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

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Abstract

Background—We sought to develop an empirical, broad-based developmental model for sex differences in risk for symptoms of alcohol use disorders, here called alcohol problems (AP).

Methods—We assessed 18 risk factors in five developmental tiers in both members of 1,377 opposite sex dizygotic twin pairs from the Virginia population-based twin registry. Analyses were conducted by structural modeling, examining within-pair differences.

Results—The best-fitting model explained 73% of the variance in men and 71% in women for last year AP. 49% of paths differed significantly across sexes. Ten variables had appreciably different predictive effects on AP in males versus females. Three were stronger in females: familial risk, early onset anxiety disorders, and nicotine dependence. Seven predictors had a stronger total effect in males: novelty seeking, conduct disorder, childhood sexual abuse, parental loss, neuroticism, low self-esteem, and low marital satisfaction.

Conclusions—In a co-twin control design, which matches sisters and brothers on genetic and familial-environmental background, we found numerous sex differences in predictors of last year AP. Factors that were more prominent in men and in women were diverse, reflecting both internalizing and externalizing psychopathology. The model was slightly more successful at predicting AP in men than in women.

Keywords

alcohol problems; development; sex differences; personality; parental loss

Alcohol use (AU) and alcohol use disorders (AUDs) are prototypical complex traits, influenced by a wide range of variables including genetic factors (Hagele et al. 2014; Heath et al. 1997; Prescott and Kendler 1999), childhood sexual and physical abuse (Fergusson and Mullen 1999), personality (Sher et al. 1999), internalizing disorders and symptoms (Kessler et al. 1997; Sher et al. 2005), externalizing disorders and traits (Heron et al. 2013), prior nicotine dependence (Sher et al. 1996), marital status (Kendler et al. 1992), and stressors in adult life (Cooper et al. 1992a; Lee et al. 2012). Risk factors measured in early to mid-childhood (Caspi et al. 1996; Dubow et al. 2008; Englund et al. 2008; Manzardo et al.

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2005;Pitkanen et al. 2008) can predict levels of AU and symptoms of AUD in adulthood suggesting that a thorough understanding of the etiology of AUDs will require a developmental perspective (Windle 1999;Zucker 2006). Several prior attempts have been made to develop empirical broad-based models for the etiology of AUDs (e.g., (Dubow et al. 2008;Fergusson et al. 1995;Kendler et al. 2011b;Ohannessian and Hesselbrock 2008)).

Sex is probably the strongest and most widely replicated risk factor for AUDs with a large male excess seen in every population examined (Helzer and Canino 1992). Furthermore, a substantial literature suggests important potential sex differences in the etiologic pathways to AUDs (Nolen-Hoeksema 2004;Wilsnack et al. 2000). However, we are unaware of any prior effort to examine a broad-based empirical developmental model for AUDs focused on sex differences in pathways of risk. In this report, we produce such a model using opposite-sex twin pairs from the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders (VATSPSUD)(Kendler and Prescott 2006). By focusing on comparisons within these twin pairs, we are able to control for average genetic liability as well as a wide range of familial-environmental variables.

The primary aim of these analyses is to examine sex differences in the strength of specific AUD predictors. As reviewed elsewhere (e.g., (Nolen-Hoeksema 2004); (Nolen-Hoeksema and Hilt 2006)), previous studies have suggested that some risk factors, such as negative affect or antisocial behavior, are differentially associated with AUP across the sexes. The nature of the current analyses enables us to explore sex differences in the total effects and in their mediational pathways. The comprehensive nature of the models employed here represents a potentially critical advantage over most previous studies, in that the effect of any individual risk factor can be seen in the context of a wide range of other predictors.

METHODS

Sample

Our data were from a two-wave study of male-male and male-female pairs from the Virginia Twin Registry formed by a search of all Virginia birth certificates. Twins were eligible if one or both members were successfully located, were a member of a multiple birth including at least one male, were Caucasian, and born between 1940 and 1974 (Brown et al. 1990). Of 9,417 eligible individuals for the first wave (male-female wave 1 or MF1), interviews were completed, typically by telephone, with 6,814 (72.4%). At least one year later, we re-contacted the twins and completed a second-wave interview (MF2), mostly face-to-face, in 5,629 (82.6% of those eligible). Signed informed or verbal consent were, respectively, obtained prior to all face-to-face and telephone interviews.

This report is based on the 1,377 male-female pairs where both members completed the MF1 interview, and 13 unpaired male and 9 unpaired female twins. At this interview, subjects had a mean (SD) age and years of education of 35.2 (8.9) and 13.6 (2.4). Interviewers were clinically trained. Each interview was reviewed twice for completeness. Members of a twin pair were interviewed by different interviewers.

Outcome Variable

Our model predicted one or more symptoms of DSM-IV alcohol abuse or alcohol dependence (American Psychiatric Association 1994) reported in the year prior to the MF1 interview. We define this outcome as “Alcohol Problems” (AP). Six percent of our sample met criteria for last-year AP, which was treated as a dichotomous variable, assuming an underlying normal liability.

Model Variables

The variables here examined were adapted from those used in our prior developmental models for major depression (Kendler et al. 2002;Kendler et al. 2006;Kendler and Gardner 2014) and alcohol use disorders (Kendler et al. 2011b) in the VATSPSUD. As previously described (Kendler et al. 2002;Kendler et al. 2006;Kendler et al. 2011b;Kendler & Gardner 2014), we organized our predictor variables into “tiers” approximating five developmental periods: childhood (familial risk, low parental warmth, childhood sexual abuse and parental loss), early adolescence (neuroticism, novelty seeking, low self-esteem, and early onset anxiety disorder), late adolescence (conduct disorder, lifetime traumas, and drug use disorder and nicotine dependence), adulthood (divorce, past history of MD, and social isolation), and last year (marital satisfaction, difficulties and drinks per month). Drug use disorders and nicotine dependence were connected to each other by residual correlations. All variables were treated as categorical or ordinal as the nature of the model was too complex to achieve convergence if we added continuous variables. We chose the categories for each variable to maximize their ability to predict the ultimate outcome of AP. We summarize each risk factor below.

Familial Risk for AUDs was based on twin and co-twin report on alcohol dependence in mother and father. Scored as 0 (no positive reports), 1 (1 positive report) and 2 (2 or more positive reports).

Low Parental Warmth was assessed using a modified version of the Parental Bonding Instrument (Parker et al. 1979). Each twin had four scores: self-report of father’s and mother’s warmth, and cotwin’s report of father’s and mother’s warmth to twin. The measure was scored as a trichotomy with 23% in the low parental warmth category, 34% in the moderate category, and 43% in the high parental warmth category.

Childhood Sexual Abuse (CSA) was taken from a single item in the MF1 interview “Have you ever been sexually abused or molested?” If a positive response was given, the age at which this first occurred was recorded. In this report, CSA was considered present if the age given was prior to 16.

Parental Loss was a binary measure scored 1 if the twin reported that one or more parents left the nuclear home due to death, divorce or parental separation prior to age 17.

Neuroticism was assessed by the Short-Scale (12-item) from the EPQ-R (Eysenck et al. 1985) obtained at MF1. We scored it as a 5 level ordinal measure: 0 – 20%, 1- 31%, 2 – 21%, 3 -16%, and 4 -12%.

Novelty seeking was assessed with a modification of Cloninger's scale (Cloninger et al. 1991) and scored as a 4 level ordinal variable: 0 – 53%, 1 - 29%, 2 – 14%, and 3 - 4%.

Low self-esteem was assessed using the full Rosenberg's self-esteem scale (Rosenberg 1965) obtained at MF1, reversed-scored so that higher scores reflected lower self-esteem and ordinalized into three categories with the following %s: 0=89%, 1=6%, 2=5%.

Early Onset Anxiety Disorder was a binary variable scored 1 for subjects with an onset, prior to age 18, of panic disorder, generalized anxiety disorder or any form of phobia as assessed at the MF2 interview using diagnostic criteria outlined previously (Kendler et al. 2002).

Conduct Disorder was treated as a four category ordinal variable based on the number of DSM-IV conduct disorder criteria met prior to age 18 that were endorsed at MF1. The variable had the following distribution: 0=58%, 1=22%, 2=16%, and 3=4%.

Lifetime Traumas reflected the number of items reported at the MF1 interview that assessed exposure to combat, life-threatening accident, natural disaster, severe injury, physical assault, and being threatened with weapon. The distribution was skewed so it was treated as a 4-level ordinal variable: 0=40%, 1=29%, 2=16%, and 3=15%.

Lifetime drug abuse or dependence according to DSM-IV criteria (American Psychiatric Association 1994) was assessed at the MF2 interview and scored as a binary variable.

Nicotine dependence as assessed by a score of 7 on the Fagerström Tolerance Questionnaire (Fagerstrom and Schneider 1989) collected at MF2.

Ever Divorced was a binary measure scored 1 for individuals who reported a lifetime history of divorce or annulment at the MF1 interview.

Prior History of Major Depression (MD) was a binary measure assessed at the MF1 interview recording a depressive episode experienced prior to the last year meeting DSM-IV criteria (American Psychiatric Association 1994).

Social isolation was assessed from items administered at MF1 designed to evaluate social support (Schuster et al. 1990). A factor analysis of these items yielded one factor that reflected the frequency of social interactions with the co-twin, family, friends, church attendance, and meetings of social groups. We treated this as a three-level ordinal variable reflecting increasing levels of isolation: 0 – 14%, 1 – 69%, 2 – 17%.

Low Marital Satisfaction was constructed using 7 items assessing the level of marital satisfaction in the last year at the MF2 interview, obtained from the Social Interaction Scale (Schuster et al. 1990). We generated three classes: 1=married, high satisfaction, 47%, 2=unmarried, 40%, and 3=married, low satisfaction, 13%.

Last Year Difficulties was an ordinalized sum of stressful life events reported in past year at the MF1 interview.

Drinks per month was constructed from items assessing in the last year the average number of days per month the individual had an alcoholic drink (defined as “a bottle of beer, one glass of wine, or one shot of liquor”) and the number of drinks per day they typically had when they drank. From these, we constructed 6 categories: 0 (0-9 drinks) 63%, 1 (10-24 drinks) 13%, 2 (25-39 drinks) 7%, 3 (40-59) 7%, 4 (60-99) 5%, 5 (100+) 5%.

Statistical Methods

Model fitting was done using Mplus version 6.11 (Muthen and Muthen 2010) using weighted least squares and focused on within-pair differences. Fit was assessed by Akaike’s Information Criterion (Akaike 1987) and the model was developed path by path, starting with paths from all variables to APs and moving up the model variable by variable. At each step, three tests of model fit were performed: Could the path be fixed to zero in males? Could the path be fixed to zero in females? If both paths were non-zero, could they be fixed equal to each other? Once we had tested every possible path in the model, the same steps were iterated three more times to identify a parsimonious model without compromising explanatory power.

We utilized three fit-indices which reflect the success of the model in balancing explanatory power and parsimony: The Tucker-Lewis Index (TLI) (Tucker and Lewis 1973) and the Comparative Fit Index (CFI) (Bentler 1990) with values ≥ 0.95 indicating good fitting models. For the mean square error of approximation (RMSEA) (Steiger 1990), values of 0.05 are considered good approximations.

RESULTS

Model Fitting

The proportion of male and female members of the DZ opposite sex twin pairs who met criteria for AP in the year prior to interview was, respectively, 8.0 and 3.9%. Of the 1,377 complete pairs interviewed, 1,221 were concordant for no AP and 6 were concordant for both having AP. Most informative for our analyses were the 150 pairs discordant for AP. In 103 and 47 of these pairs, respectively, the individual with AP was the male and female twin.

Our best fit structural model for predicting AP in these twin pairs included 181 free parameters including paths (one-headed arrows) and correlations (two-headed arrows). It explained 72.7% (SE=3.9%) and 70.5% (SE=3.9%) of the variance in liability to AP in, respectively, males and females. The model fit indices were very good (CFI=1.00, TLI=1.00, RMSEA =.00).

Parameter estimates from the best fit models in males and females are given, respectively, in figures 1 and 2. Parameters estimated to be equal across sexes, greater in females than males, and greater in males than females are depicted in black, red and blue, respectively. If a path is not present between two variables, that is because it was estimated to have a zero value.

Appendix II contains the best fit model estimate for all these paths, their statistical significance and the equality or non-equality of that path across sexes. 19 paths were estimated at zero in males versus 18 in females.

Sex differences in pathways to AP in our model can be examined in various ways of which we illustrate three: i) individual paths, ii) all outflow paths from risk variables, and iii) total effect of risk variables on liability to major depression.

Individual Paths

A number of individual paths stood out as having substantial sex differences of which we here give several examples. Familial risk and nicotine dependence both have direct and relatively robust effects on AP in females and not in males. By contrast, low self-esteem and conduct disorder have direct effects on APs in males but not females. Both lifetime traumas and low marital satisfaction impact directly on drinks per month in males but not females. Familial risk for AUDs has a strong direct effect on early onset anxiety disorders in females but not in males.

Outflow Paths from Risk Variables

We next examine sex differences in the outflow of paths from individual risk factors. This is easy to do in the figures by comparing the number of red paths coming from each risk variable in females (figure 1) versus the blue paths coming from these same variables in males (figure 2). We can simply classify variables into those with more red than blue paths, and more blue than red paths emanating from them. The former and latter are likely more important contributors to the etiologic pathway to APs in females and in males, respectively. By this approach, familial risk, low parental warmth, novelty seeking, early onset anxiety, nicotine dependence, history of divorce, and low marital satisfaction contribute more strongly to the pathway to APs in females. Childhood sexual abuse, neuroticism, conduct disorder, lifetime traumas, and drug use disorder contribute more strongly to the AP pathway in males.

Total Effect of Risk Variables on Liability to Alcohol Problems

The most comprehensive way to compare the risk factors across the sexes is to examine their total direct and indirect contribution to AP in females versus males. We do this in table 1, which depicts the total effect of the 18 predictor variables on the liability to APs. We divided these 18 variables into three groups. For eight variables, the absolute difference in their total direct and indirect impact on APs was <0.02 , which we considered to reflect minimal sex differences. For three variables, the absolute value of the differences was between 0.02 and 0.05, which reflects modest sex differences. Seven of the variables had an absolute difference of ≥ 0.05 , which we considered to demonstrate moderate to strong sex differences.

Of the three variables with modest sex differences, one had a stronger total effect in females (early onset anxiety disorders) and two had stronger effects in males (novelty seeking and conduct disorder). We can also trace the paths of these variables to risk for AP in the two sexes, giving us insight to the differences in etiological pathways. As seen in table 1, the

stronger effect of early onset anxiety disorders in females was largely mediated through lifetime trauma and nicotine dependence while the stronger effect of conduct disorder in males occurred mainly through its impact on difficulties and drinks per month.

Of the seven variables with moderate or strong sex differences, two had stronger effects in females: familial risk and nicotine dependence. Five had stronger effects on AP in males: childhood sexual abuse, parental loss, neuroticism, low self-esteem, and low marital satisfaction. These findings were due to a large range of mediational mechanisms among which four are illustrative. In females, the stronger effect of familial risk is in part mediated through early onset anxiety disorders. In males, prominent mediators include novelty seeking for the effects of parental loss, nicotine dependence for neuroticism, and drinks per month for low marital satisfaction.

Direct Versus Indirect Associations

The correlations depicted in table 1 reflect both the direct path between the variables plus all the indirect paths mediated by other variables in the model. By contrast, the path estimates in figure 1 reflect only the direct relationship adjusting for all the other variables in the model. Therefore, a comparison between the values in the table and figure gives us an estimate of the proportion of the total correlation between any two variables in the model that results from direct effects versus total indirect effects. For example, from table 1, the total correlation between familial risk and AP is +0.16 in females while the direct path between these two variables from figure 2 is +0.13. This suggests that 81% (.13/.16) of effect of familial risk factors for AUD on AP in our model is direct and 19% indirect, mediated by factors such as lifetime traumas, early onset anxiety disorders and conduct disorder. These results can be usefully contrasted with those obtained for childhood sexual abuse in males where the total correlation is +0.22 and the direct path is zero. Our model predicts that all the association between childhood sexual abuse and AP in males is indirect, mediated by a range of variables including conduct disorder, past major depression, low self-esteem, and social isolation.

DISCUSSION

We sought in this report to clarify sex differences in the etiologic pathways to AP as measured in the last year in a sample of 1,377 complete opposite-sex dizygotic twin pairs ascertained from a population-based registry. We studied a wide array of risk factors, assessed in two personal interviews at least a year apart. From these variables, we constructed a developmental path model with the goal of predicting the occurrence of AP in the year prior to our first interview. Most of the information in these analyses came from the 150 twin pairs who were discordant for the experience of last year AP.

While many in psychiatry have recognized the importance of developing bio-psychosocial (Engel 1977), multi-level (Schaffner 1994) or integrative (Kendler 2005) etiological models for our major syndromes, the empirical implementation of such an approach is challenging at both the stage of data collection and analysis. Indeed, our efforts suffer from a number of important limitations outlined below. However, models in science do not need to be complete or true to be useful (Wimsatt 2007).

Our best model fit the data very well and explained nearly three quarters of the total variance in risk for AP in males and females. Using statistical criteria, 49% of the paths in this model differed between the sexes. We suggested three different levels at which the results of this model could be usefully examined. The first two utilized visual inspection to detect individual factor paths with clear sex differences or the risk factors themselves that originated paths which were overall of stronger effect in males (figure 1) or in females (figure 2). Using these informal methods, it could be seen that familial risk and nicotine dependence both have direct and relatively robust effects on AP in females but not in males with the opposite pattern being seen for low self-esteem and conduct disorder. Early onset anxiety disorder is more strongly connected to other risk factors in females than males while the opposite pattern is seen for low marital satisfaction.

However, we focused on a comprehensive statistical view of the individual risk variables that assessed their total direct contributions to liability to AP. Focusing on total effects, our 18 risk variables for AP could be usefully divided into three groups with no, modest and moderate to large sex differences. Eight of the variables fell into the first category with similar total effects across sexes. Of the 10 risk factors in the second and third groups, 7 had a stronger total impact in males and only 3 in females.

The factors that have a greater effect size in men than in women (novelty seeking, conduct disorder, childhood sexual abuse, parental loss, neuroticism, low self-esteem, and low marital satisfaction) span the externalizing and internalizing spectrums, as well as environmental risks. Though speculative given the nature of the available data, it is possible that coping styles play a role in the associations between low self-esteem and neuroticism with AP. Men are more likely to engage in avoidant coping (Cooper et al. 1992b), which has been more strongly associated with alcohol misuse in men than in women (Cooper et al. 1992b). Given social stigma against men who experience low self-esteem or high neuroticism, these men could be more inclined to cope through the misuse of alcohol (Nolen-Hoeksema 2004). Furthermore, drinking motives could mediate the association between internalizing constructs and AP: men are more likely to report self-medication motives (e.g., drinking to cope, drinking to relieve depression) than are women (Nolen-Hoeksema 2004), which in turn predicts alcohol misuse (Nolen-Hoeksema and Harrell 2002; Rutledge and Sher 2001).

Externalizing behaviors/problems (novelty seeking, conduct disorder) have previously been implicated as risk factors for AP in men (Brady and Randall 1999). In the current study, total effect sizes were higher among men, though the factors mediating the effects of externalizing behavior were similar across genders. Previous studies have found that girls who exhibit conduct problems are far less likely to fall into the early-onset persistent class of problems (Eme 2007): their problem behavior is more likely to remit than boys', among whom it can be considered a harbinger of later poor outcomes. The effects of early childhood stressors (parental loss, CSA) on adult AP are also stronger among men, and these effects are mediated in part through externalizing factors. This underscores the complex cascade through which AP develops over the life course: early stressors lead to later problem behavior, which in turn leads to AP (or other psychiatric outcomes, such as major depression (Kendler & Gardner 2014)).

Family history was more predictive of AP among women than men. Family history includes both genetic and non-genetic risk - e.g., parental modeling of alcohol misuse, unstructured or negligent parenting due to alcohol misuse, etc. – and these factors are seemingly more “toxic” for girls than for boys. The current analysis does not allow us to disentangle the different aspects of risk conferred by family history of AP. Family history’s impact on women’s AP was mediated by two individual-level factors - early onset anxiety disorder and conduct disorder, both of which are genetically and environmentally correlated with AP (Kendler et al. 1995; Kendler et al. 2011a; Rose et al. 2004) – thus, it seems likely that both biological and environmental components of family history are relevant.

It is notable that, although effect sizes are higher for males across a wider range of predictors, the total variance accounted for is quite similar across the sexes. This suggests that, with few exceptions (e.g., nicotine dependence or low marital satisfaction), the same factors are useful for predicting AP in both sexes though the magnitude of their predictive utility varies. Unfortunately, efforts to contextualize our findings within the extant literature are stymied by the fact that few if any similar efforts have examined a similar research question, with comparable measures of risk factors, in a SEM framework. Most have reported odds ratios, making it difficult to determine whether the magnitude of effect differs across the sexes after accounting for sex differences in the base rates of risk factors and outcome. However, a study examining sex differences in pathways to major depression in the current sample (Kendler & Gardner 2014) found a similar pattern: for the most part, risk factors were associated with outcome in both sexes, though the predictive utility of any given risk factor varied across sexes. Notably, the magnitude of sex differences varies widely across the different outcomes; for example, the effect of low self-esteem on major depression was quite similar across the sexes, while in the current study, its effect is much stronger among men. This further contributes to the assertion that risk for psychiatric and substance use outcomes in adulthood is nuanced: while “bad things beget bad things,” the manner in which they do so varies across outcome and, as demonstrated here, sex.

Limitations

These results should be considered in the context of five potential methodological limitations. First, our model assumes a causal relationship between predictor and dependent variables. The validity of this assumption varies across our model. Some of the inter-variable relationships that we assume take the form of $A \rightarrow B$ may be truly either $A \leftarrow B$ or, more likely, $A \leftrightarrow B$.

Second, a number of our risk factors were assessed using long-term memory and might be influenced by recall bias. Within the limits of a two-wave design with a cohort in mid-adulthood, we minimized this problem by using multiple reporters (e.g., familial risk, parental warmth), objective events less susceptible to recall bias (e.g., parental loss, divorce), and measuring a number of key constructs over the last year (including low marital satisfaction and drinks per month), reducing the time frame of recall.

Third, our model assumes that multiple independent variables act additively and linearly in their impact on risk for AP. This is unlikely to be entirely true.

Fourth, this sample consisted of adult white twins born in Virginia. With respect to the rates of psychopathology, twins are probably representative of the general population (Kendler et al. 1996; Kendler & Prescott 2006). Lifetime prevalence rates for alcohol dependence were slightly higher in males and females in VATSPSUD (24.9 and 11.4%, respectively) than in the National Comorbidity Survey (20.1 and 8.2%) while rates of alcohol abuse were nearly identical (VATSPSUD – 12.7 and 5.9%, National Comorbidity Survey – 12.5 and 6.4%).

Fifth, our ultimate dependent variable was AP and not a diagnosis. This was a result of the rarity of symptoms of AUDs in the last year in the females in our sample. While more desirable for a number of reasons, a study of sex differences in last year AUD would have required a considerably larger twin sample than was available to us.

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Appendix

Paths from A Developmental Model for Alcohol Problems

Path to	from	Males	Females
neur	fralc	0.085(0.082)*	-
neur	lpw	0.103(0.099)***	= 0.103(0.100)***
neur	csa	0.190(0.182)***	= 0.190(0.185)***
neur	prl	0.070(0.067)^	-
ns	csa	0.114(0.111)***	= 0.114(0.112)***
ns	prl	0.151(0.147)***	-
ns	neur	0.098(0.099)***	= 0.098(0.100)***
sest	csa	0.321(0.245)***	= 0.321(0.231)***
sest	ns	0.121(0.095)*	-
sest	neur	0.644(0.514)***	0.815(0.605)***
eanx	fralc	-	0.201(0.185)***
eanx	csa	0.191(0.171)***	= 0.191(0.176)***
eanx	neur	0.198(0.185)***	= 0.198(0.188)***
eanx	ns	-	0.133(0.125)**
eanx	sest	0.181(0.211)***	-
cd	fralc	-	0.101(0.088)*
cd	lpw	0.119(0.103)***	= 0.119(0.103)***
cd	csa	0.242(0.211)***	= 0.242(0.210)***
cd	prl	0.136(0.103)***	= 0.136(0.118)***
cd	neur	0.149(0.135)***	= 0.149(0.133)***
cd	ns	0.283(0.254)***	= 0.283(0.249)***
trm	fralc	0.090(0.085)***	= 0.090(0.082)***
trm	lpw	-	0.073(0.066)*
trm	csa	0.109(0.103)**	= 0.109(0.100)**

Path to	from	Males	Females
trm	eanx	-	0.142(0.140)***
trm	cd	0.241(0.261)***	= 0.241(0.253)***
psu	lpw	0.100(0.089)**	= 0.100(0.086)**
psu	ns	0.146(0.134)***	= 0.146(0.126)***
psu	sest	-	0.070(0.083)*
psu	eanx	0.100(0.099)*	-
psu	cd	0.335(0.341)***	= 0.335(0.329)***
psu	trm	-	0.174(0.163)***
nic	fralc	0.131(0.122)**	-
nic	neur	0.085(0.083)*	-
nic	sest	0.093(0.113)**	= 0.093(0.121)**
nic	eanx	-	0.093(0.095)*
nic	cd	0.146(0.155)***	= 0.146(0.158)***
nic	trm	0.143(0.140)***	= 0.143(0.147)***
evdiv	mpw	-	0.148(0.133)***
evdiv	trm	0.164(0.164)***	0.264(0.261)***
evdiv	nic	0.248(0.252)***	= 0.248(0.237)***
phmd	csa	0.275(0.213)***	= 0.275(0.227)***
phmd	neur	0.290(0.234)***	= 0.290(0.246)***
phmd	eanx	0.138(0.119)***	= 0.138(0.123)***
phmd	trm	0.140(0.115)***	= 0.140(0.127)***
phmd	psu	0.182(0.159)***	-
phmd	evdiv	0.359(0.295)***	0.233(0.214)***
si	lpw	0.165(0.159)***	= 0.165(0.156)***
si	csa	0.105(0.101)*	-
si	neur	-	0.088(0.085)**
si	psu	-	0.123(0.136)**
si	evdiv	0.146(0.149)***	= 0.146(0.153)***
ms	lpw	0.094(0.091)***	= 0.094(0.089)***
ms	neur	0.125(0.127)***	-
ms	ns	0.150(0.150)***	= 0.150(0.143)***
ms	sest	-	0.128(0.168)***
ms	evdiv	-	0.165(0.173)***
diffs	csa	0.193(0.163)***	= 0.193(0.160)***
diffs	neur	0.112(0.098)***	= 0.112(0.095)***
diffs	ns	0.090(0.078)**	0.172(0.144)***
diffs	eanx	-	0.092(0.083)**
diffs	cd	0.108(0.104)***	= 0.108(0.103)***
diffs	trm	0.224(0.200)***	= 0.224(0.203)***
diffs	psu	0.106(0.100)***	-
diffs	evdiv	-	0.062(0.057)*
diffs	phmd	0.122(0.132)***	= 0.122(0.122)***

Path to	from	Males	Females
diffs	ms	0.072(0.062)*	-
drinks	ns	0.197(0.188)***	= 0.197(0.188)***
drinks	cd	0.094(0.100)***	= 0.094(0.102)***
drinks	trm	0.068(0.067)*	-
drinks	psu	0.117(0.123)***	= 0.117(0.129)***
drinks	si	0.082(0.079)***	= 0.082(0.082)***
drinks	ms	0.089(0.085)**	-
alcprb	fralc	-	0.230(0.125)***
alcprb	sest	0.387(0.265)***	-
alcprb	cd	0.144(0.086)*	-
alcprb	nic	-	0.427(0.246)***
alcprb	diffs	0.177(0.110)***	= 0.177(0.116)***
alcprb	drinks	1.267(0.713)***	= 1.267(0.731)***

= - path is equal in males and females; p<0.05;

**
p<0.01,

p<0.001;

^
maintained in model due to change in AIC (Akaike 1987).

Abbreviations – fralc – familial risk of alcohol; lpw – low parental warmth; csa – childhood sexual abuse; prl – parental loss; neur – neuroticism; ns – novelty seeking; sest – low self-esteem; eanx – early onset anxiety; cd – conduct disorder; trm – traumas; psu – drug use disorders; nic – nicotine dependence; ed- ever divorced; phmd – prior history of major depression; - si – social isolation; ms – low marital satisfaction; diff – difficulties; drinks – drinks per month; alcprb – alcohol problems.

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FIGURE 1.

Path estimates for best-fit model for causal pathways to last year alcohol problems (defined as meeting one or more criteria for DSM-V alcohol use disorder) in males. Parameters estimated to be equal across sexes, greater in females than males and greater in males than females are depicted in black, red and blue, respectively. If a path is not present between two variables, that is because it was estimated to have a zero value. Appendix II contains the best fit model estimate for all these paths, their statistical significance and the equality or non-equality of that path across sexes. The test of equality across sexes was based on raw path coefficients. However, for ease of interpretation and a consistent measure of effect size, we report standardized path coefficients. Thus paths that are depicted as equal (using raw coefficients) can differ slightly using standardized paths.

Figure 2.

Path estimates for best-fit model for causal pathways to last year alcohol problems (defined a meeting one or more criteria for DSM-V alcohol use disorder) in females. Parameters estimated to be equal across sexes, greater in females than males and greater in males than females are depicted in black, red and blue, respectively. If a path is not present between two variables, that is because it was estimated to have a zero value. Appendix II contains the best fit model estimate for all these paths, their statistical significance and the equality or non-equality of that path across sexes. The test of equality across sexes was based on raw path coefficients. However, for ease of interpretation and a consistent measure of effect size, we report standardized path coefficients. Thus paths that are depicted as equal (using raw coefficients) can differ slightly using standardized paths.

Table 1

Summary of Results from our Model Predicting Sex Differences in the Risk for Alcohol Problems in the Last Year from 18 Risk Factors Organized in a Developmental Cascade

Variable	Total Effect on Males	Total Effect on Females	Difference	Magnitude of Sex Differences	Major Meditational Paths from the Variable for which Effects in the Two Sexes were		
					Equal (Male = Female)	Male > Female	Female > Male
Familial Risk	.024	.156	F>M .132	Strong	LTR	N, ND	EOAD, CD
Low Parental Warmth	.069	.055	M>F .014	Minimal	CD, LMS, DUD		LTR, DIV
Childhood Sexual Abuse	.216	.128	M>F .088	Moderate	EOAD, CD, PMD, LSE, DIFF, LTR	SI	
Parental Loss	.078	.021	M>F .057	Moderate	CD	N, NS	
Neuroticism	.218	.098	M>F .120	Strong	CD, DIFF, PMD	ND, LMS,	SI
Novelty Seeking	.249	.218	M>F .031	Modest	LMS, CD, DUD, DPM		DIFF
Low Self-Esteem	.267	.039	M>F .228	Strong	ND		DUD, LMS
Early Onset Anxiety Disorder	.012	.047	F>M .035	Modest	PMD	DUD	LTR, ND
Conduct Disorder	.223	.181	M>F .042	Modest	DIFF, DPM		
Lifetime Traumas	.074	.084	F>M .010	Minimal	DIFF, PMD	DPM	DIV
Drug Use Disorder	.101	.103	F>M .002	Minimal	DPM, ND	PMD, DIFF	SI
Nicotine Dependence	.003	.251	F>M .248	Strong	DIV		
Ever Divorced	.013	.019	F>M .006	Minimal			LMS, DIFF
Past History of Major Depression	.015	.014	M>F .001	Minimal	DIFF		
Social Isolation	.056	.060	F>M .004	Minimal	DPM		
Low Marital Satisfaction	.067	.000	M>F .067	Moderate		DIFF, DPM	
Difficulties	.110	.116	F>M .006	Minimal			
Number of Drinks per Month	.713	.731	F>M .018	Minimal			

FR – familial risk, LPW – low parental warmth, CSA – childhood sexual abuse, PL – parental loss, N – neuroticism, NS – novelty seeking, LSE – low self-esteem, EOAD – early onset anxiety disorder, CD – conduct disorder, LTR – lifetime traumas, DUD – drug use disorder, ND – nicotine dependence, AUD – alcohol use disorder, DIV – history of divorce, PMD – past history of major depression, SI – social isolation, LMS – low marital satisfaction, DIFF – difficulties and DPM – drinks per month.

<0.02, minimal; .02-.05 modest; .05-.10 moderate, > 0.10 strong