate cancer but which in a posteriori analyses hinted at a possible relationship with high-quantity/low-frequency drinking (Platz et al. 2004).

In identifying areas for future research, Dr. Giovannucci discussed the importance of studying cancer–nutrient interactions, particularly for colon cancer. For example, the epidemiologic literature has consistently shown an interaction between alcohol and folate, a nutrient that seems to be protective at higher levels of drinking (Ferrari et al. 2007; Jiang et al. 2003). This suggests that the excess risk of cancer resulting from alcohol use potentially could be modified by a nutrient or combination of nutrients.

Further study also is needed to better understand the role of genetics and family history in cancer risk. The genes involved in alcohol metabolism (Yokoyama et al. 2001) and nutrient metabolism (for example, the gene *methylenetetrahydrofolate reductase* [*MTHFR*] for folate as well as other genes involved in the one-carbon metabolism pathway) are other areas that warrant additional study. Determining the molecular characteristics of tumors, such as tumor subtypes classified by level of methylation, which might reflect defects in one-carbon metabolism (Schernhammer et al. 2010), is another area that requires further investigation. In addition, little research has been conducted with cancer survivors, a group that may be especially willing to modify their drinking habits.

Finally, as noted by Dr. Giovannucci, alcohol increases the risk for many cancers, but not all. Recent studies have found that alcohol is associated with a lower risk of kidney cancer (Lee et al. 2007) and non-Hodgkins lymphoma

Future Research Ideas, Large and Small, for Consideration

In addition to the full panel discussions, panelists were asked to consider directions for future studies—both large and small. Specifically, the panelists described what studies they would suggest for future research and how they would refine those visions when funds are limited. Selected noteworthy examples are described below.

- A randomized trial to evaluate alcohol consumption and risk of multiple clinical outcomes with sufficient power to evaluate prespecified genetic environmental interactions would be ideal. However, with limited resources, it might be more realistic to use a hybrid design, with a prospective cohort study and a smaller nested trial. For example, a trial might evaluate if recommending moderate alcohol consumption, versus no recommendation, had an effect on cardiovascular and stroke outcomes among patients with a high risk for vascular problems.

- Clinical trials to establish the effects of alcohol consumption on clinical cardiovascular and cancer outcomes. A large-scale trial using high-risk populations with standardized exposure to alcohol would be ideal. A more practical approach would be to conduct shorter trials with subclinical measures of both cardiovascular disease and, to a lesser degree, cancer, using such techniques as serial computed tomography angiography and colonography.

- Studies to identify factors that influence the risk for liver disease among moderate drinkers. A large, prospective study would be ideal and would include serial measures of genomic, dietary, anthropometric, and behavioral risk factors obtained as objectively as possible, coupled with serial noninvasive measures of liver disease using magnetic resonance imaging for fat and fibroscan for fibrosis. Such a cohort could additionally fold in cardiovascular disease risk factors and clinical and subclinical cardiovascular disease. Among other things, this study would help to address the simultaneous associations of alcohol consumption with lower risk of cardiovascular disease but higher risk of fatty liver, which is associated with a higher risk for cardiovascular disease. Although of more limited utility, a cross-sectional study with the same measures would also be of clear import.

- Studies to verify estimates of drinking patterns. This is particularly important as self-reported estimates form the basis for epidemiological studies but have yet to be validated, particularly in the context of eating patterns, portion sizes, and health beliefs.

- Studies of how alcohol ingestion impacts energy balance in both moderate and binge drinkers.

- Studies to better understand the risk factors underlying alcohol-related chronic disease. These factors range from fixed characteristics, such as genetics and ethnic background, to broader modifiable behaviors, such as diet, exercise, or smoking. An ideal study would be multifaceted and include both disease-specific and composite global endpoints, such as healthy aging or survival free of chronic disease. A more limited study could simply compile data from the dozens of cohort studies worldwide where much of this data already have been collected. A more comprehensive effort would use ongoing studies prospectively to incorporate novel measures of drinking patterns, biomarkers of health status, or greater assessment of quality of life and mental health.

(Kroll et al. 2012). Understanding how these two cancers differ from others is another area requiring additional research.

Dr. Giovannucci suggested the following future opportunities for alcohol and cancer research:

- Effects of drinking patterns on cancer risk;
- Nutrient interactions;
- Genetic susceptibility (genes related to alcohol metabolism, genes related to one-carbon metabolism);
- Tumor subtypes;
- Cancer survivors; and
- Pathways that might explain the limited protective aspects of alcohol consumption.

Diabetes

Evidence that alcohol can impact diabetes has been consistent over several studies. Results from the Nurses' Health Study (Stampfer et al. 1988), the Health Professionals Follow-up Study (Conigrave et al. 2001), a systematic review (Howard et al. 2004), and two meta-analyses (Baliunas et al. 2009; Koppes et al. 2005) all show that moderate drinking is associated with a lower risk of diabetes. Heavy drinking, on the other hand, seems to lead to an increased risk of diabetes, although sample sizes generally have been too small to draw firm conclusions.

Dr. Eric Rimm described specific areas of research that warrant further study. For example, only about 30 to 50 percent of alcohol's beneficial effects on diabetes can be linked to biomarkers studied to date. In addition to its overall effect on insulin sensitivity (Davies et al. 2002), moderate alcohol consumption improves adiponectin, a fat-tissue hormone associated with insulin sensitivity; inflammatory status (Joosten et al. 2008); and HDL cholesterol. With regard to metabolic studies, he noted the value of using short-term feeding studies because they provide an opportunity to control and simultaneously examine drinking (for example, with meals or without) and diet (for example, high versus low glycemic load) (Mekary et al. 2011). He also discussed the importance of studying genetic predisposition (Beulens et al. 2007).

In addition to these areas, Dr. Rimm suggested several future opportunities for alcohol and type 2 diabetes research:

- Pool large cohort studies to maximize power to look at subpopulations where alcohol may be most detrimental or most beneficial.
- Pool data from large cohort studies with genetic information on alcohol metabolizing and diabetes-related genes to examine the interactions between alcohol, genetic predisposition, and diabetes risk.
- Conduct metabolic studies specifically within subgroups to examine how alcohol modifies risk based on lifestyle characteristics, such as body mass index, diet, and physical activity.

Stroke and Cognition

Several important findings on the effects of alcohol consumption on the incidence of stroke have emerged from the Northern Manhattan Study, a prospective, multiethnic cohort study (Elkind et al. 2006; Sacco et al. 1999). In that study, subjects with the lowest risk for ischemic stroke consumed, on average, two drinks per day. Those effects were similar among drinkers of wine, beer, and liquor. In contrast, no protective effect was found for hemorrhagic stroke.

The study's principal investigator, Dr. Ralph Sacco, presented the results of two meta-analyses. One found the greatest protection against all strokes combined was most evident at a lower level of drinking, less than or equal to one drink per day (Ronksley et al. 2011). Other analyses compared results from ischemic with hemorrhagic strokes (Reynolds et al. 2003). For ischemic stroke, moderate drinking was protective, whereas heavy drinking was associated with an increased risk; for hemorrhagic stroke, heavy drinking increased risk (although sample size was insufficient to study the effects of moderate drinking on hemorrhagic stroke).

The heterogeneity of strokes underscores the importance of studying stroke subtypes. Both ischemic strokes (the majority of all strokes) and hemorrhagic strokes (about 17 percent of all strokes) have subtypes with differing etiologies that may respond differently to alcohol consumption. Little research has been conducted on these subtypes, partly because of the small numbers of each that occur within most studies and the need for relatively large samples to obtain sufficiently precise estimates of risk. Numerous subclinical markers of stroke, such as endothelial function, currently are being pursued by researchers (Suzuki et al. 2009).

Cognition

The prevalence of cognitive impairment is growing rapidly as the population ages, and, like stroke, cognitive impairment is not a single disease or condition. Studies of alcohol use and cognition have examined a variety of outcomes, including Alzheimer's disease, cognitive function, dementia, and mild cognitive impairment (Lee et al. 2010). Studies and meta-analyses generally show that moderate drinking is associated with a decreased risk of dementia (Mukamal et al. 2003*b*; Peters et al. 2008), Alzheimer's disease (Peters et al. 2008), vascular dementia (Peters et al. 2008), and cognitive

Recommendations for Strengthening Studies

In addition to offering ideas for future studies, the Expert Panel also made recommendations for strengthening research in the field. Specific suggestions include:

1. Standardize alcohol consumption measurement in prospective and retrospective studies of alcohol and chronic disease to the greatest degree possible. Standardized measures:

   a. Should include consumption quantity, frequency, and binge drinking (i.e., basic drinking patterns).

   b. Should consider drinking over the lifespan (for example, during youth, middle age, menopause, and during time of heaviest drinking) as the critical time periods for effects of alcohol on chronic disease development are uncertain.

   c. Are available from NIAAA and from the NIH/National Human Genome Research Institute Phenx Toolkit: http://www.niaaa.nih.gov/Resources/Research Resources/Pages/TaskForce.aspx; https://www.phenx.org/Default.aspx?tabid=36

2. Strongly encourage collection of biological material and broad consent for genetic studies in all clinical trials and in as many population studies as possible.

3. Objectively validate standardized alcohol measures using novel technologies as they become available. Examples may include implantable biosensors and point-of-care devices with wireless transmission capability.

4. Develop new biomarkers for moderate alcohol consumption to complement those used for heavy drinking.

5. Identify surrogate markers for chronic disease (including measures of subclinical disease) that will have utility in small-scale studies and for elucidating mechanisms and pathways linking alcohol to chronic disease.

6. Pool data from existing cohort studies to facilitate examination by population subgroups, including but not limited to age, lifespan phase, race/ethnicity, menopausal status, body mass index/anthropometrics, dietary intake/nutritional status, smoking status, physical activity/fitness, cancer survivorship, and age of drinking onset. Pooled data also may facilitate studies of rare or understudied outcomes such as liver disease.

   a. Standardized alcohol questions should be used where possible.

   b. Confounding and interaction should be considered to ensure robust estimates and define susceptible subgroups.

   c. Targeted sub-studies within large cohorts should be considered as a cost-efficient way to better understand and explain results in the full cohort. For example, when data on alcohol consumption are not gathered in enough detail in the original study, targeted follow-up studies may be used among stratified subsets of subjects to collect biological samples and to obtain more detailed data on consumption for extrapolating to the parent study.

7. Include associations between alcohol dependence/abuse and chronic disease outcomes. Studies using pooled data or sub-studies within large cohorts may have the power to address these drinking problems. Data on period of maximum drinking could be important, particularly given the marked variation in alcohol intake during the lifespan.

8. Perform studies in understudied areas, including but not limited to the effects of alcohol on diabetes, obesity, cognition, healthy aging, and food intake.

9. Focus on relationships between drinking patterns and chronic disease. Drinking patterns include but are not limited to basic patterns such as usual quantity, frequency, and binge drinking as well as when, where, and with whom alcohol was consumed and whether it was consumed with a meal.

10. Encourage clinical trials across the spectrum of chronic disease from studies that examine key physiological parameters and intermediate studies such as feeding studies that examine surrogates or subclinical

phenotypes to practical trials that examine chronic disease outcomes.

a. Physiologic studies are preferred when epidemiologic evidence is relatively limited.

b. Practical trials are preferred when there is extensive evidence from physiological and epidemiological studies.

11. Encourage studies examining the interactions between the genetics that predispose individuals to drink and the genetics that modify how alcohol affects chronic disease.

12. Encourage studies of carefully defined homogeneous phenotypes. For example, studies are needed to clarify the effects of alcohol on thrombotic versus embolic ischemic stroke, Alzheimer's disease versus other dementias, specific eye diseases, etc.

13. Encourage studies on moderate drinking patterns and metabolism ranging from total energy and macronutrient metabolism to specific metabolic pathways for small molecules such as vitamins, amino acids, sugars, and steroids and their products and precursors.

14. Examine the effectiveness of communication messages about drinking. Studies may include, but are not limited to, how to disseminate cost-benefit messages, individualized messages based on patient demographic and clinical history, and guidance for health care professionals on how to advise patients.

15. Encourage the use of natural experiments to examine whether policy interventions or alcohol intervention studies might change the relationship between alcohol and chronic disease.

decline (Peters et al. 2008). According to Dr. Sacco, there currently is great interest in vascular risk factors for dementia, yet little alcohol research has been done in that area.

Other future opportunities for research into alcohol and chronic neurological disease noted by Dr. Sacco include the following:

- Cohort studies with careful end point adjudication to separate ischemic stroke subtypes and different etiologies of dementia and cognitive impairment;
- Examination of interactions with race and ethnicity and other neurological risk factors;
- Comparison of associations across beverage types for neurological outcomes; and
- Understanding protective alcohol mechanisms including inflammatory relationships, subclinical measures and biomarkers, and gene–environment interactions.

Chronic Liver Disease

Chronic liver disease has long been associated with alcohol consumption and includes alcoholic liver disease, hepatitis C, and nonalcoholic steatohepatitis. Despite this clear association, however, there is a lack of strong clinical measures to describe and predict the progression of chronic liver disease. Dr. James Everhart noted that the course of alcoholic liver disease is several decades in duration and begins as simple steatosis (fatty liver) before progressing to more advanced stages including steatohepatitis, alcoholic cirrhosis, and, eventually, liver failure.

Dr. Everhart noted that alcoholic liver disease may be overrepresented in terms of mortality because of the current classification system. Histologically, alcoholic fatty liver and nonalcoholic fatty liver look similar (Scaglioni et al. 2011), and patients with otherwise similar multiple risk factors and histology may be classified as having alcoholic liver disease rather than nonalcoholic steatohepatitis simply because they do or do not drink. According to Dr. Everhart, the current strict separation of alcoholic and nonalcoholic fatty liver disease limits epidemiology, public health, and clinical understanding.

In examining the effects of drinking amounts on liver disease, little association has been found between moderate drinking and alcoholic liver disease, and only a minority of very heavy drinkers develops alcoholic liver disease, although the reason is not clear. It is possible that drinking patterns and diet each play a role in risk. More information also is needed to determine if drinking at times other than during meals could increase risk.

Other factors that put people at higher risk for liver disease include being obese, using cannabis, having diabetes,

and being female (Hart et al. 2010). Conversely, coffee consumption seems to lower risk and smoking seems to have no effect on the development of chronic liver disease. Genetic susceptibility is another important risk factor for liver disease. For example, a variant in one gene, *PNPLA3*, originally associated with fatty liver, has been strongly associated with alcoholic liver disease. Again, additional research is needed to determine how these factors influence alcohol's effects.

Dr. Everhart suggested several future opportunities for alcohol and chronic liver disease research:

- Improve the current chronic liver disease classification scheme;
- Develop reliable and accurate measures of progressive liver disease that can be applied serially;
- Implement better measures of alcohol consumption and its patterns to study drinking patterns and interactions between drinking and diet;
- Evaluate how genetics may influence the link between alcohol consumption and the risk of liver disease; and
- Identify determinants of chronic liver disease among heavy drinkers.

Genetics

Chronic diseases tend to run in families yet do not follow a simple genetic pattern; that is, they are complex and polygenic. Identifying the genes that affect chronic disease risk can be hampered by multiple factors, including phenotypic complexity, multiple genes with small effects, environmental variability, gene–gene interactions, and gene–environment interactions. Alcohol's role in chronic disease likely reflects a gene–environment interaction in which risk is influenced by genes, by lifestyle choices, and by a combination of both. In addition, as noted by Dr. Howard J. Edenberg, most of the variations in genes related to alcohol and chronic disease likely have only small effects, making those genetic influences especially difficult to identify.

One way of overcoming these difficulties, as proposed by Dr. Edenberg, is to obtain large sample sizes by combining data from multiple epidemiologic studies. This enables investigators to examine gene–environmental associations using secondary data analyses. The drawback is that studies typically ask different questions about alcohol use and often include different time frames, often collect no data on drinking problems, and may not obtain appropriate consent for genetic testing. Dr. Edenberg suggested a number of strategies to manage these obstacles. For example, investigators could be encouraged to incorporate standardized alcohol consumption questions, particularly for patterns of consumption, and to obtain DNA samples using proper consent for genetic studies, where appropriate. Existing studies also could be enhanced through targeted ancillary studies in which key subsets of subjects are re-contacted to provide more detailed or standardized information. The payoffs from such steps could lead to the discovery of key genes and pathways that reveal mechanisms and potential targets for therapy. Even if the effect of a variant is small, the pathway it leads to could be of major importance.

Dr. Edenberg suggested several future opportunities for the genetics of alcohol and chronic disease research:

- Design and incorporate more detailed alcohol exposure measures that include patterns of consumption and drinking problems;
- Search out ongoing and planned studies to;
  - Partner to incorporate exposure measures as early as possible;
  - Target follow-up and additional studies to gather more detailed exposure information and genetic samples; and
  - Encourage collection of samples with consent for genetic studies.

Eating Behaviors

The link between alcohol intake and eating behaviors is not well known. Studies generally show that alcohol calories, when added to the diet, increase total energy intake (Yeomans 2010). Yet despite the fact that alcohol is an energy source, is largely uncompensated (i.e., supplements rather than replaces other calories), may weaken feeding controls, and spares fat for storage, little evidence exists that moderate drinking is associated with increased body mass index or weight gain (Liangpunsakul 2010; Liu et al. 1994; Wang et al. 2010) (although a French study did show such an effect [Lukasiewicz et al. 2005]). On the other hand, certain drinking patterns, particularly binge drinking, have been associated with higher body mass index (Arif and Rohrer 2005; Breslow and Smothers 2005), although impulsivity related to both eating and drinking could be an alternative explanation. According to Dr. Richard Mattes, determining alcohol's effects on eating behaviors is further confounded by beverage consumption itself and the fact that energy compensation for fluids is less than for semisolid or solid foods (Mattes 1996; Mourao et al. 2007).

He also suggested that what people think they are eating may be more important in terms of appetitive sensations than its true energy value, noting current research showing that manipulating food form (liquid or solid) can alter a person's expectation of how filling that food will be.

Dr. Mattes suggested several research opportunities for future studies on ingestive behavior and alcohol-related

chronic disease research, particularly in controlled experimental designs:

- Clarify the role of moderate alcohol consumption on energy balance;
- Assess which properties of alcohol contribute to hunger and satiety;
- Ascertain the true biological energy value of alcohol;
- Test the role of drinking patterns on energy balance; and
- Determine the effects of different levels of alcohol consumption on body composition and energy balance.

Technology

A number of promising technologies and medical devices currently are under development by the National Institute of Biomedical Imaging and Bioengineering and others that may enhance alcohol-related chronic disease research in the future. Dr. John Haller reviewed the research on three areas: sensors, point-of-care (POC) diagnostic devices, and imaging technologies and bioinformatics tools.

Sensors are used to detect and quantitate clinically relevant analytes. Examples include BioMEMs, microfluidics (Chin et al. 2011), and nanoscale technologies, including micro-total analysis systems, arrays, and biochips. These multifunctional devices can measure multiple analytes across a variety of diseases using a platform the size of a credit card.

Such technologies then can be combined into POC tests, which are defined as diagnostic testing at or near the site of patient care (rather than at centralized laboratories). Benefits include earlier diagnosis of disease and the ability to monitor patients at home. For example, POC tests for alcohol include a breath test and saliva-testing devices (http://www.aacc.org/events/online_progs/documents/AlcoholTesting1.2.pdf); SpectRx, a wristwatch-type device; and Giner, a WrisTas transdermal sensor for measuring alcohol consumption (Marques and McKnight 2009). Dr. Haller also reviewed implantable monitors and a tattoo using nanosensors that reside under the skin. By shining a light on the tattoo the subject enables tracking of sodium and glucose levels by portable digital devices, including smartphones. In the future, such a technology could be used to track alcohol consumption.

Biomedical imaging of the brain is another area where advances could be applied to the study of alcohol and chronic disease. Most radiology images (e.g., magnetic resonance imaging [MRI], computerized tomography) show anatomy/morphology. These images generally capture the late stages of chronic disease. An alternative approach would be to examine the physiological function (e.g., neuroreceptors) using nuclear imaging (e.g., positron emission tomography and single-photon emission computed tomography). Magnetic resonance spectroscopy can image relative chemical composition. MRI diffusion tensor imaging can image white matter tracts (connectivity), and functional MRI can image relative blood flow, a marker of neural activity. These structural and functional neuroimaging methods currently are being used in alcohol research (Buhler and Mann 2011). Dr. Haller noted that informatics (data modeling, simulation, and analysis) also will have a significant role in making sense of the large amounts of high-dimension data now available.

Dr. Haller had the following suggestions regarding alcohol-related chronic disease research:

- Among the variety of technologies and medical devices that exist for the study of individuals and populations, those of particular interest might include sensors, POC diagnostic devices, imaging technologies, and bioinformatics tools;
- A better alternative to the "hammer-in-search-of-a-nail" approach in imaging is to define the clinical problem of interest first, then find the appropriate tools to address the problem or chronic disease under study;
- Alcohol and chronic disease epidemiology could be improved through the use of new sensors (including POC diagnostics, sensors embedded in the home or implanted in the body) to enhance alcohol measurement and by techniques that can image physiological function early in the course of chronic disease; and
- Technological advances will inevitably produce vast amounts of data about individuals and populations, but they require new informatics tools that enable meaningful use of the data in wide varieties of research settings.

Summary

This NIAAA workshop provided an excellent forum for summarizing the current state of the field and for identifying future research opportunities. Although by no means exhaustive, the ideas provided here highlight areas in need of additional study and offer a roadmap for moving forward across a variety of methodological approaches and content areas. NIAAA would like to thank all of the presenters for their insight and for taking the time to participate in this unique workshop. Our hope is that the ideas presented here will stimulate additional research and further advance our understanding of the role of alcohol in chronic disease. ■

Additional Resources

The agenda, roster of speakers, and speaker's abstracts can be obtained from the author. A copy of the meeting transcript also is available from the author, upon request.

Financial Disclosure

The authors declare that they have no competing financial interests.

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The World Health Organization's Global Monitoring System on Alcohol and Health

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With growing awareness of the impact of alcohol consumption on global health (Rehm et al. 2004; World Health Organization [WHO] 2002, 2009) the demand for global information on alcohol consumption and alcohol-attributable and alcohol-related harm as well as related policy responses has increased significantly. Public health problems attributable to harmful alcohol consumption have become the focus of several World Health Assembly resolutions, including one adopted in 2005 that requested the Director-General of the WHO "to strengthen global and regional information systems through further collection and analysis of data on alcohol consumption and its health and social consequences, providing technical support to Member States and promoting research where such data are not available" (WHO 2005). Monitoring and surveillance are crucial in setting objectives for national alcohol plans and in evaluating success (for more details see Rehm and Scafato 2011). In recognition of the increasing demand from WHO Member States for global health information, the WHO's 11th General Programme of Work called for monitoring health situations and assessing trends as one of six core functions for the period 2006–2015 (WHO 2006).

In 2010, the World Health Assembly endorsed the Global Strategy to Reduce the Harmful Use of Alcohol (WHO 2010), which targeted the monitoring and surveillance of harmful alcohol consumption and alcohol-attributable harm as one of 10 areas for action. The Global Strategy also identified production and dissemination of knowledge as one of the key components for global action (WHO 2010).

Most recently, the Political Declaration of the High-level Meeting of the United Nations General Assembly on the Prevention and Control of Non-Communicable Diseases (NCDs) mandated the development of a global monitoring framework, including indicators, and a set of voluntary global targets for the prevention and control of NCDs. This mandate explicitly mentioned the harmful use of alcohol as one of the four common risk factors for NCDs along with tobacco use, unhealthy diet, and lack of physical activity (United Nations 2011). This work yielded a set of nine voluntary targets, including at least a 10 percent relative reduction in the harmful use of alcohol and a set of 25 indicators, including the following possible indicators for monitoring the harmful use of alcohol as appropriate, within the national context: (1) total (recorded and unrecorded) alcohol per capita consumption (among those ages 15 and older) within a calendar year in liters of pure alcohol; (2) age-standardized prevalence of heavy episodic drinking among adolescents and adults; and (3) alcohol-related morbidity and mortality among adolescents and adults (WHO 2012). Inclusion of the alcohol target and indicators in the global monitoring framework for NCDs and their risk factors will increase the demand for high-quality global data on alcohol consumption and alcohol-related harm and attention to the WHO monitoring activities in this area.

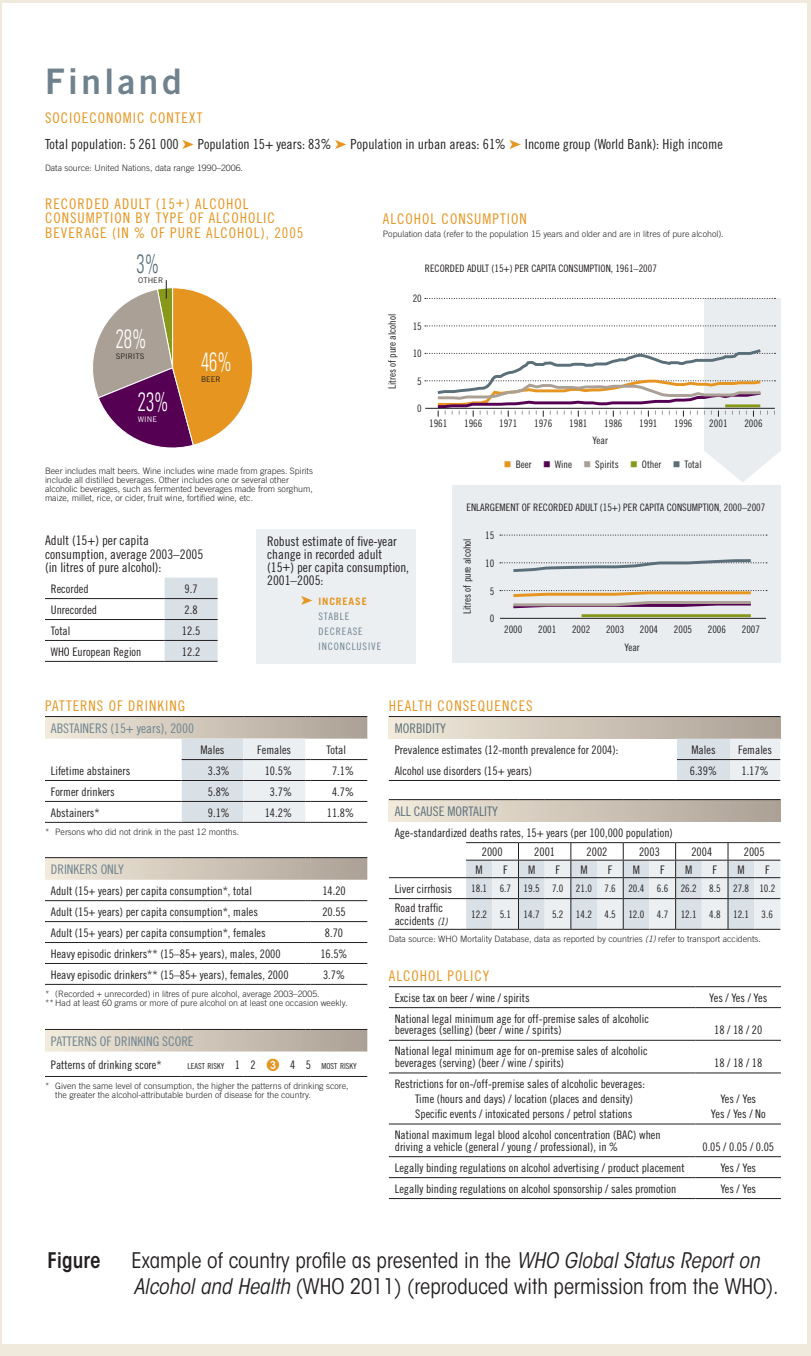
History of the WHO Global Monitoring System on Alcohol and Health

The WHO Program on Substance Abuse established the Global Alcohol Database in 1996, creating the world's largest single source of information

on levels and patterns of alcohol consumption, its health consequences, and policy responses in WHO Member States. Prior to this, WHO monitoring of alcohol and health activities largely was focused on collecting countries' alcohol policy and prevention program data (Moser 1974, 1980, 1992). With the establishment of the Global Alcohol Database, the WHO Secretariat started to implement regular global questionnaire surveys on alcohol and health among the governmental officials of WHO Member States nominated to provide information to WHO in the areas of alcohol consumption, alcohol-related harm, and policy responses. The data collection tools were developed by WHO staff in collaboration with external experts. The first *Global Status Report on Alcohol* was published in 1999 (WHO 1999), followed by the *Global Status Report on Alcohol and Young People* (WHO 2001). In 2004, the WHO produced two global status reports based on the data collected from Member States and other sources during 2002: one on alcohol consumption and related harm (WHO 2004*a*) and the second focused on alcohol policy (WHO 2004*b*). The latest *Global Status Report On Alcohol and Health* contained newly developed country profiles (see figure) based on 30 key indicators related to alcohol consumption, health consequences, and policy responses (WHO 2011). The reports also provided valuable information on levels and patterns of alcohol consumption at global and regional levels, and contained estimates of alcohol-attributable disease burden. In 2006, the WHO Expert Committee on Problems Related to Alcohol Consumption recommended the establishment of a global information system on alcohol, based on the current WHO Global Alcohol Database, to continue efforts to collect, compile, and analyze alcohol monitoring and surveillance information based on comparable data and agreed definitions (WHO 2007).

WHO Global Information System on Alcohol and Health

The WHO created the Global Information System on Alcohol and



Finland

SOCIOECONOMIC CONTEXT

Total population: 5 261 000 ➤ Population 15+ years: 83% ➤ Population in urban areas: 61% ➤ Income group (World Bank): High income

Data source: United Nations, data range 1990–2006.

RECORDED ADULT (15+) ALCOHOL CONSUMPTION BY TYPE OF ALCOHOLIC BEVERAGE (IN % OF PURE ALCOHOL), 2005

Beer includes malt beers. Wine includes wine made from grapes. Spirits include all distilled beverages. Other includes one or several other alcoholic beverages, such as fermented beverages made from sorghum, maize, millet, rice, or cider, fruit wine, fortified wine, etc..

ALCOHOL CONSUMPTION

Population data (refer to the population 15 years and older and are in litres of pure alcohol).

Adult (15+) per capita consumption, average 2003–2005 (in litres of pure alcohol):

Recorded	9.7
Unrecorded	2.8
Total	12.5
WHO European Region	12.2

Robust estimate of five-year change in recorded adult (15+) per capita consumption, 2001–2005:

➤ INCREASE
STABLE
DECREASE
INCONCLUSIVE

PATTERNS OF DRINKING

ABSTAINERS (15+ years), 2000

	Males	Females	Total
Lifetime abstainers	3.3%	10.5%	7.1%
Former drinkers	5.8%	3.7%	4.7%
Abstainers*	9.1%	14.2%	11.8%

* Persons who did not drink in the past 12 months.

DRINKERS ONLY

Adult (15+ years) per capita consumption*, total	14.20
Adult (15+ years) per capita consumption*, males	20.55
Adult (15+ years) per capita consumption*, females	8.70
Heavy episodic drinkers** (15–85+ years), males, 2000	16.5%
Heavy episodic drinkers** (15–85+ years), females, 2000	3.7%

* (Recorded + unrecorded) in litres of pure alcohol, average 2003–2005.
** Had at least 60 grams or more of pure alcohol on at least one occasion weekly.

PATTERNS OF DRINKING SCORE

Patterns of drinking score* LEAST RISKY 1 2 3 4 5 MOST RISKY

* Given the same level of consumption, the higher the patterns of drinking score, the greater the alcohol-attributable burden of disease for the country.

HEALTH CONSEQUENCES

MORBIDITY

Prevalence estimates (12-month prevalence for 2004):	Males	Females
Alcohol use disorders (15+ years)	6.39%	1.17%

ALL CAUSE MORTALITY

Age-standardized deaths rates, 15+ years (per 100,000 population)

	2000		2001		2002		2003		2004		2005	
	M	F	M	F	M	F	M	F	M	F	M	F
Liver cirrhosis	18.1	6.7	19.5	7.0	21.0	7.6	20.4	6.6	26.2	8.5	27.8	10.2
Road traffic accidents *(1)*	12.2	5.1	14.7	5.2	14.2	4.5	12.0	4.7	12.1	4.8	12.1	3.6

Data source: WHO Mortality Database, data as reported by countries *(1)* refer to transport accidents.

ALCOHOL POLICY

Excise tax on beer / wine / spirits	Yes / Yes / Yes
National legal minimum age for off-premise sales of alcoholic beverages (selling) (beer / wine / spirits)	18 / 18 / 20
National legal minimum age for on-premise sales of alcoholic beverages (serving) (beer / wine / spirits)	18 / 18 / 18
Restrictions for on-/off-premise sales of alcoholic beverages:	
Time (hours and days) / location (places and density)	Yes / Yes
Specific events / intoxicated persons / petrol stations	Yes / Yes / No
National maximum legal blood alcohol concentration (BAC) when driving a vehicle (general / young / professional), in %	0.05 / 0.05 / 0.05
Legally binding regulations on alcohol advertising / product placement	Yes / Yes
Legally binding regulations on alcohol sponsorship / sales promotion	Yes / Yes

Figure Example of country profile as presented in the *WHO Global Status Report on Alcohol and Health* (WHO 2011) (reproduced with permission from the WHO).

Health (GISAH) to collect, compile, analyze, and disseminate global information on alcohol and health. From the very beginning of its development by the WHO Department of Mental Health and Substance Abuse in collaboration with the Centre for Addiction and Mental Health (CAMH) in Canada, the global information system was conceived as integrated with the regional information systems on alcohol, although at that time such a system existed only in the WHO European region. GISAH now is part of the WHO Global Health Observatory and integrates four regional information systems from countries in the Americas, Europe, Southeast Asia, and Western Pacific regions (http://www.who.int/gho/alcohol/en/index.html). The GISAH functions as one single data repository, with common data collection and data quality–control procedures to prevent discrepancies between the global and regional information systems on alcohol and health.

Within GISAH, data are organized under a broad set of seven categories of indicators: levels of alcohol consumption; patterns of consumption; harms and consequences; economic aspects; alcohol control policies; prevention, research, and treatment resources; and youth and alcohol.

GISAH currently encompasses more than 150 alcohol-related indicators, with data for more than 225 countries and territories and includes indicators that are comparable across countries. The information on prevention and treatment resources is presented in another information system (i.e., Resources for the Prevention and Treatment of Substance Use Disorders) (http://www.who.int/gho/substance_abuse/en/index.html), which also is a part of the WHO Global Health Observatory.

Since its development, the GISAH and its regional components have become the central global information tool for dynamic presentation of worldwide data on levels and patterns of alcohol consumption, alcohol-attributable health and social consequences, and policy responses at all levels. The WHO Global Strategy to reduce the harmful use of alcohol explicitly mentions strengthening the GISAH and developing or refining appropriate data-collection mechanisms, based on comparable data and agreed indicators and definitions, as the key activity of the WHO Secretariat in support of WHO Member States in producing and disseminating knowledge on alcohol and health (WHO 2010).

Among the remaining key challenges for improving international comparisons of data on alcohol consumption and alcohol-attributable health consequences are the following: (1) national monitoring systems on alcohol and health in many countries are weak, fragmented or lacking; (2) difficulties exist in estimating consumption of informally and illicitly produced alcohol; (3) poor comparability of indicators used in different jurisdictions; (4) limited geographical representation of studies on the association of alcohol consumption with health outcomes; and (5) a paucity of international multicountry research projects on alcohol epidemiology using common research protocols.

Processes and Procedures Underlying the WHO GISAH

Data sources for the GISAH include results of the WHO Global Survey on Alcohol and Health; government documents and national statistics available in the public domain; data from the Global Burden of Disease Project; data from national and international surveys including questions on alcohol consumption and related harm from the WHO STEPS (http://www.who.int/chp/steps/instrument/ en/index.html) survey instrument; and data in the public domain from economic operators in alcohol production and trade, including industry-supported organizations, published scientific articles, data from the United Nations (UN) Food and Agricultural Organization (FAO) and other UN agencies, and intergovernmental organizations such as Organization International de la Vigne et du Vin. The Canadian CAMH conducts passive surveillance of the relevant published as well as grey literature. The WHO Secretariat convenes regular meetings with key data providers on alcohol consumption to discuss and triangulate available data for achieving better estimates when national data are either unavailable or incomplete.

The WHO Global Survey on Alcohol and Health, a key data-collection mechanism, is implemented in collaboration with WHO regional and country offices, the Canadian CAMH and several other academic centers and institutions. The WHO Global Survey Instrument on Alcohol and Health, developed by WHO in collaboration with all partners involved in the survey, is forwarded to all WHO Member States through the WHO regional and country offices for completion by focal points and national counterparts explicitly nominated by governments to collaborate with WHO on this activity. For countries belonging to the European Union (EU), the survey is implemented in collaboration with and support from the European Commission. In 2008, the survey instrument contained 69 questions grouped into three sections: (1) alcohol policy; (2) alcohol consumption; and

(3) alcohol-related health indicators. The questionnaire was developed in English and translated into French, Portuguese, Russian, and Spanish. In 2008, completed questionnaires were received from 84 percent of WHO Member States, representing 97 percent of the world's population. In 2012, 177 Member States participated in the survey, which represented a 90 percent response rate and covered 98 percent of the world population.

In 2012, the survey tool was modified to strengthen the alcohol policy section in line with the main suggested areas for national action specified in the WHO Global Strategy to reduce the harmful use of alcohol. In 2012 the survey was partially implemented using the Web-based data-collection tool.

Alcohol Per Capita Consumption

One of the most important indicators of alcohol consumption in the Global Survey on Alcohol and Health is per capita consumption (among those aged 15 and older) in liters of pure alcohol. Notwithstanding some limitations associated with its aggregate-level nature (Bloomfield et al. 2003), alcohol per capita consumption is a key indicator for measuring levels of alcohol exposure in populations (WHO 2000, 2007). Despite the potential measurement bias in unrecorded consumption, per capita consumption is considered the most reliable and valid indicator for alcohol consumption in a population (Gmel and Rehm 2004) and is particularly appropriate for monitoring purposes. Population-based survey data are extremely important for further estimates of alcohol consumption in different age and gender groups but currently cannot be considered as a valid and reliable basis for estimates of alcohol per capita consumption at country, regional, and global levels. Surveys are thought to underestimate per capita consumption by more than 50 percent (Midanik 1988, 1982; Rehm et al. 2007) and survey errors are larger (Shield and Rehm 2012).

The alcohol per capita consumption indicator is based on the estimates of per capita consumption of recorded and unrecorded alcohol, the latter referring to alcohol that is not taxed and is outside the usual system of governmental control, because it is produced, distributed, and sold outside formal channels and, therefore, not registered by routine data collection (Rehm et al. 2003, 2007). It is critical to include unrecorded consumption in the estimates of overall levels of alcohol exposure in populations, because more than one-fourth of global consumption stems from unrecorded alcohol (WHO 2011). However, contrary to some conjectures, unrecorded consumption does not seem to be linked to more health problems than recorded consumption, if volume and patterns of drinking are controlled for (Rehm et al. 2010). Recorded consumption can be measured via sales and taxation or via production, export, and import. Many national governments regularly monitor alcohol per capita consumption, and reliable data is available from a significant number of countries, though predominantly high-income. These national statistics, if based on validated methodology, are given highest preference in reporting in GISAH. However, even if data on alcohol consumption are unavailable from national statistics, *per capita* consumption can be estimated, either via industry data in the public domain, or by using data supplied from by the FAO and its statistical database (FAOSTAT) (http://faostat3.fao.org/home/index.html). An algorithm is used by the WHO Secretariat to decide which statistics to give preference to, depending on the validity of the data (see http://who.int/gho/gisah).

Unrecorded consumption obviously is harder to estimate and monitor at the country level. Only a few countries have regular monitoring of unrecorded consumption. For all others, unrecorded alcohol consumption is estimated based on one-time studies and expert opinion. For the 2012 Global Survey on Alcohol and Health an additional questionnaire component on unrecorded alcohol consumption has been developed and implemented based on the principles of the Delphi survey methodology (for a description, see Linstone and Turoff 1975; Rehm and Gadenne 1990). The questionnaire in this component covers estimates of unrecorded alcohol consumption in its major categories, such as home production (of spirits, wine, and beer), alcohol brought over the border (smuggling, duty free, and cross-border shopping), illegal production (including counterfeit alcoholic beverages), and surrogate alcohol (liquids usually containing ethanol and industrial spirits not intended for consumption as beverages). The questionnaire also addresses perceived importance of unrecorded alcohol consumption from a public health perspective as well as the measures implemented at the country level to reduce the public health impact of illicit and informally produced alcohol in line with a set of policy options and interventions listed in the Global Strategy to reduce the harmful use of alcohol (WHO 2010).

Tourist consumption also is being considered in estimating alcohol per capita consumption in populations, where tourist consumption is significant (because the number of tourists per year is at least the num-

ber of inhabitants) and is not balanced by drinking by national inhabitants abroad during vacations. This mainly is the case for smaller countries.

Alcohol per capita consumption is one example of the approximately 200 indicators monitored via the GISAH at the country, regional, and global levels.

Data Validation

Before releasing the national, regional, and global data on alcohol consumption, alcohol-related harm, and policy responses, the WHO Secretariat undertakes an intensive process of data validation by compiling country profiles with all the available data for key indicators and forwarding the country profiles to each country for validation. At this stage, any discrepancies are resolved by considering new data for the periods covered in the survey, further triangulation of available information, and building consensus around disputed qualitative indicators. After the validation process, the data are uploaded in the WHO GISAH and subsequently presented in the WHO global status reports on alcohol and health.

Further Developments

Both the depth of the GISAH and the rigor of data collection and validation make it an indispensable tool for policy development and evaluation, as well as for global research (e.g., the Global Burden of Disease 2010 estimates were based on WHO global monitoring [Lim et al. 2012; Shield et al. 2013]). One of the key tasks for the WHO in the area of global monitoring and surveillance on alcohol and health is to support the development of effective national systems for monitoring alcohol consumption, its health and social consequences and related policy responses, while also strengthening national capacity for analyzing and disseminating the information, also through the WHO's global and regional information systems on alcohol and health. To further improve comparability of data generated in countries, consistent data collection mechanisms, agreed indicators and definitions, and enhanced dissemination of data is needed. The new alcohol module in the WHO STEPS instrument (http://www.who.int/chp/steps/instrument/en/index.html), which is the main data collection tool used in WHO surveillance activities on risk factors for chronic diseases, is an attempt to prioritize some well-defined key indicators and improve consistency between the relevant national surveillance activities and the WHO global monitoring system on alcohol and health. Work continues on WHO tools for alcohol epidemiology and monitoring, such as the *International Guide for Monitoring Alcohol Consumption and Related Harm* (WHO 2000).

One of the challenges for the WHO global monitoring system on alcohol and health continues to be a time lag between the alcohol exposure data collected from countries and their dissemination through GISAH and WHO global and regional status reports on alcohol and health. Efforts to reduce this time lag will involve data collection through Web-based data collection tools, optimizing data validation and dissemination procedures, as well as strengthening partnerships and resource mobilization for effective functioning of the global monitoring system.

The ultimate objective for the WHO global monitoring system on alcohol and health is strengthening the link between monitoring activities and policy development and evaluation. This system, which includes the global surveys, GISAH, and WHO global status reports on alcohol and health, is the central mechanism for monitoring implementation of the WHO global strategy to reduce the harmful use of alcohol and report on its implementation to WHO Member States (WHO 2013), other constituencies, and the public health community at large. ■

Note: The views expressed in this article are those of the authors and, except as specifically noted, do not represent the official policies or positions of the WHO.

Financial Disclosure

The authors declare that they have no competing financial interests.

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Alcohol and Mortality

Global Alcohol-Attributable Deaths From Cancer, Liver Cirrhosis, and Injury in 2010

Jürgen Rehm, Ph.D., and Kevin D. Shield, MH.Sc.

Alcohol consumption has long been recognized as a risk factor for mortality. By combining data on alcohol per capita consumption, alcohol-drinking status and alcohol-drinking patterns, risk relationships, and mortality, the Comparative Risk Assessment Study estimated alcohol-attributable mortality for 1990 and 2010. Alcohol-attributable cancer, liver cirrhosis, and injury were responsible for the majority of the burden of alcohol-attributable mortality in 1990 and 2010. In 2010, alcohol-attributable cancer, liver cirrhosis, and injury caused 1,500,000 deaths (319,500 deaths among women and 1,180,500 deaths among men) and 51,898,400 potential years of life lost (PYLL) (9,214,300 PYLL among women and 42,684,100 PYLL among men). This represents 2.8 percent (1.3 percent for women and 4.1 percent for men) of all deaths and 3.0 percent (1.3 percent for women and 4.3 percent for men) of all PYLL in 2010. The absolute mortality burden of alcohol-attributable cancer, liver cirrhosis, and injury increased from 1990 to 2010 for both genders. In addition, the rates of deaths and PYLL per 100,000 people from alcohol-attributable cancer, liver cirrhosis, and injury increased from 1990 to 2010 (with the exception of liver cirrhosis rates for women). Results of this paper indicate that alcohol is a significant and increasing risk factor for the global burden of mortality. **KEY WORDS: Alcohol consumption; alcohol burden; alcohol-attributable mortality; alcohol-attributable fractions; global alcohol-attributable mortality; risk factor; cancer; liver cirrhosis; injury; burden of disease; Global Burden of Disease and Injury study**

Alcohol and Mortality

Alcohol is causally linked to more than 200 different diseases, conditions, and injuries (as specified in the *International Classification of Diseases, Revision 10* [ICD-10] three-digit codes [see Rehm 2011; Rehm et al. 2009; Shield et al., 2013*c* [pp. 155–173 of this issue]). All of these disease, condition, and injury categories cause mortality and disability, and, thus, alcohol consumption causes a net burden of mortality and disability (Rothman et al. 2008). However, certain patterns of alcohol consumption are protective for ischemic diseases (Roerecke and Rehm 2012*a*) and diabetes (Baliunas et al. 2009), and, thus, alcohol can prevent death and disability from these causes. The total mortality and disability caused by and prevented by the consumption of alcohol is calculated by comparing the expected mortality under current conditions to a counterfactual scenario where no one has consumed alcohol (Ezzati et al. 2006; Walter 1976). Although the counterfactual scenario seems unrealistic as almost one-half of the global population consumes alcohol (for the most up-to-date statistics on alcohol consumption, see Shield et al. 2013*b*; World Health Organization 2011*a*), recent natural experiments in countries where there has been a considerable reduction in alcohol consumption showed a clear reduction in mortality (e.g., Russia) (Leon et al. 1997; Neufeld and Rehm 2013). Accordingly, the calculations of the deaths and disability caused by alcohol consumption seem to correspond to real phenomena and, thus, could predict an approximate level of reduction in mortality if alcohol consumption were to be reduced.

This article outlines the alcohol-attributable mortality burden from three major causes: cancer, liver cirrhosis, and injury. All three categories have long been identified as causally linked to alcohol consumption. With respect to cancer, in 1988 the International Agency for Research on Cancer established alcohol as a carcinogen (International Agency for Research on Cancer 1988), and in its latest monograph has found alcohol consumption to be causally associated with oral cavity, pharynx, larynx, esophagus, liver, colon, rectum, and female breast cancers (International Agency for Research on Cancer 2010, 2012). Studies have shown that stomach cancer may be associated with alcohol consumption, but evidence on the causal relationship between stomach cancer

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and alcohol consumption is not yet conclusive (International Agency for Research on Cancer 2012; Rehm and Shield, in press). Biologically, it has been established that ethanol, and not other ingredients of alcoholic beverages, is the ingredient that mainly causes cancer (Lachenmeier et al. 2012), with acetaldehyde (the first metabolite of ethanol) likely being the most important biological carcinogen (International Agency for Research on Cancer 2010, 2012; Rehm and Shield, in press). In addition, observational studies have found a clear dose-response relationship between alcohol consumption and the risk of cancer, with no observed threshold for the effect of alcohol, as an elevated risk of cancer has been observed even for people who consume relatively low amounts of alcohol (Bagnardi et al. 2013; Rehm et al. 2010*a*).

Liver cirrhosis has been associated with alcohol consumption, especially heavy consumption, since the seminal work of Benjamin Rush (Rush 1785). The causal link between alcohol consumption and liver cirrhosis is so strong and important that the World Health Organization has created a specific category for alcoholic liver cirrhosis (World Health Organization 2007). As with cancer, there is a dose-response relationship between alcohol consumption and the risk of liver cirrhosis, with no lower threshold being observed (Rehm et al. 2010*c*); however, the majority of the effect can be seen for heavy drinking (Rehm et al. 2010*c*).

The risk of injury also has been causally linked to alcohol consumption, with this relationship fulfilling all of the classic Bradford Hill criteria (e.g., consistency of the effect, temporality, a dose-repsonse relationship with the risk of an injury [biological gradient]) (Rehm et al. 2003*a*). The effect of alcohol on injury is acute; the level of risk for both intentional and unintentional injuries is clearly linked to blood alcohol level (Taylor and Rehm 2012; Taylor et al. 2010), with a very low threshold (Eckardt et al. 1998). There also is an association between average consumption of alcohol and injury (Corrao et al. 2004).

Alcohol-attributable cancer, liver cirrhosis, and injury constitute the majority of the burden of alcohol-attributable mortality. Collectively, they were responsible for 89 percent of the net burden of alcohol-attributable mortality (i.e., the mortality rate after including the beneficial effects of alcohol on ischemic diseases and diabetes) and for 79 percent of the gross burden of alcohol-attributable mortality (Shield et al. 2013*a*) in the United States in 2005, for people 15 to 64 years of age. Additionally, they were responsible for 91 percent of the net alcohol-attributable mortality and 79 percent of the gross alcohol-attributable mortality in the European Union (Rehm et al. 2012) and 80 percent of the net alcohol-attributable mortality and 72 percent of the gross alcohol-attributable mortality globally (Rehm et al. 2009) in 2004. This article does not review the other causes of alcohol-attributable deaths included in the latest Comparative Risk Assessment (CRA) Study (Lim et al. 2012). The CRA study estimates as published in December contained significant errors in the calculation of alcohol-attributable cardiovascular deaths, estimating that 33 percent of all ischemic heart disease deaths were attributed to alcohol, which is an impossibility as the relationship between alcohol consumption and this disease category is mainly protective (for details on relationship between alcohol and heart disease, see Roerecke and Rehm 2010, 2012*b*). A comparison with other alcohol-attributable disease and protective effects will thus only be possible once the corrected CRA results are published.

Methodology Underlying the Estimation of the Mortality Burden of Alcohol-Attributable Diseases and Injuries

The number of alcohol-attributable cancer, liver cirrhosis, and injury deaths in 1990 and 2010 were estimated using alcohol-attributable fractions (AAFs) (Benichou 2001; Walter 1976, 1980). AAFs are calculated by comparing the population risk of a disease under current conditions to a counterfactual scenario where no one has consumed alcohol. This is achieved by using information on the distribution of levels of alcohol consumption and the associated relative risks (RRs) (i.e., risks of disease for different levels of alcohol consumption versus abstainers). These calculated AAFs then were applied to mortality data obtained from the 2010 Global Burden of Disease (GBD) Study for 1990 and 2010 (Lim et al. 2012). Mortality data for 1990 and 2010 were modelled using data on mortality from 1980 to 2010. Data on mortality were imputed for those countries with little or no data by using data from other countries and were smoothed over time (in addition to other data corrections procedures that corrected for cause of death recording errors) (Lozano et al. 2012).

Calculating the Alcohol-Attributable Mortality Burden of Cancer and Liver Cirrhosis

Alcohol consumption is causally related to mouth and oropharynx cancers (ICD-10 codes: C00 to C14), esophageal cancer (C15), liver cancer (C22), laryngeal cancer (C32), breast cancer (C50), colon cancer (C18), and rectal cancer (C20). Alcohol RR functions for cancer were obtained from Corrao and colleagues (2004) (For information about the causal relationship between alcohol and cancer, see Baan et al. 2007; International Agency for Research on Cancer 2010.) The alcohol RR for liver cirrhosis (ICD-10 codes: K70 and K74) was obtained from Rehm and colleagues (Rehm et al. 2010*c*). The above-noted RRs were modelled based on drinking status and average daily alcohol consumption among drinkers. The same RRs were used to estimate the AAFs by country, sex, and age for 1990 and for 2010.

Alcohol-drinking statuses and adult (people 15 years of age and older) per capita consumption data for 1990 were obtained from various population surveys (Shield et al. 2013*b*), and the Global Information System on Alcohol and Health (available at: http://apps.who. int/ghodata/?theme=GISAH), respectively. Data on drinking status and adult per

capita consumption for 2010 were estimated by projections (performed using regression analyses) using data from years prior to 2010 (Shield et al. 2013*b*). Average daily alcohol consumption was modelled using a gamma distribution (Rehm et al. 2010*b*) and data on per capita consumption for 1990, which was projected to 2010 (Shield et al. 2013*b*). (For more information on the methodology of how alcohol consumption was modelled, see Kehoe et al. 2012; Rehm et al. 2010*b*). This paper presents alcohol consumption data from 2005, the latest year with actual data available.

Calculating the Alcohol-Attributable Mortality Burden of Injuries

The burden of injury mortality attributable to alcohol consumption was modelled according to methodology outlined by Shield and colleagues (2012), using risk information obtained from a meta-analysis (Taylor et al. 2010) and alcohol consumption data from 1990 and 2010. The risk of an injury caused to the drinker over a year was calculated based on alcohol consumed during normal drinking occasions and alcohol consumed during binge-drinking occasions. Alcohol-attributable injuries caused to nondrinkers also were estimated (Shield et al. 2012).

Global Consumption of Alcohol

In 2005 adult per capita consumption of alcohol was 6.1 litres of pure alcohol. Figure 1 shows the adult per capita consumption of alcohol by country. Alcohol consumption per drinker in 2005 was 17.1 litres (9.5 litres per female drinker and 20.5 litres per male drinker). Of all adults, 45.8 percent were lifetime abstainers (55.6 percent of female adults and 36.0 percent of male adults), 13.6 percent were former drinkers (13.1 percent of female adults and 14.1 percent of male adults), and 40.6 percent were current drinkers (31.3 percent of female adults and 49.9 percent of male adults). The global pattern of drinking score (a score from 1 to 5 that measures the harmfulness of alcohol drinking patterns, with 1 being the least harmful and 5 being the most harmful [Rehm et al. 2003*b*]) was 2.6 in 2005 and ranged from 4.9 for Eastern Europe to 1.5 for Western Europe. Thus, alcohol consumption in Eastern Europe can be characterized by fre-

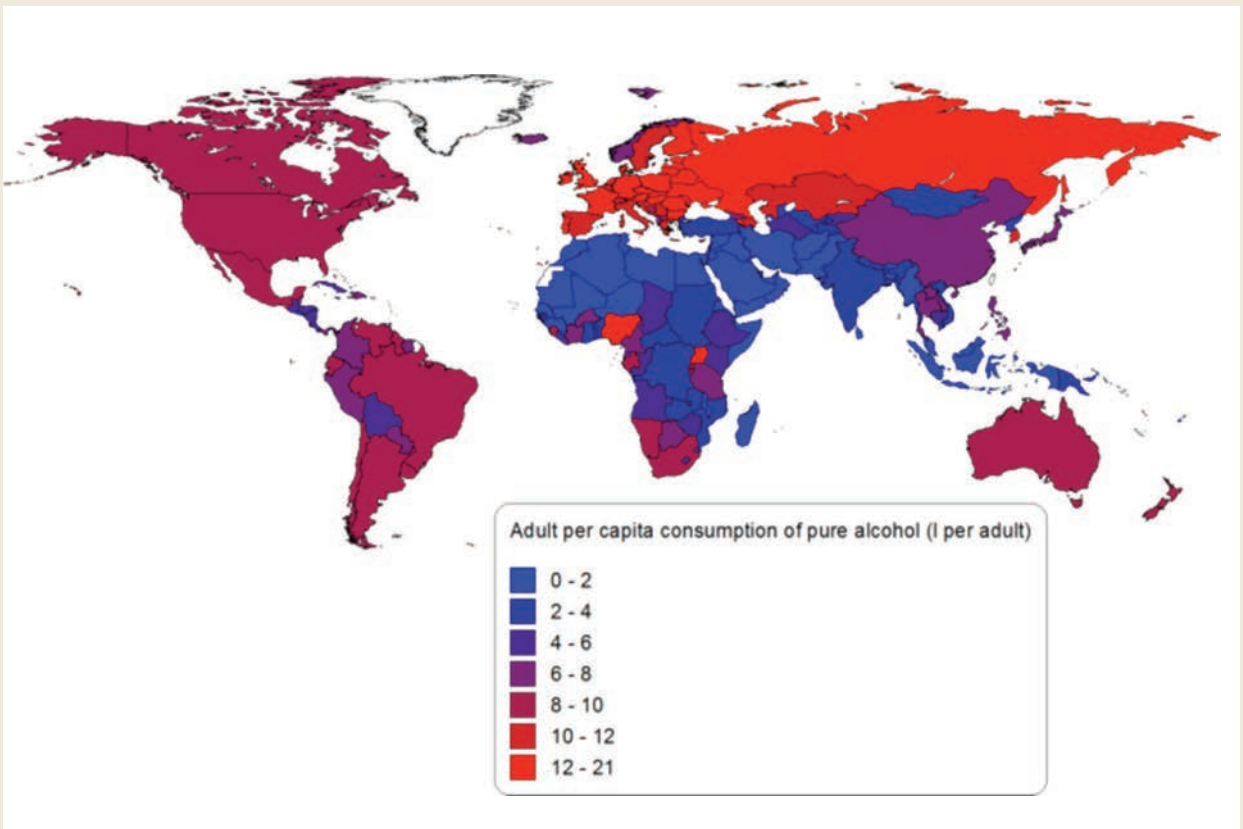

Figure 1 Adult per capita consumption of pure alcohol by country in 2005.

NOTE: More detailed information can be obtained from the author.

quent heavy alcohol consumption outside of meals and drinking to intoxication.

Global Alcohol-Attributable Mortality From Cancer

In 2010, alcohol-attributable cancer caused 337,400 deaths (91,500 deaths among women and 245,900 deaths among men) and 8,460,000 PYLL (2,143,000 PYLL among women and 6,317,000 PYLL among men). This burden is equal to 4.9 deaths per 100,000 people (2.7 deaths per 100,000 women and 7.1 deaths per 100,000 men) and 122.8 PYLL per 100,000 people (62.8 PYLL per 100,000 women and 181.9 PYLL per 100,000 men). Stated another way, alcohol-attributable cancer was responsible for 4.2 percent of all cancer deaths in 2010 and 4.6 percent of all PYLL caused by cancer. Figure 2 shows the number of alcohol-attributable cancer deaths per 100,000 people by region in 2010. Eastern Europe had the highest burden of mortality and morbidity from alcohol-attributable cancer, with 10.3 deaths and 272.0 PYLL per 100,000 people. North Africa and the Middle East had the lowest mortality burden of alcohol-attributable cancer, with 0.6 deaths and 17.1 PYLL per 100,000 people.

In 1990, alcohol-attributable cancer caused 243,000 deaths worldwide (70,700 deaths among women and 172,300 deaths among men) and 6,405,700 PYLL (1,762,200 PYLL among women and 4,643,500 PYLL among men). This mortality burden is equal to 4.6 deaths per 100,000 people (2.7 deaths per 100,000 women and 6.5 deaths per 100,000 men) and 120.8 PYLL per 100,000 people (67.0 PYLL per 100,000 women and 173.9 PYLL per 100,000 men) caused by alcohol-attributable cancer. From 1990 to 2010 the absolute mortality burden of alcohol-attributable cancer (measured in deaths and PYLL) and the rates of deaths and PYLL per 100,000 people have each increased.

Global Alcohol-Attributable Mortality From Liver Cirrhosis

In 2010, alcohol-attributable liver cirrhosis was responsible for 493,300 deaths worldwide (156,900 deaths among women and 336,400 deaths among men) and 14,327,800 PYLL

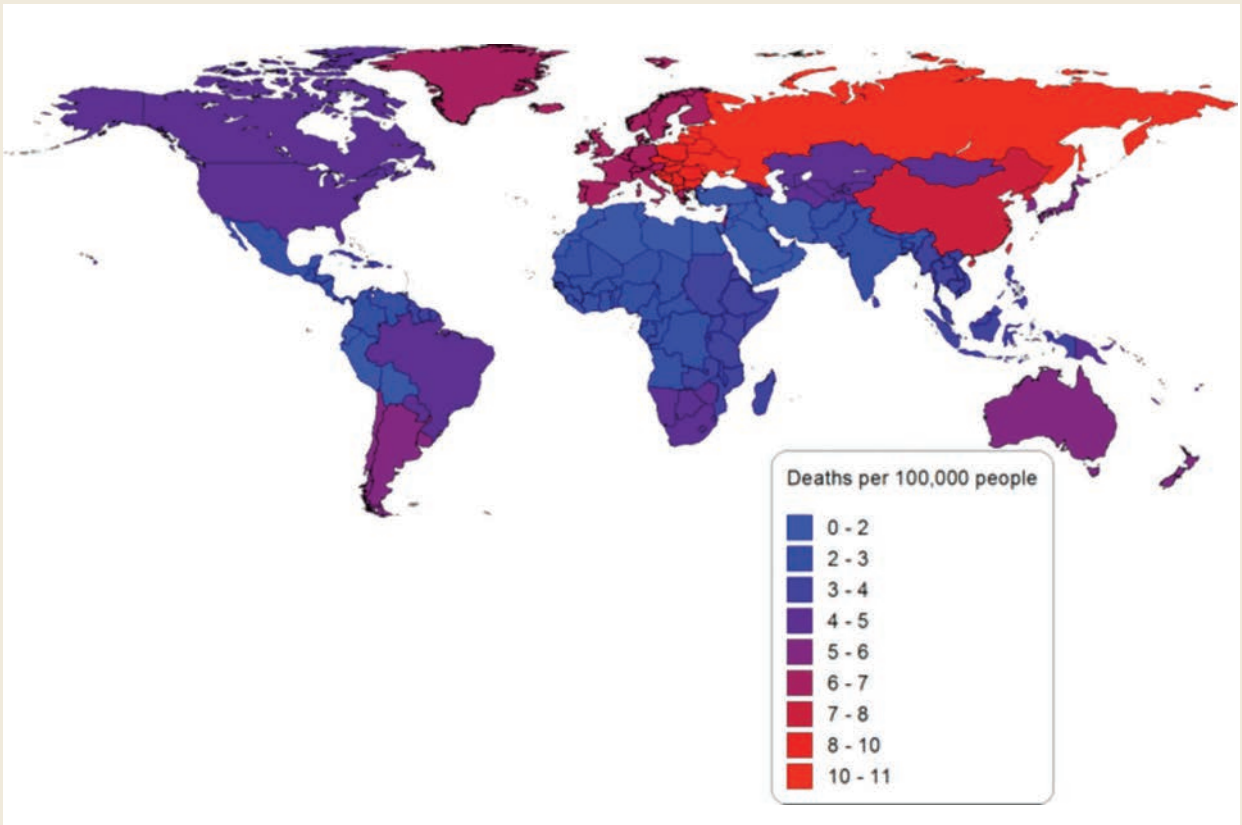

Figure 2 Alcohol-attributable cancer deaths per 100,000 people in 2010 by global-burden-of-disease region.

NOTE: More detailed information can be obtained from the author.

(4,011,100 PYLL among women and 10,316,800 PYLL among men). This mortality burden is equal to 7.2 deaths per 100,000 people (4.6 deaths per 100,000 women and 9.7 deaths per 100,000 men) and 208.0 PYLL per 100,00 people (117.5 PYLL per 100,000 women and 297.0 PYLL per 100,000 men) caused by alcohol-attributable liver cirrhosis in 2010. Overall, in 2010 alcohol-attributable liver cirrhosis was responsible for 47.9 percent of all liver cirrhosis deaths and 47.1 percent of all liver cirrhosis PYLL. Figure 3 outlines the number of alcohol-attributable liver cirrhosis deaths per 100,000 people by region in 2010, showing strong regional variability.

In 1990, alcohol-attributable liver cirrhosis was responsible for 373,200 deaths worldwide (125,300 deaths among women and 247,900 deaths among men) and 10,906,200 PYLL (3,253,300 PYLL among women and 7,652,900 PYLL among men). That is, 7.0 deaths per 100,000 people (4.8 deaths per 100,000 women and 9.3 deaths per 100,000 men) and 205.7 PYLL per 100,000 people (123.7 PYLL per 100,000 women and 286.6 PYLL per 100,000 men) were caused by liver cirrhosis attributable to alcohol consumption. From 1990 to 2010, the absolute mortality burden of alcohol-attributable liver cirrhosis (measured in deaths and PYLL) and this mortality burden per 100,000 people have each increased (except for women, where alcohol-attributable liver cirrhosis deaths and PYLL per 100,000 decreased slightly).

Global Alcohol-Attributable Mortality From Injury

Globally in 2010, alcohol-attributable injuries were responsible for 669,300 deaths (71,100 deaths among women and 598,200 deaths among men) and 29,110,600 PYLL (3,060,200 PYLL among women and 26,050,400 PYLL among men). This mortality burden is equal to 9.7 deaths per 100,000 people (2.1 deaths per 100,000 women and 17.2 deaths per 100,000 men) and 422.6 PYLL per 100,000 people (89.6 PYLL per 100,000 women and 750.0 PYLL per 100,000 men). Overall, in 2010 alcohol-attributable injuries were responsible for 13.2 percent of all injury deaths and 12.6 percent of all injury PYLL. Figure 4 outlines the number of alcohol-attributable injury deaths per 100,000 people in 2010. Eastern Europe had the greatest mortality burden of alcohol-attributable injuries, with 76.7 deaths and

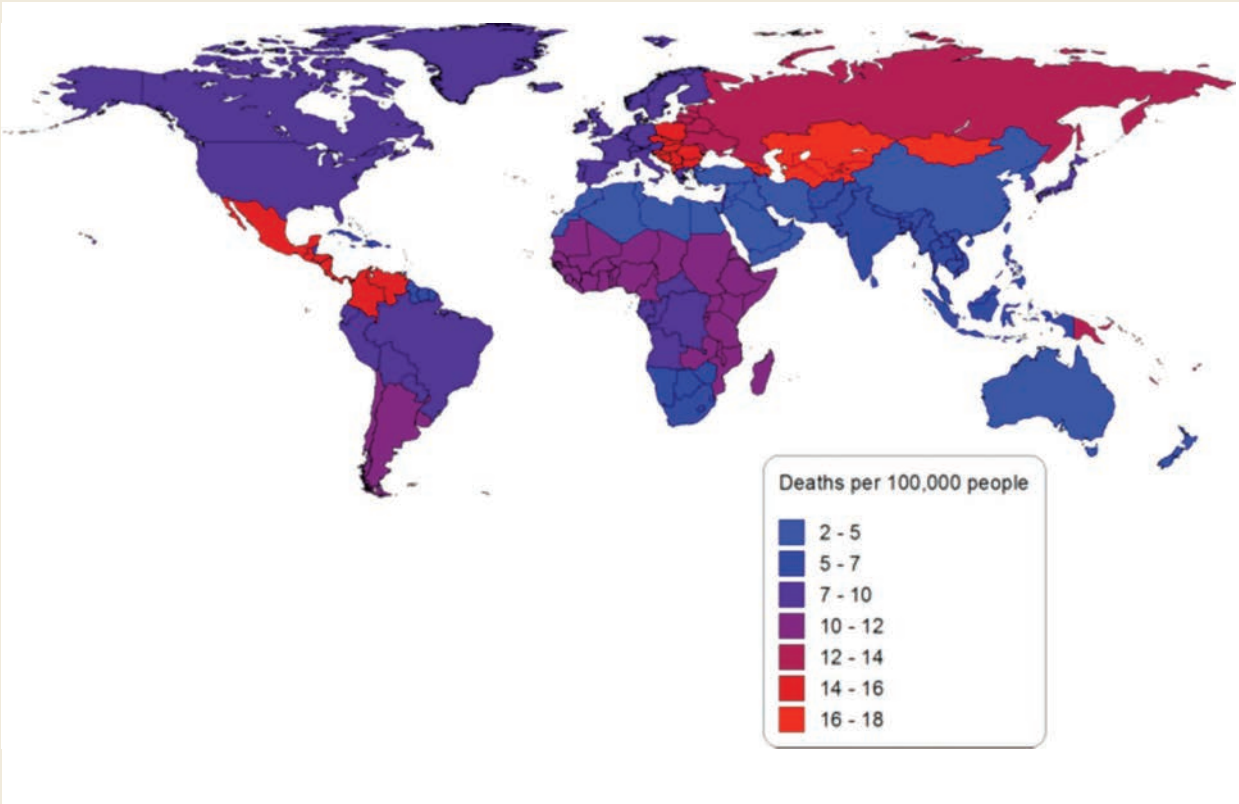

Figure 3 Alcohol-attributable liver cirrhosis deaths per 100,000 people in 2010 by global-burden-of-disease region.

NOTE: More detailed information can be obtained from the author.

3,484.7 PYLL per 100,000 people, whereas North Africa and the Middle East had the lowest mortality burden, with 2.0 deaths and 117.2 PYLL per 100,000 people.

In 1990, alcohol-attributable injuries were responsible for 485,100 deaths (54,700 deaths among women and 430,400 deaths among men) and 21,934,800 PYLL (2,409,100 PYLL among women and 19,525,700 PYLL among men), equal to 9.2 deaths (2.1 deaths per 100,000 women and 16.1 deaths per 100,000 men) and 413.8 PYLL per 100,000 people (91.6 PYLL per 100,000 women and 731.3 PYLL per 100,000 men). The absolute number of alcohol-attributable injury deaths and PYLL and the number of alcohol-attributable injury deaths and PYLL per 100,000 people each increased from 1990 to 2010.

Appendix 1 presents the number and percentage of alcohol-attributable cancer, liver cirrhosis, and injury deaths and PYLL by GBD study region for 1990 and 2010. Appendix 2 presents the number of alcohol-attributable cancer, liver cirrhosis, and injury deaths per 100,000 people. Unlike figures 1, 2, and 3, the figures in Appendix 2 use the same scale for each cause of death.

Global Alcohol-Attributable Cancer, Liver Cirrhosis, and Injury Mortality As Part of Overall Mortality

In 2010, alcohol-attributable cancer, liver cirrhosis, and injury caused 1,500,000 deaths (319,500 deaths among women and 1,180,500 deaths among men). This represents 2.8 percent of all deaths (1.3 percent of all deaths among women and 4.1 percent of all deaths among men), or 21.8 deaths per 100,000 people (9.4 deaths per 100,000 women and 34.0 deaths per 100,000 men). In 1990, alcohol-attributable cancer, liver cirrhosis, and injury caused 1,101,400 deaths (250,800 deaths among women and 850,600 deaths among men), representing 20.8 deaths per 100,000 people (9.5 deaths per 100,000 women and 31.9 deaths per 100,000 men). The table outlines the mortality burden (measured in deaths and PYLL) of alcohol-attributable cancer, liver cirrhosis, and injury for 1990 and 2010 by age and by sex. Compared with the mortality burden in 1990, the absolute number of alcohol-attributable deaths from cancer, liver cirrhosis, and injury in 2010 is higher, and the rate of deaths per 100,000 also increased for men but decreased slightly for women in 2010.

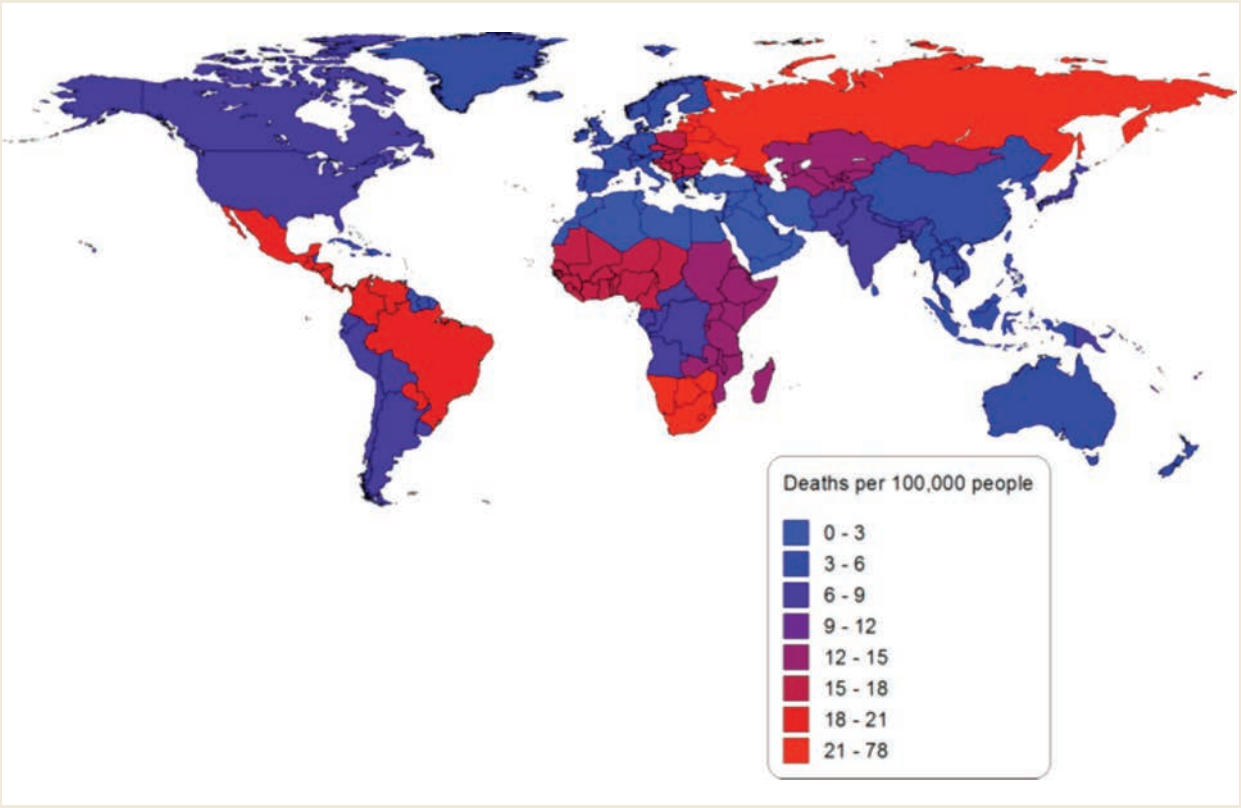

Figure 4 Alcohol-attributable injury deaths per 100,000 people in 2010 by global-burden-of-disease region.

NOTE: More detailed information can be obtained from the author.

The burden of mortality from alcohol-attributable cancer, liver cirrhosis, and injury led to 51,898,400 PYLL (9,214,300 PYLL among women and 42,684,100 PYLL among men) in 2010 and 39,246,800 PYLL (7,424,600 PYLL among women and 31,822,100 PYLL among men) in 1990. This mortality burden represents 3.0 percent (1.3 percent for women and 4.3 percent for men) of all PYLL in 2010 and 2.0 percent (0.9 percent for women and 2.9 percent for men) of all PYLL in 1990. In 2010, alcohol-attributable cancer, liver cirrhosis, and injury led to 753.4 PYLL per 100,000 people (269.8 PYLL per 100,000 women and 1,228.9 PYLL per 100,000 men) and to 740.4 PYLL per 100,000 people (282.2 PYLL per 100,000 women and 1,191.9 per 100,000 men) in 1990. Again, the overall rates of PYLL per 100,000 people increased, but this effect was attributed to increases for men, coupled with slight decreases for women.

Measurement Limitations

The methods used to estimate the number of alcohol-attributable cancer, liver cirrhosis, and injury deaths and PYLL have limitations as a result of the available data on mortality and the measurement of alcohol consumption and RRs. Most low- and middle-income countries do not have reliable mortality data and measurement of adult mortality in these countries (through verbal autopsies or surveys) is infrequent. Therefore, estimates of mortality and PYLL have a large degree of uncertainty (Wang et al. 2012). Additionally, for high-income countries, information concerning the cause of death has long been acknowledged as containing inaccuracies (James et al. 1955), and more recent studies have confirmed considerable degrees of error in this information (Nashelsky and Lawrence 2003; Shojania et al. 2003). To adjust for inaccuracies and inconsistencies in mortality data,

Table 1 Deaths and Years of Life Lost (YLL) From Cancer, Liver Cirrhosis, and Injuries Attributable to Alcohol Consumption in 1990 and 2010

Year	Gender	Age (Years)	Deaths	% Of All Deaths	YLL	% Of All YLL
1990	Women	0 to 15	4,000	0.1	324,400	0.1
		15 to 34	22,300	1.5	1,349,500	1.5
		35 to 64	128,700	2.9	4,437,000	3.0
		65+	95,800	1.0	1,313,800	1.1
		Total	250,800	1.2	7,424,600	0.9
	Men	0 to 15	6,700	0.1	540,400	0.1
		15 to 34	174,400	8.4	10,547,900	8.4
		35 to 64	502,600	7.4	18,167,100	7.8
		65+	166,800	1.8	2,566,700	2.0
		Total	850,600	3.4	31,822,100	2.9
	Total	**Total**	**1,101,400**	**2.4**	**39,246,800**	**2.0**
2010	Women	0 to 15	3,800	0.1	313,800	0.1
		15 to 34	28,800	1.7	1,741,700	1.7
		35 to 64	162,000	3.1	5,570,800	3.1
		65+	124,800	0.9	1,587,900	1.1
		Total	319,500	1.3	9,214,300	1.3
	Men	0 to 15	6,100	0.1	492,400	0.1
		15 to 34	214,900	8.5	12,972,300	8.5
		35 to 64	709,200	7.9	25,549,800	8.2
		65+	250,300	1.9	3,669,500	2.2
		Total	1,180,500	4.1	42,684,100	4.3
	Total	**Total**	**1,500,000**	**2.8**	**51,898,400**	**3.0**

NOTE: More detailed information can be obtained from the author.

the 2010 GBD study modelled the number of deaths mathematically (Wang et al. 2012).

Survey data measuring alcohol consumption, patterns of alcohol consumption, and the prevalence of lifetime abstainers, former drinkers, and current drinkers also are susceptible to numerous biases (Shield and Rehm 2012). To correct for the undercoverage that is observed when alcohol consumption is measured by population surveys (as compared with per capita consumption of alcohol), alcohol consumption was modelled by triangulating per capita and survey data (see above). Total alcohol consumption was set to 80 percent of per capita consumption in order to account for alcohol produced and/or sold, but not consumed, and to account for the undercoverage of the alcohol consumption typically observed in studies that calculate the alcohol RRs (Rehm et al. 2010*b*). Additionally, although alcohol was measured using adult per capita consumption and most people 14 years and younger do not consume alcohol or binge regularly, some adolescents 10 to 14 years of age report previously trying alcohol and previously being intoxicated (Windle et al. 2008).

The CRA was based on alcohol RR functions that typically were differentiated by sex and adjusted for age, smoking status, and other potentially confounding factors. The use of adjusted RR functions may introduce bias into the estimated number of deaths and PYLL that would not have occurred if no one had ever consumed alcohol (Flegal et al. 2006; Korn and Graubard 1999; Rockhill and Newman 1998). However, most of the published literature on alcohol-as-a-risk-factor–only reports adjusted RRs, and, thus, the use of unadjusted alcohol RRs for the CRA study would have led to imprecise estimates as a result of leaving out most of the studies. The bias of using adjusted RRs is likely to be small, as most analyses of the estimated RRs show no marked differences after adjustment for the potentially confounding factors and effect measure modifiers. Future CRA studies may require more complex modelling techniques for alcohol if other dimensions of alcohol consumption, such as irregular heavy-drinking occasions, impact RR estimates.

Finally, this analysis did not account for a lag time for the calculation methods used in this paper. This is especially a problem for cancer, which has a lag time of 15 to 20 years (Holmes et al. 2012; Rehm et al. 2007). In other words, the alcohol-attributable deaths and PYLL in 2010 actually are based on consumption patterns from 1990 to 1995, but in this paper were estimated based on consumption in 1990 and 2010. Although liver cirrhosis also is a chronic disease that develops over time like cancer (Rehm et al. 2013*a*), the impact of population-level consumption on liver cirrhosis deaths can be quite abrupt. For example, Gorbachev's anti-alcohol campaign was reflected in a clear reduction in Russia's liver cirrhosis mortality (Leon 1997). Likewise, the German seizure of alcohol in France in World War II led to reduced cirrhosis mortality (Zatonski et al. 2010). Most of the effect of alcohol consumption on liver cirrhosis probably is captured within 1 year (Holmes et al. 2012). For injury, with the exception of suicide, there is no noticeable lag time as the risk of injury is associated with blood alcohol content (Taylor and Rehm 2012; see also Cherpitel 2013).

Implications of Alcohol-Attributable Mortality

In 1990 and in 2010, alcohol consumption had a huge impact on mortality. Regions such as Europe (especially Eastern Europe) and parts of Sub-Saharan Africa (especially south Sub-Saharan Africa) that have a high per capita consumption of alcohol and detrimental drinking patterns are more affected by alcohol consumption compared with other regions. It is important to note that the alcohol-attributable mortality burden is composed of two elements: AAF and the overall mortality burden of the respective disease. Accordingly, the observed overall increase from 1990 to 2010 in alcohol-attributable cancer, liver cirrhosis, and injury deaths and in PYLL can be attributed to two different sources: (1) an increase in the number of cancer, liver cirrhosis, and injury deaths (mainly attributed to increases of these deaths in low- to middle-income countries) (Lozano et al. 2012) and (2) an increase in alcohol consumption in low- to middle-income countries (Shield et al. 2013*b*).

Low- and middle-income countries have higher rates of alcohol-attributable mortality per 100,000 people, even though these countries typically have lower AAF (as their overall burden of mortality is higher). Economic wealth is correlated with overall mortality (Lozano et al. 2012), and, thus, the mortality burden per litre of alcohol consumed is highest in low-income countries, followed by middle-income countries (Rehm et al. 2009; Schmidt et al. 2010). It follows, therefore, that increases in the alcohol-attributable mortality burden in low- and middle-income countries attributed to economic growth may be able to be reduced or controlled for by implementing alcohol control policies such as taxation (Shield et al. 2011; Sornpaisarn et al. 2012*a, b,* 2013), bans on advertising, and restrictions on availability (Anderson et al. 2009; World Health Organization 2011*b*) preferably while maintaining the relatively high levels of abstention in these countries.

The typical causes of death associated with alcohol use disorders are liver cirrhosis and injuries, (i.e., exactly the categories described in this article). Liver cirrhosis and injuries, and to a lesser degree cancer, may primarily be responsible for the high proportion of alcohol-attributable mortality explained by alcohol use disorders (Rehm et al. 2013*b*); however, additional research is required to empirically confirm this hypothesis. By increasing the rate of treatment for alcohol use disorders (Rehm et al. 2013*b*), the mortality burden of alcohol-attributable diseases also can be reduced. Recent research has shown that the mortality burden associated with alcohol use disorders, albeit high, has been underestimated (see Harris and Barraclough 1998 for the first meta-analysis; and Callaghan et al. 2012; Campos et al. 2011; Guitart et al. 2011; Hayes et al., 2011; Saieva et al. 2012; Tikkanen et al.

2009 for recent papers that observed a markedly higher mortality risk than in the first meta-analysis). ■

Acknowledgements

We thank all who helped to realize the Comparative Risk Assessment for alcohol within the 2010 Global Burden of Disease and Injury study, and to especially thank Gerrit Gmel and Tara Kehoe-Chan, who helped program the alcohol-attributable fractions.

Financial Disclosure

The authors declare that they have no competing financial interests.

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Using Surveys to Calculate Disability-Adjusted Life-Years

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Mapping a certain disease into a system of disabling attributes allows researchers to compare diseases within a common framework. To quantify the total burden of morbidity (e.g., morbidity attributable to alcohol use), so-called disability weights (DWs) must be generated. General-population surveys can be used to derive DWs from health valuation tasks. This article describes the application of three psychometric methods (i.e., pairwise comparisons, ranking tasks, and visual analog scales) in general-population surveys and outlines their strengths and weaknesses. A recently proposed health valuation framework also is presented, which highlights the underlying cognitive processes from a social-judgment perspective and presents a structured data-collection procedure that seems promising in deriving DWs from general-population surveys.

To quantify the burden of a disease within a population, a health-gap measure is more useful than measures of health expectancy or quality-adjusted life-years (see Etches et al. 2006). Disability-adjusted life-years (DALYs), the most prominent of the health-gap measures, combine the burden attributable to early death and to morbidity into one single number. Alcohol affects a long list of diseases and disabilities in varying intensities, each of which can be described by a number of health-state attributes. Common measures of health outcomes include the EuroQol5D (EQ5D) (Brooks and EuroQol Group 1996), the Health Utilities Index III (HUI III) (Feeny et al. 2002), the Short-Form 36 Health Survey (SF36) (Ware and Sherbourne 1992), and the CLAssification and MEasurement System of Functional Health (CLAMES) (McIntosh et al. 2007).

Mapping a certain disease into a system of disabling attributes (e.g., physical functioning, pain, memory and thinking, etc.) enables health researchers to compare qualitatively different diseases within a common framework. To quantify the total burden of alcohol-attributable morbidity, it is necessary to provide so-called disability weights (DWs) for each of these health states, which are bounded by the DWs of 0 (for complete health) and 1 (for death). It should be noted that health states are considered, rather than diseases with labels (and their psychological and/or medical implications), when DWs are determined.

How DWs can validly be measured, defined, or (more neutrally speaking) elicited is of equal importance for the results as the question, "Who is asked to provide the DWs?" Although elicitation methods will be discussed below, this article does not focus on the question of which sources (e.g., patients, clinical experts, etc.) should be consulted to quantify DWs. Rather, this article considers only general-population surveys (i.e., telephone, face to face, or mailed) as sources of information on the disabilities associated with different health states.

How Are DWs Elicited?

Three popular methods to construct DWs stem from econometric utility theory: standard gamble (SG), time tradeoff (TTO), and person tradeoff (PTO). They all share the central idea that a respondent's point of indifference, at which he or she cannot unequivocally decide on a certain judgmental task, enables researchers to measure utility differences via the traded "goods." For example, in SG, respondents are given a choice between an outcome that is certain (i.e., remaining in ill health) and a

gamble with one better and one worse outcome (e.g., full health or death). Respondents are asked what probability of the better outcome would make them indifferent to remaining in the described state (ill health) for certain or choosing the risky option. Therefore, if they are indifferent to the ill-health state and gamble with a 0.8 probability of the better outcome (but 0.2 probability of the worse outcome), 0.8 represents the utility of the ill health.

In a TTO task, respondents are asked to consider the relative amounts of time (e.g., number of life-years) they would be willing to sacrifice to avoid a certain poorer health state (e.g., frequent headaches). Assuming a scenario of 10 years with frequent headaches, the respondent may be indifferent to this state and a shorter lifetime of 7 years, resulting in an estimated utility for the frequent-headaches health state of 0.7 (7 years divided by 10 years).

A typical PTO elicitation asks respondents to choose between two equally expensive health care treatment programs that improve quality of life or save lives for two groups of patients. The decisionmaker must choose to fund one of the two mutually exclusive programs, one of which has a fixed number of patients. Respondents are asked how many patients would need to be treated to make them indifferent to the two programs. For example, program A might extend the life of 100 healthy individuals for 1 year, whereas program B might cure 100 individuals of a chronic health condition.

All three methods are time consuming, require highly motivated respondents, and are hardly feasible without a trained interviewer or computer program. Whereas TTO has been used in face-to-face interviews in the general population quite often (e.g., Badia et al. 2001; Chevalier and de Pouvourville 2011; Dolan 1997; Greiner et al. 2005; Jelsma et al. 2003; Jo et al. 2008; Lamers et al. 2006; Lee et al. 2009; Shaw et al. 2010; Tsuchiya et al. 2002; Wittrup-Jensen et al. 2009; Zarate et al. 2008), in mail surveys only two studies (Burström et al. 2006; Lundberg et al. 1999) used TTO to quantify respondents' own health states. SG and PTO have rarely been used for eliciting health-state preferences in mailed surveys (i.e., they are usually used in face-to-face or phone interviews), and they have only been used among former patients (i.e., not the general public) (Hammerschmidt et al. 2004).

Readers are referred to Rehm and Frick (2010) for an overview on the methodological problems associated with econometric elicitation methods in this context. Recently, Wittenberg and Prosser (2011) described two additional sources of bias or mistaken responses in preference measurement in surveys: ordering errors (i.e., illogical responses, which violate a naturally given order, whereas inconsistent responses contradict each other within a person), and objections/invariance (i.e., respondents may refuse to participate because of an unwillingness to trade time [in the TTO task] or risk [in the SG task]). Furthermore, the meaning of SG results has been criticized as rather a measurement of risk attitude than a representation of subjective utility (Lenert and Kaplan 2000). TTO results as a metric for utility have been shown to vary with respondents' age, education, and current health state (Ayalon and King-Kallimanis 2010; Meropol et al. 2008; Stiggelbout et al. 1996; Voogt et al. 2005). Feasibility of PTO frequently is hampered because people tend to refuse such tasks because of their desire to avoid prejudice and discrimination (Damschroder et al. 2005).

As alternatives to the methods described above, psychometric theory provides paired comparisons, ranking tasks, and visual analogue scales as tools to elicit health-state preferences. These tools are discussed below.

Paired Comparisons

In the context of health-state valuation, a paired comparison (PC) task simply means that respondents must choose which of two given states is more disabling, worse, or dominant in some way. Because measuring via PC seems quite simple and feasible (because it is only necessary to present all health states in a consistent descriptive system), it has been applied in various surveys in the general population (Bijlenga et al. 2009; Kind 1982, 2005; Prieto and Alonso 2000; Ratcliffe et al. 2009; Stolk et al. 2010). For a recent application of PCs among an expert panel see Rehm and Frick (2013). Deriving DWs from the resulting pattern of dominance relations, by contrast, constitutes a complex statistical task for which solutions have been formulated from the theory of Thurstone scaling (Thurstone 1927), conditional logistic regression (Hosmer and Lemeshow 2000), and loglinear modeling (Critchlow and Fligner 1991).

Methodological challenges associated with PC stem from logically inconsistent judgments (e.g., A > B and B > C, but C > A) and from rapidly increasing burden of task when comparing larger numbers of health states (i.e., combinatorial explosion). Intransitive judgments (e.g., in comparing 10, 7, and 5, 10 is preferred to 7 and 7 is preferred to 5, but 5 is preferred to 10) may originate in unintended framing effects as well as in imperfect judgment (von Winterfeldt and Edwards 1986). Recently published experimental stud-

ies favor the position that excluding inconsistent ratings cannot improve the description of true preferences and therefore might to some degree be an inevitable consequence of the decisionmaking process itself (Linares 2009). To keep the number of judgments at manageable dimensions, several studies have used incomplete factorial designs (Bijlenga et al. 2009; Prieto and Alonso 2000; Ratcliffe et al. 2009).

Asking subjects to rank order several health states, but statistically analyzing rankings as PCs, was used as an alternative in several studies (Krabbe 2008; Ip et al. 2004). Rankings can be transformed into a series of PCs (Francis et al. 2002), which at first glance avoids inconsistent judgments.

Ranking Tasks

Health-state rankings (i.e., putting several health states into an ordinal sequence of disability), which also provide comparative information, require less cognitive effort for survey respondents. Furthermore, simultaneous comparisons of multiple health states might be less sensitive to biases (e.g., those provoked by arbitrarily labeled endpoints of rating scales) (Maydeu-Olivares and Böckenholt 2008). Although ranking exercises had been included in numerous valuation studies as an external comparison measure for TTO and SG, researchers had not used the resulting ordinal data (McCabe et al. 2006) for construction of DWs before the seminal article by Salomon (2003). Cardinal utilities derived from health-state rankings displayed high agreement to utilities from TTO or SG methods (Craig et al. 2009*a*, *b*; Kind 2005) and were more stable in a cross-cultural comparison than weights derived from SG (Ferreira et al. 2011).

From a more theoretical viewpoint, articles by Flynn and colleagues (2010) and Flynn (2010) have raised serious statistical concerns about the use of ranks as a substitution for econometric valuation tasks. Their critique focuses on modeling assumptions and thus seems beyond the scope of this article. Nevertheless, their argument suggests that it can be important to restrict the number of alternatives to be ranked and to pay special attention to how a respondent generates rankings. In addition, Lenert and colleagues (1998) have demonstrated that reported utilities are heavily influenced by the search process used to form a certain judgment. This matches the notion that preferences often are constructed (instead of merely obtained) in the elicitation process (Slovic 1995). Ranking tasks within self-administered questionnaires might be hampered by limited control of the mechanism respondents use to generate the rank order. This introduces at least two issues: First, it remains unclear which reference attributes the respondent uses to generate the rank order, which constricts intersubjective comparability and provokes primacy biases (i.e., the tendency to give more attention to items listed first) (Bowling 2005). Second, from a more technical perspective, statistical ranking models (such as the rank-ordered logit model) assume that rankings were obtained using a particular psychological mechanism (Flynn 2010). For free rankings, however, it remains unclear which statistical model is most appropriate to describe the ranking mechanism. Furthermore, it cannot be ensured that respondents using a self-administered questionnaire judge along repeated best/worst choices, a "ping-pong" method that was shown to produce reliable data (Louviere at el. 2008).

Visual Analog Scale

To use a visual analog scale (VAS), respondents are asked to specify their level of agreement to a statement by indicating a position along a continuous line between two endpoints. Numerous studies have used VAS responses to derive health-state values in the general population (Björk and Norinder 1999; Cleemput 2010; Devlin et al. 2003; Dolan and Kind 1996; Essink- Bot et al. 1993; Greiner et al. 2003; Johnson and Pickard 2000; Johnson et al. 1998; Leidl and Reitmeir 2011). Krabbe and colleagues (2007) proposed a methodology based on differences in VAS values, where the ranks of pairwise VAS differences are used in a multidimensional scaling analysis to estimate cardinal health-state values. However, other researchers have questioned the validity of VAS data as cardinal values (Bleichrodt and Johannesson 1997; Devlin et al. 2004; van Osch and Stiggelbout 2005) for various reasons. First, VAS tasks in which the top and the bottom endpoints are precisely defined (e.g., death versus perfect health) allow direct comparison between individuals, whereas vague labels such as "worst imaginable" and "best imaginable" hamper an interindividual comparison (Torrance et al. 2001). Second, VAS responses might be affected by a so-called end-aversion bias, the phenomenon of respondents tending to be reluctant to mark positions near the endpoints of the scale (Bleichrodt and Johannesson 1997; Robinson et al. 2001; Torrance et al. 2001). Third, a VAS score for a certain health state may depend on other states presented at the same time (i.e., context bias) (Torrance et al. 2001). Fourth, the accuracy of VAS responses may be influenced by hand preferences and which hand was used (McKechnie and Brodie 2008).

Finally, the orientation of the VAS scale (vertical versus horizontal) itself might affect the shape of the resulting score distribution (e.g., Lundqvist et al. 2009). Taken together, VAS responses therefore should be interpreted on an ordinal scale level only.

Health Valuation: A Social Judgment Perspective

Stiggelbout and de Vogel-Voogt (2008) presented a four-step framework describing respondents' cognitive processes while valuing health states: perspective/perception of the stimulus, interpretation, judgment, and formation of a manifest response (see also Rehm and Frick 2010). For each step, several mechanisms have been identified, which may affect the final response.

1. Perspective/perception of the stimulus. In a meta-analysis, Dolders and colleagues (2006) reported no significant differences in preferences when patient surveys were compared with those of the general public, whereas a more recent and more extensive meta-analysis by Peeters and Stiggelbout (2010) suggests that patients differ from the general public in their valuations. Frick and colleagues (2012) reported on the importance of social relationships as determinants of health valuation, especially for health professionals. Health states hampering social relationships are judged as more disabling. Ubel and colleagues (2003) described several factors that may contribute to these discrepancies: adaptation effects (i.e., affected patients often adapt physically and emotionally to their health state, resulting in a more positive valuation of the respective state), focusing illusion (i.e., healthy people focus on impaired attributes, largely ignoring unchanged attributes of a certain disease), and contrast effects (i.e., severely ill patients may underestimate the impact of lenient diseases, while healthy people may overestimate this impact). Conducting a survey in the general public will result in a weighted mixture of affected and healthy valuation perspective.

2. Interpretation/primary appraisal. The interpretation of a health state depends on a subject's values, goals, and beliefs, as well as on the cognitive framing (Kahneman and Tversky 1984) and/or context (Schwarz 1999) of the health-state description.

3. Judgments on health states. Like human judgments in general, these are not formed to fulfill the criteria of an exhaustive information processing. By contrast, they serve as decision rules to govern behavior (e.g., giving an answer in a questionnaire) and follow the principles of parsimony and functional pragmatism rather than coherence and rationality. Stiggelbout and de Vogel-Voogt (2008) identified various sources of biases that might be relevant in the context of health valuation, such as focusing illusion (see step 1), status quo bias (i.e., respondents are more sensitive to changes in their own health state compared with imagined health states), loss aversion (see Tversky and Kahneman 1992), or failure to anticipate negative events (i.e., poor hedonic forecasting). In addition, affects and mood are known to be highly influential during judgmental processing.

4. A deliberate editing of the response. In this last step, for example, a respondent's attempt to be compatible with perceived norms (e.g., perceived fairness, political correctness, or ethical considerations) further biases a subjective valuation (Rehm and Frick 2010).

Conclusion

Econometric elicitation methods were not originally developed for self-administered questionnaires. Given the many methodological risks of using this data collection mode, TTO, PTO, or SG elicitation methods are not recommended for paper-and-pencil surveys. Understanding the introductory scenarios and autonomously and successively approaching the point of indifference seems too complicated a task for lay respondents. Though VAS scales were developed specifically for self-administered questionnaires, their validity and reliability are too weak to measure the utilities of complex health states on the interval level. Choosing between rankings and PC tasks would mean a tradeoff between economy and validity of the measurement procedure.

Among PCs presented to respondents from the general public, those with the following characteristics seem to be most promising: (1) The number of pairs of health states should be limited (to a number determined by pre-analysis) so that annoyance effects or reactance can mostly be precluded. (2) Cognitive complexity of the health state descriptions should not exceed seven (plus or minus two) judgmental attributes (Miller 1956). However, this does not necessarily mean that health-state descriptions should be limited to seven dimensions or attributes, as respondents tend to

organize redundant information into broader superconcepts. That being said, this ability should also be evaluated prior to the survey. Applying these principles would allow surveys to pose complex vignettes to respondents. (3) To avoid biases due to the direction of a comparison (e.g., A versus B is not the same as B versus A) (Wänke 1996), presentation of health states within one comparison should be randomly balanced. To avoid order effects or carryover effects, factorial design techniques that also preclude repetitive presentations of certain health states (A versus B followed by C versus D and not by A versus C, for instance) should be used in the assignment of comparison tasks to respondents. Complex survey designs like the one proposed here require adequate techniques for statistical analysis (Hox et al. 1991). ■

Financial Disclosure

The authors declare that they have no competing financial interests.

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Stress and Alcohol

Epidemiologic Evidence

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Exposure to stress often is psychologically distressing. The impact of stress on alcohol use and the risk of alcohol use disorders (AUDs) depends on the type, timing during the life course, duration, and severity of the stress experienced. Four important categories of stressors that can influence alcohol consumption are general life stress, catastrophic/fateful stress, childhood maltreatment, and minority stress. General life stressors, including divorce and job loss, increase the risk for AUDs. Exposure to terrorism or other disasters causes population-level increases in overall alcohol consumption but little increase in the incidence of AUDs. However, individuals with a history of AUDs are more likely to drink to cope with the traumatic event. Early onset of drinking in adolescence, as well as adult AUDs, are more common among people who experience childhood maltreatment. Finally, both perceptions and objective indicators of discrimination are associated with alcohol use and AUDs among racial/ethnic and sexual minorities. These observations demonstrate that exposure to stress in many forms is related to subsequent alcohol consumption and AUDs. However, many areas of this research remain to be studied, including greater attention to the role of various stressors in the course of AUDs and potential risk moderators when individuals are exposed to stressors. **Key words: Alcohol use and abuse; alcohol use disorders; stress; stress as a cause of alcohol and other drug use; risk factors; psychological stress; stress response; coping; stressors; general life stress; catastrophe; child abuse; minority group; epidemiological indicators**

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Exposure to varying forms of stress is an integral life experience that can provoke a variety of reactions. In research on alcohol, drug, and psychiatric disorders, the term "stress" often is understood to indicate any experience denoting adversity (Dohrenwend 2000). Stress exposures consist of external stimuli that are threatening or harmful; elicit fear, anxiety, anger, excitement, and/or sadness; and are negative in impact and outcome (Sinha 2001, 2008). Mild to moderate levels of stress can present challenges that are within a person's capability to overcome, producing a sense of mastery and accomplishment that eventually result in a positive outcome. However, adverse experiences that exceed the coping abilities of the individual increase the risk for psychopathology (Lazarus 1999; Levine 2005; McEwen 2007; Selye 1976; Sinha 2008).

Just as people vary in their capabilities, stress exposures can be viewed as varying across several dimensions (see figure 1). One dimension is severity, which can range from mild (e.g., the daily hassles of family and job among healthy individuals whose basic needs are met) to severe (e.g., extreme adversity that threatens the life, physical integrity, health and home of oneself and one's loved ones). Other dimensions, not necessarily orthogonal to each other, include whether the stressor occurred during childhood or maturity, the degree to which the stressor is acute or chronic and expected or unexpected, whether the threat is emotional or physical, and the difficulty of discerning whether the stressor was the cause or consequence of the health outcome under consideration.

This article presents evidence for the effect of four categories of stressors,

including general life stress, catastrophic/fateful stress, childhood maltreatment, and minority stress, each of which encompasses a range of specific kinds of stressors (see figure 2). Each category of stressors is evaluated according to the dimensions shown in figure 1, and the extant epidemiologic evidence for the effect of each on both alcohol use and alcohol use disorders (AUDs) is reviewed.

General Life Stressors and AUDs—Evidence From National Surveys

National surveys often include some measure of general life stress that may range from common experiences, such as moving or changing jobs, to uncommon experiences, such as severe threats to personal integrity and arrest. The severity of the events often is variable; for example, a divorce that may be stressful for some individuals can be a relief for others, and the death of a relative may refer to a parent or spouse or to a distant relative with little connection to the respondent's day-to-day life. Nevertheless, the overall number of these experiences is related to alcohol outcomes (see table 1). In the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions, respondents reported on 12 general life stressors, ranging from items such as changing jobs or moving, to trouble with a boss or coworker, trouble with a neighbor, and a family member in poor health, to being the victim of a crime, being unemployed or fired from a job, and divorce or breakup of a steady relationship. The data show that the number of past-year stressors experienced was related to any current drinking, current binge drinking (i.e., consuming five or more drinks for men or four or more drinks for women at least once in the past year), and current AUDs. Among men, the relationship with each alcohol outcome steadily increased from 0 to approximately 6 stressors, after which the relationship tapered off and tended to decrease at 10 or more stressors. Among women, the relationship with each outcome generally was more linear, with increases in prevalence at each increase in past-year stressors (see table 1).

Various studies in smaller adult community samples also have found that the number of general life stressors is associated with alcohol consumption and problem alcohol use (which may not necessarily meet the criteria of an AUD) (Cole et al. 1990; King et al. 2003). However, one population-based longitudinal study of older adults (mean age 61 years) did not demonstrate long-term effects (i.e., at 1 year or more after the event) of acute stressful life events on patterns of alcohol consumption (Skaff et al. 1999). A national prospective study of 3,006 women found an increased risk of alcohol abuse after being an assault victim, with no evidence of reverse causation (i.e., that alcohol consumption alone contributed to the risk for assault) (Kilpatrick et al. 1997). However, other studies have indicated that excessive alcohol use also increases the risk for sexual assault (Abbey et al. 1994; Corbin et al. 2001); therefore, the relationship between assault and alcohol use likely is bidirectional. Finally, several general population studies have found an increase in the incidence of AUDs following job loss, particularly among men (Catalano et al. 1993; Crawford et al. 1987). It is noteworthy, however, that the context of a job loss likely is important for its impact on the risk of AUDs. For example, the meaning of the lost job may be different for a worker whose plant is shut down after he or she has worked for 30 years in the same position compared with an artist or a musician accustomed to temporary work. Nevertheless, these studies indicate that any type of job loss is associated with increased risk of AUDs.

Genetic factors may influence the relationship between exposure to general stressors and alcohol and other drug use. In a longitudinal study of 295 college students who for 2 years

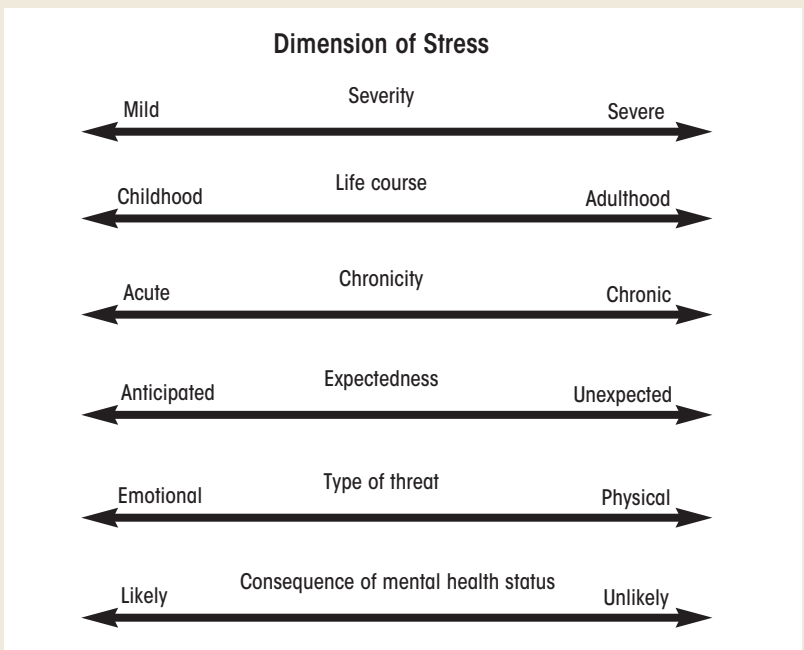

Figure 1 Dimensions of stressful experiences.

provided daily reports of stressful events as well as alcohol and drug use via the internet, those who carried two copies of a specific variant in regulatory region of the gene encoding a protein involved in the actions of the brain signaling molecule serotonin (i.e., who were homozygous for the *s* allele of 5-HTTLPR serotonin transporter promoter) were at substantially increased risk for heavy drinking and drug use if they experienced a high level of stressful life events compared with students carrying only one or no copy of this allele (Covault et al. 2007).

It also is important to note that daily exposure to interpersonal stress, such as problems at work, trouble with the police, or breakup of romantic relationships also may be influenced by having an AUD. Although these exposures likely are stressful for anyone experiencing them, they can be as much a consequence as a cause of an AUD. Therefore, teasing apart the temporal and causal directions of relationships between these adult stressors and alcohol use is a difficult task in general-population epidemiologic samples.

Substantial research on mental health in general and alcohol consumption specifically has been conducted after the terrorist attacks on the World Trade Center.

Fateful/Catastrophic Events and AUDs

With respect to the various correlated dimensions of stress in human populations described earlier, fateful/catastrophic events, such as direct exposure to a disaster or terrorism attack, typically lie on the more extreme end of the severity continuum. These stressors usually are acute and unexpected, and exposure is very unlikely to result from an individual's alcohol consumption. However, the "fatefulness" of the event may depend on the specific circumstances of the event. For example, studies of people exposed to nightclub disasters (e.g., from fires and terrorist attacks) (Kennedy et al. 2005; Mahoney et al. 2005) involve individuals who are younger and more likely to consume alcohol than the general population. The study of such events still may provide important information, but the type of individuals involved and the appropriate control group must be considered carefully. Fateful/catastrophic events can involve both physical threat to one's life and emotional threat (e.g., knowing someone lost or killed in the fateful/catastrophic incident, fear of additional exposures) and generally can occur at any point in the life course.

Both in the United States and internationally, many studies have addressed the relationship between different types of natural and man-made disasters and alcohol consumption, including studies of exposure to natural disasters, such as flooding (North et al. 2004), volcano eruptions (Adams and Adams 1984), earthquakes (Shimizu et al. 2000), and hurricanes (Cerda et al. 2011; Kohn et al. 2005). Studies also have investigated the consequences of exposure to man-made disasters, such as mass shootings (North et al. 1994; Smith et al. 1999), fire or grotesque death (Green et al. 1985; Reijneveld et al. 2003; Sims and Sims 1998), ferry disasters (Joseph et al. 1993), and nuclear accidents (Kasl et al. 1981). Studies covering a timeframe of a year or less after the disaster consistently have indicated postdisaster increases in alcohol consumption (Joseph et al. 1993; Kasl et al. 1981; Kohn et al. 2005; Reijneveld et al. 2003; Sims and Sims 1998; Smith et al. 1999). Studies with multiple and/or longer followups generally have found attenuation of this relationship over time (Joseph et al. 1993).

Several studies also have addressed alcohol consumption in response to

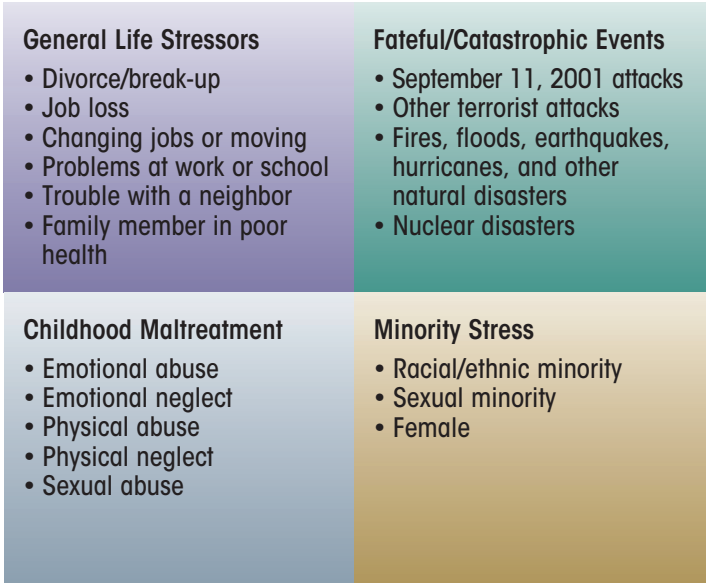

Figure 2 Four categories of stressors and examples of exposures within each stress category.

exposure to terrorism. Substantial research on mental health in general and alcohol consumption specifically has been conducted after the terrorist attacks on the World Trade Center in New York City and the Pentagon in Washington, DC, on September 11, 2001 (9/11). These studies have indicated that alcohol consumption generally increased in both New York City and elsewhere in the short term following the attacks. Thus, increased alcohol use was found among the following groups:

- Survivors of the attack on the Pentagon (Grieger et al. 2003);
- Residents of Manhattan in the one month and/or six months following the attack (Ho et al. 2002; Vlahov et al. 2002, 2004);
- Residents in the tri-State area of Connecticut, New York, and New Jersey (Melnik et al. 2002); and
- Adults from a nationally representative sample (Stein et al. 2004).

Longer-term studies showed increased alcohol consumption 1 and 2 years later among New Yorkers at greater exposure levels to the attack (Boscarino et al. 2006).

Few studies have examined alcohol use and terrorism exposure outside the United States, but two studies of adolescents in different cities in Israel found that geographic proximity to terrorist attacks was associated with greater quantity and frequency of drinking as well as with binge drinking (Schiff et al. 2006, 2007).

Several studies have been able to control for predisaster drinking levels, the lack of which had been a limitation of most of the aforementioned epidemiologic research. These studies have documented an increase in alcohol consumption following exposure to disaster independent of the consumption levels measured prior to the exposure (Cerda et al. 2011; Hasin et al. 2007*a*; Richman et al. 2004). A recent meta-analysis of 27 studies assessing substance use in response to terrorism that included studies with follow-up times ranging from 1 week to more than 2 years found a pooled effect indicating that the population level of alcohol consumption is increased following a terrorist attack (DiMaggio et al. 2009).

The research described above focuses on any alcohol consumption after disaster. Studies of AUDs and problem drinking following major disasters have been less consistent. Following the Oklahoma City bombings in 1995, North and colleagues reported no increase in incident AUDs, either in survivors of the attack (North et al. 1999) or in rescue workers (North et al. 2002). Survivors of other disasters, such as Hurricane Andrew (David et al. 1996), flooding (Green et al. 1992; North et al. 2004), and jet crashes

Table 1 Relationship Between Number of Past-Year Stressors and Prevalence of Current Drinking, Current Binge Drinking, and Current Alcohol Use Disorders Among Men and Women in the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions (*N* = 43,093).

	Men			Women		
	Current Drinking (% respondents)	Current Binge Drinking (% respondents)	Current Alcohol Use Disorders (% respondents)	Current Drinking (% respondents)	Current Binge Drinking (% respondents)	Current Alcohol Use Disorders (% respondents)
Number of past-year stressors						
0	65.9	32.0	6.1	49.0	11.9	1.8
1	70.7	41.2	9.8	58.5	13.8	3.3
2	72.8	42.7	12.0	61.6	17.7	4.7
3	77.8	52.3	18.3	68.7	24.5	7.0
4	79.0	60.8	24.6	73.8	28.8	11.5
5	84.1	61.5	30.3	74.6	33.5	11.9
6	87.7	66.1	35.0	77.6	39.2	13.7
7	87.3	69.5	35.8	76.9	36.5	21.2
8	85.6	70.7	35.1	84.0	47.7	23.9
9	96.8	66.9	56.3	86.9	46.1	33.2
10+	66.0	65.2	36.4	89.2	50.9	40.8

SOURCE: National Epidemiologic Survey on Alcohol and Related Conditions

(Smith et al. 1990), as well as a combined sample of survivors from the Oklahoma City terrorist bombing and the bombing of the U.S. embassy in Nairobi, Kenya (North et al. 2005) also showed no evidence of increases in incident AUDs. Studies assessing the impact of 9/11 found that neither living near the attack site nor knowing someone lost or killed was associated with incident alcohol problems 6 months following the attack (Vlahov et al. 2006); moreover, exposure to 9/11 was not associated with the trajectory of alcohol use and binge drinking in the 3 years following the attack (Cerda et al. 2008). In a recent pooled analysis of data from 10 different disasters, including exposure to flooding, shootings, and plane crashes, North and colleagues (2010) again reported no evidence of increased risk for incident AUDs after these events, although people with pre-existing AUDs were more likely to report increased drinking after these events.

Several studies contradict the above evidence, however, as follows:

- Evidence from survivors of Hurricane Katrina indicates elevated rates of alcohol problems compared with national and local predisaster averages (Flory et al. 2009). Furthermore, increases in binge drinking were found among those most exposed to the hurricane, controlling for prehurricane alcohol use (Cerda et al. 2011).

- Among New Yorkers interviewed at 1 and 2 years after 9/11, greater exposure levels predicted binge drinking at 1 year but not 2 years and an increase in alcohol dependence at both time points (Boscarino et al. 2006).

- Seven months after the Mount St. Helens volcano eruption, alcohol-center referrals and liquor-law violations had increased compared with the pre-eruption period (Adams and Adams 1984).

- Survivors of the Beverly Hills Supper Club fire seemed to have an increase in alcohol abuse more than 2 years after the fire (Green et al. 1985).

Thus, the literature is inconsistent on the role of fateful traumatic events in the development of AUDs. It is noteworthy, however, that studies of incident AUDs after major disasters were conducted in adult populations in which the incidence of such disorders generally is low (Hasin et al. 2007*b*). Studies of incident AUD risk following exposure to disaster in adolescent and young adult populations are necessary to comprehensively understand the relation between disaster and incident AUDs.

A substantial literature also has documented increased alcohol consumption and risk for AUDs among war veterans, especially those exposed to active combat (Hoge et al. 2006; Jacobson et al. 2008; Milliken et al. 2007; Shipherd et al. 2005). Causal inference from this literature is complicated, however, because people who perform military duty most often are young men at high baseline risk for AUDs. In addition, exposure to combat is not randomly assigned, and people who have sensation-seeking personality characteristics are more likely to both be assigned to combat and, independently, develop AUDs.

Child Maltreatment and AUDs

Childhood maltreatment includes many adverse exposures (e.g., sexual, emotional, and/or physical abuse and emotional and/or physical neglect) during the first 18 years of life. With respect to the various correlated dimensions of stress in human populations described earlier, childhood maltreatment experiences range from mild (e.g., occasionally saying hurtful things) to severe (e.g., chronic physical and/or sexual abuse). Although these stressors can be acute, they often are chronic throughout childhood; furthermore, they are very unlikely to be a consequence of alcohol consumption as they typically occur before drinking initiation. Childhood maltreatment can involve both physical threat (e.g., physical and sexual abuse or physical neglect of needs) and emotional threat (e.g., emotional abuse and neglect). These experiences are common and may account for a significant proportion of all adult psychopathology (Afifi et al. 2008; Green et al. 2010). Further, events frequently co-occur (Dong et al. 2004; Dube et al. 2002; Edwards et al. 2003; Finkelhor et al. 2007)—in other words, exposure to one type of childhood maltreatment increases the risk of exposure to others.

Epidemiologic studies addressing the impact of adverse childhood events on alcohol consumption and AUDs have employed several types of designs, including cross-sectional studies of adults with retrospective assessment of adverse childhood events, prospective cohort studies, and studies of twin and other genetically informative samples. Studies generally have shown that most forms of child maltreatment are related to higher risk of adolescent alcohol consumption (Bensley et al. 1999; Hussey et al. 2006; Sartor et al. 2007; Thornberry et al. 2001) and adult alcohol consumption and AUDs (Anda et al. 2002; MacMillan et al. 2001; Molnar et al. 2001; Nelson et al. 2006). One review documented that childhood maltreatment and other childhood stressors were associated with earlier onset of adolescent alcohol consumption and with AUDs in adulthood (Enoch 2010).

Childhood maltreatment is more likely to occur among children of alcoholics (Gilbert et al. 2009); in these cases, the parents may not only engage in harmful parenting practices (Kettinger et al. 2000; Stanger et al. 2004; Suchman et al. 2007, 2008) but also may pass along genes increasing the risk of AUDs to their offspring. Thus, the specificity of the relationship between maltreatment and alcohol use in the context of these other risk factors remains an open debate. Furthermore, psychiatric comorbidity also may confound the relationship between early maltreatment and AUDs because mal-

treatment affects the risk for multiple psychiatric disorders (Green et al. 2010; Kendler et al. 2000; Kessler et al. 1997; Widom et al. 2007*a*), and AUDs are highly comorbid with other forms of psychopathology (Hasin et al. 2007*b*). Studies using animal models, which can control for environmental factors and comorbidity, have suggested that extended stress in early life leads to later self-administration of alcohol (Cruz et al. 2008; Miczek et al. 2008). However, some epidemiologic studies suggest that the relationship between maltreatment and AUDs may be at least partially confounded by family history of alcohol problems. For example, a prospective cohort study that compared court-recorded cases of abuse and neglect with matched community controls in the Midwest found no remaining association between early abuse and adult AUDs[1] after controlling for family history of alcohol problems among men (Widom et al. 1995, 2007*b*); only among women physical neglect remained associated with AUDs.

However, several studies that controlled for family history of alcoholism have indicated a persistent relationship between childhood adverse events, including parental divorce (Pilowsky et al. 2009; Thompson et al. 2008) and death of a parent or foster home placement (Kendler et al. 1996; Pilowsky et al. 2009), and adult risk for AUDs. Another study documented strong and significantly increased odds of AUDs based on retrospective assessment of childhood sexual abuse among same-sex twins in Australia (Nelson et al. 2002), even after controlling for family background variables such as parental alcohol problems. Finally, recent data from a population-based study of twins in Virginia reported that participants who reported any maltreatment were 1.74 times as likely to experience an AUD in adulthood as were people who did not report maltreatment, and although controlling for family-level risk factors substantially attenuated the observed association, a direct effect remained after control (Young-Wolff et al. 2011).

Research now is examining specific genetic variations (i.e., polymorphisms) as moderators of the relationship between child maltreatment and AUDs. The finding that functional polymorphisms in the gene encoding the monoamine oxidase A enzyme (MAOA) (Caspi et al. 2002) interact with childhood maltreatment to predict antisocial behavior in adulthood stimulated research on whether this effect generalizes to substance use disorders; however, thus far, the findings could not be replicated (Young et al. 2006). Other studies have focused on the previously mentioned serotonin transporter promoter variant, 5-HTTLPR, and its interaction with stressful experiences in a wide variety of psychiatric outcomes after researchers detected such an interaction for major depression (Caspi et al. 2003). This DNA sequences exists in two alleles, *l* and *s* alleles; thus, a person can carry either two *l* or two *s* alleles (i.e., be homozygous for *l* or *s*) or one *l* and one *s* allele (i.e., be heterozygous). One study found that youth with court-documented maltreatment were at higher risk for early-onset alcohol use if they had the heterozygous (*s/l*) genotype compared with the *l/l* genotype (Kaufman et al. 2007). In another youth study, the effect of the same heterozygous genotype on increased risk for substance use was attenuated in families providing involved-supportive parenting (Brody et al. 2009*a*). In an innovative approach involving random assignment of the environment, the investigators then randomized at-risk families to an intervention designed to increase involved-supportive parenting or a control condition (Brody et al. 2009*b*). Among those with the heterozygous 5-HTTLPR genotype, children in treated families had less substance use at followup compared with children of the control families (Brody et al. 2009*b*). Taken together, these studies suggest that the risk for later alcohol outcomes is affected by an interaction of stressful early home environments and genetic vulnerability.

Minority Stress and AUDs

Minority stress is defined as exposure to specific stressors that result from a person's minority status, especially prejudice and discrimination events (Meyer 2003*b*; Williams et al. 2003). These events range from mild (e.g., daily hassles, such as being followed in a store) to more severe (e.g., being a victim of a violent crime) and include both emotional (e.g., workplace harassment [Waldo 1999]) and physical (e.g., hate crimes [Herek 2009]) threats to self. Minority status cannot be attributed to having an AUD, making one aspect of interpretation straightforward in studies in this area. Although minority stress can involve acute events, it most frequently is viewed as a chronic exposure that occurs across the entire life course (Williams et al. 2003). Finally, minority stressors vary with respect to whether they are expected. Research has indicated that although many stressors that members of minority groups confront are unanticipated, one consequence of repeated exposure to discrimination is that people begin to expect rejection based on their stigmatized identity (Mendoza-Denton et al. 2002).

Racial/Ethnic Minorities

According to minority stress models, the stress resulting from prejudice and discrimination should lead to elevations in alcohol use among minority group members. Patterns of alcohol use among racial/ethnic minorities, however, fail to correspond to these predictions. Although Native Americans have higher rates of alcohol consumption and AUDs compared with non-Hispanic Whites (Hasin et al. 2007*b*), several large surveys have indicated lower rates of alcohol consumption and AUDs among non-Hispanic Blacks, Asians, and Hispanics compared with Whites (Breslau et al. 2006; Hasin et al. 2007*b*; Kessler et al. 1994). These

[1] AUDs in this study were defined according to the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* (DSM–III–R).

minority groups also have lower rates of other psychiatric disorders (e.g., major depression), leading to what has been called the "minority paradox" (Williams 2001) in mental health research—that is, minority groups such as Blacks and Hispanics have lower rates of psychiatric and substance disorders despite greater exposure to institutional and interpersonal discrimination that has been shown to engender substantial stress via biological (Lewis et al. 2006) and psychological (Hatzenbuehler 2009) mechanisms. In contrast to these findings from between-group studies, within-group studies consistently show that perceived discrimination is associated with alcohol outcomes. This association has been found in Blacks (McLaughlin et al. 2010*b*; Taylor and Jackson 1990; Yen et al. 1999), Filipino Americans (Gee et al. 2007) and Asian-American adolescents (Yoo et al. 2010).

Sexual Minorities

In contrast to racial/ethnic minorities, lesbian, gay, and bisexual (LGB) individuals have higher rates of substance use and substance use disorders than their heterosexual peers (Garofalo et al. 1998; Russell et al. 2002; Ziyadeh et al. 2007); this difference applies to both adolescents (Eisenberg and Wechsler 2003; Hatzenbuehler et al. 2008) and adults (Burgard et al. 2005; Cochran et al. 2000; Drabble et al. 2005). Although research has tended to primarily examine perceived discrimination as a risk factor for internalizing psychopathology, such as depression and anxiety, recent studies also have shown higher levels of alcohol use (Hatzenbuehler et al. 2011) and AUDs (McCabe et al. 2010) among LGBs who perceive that they have experienced higher levels of discrimination.

Because of their design, these studies cannot rule out reverse causality—that is, that individuals with alcohol problems may perceive and report greater discrimination. In order to address some of these methodological limitations of subjective measures of discrimination, recent studies have developed novel measures for operationalizing objective stressors that LGB individuals confront, including institutional forms of discrimination (e.g., anti-marriage laws or employment discrimination policies). Because these institutional stressors occur outside the control of LGB individuals, they are not confounded with mental health status and therefore provide a stronger test of the effect of discrimination on mental health than measures of subjective stress. Studies are beginning to document the relationship between these objective stressors and LGB health, including alcohol use. For example, a recent study examined the impact of State-level ballot initiatives banning gay marriage on the prevalence of psychiatric and substance use disorders in LGB populations (Hatzenbuehler et al. 2010). The results indicated that LGB respondents living in States that passed such bans in 2004 had significantly greater increases in psychiatric disorders and AUDs than did LGB respondents in States that did not pass such bans (Hatzenbuehler et al. 2010). This research demonstrates the potential importance of incorporating more objectively-defined indices of social stress into research on alcohol use among minority populations. Indeed, an examination of how and why such social stressors contribute to the development and maintenance of AUDs within LGB populations represents a crucial avenue for future inquiry.

Conclusion

The psychological and psychiatric effects of stress remain an important mechanism for individual differences in all areas of mental health. Substantial evidence exists that fateful/catastrophic events, such as exposure to disaster and terrorism; childhood adversities, such as maltreatment; interpersonal stressors, such as divorce and job loss; and chronic minority stress affect alcohol consumption and AUDs. Although these data demonstrate the importance of stress in the development of alcohol problems in human populations, substantial work remains to be done in these areas. Refined measures of stress exposures; careful assessment of confounding and reverse causation; an examination of AUD course, including relapse; and the potentiating of stress effects by genetic vulnerability, personality factors, macrosocial factors, and other important biological and social domains remain important topic areas in need of more epidemiologic study. Exploring the epidemiology of stress in human populations can help integrate and translate work in experimental human and animal models in order to demonstrate the real-world effects of these common yet often devastating exposures on alcohol use and misuse. ■

Acknowledgements

This research was supported in part by National Institute on Alcoholism and Alcohol Abuse grants K05–AA–014223 and U01–AA–018111 (to Dr. Hasin), National Institute of Drug Abuse fellowship F31–DA–026689 (to Dr. Keyes), the Robert Wood Johnson Health and Society Scholars program (to Dr. Hatzenbuehler), and New York State Psychiatric Institute (to Dr. Hasin). We would like to thank Philip Bender for assistance in manuscript preparation.

Financial Disclosure

The authors declare that they have no competing financial interests.

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