Genes, Environments, and Sex Differences in Alcohol Research

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ABSTRACT. Objective: The study of sex differences has been identified as one way to enhance scientific reproducibility, and the National Institutes of Health (NIH) have implemented a new policy to encourage the explicit examination of sex differences. Our goal here is to address sex differences in behavioral genetic research on alcohol outcomes. **Method:** We review sex differences for alcohol outcomes and whether the source and magnitude of genetic influences on alcohol consumption and alcohol use disorder (AUD) are the same across sexes; describe common research designs for studying sex-specific gene-by-environment interaction ($G \times E$) effects; and discuss the role of statistical power

and theory when testing sex-specific genetic effects. **Results:** There are robust sex differences for many alcohol outcomes. The weight of evidence suggests that the source and magnitude of genetic influences on alcohol consumption and AUD are the same across sexes. Whether there are sex-specific $G \times E$ effects has received less attention to date. **Conclusions:** The new NIH policy necessitates a systematic approach for studying sex-specific genetic effects in alcohol research. Researchers are encouraged to report power for tests of these effects and to use theory to develop testable hypotheses, especially for studies of $G \times E$. (*J. Stud. Alcohol Drugs*, 78, 494–501, 2017)

RECENT CONCERNS REGARDING the reproducibility of science have prompted growing interest in what investigators can do to increase confidence in findings that will ultimately inform preventive interventions to improve health (Begley & Ellis, 2012; Open Science Collaboration, 2015). National Institutes of Health (NIH) leadership recently identified examination of sex differences as central to a reproducible science (Collins & Tabak, 2014), and the NIH now expects “that scientists will account for the possible role of sex as a biological variable in vertebrate animal and human studies” (notice no. NOT-OD-15-102). Our objective here is to address sex differences in behavioral genetic research on alcohol outcomes. We begin with an overview of sex differences in alcohol outcomes, review whether there are sex differences in the magnitude or source of genetic influences on alcohol outcomes, and then describe common research designs for investigating sex-specific gene-by-environment interaction ($G \times E$) effects. We conclude with a discussion of the challenge that statistical power poses when studying

sex-specific genetic effects, as well as the role of theory for guiding research in this area.

Terminology

The term *sex* typically refers to an individual’s biological status (male, female, or intersex), and the term *gender* typically refers to the attitudes, feelings, and behaviors associated with biological sex in a particular culture (American Psychological Association, 2012). In human alcohol research, it is difficult to distinguish between differences that have a purely biological or social/cultural origin. In view of this, we use the term *sex differences* for brevity throughout this article but note that this term broadly encompasses sex and gender differences. We return to the need for more systematic attention to the distinctions between sex and gender later.

Sex differences in alcohol outcomes

Epidemiological studies provide ample evidence for sex differences in alcohol outcomes across the drinking career (Nolen-Hoeksema, 2004; Nolen-Hoeksema & Hilt, 2006; Windle, 2016). In a review of findings from the well-characterized U.S. Monitoring the Future sample (Windle, 2016), more early adolescent (eighth grade) females report alcohol use in the past year, alcohol use in the past 30 days, binge or heavy episodic drinking in the past 2 weeks, and past-year drunkenness compared with males. By 10th grade, these

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alcohol indicators converge across the sexes; by 12th grade, more males report binge drinking in the past 2 weeks and being drunk in the past 12 months than do females. Similar trends are observed in European samples; adolescent females drink more frequently than males in early adolescence, but this trend reverses in early adulthood (Ahlstrom & Osterberg, 2004/2005).

Analyses of 16 general population surveys from 10 countries indicate that males and females do not differ in their likelihood of being a current drinker (Wilsnack et al., 2000); however, there are consistent sex differences in drinking behaviors. Compared with females, males report drinking more frequently and in greater quantities, and have higher rates of heavy episodic drinking (5+ drinks per occasion) and adverse drinking consequences (Wilsnack et al., 2000). Recent findings from the 2012–2013 National Epidemiologic Survey on Alcohol and Related Conditions III (NESARC III; Grant et al., 2015) document robust sex differences in alcohol use disorder (AUD) diagnoses in the United States. The 12-month prevalence of any AUD according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5; American Psychiatric Association, 2013), was 10.4% for females and 17.6% for males, representing an adjusted odds ratio (adjusted for race/ethnicity, age, marital status, educational level, annual family income, urbanicity, and region) of 1.9 for males. Sex differences in patterns and rates of AUD have considerable personal and social costs. Worldwide, 7.6% of males' deaths and 4.0% of females' deaths were attributable to alcohol in 2012 (World Health Organization [WHO], 2014).

Some have noted that the magnitude of sex differences in alcohol outcomes is declining (Keyes et al., 2011; WHO, 2014). This convergence appears to be driven by decreases in males' drinking frequency and the number of males meeting criteria for AUDs, alongside increases in females' drinking frequency and stability in the number of females meeting criteria for AUDs (White et al., 2015). The uptick in females' drinking and alcohol abuse has been attributed to their increased participation in society and economic opportunity (Keyes et al., 2011; White et al., 2015; WHO, 2014). The secular trends associated with changing rates of alcohol use and AUD in females underscore the important role of the environment for alcohol outcomes, and the need to understand the joint effects of genetic and environmental influences. We return to the topic of gene–environment interplay in a later section.

Are there sex differences in the magnitude or source of genetic influence on alcohol outcomes?

Genetically informed designs can be used to examine the extent to which there are sex differences in the genetic influences on alcohol outcomes. There are two forms of sex-specific genetic differences (Neale & Cardon, 1992).

Quantitative sex differences refer to differences in the degree to which additive genetic factors account for variation in an outcome in males and females. *Qualitative sex differences* refer to differences in the source of genetic variation across males and females. As summarized in Figure 1, quantitative and qualitative sex differences can be studied simultaneously in twin samples that include dizygotic (DZ; twins who share half of their segregating genes on average) opposite-sex twin pairs. Twin pair correlations provide the information for testing this statistical model. If there are no quantitative sex differences, meaning that genetic factors have the same magnitude of effect in both sexes, then the ratio of the monozygotic (MZ; twins who share 100% of their segregating genes) to DZ twin pair correlations will be the same across male–male and female–female pairs [i.e., $(r_{MZ_{male}}:r_{DZ_{male}}) = (r_{MZ_{female}}:r_{DZ_{female}})$]. If there are no qualitative sex differences, meaning that the same genes contribute to an outcome in males and females, then the opposite-sex DZ twin pair correlation would lie between the correlations of the male–male DZ and female–female DZ pairs. But, if there are qualitative sex differences, then the opposite-sex DZ twin pair correlation would be significantly lower than that of the male–male and female–female DZ pairs.

Quantitative sex differences can also be studied using adoption designs. For example, a quantitative sex difference would be suggested if the resemblance for AUD between biological parents and their adopted-away sons differs from the resemblance between biological parents and their adopted-away daughters. Qualitative sex differences can also be examined in family and adoption studies of sex-dependent transmission. Stronger resemblance between AUD probands and their same-sex biological relatives compared with their opposite-sex biological relatives would suggest that there are qualitatively different familial factors (genetic factors in a study of biological parents and their adopted-away offspring; and genetic and/or environmental factors in an intact family-based sample) that contribute to alcohol outcomes. However, as noted by Prescott (2002), the limited number of women with AUD has precluded strong tests of sex-specific genetic effects using these alternative designs.

Adult alcohol consumption. There is mixed evidence for sex differences in the genetic influences on patterns of alcohol consumption (for a detailed review of genetic influences on alcohol consumption, see Dick et al., 2009). In a sample of Australian twin pairs, Heath et al. (1991) found evidence for sex-specific genetic influences on patterns of alcohol consumption (separate measures of frequency and quantity). However, the sample ($n = 3,810$ twin pairs) lacked power to discriminate between a model where the source of genetic influences differed for males and females (a qualitative sex difference), and an alternative model where the magnitude of genetic influences differed between males and females (a quantitative sex difference). For both of these models, the heritability of females' alcohol frequency and quantity was

FIGURE 1. General twin ACE model summarizing the types of sex-specific genetic effects that can be examined when opposite-sex twin pairs are included (corresponding ACE models for same-sex monozygotic and dizygotic twin pairs are not shown). A = additive genetic factors; C = common environmental factors; E = unique environmental factors. A_h denotes additive genetic influences that are specific to males, indicating a qualitative sex difference. Quantitative sex differences are indicated when the magnitude of the additive genetic variance components differs between males ($_m$) and females ($_f$). Subscripts $_1$ and $_2$ denote the first and second members of the twin pair.

estimated as 66% and 57%, respectively. In contrast, the heritability of alcohol frequency and quantity varied between 42%–75% and 24%–61% for males under these two models (confidence intervals were not available for these estimates).

A formal test of quantitative sex differences for the heritability of past-year alcohol consumption in a sample of 3,049 female and 1,070 male twins was not significant (Prescott et al., 1994). In a more recent study of 2,862 young adult twins (ages 20–22 years), the heritability of a heaviness of alcohol consumption measure did not differ significantly between the sexes, nor was there any evidence of qualitative sex differences (Seglem et al., 2016). To summarize, these studies provide no clear evidence that genetic influences on alcohol consumption are larger in one sex compared with the other, nor evidence that there are sex-specific sources of genetic influence on alcohol consumption.

Alcohol use disorder. The field's understanding of sex differences in the genetics of AUD has evolved over the years, which is in part attributable to a greater number of females now included in genetically informed AUD research (Heath et al., 1997). The most comprehensive test of genetic differences in the heritability of AUD to date comes from the Verhulst et al. (2015) meta-analysis of twin and adoption studies of AUD across clinically ascertained and registry-

based samples. They found that genetic factors account for roughly 50% of the variance in AUD, and this estimate applies to both males and females. Thus, in contrast to mixed findings from earlier studies (McGue et al., 1992; Prescott, 2001; Prescott et al., 1999), more recent meta-analytic evidence suggests that there are not quantitative sex differences for AUD. Furthermore, there was no evidence of qualitative sex differences in the Verhulst et al.'s (2015) meta-analysis, which is consistent with previous findings from a review of well-controlled family studies of sex-dependent transmission (Merikangas, 1990).

One exception to these conclusions is a recent analysis of Swedish national data for 787,916 twin and sibling pairs, which found evidence for both quantitative and qualitative sex differences for AUD (Kendler et al., 2016). They found that genetic factors accounted for 57%, 95% CI [40%, 69%] of the variance in males' AUD and 22%, 95% CI [7%, 47%] of the variance in females' AUD (Kendler et al., 2016). The genetic correlation for males and females was +0.91, indicative of modest sex-specific genetic sources of influence. Kendler et al. (2016) speculate that these qualitative and quantitative sex differences may reflect social factors that make alcohol exposure and heavy alcohol use different for males and females in Sweden. We discuss approaches to

study potential sex differences in how environmental factors change the magnitude and source of genetic influences in the next section.

Investigating sex-specific Gene $\times$ Environment effects

There is increasing recognition that genetic and environmental influences for many outcomes are likely to interface in complex ways. In studies of $G \times E$ effects, the goal is to understand whether and how measured environmental factors moderate genetic influences on a behavior. A longstanding motivation for researchers in the area of $G \times E$ effects is to understand how environmental factors constrain or amplify individual differences, or the degree to which individual difference factors influence susceptibility to environmental influences (Belsky et al., 2009). Identifying whether these effects are sex specific is a natural extension of this work.

Quantitative sex-specific $G \times E$ effects. One type of sex-specific $G \times E$ effect is one of magnitude (i.e., whether the strength of a $G \times E$ effect differs for males and females). So, it may be the case that a particular environment, such as marital status, moderates genetic influences on alcohol outcomes for one sex but not the other. Or, the moderation effects may be stronger in one sex as compared with the other. These sex-specific magnitude effects (i.e., quantitative differences) are most often studied using twin and measured genetic study designs.

Quantitative sex-specific $G \times E$ effects in twin studies. In the context of a twin study, quantitative sex-specific $G \times E$ effects can be examined by comparing relatives of different genetic relatedness. The key question is whether genetic variance, as indicated by the ratio of MZ:DZ twin pair correlations, changes across levels of an environmental factor (e.g., religiosity, peer deviance, marital status, or parental monitoring), and whether these changes differ between males and females. Typically, changes in unstandardized genetic variance are examined in studies of latent $G \times E$ because changes in standardized genetic variance (i.e., heritability, or the proportion of overall variance accounted for by genetic factors) can be misleading (Purcell, 2002; Young-Wolff et al., 2011). This is because the overall variance in an outcome can change across levels of the environment, making it difficult to discern whether changes in heritability are attributable to changes in genetic variance or simply to changes in the overall variance of the outcome. Despite the ambiguity in interpreting standardized variance components in $G \times E$ research, there is still some inconsistency in whether authors report unstandardized versus standardized variance components.

There are only a small number of published twin studies testing quantitative sex-specific $G \times E$ effects (van der Zwaluw & Engels, 2009; Young-Wolff et al., 2011), underscoring the need for more systematic research in this area. We highlight one example here. In a $G \times E$ study of Dutch

adolescents' alcohol initiation, Koopmans et al. (1999) found that a religious upbringing moderated genetic influences on initiation in a sex-specific manner. The degree to which standardized genetic influences accounted for variance in alcohol initiation was higher ($h^2 = 40\%$) among females with a nonreligious upbringing compared to females with a religious upbringing ($h^2 = 0\%$). In males, the degree to which genetic influences accounted for variance in alcohol initiation did not differ as a function of religious upbringing. Thus, on a standardized scale, there is a $G \times E$ effect for females (but not males), whereby being raised in a religious household inhibits the expression of genetic predispositions for alcohol initiation. It is not clear whether this $G \times E$ effect is attributable to sex-specific differences in genetic variance in the religious and nonreligious groups (i.e., the ratio of MZ:DZ correlations changes as a function of religious upbringing for females [but not males]), or whether this reflects a sex-specific difference in the proportion of total variance accounted for by genetic factors in the religious and nonreligious groups (i.e., the ratio of MZ:DZ correlations is the same across religious upbringings, but there is less variance in alcohol initiation among females with a religious upbringing).

Quantitative sex-specific $G \times E$ effects using measured genotypes. Measured genetic studies provide another way to test sex-specific $G \times E$ effects by examining whether there are sex differences in the association between a particular genotype and outcome across levels of the environment. In one example, Perry and colleagues (2013) used data from the Collaborative Study on the Genetics of Alcoholism to look at whether there were sex-specific $G \times E$ effects for *GABRA2*, which codes for the receptor for the central nervous system inhibitory neurotransmitter GABA α 2 subunit. They found that males who had the high-risk *GABRA2* genotype and who experienced more daily uplifts (i.e., pleasurable experiences at work and home) had a lower probability of alcohol dependence compared with males who had the high-risk genotype and who experienced fewer daily uplifts. In contrast, the probability of alcohol dependence for females did not differ as a function of either their genotype or the number of uplifts experienced. This suggests that an environment characterized by these types of social support mitigates the alcohol dependence risk associated with the A-allele for this variant for males, but not females.

There is controversy surrounding research on measured $G \times E$ effects (Dick et al., 2009, 2015; Duncan & Keller, 2011; Eaves & Verhulst, 2014; Young-Wolff et al., 2011) involving issues such as the selection of candidate genes or genetic variants, statistical power, and correction for multiple testing. Of particular concern is the selection and analysis of single genes or genetic variants in view of the fact that AUDs are polygenic (Edenberg & Foroud, 2014), meaning that many genes and genetic variants are likely to be involved. There are now several methods for characterizing genetic risk

across multiple variants and genes. Among the best-established methods are genome-wide pruning-and-thresholding, linear mixed models, and linkage disequilibrium scoring (Dudbridge, 2016; Wray et al., 2014). Polygenic scores derived from these methods can be carried forward into studies of $G \times E$ effects, although this is only appropriate when the hypothesis is that the environment under study will moderate the majority of genes involved in the outcome in the same direction. Genome-wide polygenic $G \times E$ effects have been examined in alcohol and substance use research (Meyers et al., 2013; Musci et al., 2015; Salvatore et al., 2014, 2015), but to our knowledge have not yet been systematically applied to questions of sex-specific $G \times E$ effects.

Qualitative sex-specific $G \times E$ effects. A less commonly studied question is whether environmental factors moderate sex-specific sources of genetic influence for alcohol outcomes (i.e., qualitative sex differences). It is possible that environmental factors may moderate different sets of genes for males and females. This possibility can be studied using either a twin study that includes same- and opposite-sex DZ twin pairs, an adoption study that includes AUD information for both biological parents, or in a measured genetic framework. Investigating whether environmental factors moderate different sets of genes for males and females is likely to be challenging in view of the large sample sizes required. This is particularly true for measured $G \times E$ effects. Large sample sizes are required for even simple genetic association studies, and gene identification for AUD has been slow, with the exception of the alcohol-metabolizing enzyme genes (Hart & Kranzler, 2015). Whether genetic effects that interact with environmental factors in a sex-specific manner will be identified remains unknown; but, if they exist, identifying such effects could help refine prevention and intervention efforts.

A note on measuring the "environment" when studying $G \times E$ effects. We note that many of the environmental exposures examined in alcohol $G \times E$ research (e.g., stressful life events, parenting, marital quality, social support, and peer interactions) are under a modest to moderate degree of genetic influence (Kendler & Baker, 2007). It is possible that genes that predispose individuals to higher levels of alcohol consumption or problems may also contribute to one's exposure to risky environments (i.e., gene-environment correlation). For this reason, examining and statistically accounting for gene-environment correlation in tests of $G \times E$ effects is important to reduce potential confounds.

Power: An important concern in tests of sex-specific genetic effects

Achieving the NIH's goal to consider sex as a biological variable can be met in several ways. The most straightforward starting point is to make the examination of sex effects a standard supplement to any latent or measured genetic study. Collecting genetically informative data requires a

large investment; thus, it is likely that many tests of sex differences will be conducted in genetically informative archival data sets. For this reason, it will be important for researchers to examine and report their achieved power for sex-specific genetic effects across both latent and measured genetic studies. Researchers are also encouraged to clarify whether there was adequate power to detect sex differences when interpreting and discussing results. A major concern is that many samples will be insufficiently powered to detect sex-specific effects, particularly in the growing area of measured $G \times E$ research (Young-Wolff et al., 2011). For this reason, explicitly addressing issues of power when interpreting results is especially important to help readers distinguish between instances where there was adequate power to detect a sex-specific effect but none was found, and instances where there was inadequate power to detect a sex-specific effect.

To demonstrate that power is a major concern for tests of sex-specific measured $G \times E$ effects, we conducted power analyses to determine the sample size needed to have sufficient power ($\beta = .80$, $\alpha = .05$) to detect hypothetical effects for alcohol consumption. For this example, we examined marital status as the environment, and used previously published data on alcohol use as a function of marital status and sex as reported in Power et al. (1999) and Curran et al. (1998) to inform the analysis. We constructed two hypothetical sex-specific $G \times E$ effects for a C/T (cytosine/thymine) single-nucleotide polymorphism. In the first example (Figure 2, Panel A), different alleles confer risk for males and females. In the second example (Figure 2, Panel B), the same allele confers risk across the sexes, but the effect is greater for males. These correspond to effect sizes (η^2) of .0034 and .0043, and power of .80 was achieved with $N = 2,004$ and $N = 1,584$, respectively. These calculations assume a balanced design with an equal number of people for each configuration of sex, marital status, and genotype. In reality, of course, it would be difficult to achieve a balanced design. The likely limited statistical power to test for sex differences in archival samples raises concerns about type I error, particularly for tests of sex-specific measured $G \times E$ effects.

The need for theory to guide tests of sex-specific genetic effects

The challenges associated with power mean that the approach of routinely testing for sex-specific genetic effects, and especially sex-specific $G \times E$ effects, may produce a fragmented catalog of underpowered effects without a framework for interpreting them. One promising alternative approach is to leverage theory and evidence regarding sex differences from disciplines such as psychology, sociology, anthropology, neurobiology, and physiology (including evidence from preclinical research in nonhuman animals) to generate testable hypotheses. For example, it is known that there are sex differences in exposures to many of the

FIGURE 2. Two hypothetical sex-specific gene-by-environment interaction effects for a C/T (cytosine/thymine) single-nucleotide polymorphism. In Panel A, different alleles confer risk for males and females. In Panel B, increasing copies of the T allele confer risk for divorced males and females, but the effect is greater for males.

environments that have been examined in $G \times E$ studies of alcohol outcomes, including parental monitoring (Barnes et al., 1997; Svensson, 2003), stressful life events (Kessler & McLeod, 1984), and the health-protecting benefits of marriage (Kiecolt-Glaser & Newton, 2001).

Likewise, there are sex differences in processes including alcohol metabolism (Mancinelli et al., 2009), levels of reproductive- and stress-related hormones (Witt, 2007), subjective and neurobiological responses to alcohol intoxication (Wang et al., 2003), and genetic factors shared between AUD and endophenotypes such as alcohol sensitivity (Heath et al., 1999). Bringing together theory and evidence about how alcohol-related environments and processes differ across the sexes may help build a cohesive body of knowledge about the pathways from sex-specific genetic effects to clinically significant AUD outcomes (Short et al., 2013). This approach

highlights the need for interdisciplinary perspectives in alcohol training programs in order to fully integrate across these areas. A theoretically informed approach also underscores the importance of explicitly distinguishing between sex and gender differences, as these terms have often been used interchangeably in the past. We refer readers to the Sex and Gender Equity in Research (SAGER) guidelines for information on conceptualizing, studying, and reporting sex and gender differences in their research (Heidari et al., 2016).

Conclusions

Epidemiological studies document robust sex differences for many alcohol outcomes. The weight of evidence from genetically informed studies suggests that the source and magnitude of genetic influences on alcohol outcomes are

likely the same across sexes. Whether there are sex-specific $G \times E$ effects has received less attention to date. The new NIH policy to address sex differences necessitates a systematic approach for this area of research. For this reason, we recommend reporting power analyses for tests of sex-specific genetic effects, and integrating theory and evidence across multiple disciplines to develop testable hypotheses in order to build a coherent body of knowledge about potential sex-specific genetic effects. Despite the practical challenges associated with studying sex differences in genetically informed alcohol research, the knowledge that stands to be gained has important implications for the etiology, prevention, and treatment of alcohol use disorder in males and females.

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