

# Commentary: Sex Differences in the Pathways to Symptoms of Alcohol Use Disorder: A Study of Opposite-Sex Twin Pairs

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KENDLER AND COLLEAGUES (2015) identify a lattice of risk and protective factors that underlie liability to alcohol problems (AP) in opposite-sex siblings. The authors examine the interplay between 18 risk and protective factors, broadly classified into 5 developmentally relevant domains relating to childhood (e.g., childhood abuse, familial risk), early adolescence (e.g., neuroticism), late adolescence (e.g., conduct disorder, lifetime traumas), adult (e.g., divorce), and last year (e.g., drinks/month). Their Figs 1 and 2, illustrating results from comprehensive and computationally intensive structural equation models, are more reminiscent of a subway grid or an anatomical model of human vasculature than the typical bar charts found in epidemiological studies. These figures outline several unique routes via which liability to AP develop in men and women. For instance, familial risk and nicotine dependence were found to have stronger links with AP in females, while conduct disorder and low self-esteem were found to exert a more pronounced influence among males. Importantly, this assortment of 18 parameters explained an impressive 71–73% of the variance in liability to alcohol use problems (AUP).

In particular, the study has 2 innovative features. First, the authors leverage the genetic and familial matching afforded by dizygotic opposite-sex sibling pairs. In traditional discordant twin analyses, such pairs are less useful because traditional exposures and outcomes studied in addiction (e.g., the association between early onset alcohol use and later alcohol dependence) are confounded with sex (Prescott and Kendler, 1999). However, Kendler and colleagues (2015) show the utility of these pairs for the study of the origins of sex differences in AP. Second, the authors

allow the developmental contributors to interface with each other, estimating direct and indirect paths. For instance, familial risk is among the most robust predictors of AP, and arguably, more prognostic than any genetic variant identified to date (Yan et al., 2014). Yet, the current study shows that only about 80% of its relationship with AP is direct. The remainder, albeit modest, is attributable to its interface with lifetime trauma, neuroticism, nicotine dependence, anxiety, and conduct disorder.

While the partial matching for genes identical by descent is a notable strength, it also raises the intriguing question of whether existing research is adequately addressing the putative role of sex differences in genetic analyses. The classical twin analysis directly utilizes data on opposite-sex twin pairs to examine *qualitative* sex differences, that is, whether the same or different genes influence heritable (and shared environmental) variation in men and women (Neale and Cardon, 1992). This is different from *quantitative* sex differences, or the test of whether the magnitude of heritable variation is sex invariant. For AUP, little support exists for quantitative sex differences (i.e., about 50 to 60% heritability in men and women). However, evidence of whether the genetic influences that comprise these heritability estimates overlap has been inconclusive. For instance, Prescott and colleagues (1999) found that unlike the genetic sharing of 0.5 that is expected for DZ twin pairs, the genetic correlation in opposite-sex pairs, when freely estimated, was 0.20 to 0.24. However, this qualitative sex difference was not identified by Heath and colleagues (1997).

Genomic studies can also benefit from additional consideration of sex. For instance, while all genomewide association studies include the main effects of sex as a covariate, few have considered the joint analysis of the single nucleotide polymorphism (SNP) and SNP  $\times$  Sex term. This 2 degree of freedom test has been powerful in uncovering gene–environment interactions for other environmental factors (Hancock et al., 2012). It was also employed in one of the earliest GWAS of nicotine dependence, the candidate gene component of which was one of the first studies to identify the role of rs16969968 in the etiology of smoking (Saccone et al., 2007). While the effects of rs16969968, the strongest and most replicable genetic signal for tobacco smoking to date, have been noted in men and women, other SNPs have been

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noted to exert sex-specific effects (Saccone et al., 2007). Such analyses necessitate large sample sizes, which are already being accrued for AP. Indeed, the recent identification of genome-wide significant findings for alcohol-related phenotypes (Bierut et al., 2010; Edenberg et al., 2010; Gelernter et al., 2014; Kapoor et al., 2014; Wang et al., 2013) prompts the investigation of sex-specific genomic effects. Nontwin sibling pairs might also provide an avenue for increased sample sizes (e.g., COGA, OZALC; Heath et al., 2011; Kapoor et al., 2014); however, contending with sibling age differences may present challenges.

The developmental patterns underlying sex differences are also worthy of careful study. Sex differences in patterns of drinking come to the fore during late adolescence, which is when males and females, particularly siblings, diverge in their individual experiences (e.g., leaving home; Brown et al., 2008). For example, drinking frequency is more heritable in young adult women, but not in men, residing in regions with high (vs. low) alcohol sales ( $h^2 = 0.61$  vs.  $0.25$ ) (Dick et al., 2001). Earlier sources are of note as well that the developmentally driven sex differences are evident in brain maturation (De Bellis et al., 2001) which is associated with alcohol use and alcohol use disorders (Brown and Tapert, 2004). Such age  $\times$  sex interactions remain relatively unexplored, as simple covariates and more importantly, as moderators of genetic liability in genomic analyses.

Future research should also target whether the profile of symptoms that constitute AP differ across men and women. For instance, Saha and colleagues (2006) have noted that criteria like withdrawal, neglect roles and larger/longer appear to represent a greater degree of illness severity in men than in women, while the converse was true for hazardous use and social/interpersonal problems. Such an exploration may serve to be even more interesting within opposite-sex twin pairs. Even when the pairs are concordant for AP, is the extent of AP and symptoms that constitute it similar or different across genetically related subjects? The discordant pairs are, perhaps, even more exciting: Do different symptoms comprise AP in women with an unaffected versus an affected brother? The panoply of hypotheses that can be tested with this impressive study design is extensive.

Much like their prior study of major depression, Kendler and colleagues (2002) illustrate here how complex pathways underlie complex phenotypes. This roadmap of sex-invariant and sex-specific influences deserves further replication so that it may be better generalized. Inasmuch as one might hesitate to explore the labyrinthine New York subway system without a map, the study by Kendler and colleagues (2015) thus might serve as guide for future research aimed at delineating sex differences in liability to AP.

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