Published in final edited form as:

Soc Psychiatry Psychiatr Epidemiol. 2018 December ; 53(12): 1381–1389. doi:10.1007/s00127-018-1563-5.

The role of parent and offspring sex on risk for externalizing psychopathology in offspring with parental alcohol use disorder: A national Swedish study

E.C. Long, PhD^{1,*}, S.L. Lönner, PhD², J. Sundquist, MD, PhD^{2,5}, K. Sundquist, MD, PhD^{2,5}, and K.S. Kendler, MD^{1,3,4}

¹Virginia Institute for Psychiatric and Behavioral Genetics, Richmond, VA, USA

²Center for Primary Health Care Research, Lund University, Malmö, Sweden.

³Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, USA

⁴Department of Human and Molecular Genetics, Virginia Commonwealth University, Richmond, VA, USA

⁵Department of Family Medicine and Community Health, Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, New York, USA

# These authors contributed equally to this work.

Abstract

PURPOSE.—The substantial literature showing that offspring of parents with alcohol use disorder (AUD) are at increased risk for externalizing psychopathology rarely examines the differential effects of parental and offspring sex. This literature also has other important limitations, such as modest sample sizes and use of unrepresentative samples. Using a large, nationwide Swedish sample, we aim to investigate the roles of parental and offspring sex in externalizing psychopathology among offspring with parental AUD.

METHODS.—AUD diagnosis and externalizing measures were obtained from national registries. Associations between outcomes and parental AUD were examined using logistic regressions. Parental and offspring sex effects were examined with interaction terms.

RESULTS.—Risks for externalizing disorders were increased in sons and daughters with parental AUD, with significant differences between sons and daughters for criminal behavior; maternal AUD had a greater impact than paternal AUD (regardless of offspring sex), but having two parents with AUD increased risk for all outcomes substantially more than having one parent; and maternal AUD increased risk of drug abuse for daughters more than sons, while paternal AUD increased risk of AUD and criminal behavior for sons more than daughters.

*Corresponding author: Elizabeth Long, Virginia Commonwealth University, Virginia Institute for Psychiatric and Behavioral Genetics, Box 980126, Richmond, VA 23298-0126 (USA); longe@vcu.edu.

Conflict of Interest: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical Standards Statement: The study has been approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

CONCLUSIONS.—Offspring of parents with AUD are at increased risk for externalizing psychopathology. Maternal and paternal AUD differentially affected sons' versus daughters' risks for AUD, drug abuse, and criminal behavior. The transmission of psychopathology within the externalizing spectrum appears to have sex-specific elements.

Keywords

parental alcohol use disorder; externalizing disorders; sex differences; children of alcoholics

Introduction

Over the past 30 years, empirical evidence has consistently shown that offspring of parents with a history of alcohol use disorder (AUD) are at increased risk for externalizing disorders [1], such as substance use disorders [2, 3] and attention deficit hyperactivity disorder (ADHD) [4]. Given that externalizing disorders are common and associated with significant adverse societal costs [5–10], understanding whether this parent-child transmission of externalizing psychopathology differs by sex of the parents or offspring is critical for informing etiology and improving intervention efforts. Understanding the role of sex is also important because of the higher prevalence of externalizing disorders in men [11]. However, many of the extant studies investigating risk for externalizing disorders among offspring with parental AUD do not account for sex of offspring or parents. The studies that have examined offspring sex effects produced mixed results [3, 12, 13]. For example, there is some evidence that sons are more vulnerable than daughters to externalizing symptoms [13–16], but there is also evidence that daughters with parental AUD had a greater increased risk for AUD than sons [16].

Of the limited research investigating the differential effects of maternal vs. paternal AUD on sons vs. daughters, there is conflicting evidence for within- versus opposite-sex transmission. While Pollock and colleagues [17] showed that daughters of mothers with AUD had elevated rates of AUD themselves, two other reports showed evidence for opposite-sex transmission of problems [18, 19]. Finally, at least four studies did not find significant effects of parental or offspring sex when examining internalizing symptoms, general maladjustment, alcohol use, and alcohol problems [1, 12, 20, 21]. Thus, the question of whether maternal vs. paternal AUD differentially affects sons vs. daughters remains largely unclear.

Additionally, there are a number of other limitations in this literature. These include use of unrepresentative samples, such as college students, which may be a particularly resilient population, and help-seeking samples [22, 23], as well as frequent use of small sample sizes. Indeed, a recent review [22] noted that 47% of the included studies did not have enough power to reliably detect moderate effects, and only three could reliably detect small effects [15, 24, 25].

The present study aims to clarify the roles of parental and offspring sex in risk for externalizing psychopathology among offspring of parents with AUD while addressing some limitations of previous research by using a large, nationwide Swedish sample that is population-based rather than restricted to unrepresentative samples. To our knowledge, this

is the largest study of its kind, which will increase the reliability and precision of the results. Given that the extant literature has produced conflicting results, we do not have a solid basis to make any specific hypotheses. Rather, our research questions are exploratory in nature. We investigate two main questions: (1) Does parental AUD affect risk for externalizing psychopathology among sons vs. daughters differently? (2) Does maternal AUD vs. paternal AUD affect risk for externalizing psychopathology among sons vs. daughters differently?

Methods

Sample

We linked Swedish National Registers by the unique identification number (replaced with anonymized serial numbers) assigned at birth or immigration to all Swedish inhabitants. The following sources were used to construct our analysis data set: The Multi Generation Register (linking individuals born after 1932 to their parents); the Swedish Census (information on household and education every five years from 1960 to 1990); the Total Population Register (annual data on family from 1990 to 2013); the Longitudinal Integration Database for Health Insurance and Labor Market Studies (information on parental education from 1990 to 2012); the Swedish Hospital Discharge Register (hospitalizations from 1964 to 2012); the Swedish Outpatient Register (medical diagnosis in open care clinics from 2001 to 2012); the Swedish Prescribed Drug Register (prescriptions from July 2005 to December 2013); the Swedish Crime Register (all convictions in lower court from 1973 to 2012); the Suspicion register (individuals strongly suspected of a crime from 1995 to 2012); the Swedish Mortality Register from 1973 to April 2014 (causes and timing of death); and the National School Register. The present analyses included 1,007,333 Swedish-born males and females, born between 1972 and 1982, who did not die or emigrate before age 25 and with at least one biological parent registered, on whom we had information on the parental education variable at age 16.

Measures

We examined four measures of externalizing psychopathology in the proband before age 30: alcohol use disorder (AUD), criminal behavior (CB), drug abuse (DA), and attention deficit hyperactivity disorder (ADHD). AUD was identified from medical registers using ICD codes, prescribed drugs, and criminal records (for a more detailed description see [26]). DA was identified based on medical diagnoses, convictions and suspicions, and prescribed drugs [27]. CB was identified based on convictions in lower court and includes violent crime, property crime, and white-collar crime [28]. ADHD was defined by ICD-9: 314, and ICD-10: F90. AUD, DA, CB, and ADHD were dichotomous variables (present, as defined by at least one registration, or absent).

Parental AUD was defined as an AUD registration in the parent before the probands reached age 18. We include AUD in both parents, maternal only, and paternal only. As a proxy for socioeconomic status during childhood, we used highest level of parental education categorized as low (compulsory school only or missing information), mid (high school), or high (university). We also included rates of offspring living with their mother only, their

father only, or both parents, at age 15 to get a proxy for household composition. We secured ethical approval from the Regional Ethical Review Board of Lund University.

Statistical analyses

Logistic regression models were used to estimate the association between the four externalizing outcomes (AUD, DA, CB, and ADHD) and parental AUD, adjusting for birth year and highest parental education. We also included offspring sex as a covariate in all models to account for differences in base rates of the externalizing disorders. First, we examined the association with parental AUD and tested for offspring sex differences by including a parental AUD by offspring sex interaction, i.e.:

$$\log\left(\frac{P(Y=1)}{1-P(Y=1)}\right) = \beta_0 + \beta_1 byear + \beta_2 EDU_{low} + \beta_3 EDU_{mid} + \beta_4^{sex} + \beta_5 AUD_{par} + \beta_{45}^{sex} \cdot AUD_{par}$$

To facilitate interpretation, the associations between parental AUD and offspring externalizing behavior are presented by offspring sex as odds ratios (ORs), represented by $\exp(\beta_5)$ for females and $\exp(\beta_5 + \beta_{45})$ for males. The interaction terms correspond to the differences between sexes and represent a test for sex differences. Supplementary Table 1 includes all estimated parameters presented in two ways: with offspring sex-specific effects (Parameterization A) and with all parameters, including the interaction term (Parameterization B).

Next, we included both maternal and paternal AUD to investigate whether parental sex has a differential impact on sons versus daughters. Three interactions were included: maternal by paternal AUD, maternal AUD by offspring sex, and paternal AUD by offspring sex, i.e.:

$$\log\left(\frac{P(Y=1)}{1-P(Y=1)}\right) = \beta_0 + \beta_1 byear + \beta_2 EDU_{low} + \beta_3 EDU_{mid} + \beta_4^{sex} + \beta_5 AUD_{mo} + \beta_6 AUD_{fa} + \beta_{45}^{sex} \cdot AUD_{mo} + \beta_{46}^{sex} \cdot AUD_{fa} + \beta_{56} AUD_{mo} \cdot AUD_{fa}$$

As above, we present the associations between maternal, paternal, or both maternal and paternal AUD and offspring externalizing behavior by offspring sex as ORs. The ORs for females and males with only maternal AUD are: $\exp(\beta_5)$ and $\exp(\beta_5 + \beta_{45})$, respectively. For females and males with only paternal AUD, the ORs are: $\exp(\beta_6)$ and $\exp(\beta_6 + \beta_{46})$, respectively. Finally, for females and males with both maternal and paternal AUD, the ORs are: $\exp(\beta_5 + \beta_6 + \beta_{56})$ and $\exp(\beta_5 + \beta_6 + \beta_{45} + \beta_{46} + \beta_{56})$. The interaction terms correspond to the differences between sexes and how the sum of maternal and paternal AUD is modified when both parents are affected. All parameter estimates are presented in Supplementary Table 2 with the two parametrizations described above. All ORs are presented with 95% confidence intervals (CIs). The estimates of maternal and paternal AUD were compared using Wald's tests. All models were run in SAS software version 9.3 [29].

Results

Descriptive Statistics

The prevalences for the externalizing psychopathology measures among those with parental AUD and no parental AUD are shown in Table 1, stratified by sex of the offspring, along with descriptive statistics for the covariate of parental education. Sons had higher prevalences of all four measures compared to females, which is consistent with the literature [30,31]. Across the board though, sons and daughters in the parental AUD group had higher prevalences of externalizing psychopathology compared to the no parental AUD group. These prevalences were higher for offspring with maternal AUD compared to paternal AUD.

Also shown in Table 1 are the rates of household composition. Regardless of whether the mother or father had AUD, both sons and daughters were more likely to live with their mother in cases of parental AUD.

Associations between parental AUD and externalizing psychopathology by offspring sex

The estimated associations between parental AUD and risk for externalizing psychopathology among sons and daughters are shown in Figure 1 (with all parameter estimates in Supplementary Table 1). As shown, the risks for AUD, DA, CB, and ADHD were all significantly increased for both sons (ORs ranging from 2.59 to 2.92) and daughters (ORs ranging from 2.41 to 3.26) with parental AUD. The associations for sons' and daughters' CB (OR of 2.69 vs. 2.41, respectively) were significantly different, as indicated by the significant interaction term. However, the associations for sons' vs. daughters' AUD, DA, and ADHD were not significantly different.

Associations between parental AUD and externalizing psychopathology by parental and offspring sex

The estimated associations between maternal/paternal AUD and risk for externalizing psychopathology among sons and daughters are shown in Figure 2 (with all parameters estimates shown in Supplementary Table 2). The risks for AUD, DA, CB, and ADHD were all significantly increased among sons and daughters with maternal and paternal AUD. These effects were stronger when both parents had AUD. Examination of differences in the ORs for maternal AUD compared to paternal AUD indicates that maternal AUD had a stronger impact than paternal AUD.

Examination of the interactions showed a significant paternal AUD by offspring sex interactions for AUD, suggesting that paternal AUD influences the development of AUD in sons vs. daughters differently. Further, direct comparisons of the effects of maternal vs. paternal AUD as per the Wald's tests were significantly different for sons' AUD ($p = 0.04$) and for daughters' AUD ($p < 0.01$). Thus, paternal AUD increased risk slightly more for sons (OR = 2.86) than daughters (OR = 2.57), while the increased risk for AUD from maternal AUD was similar for both sons and daughters.

For DA, there was a significant maternal AUD by offspring sex interaction, providing evidence that maternal AUD influences the development of DA in sons vs. daughters

differently. The Wald's test further showed that the effects of maternal vs. paternal AUD were significantly different for daughters' DA ($p = 0.01$). Accordingly, maternal AUD increased risk for DA more for daughters (OR = 3.98) than sons (OR = 3.05), while the increased risk for DA from paternal AUD was similar for both sons and daughters.

For CB, there was a significant paternal AUD by offspring sex interaction, showing evidence that paternal AUD influences the development of CB in sons vs. daughters differently. However, while the OR was slightly higher for sons (OR = 2.71) than for daughters (OR = 2.34), this difference was not significant as per the Wald's test.

Neither of the two interactions of maternal AUD by offspring sex and paternal AUD by offspring sex were significant for ADHD. Neither of the Wald's test for sons' and daughters' ADHD were significant. As such, risk for ADHD was increased regardless of parental and offspring sex.

Discussion

Using a large, nationwide Swedish sample, we sought to clarify the roles of parental and offspring sex in risk for externalizing psychopathology (AUD, DA, CB, and ADHD) among offspring of parents with AUD. Three key findings are noteworthy.

First, we showed a two- to three- fold increased risk for AUD, DA, CB, and ADHD among both sons and daughters with parental AUD (of either sex) compared to individuals with no history of parental AUD. These findings are consistent with the substantial amount of previous research showing that children of parents with a history of AUD are at increased risk for externalizing disorders [1–4, 13, 32–35], but we have increased their reliability, precision, and power to detect small effects by using a large, population-based sample. The only significant difference between sons and daughters was for CB. Sons were at greater increased risk than daughters, which is consistent with the literature indicating that sons with parental AUD are more vulnerable to externalizing symptoms [13–16].

Second, analyzing the effect of maternal vs. paternal AUD allowed us to investigate whether affected mothers have a greater impact on their children than affected fathers, or vice versa. We showed that maternal AUD consistently conferred a greater risk than paternal AUD overall for both sons and daughters. One likely explanation for this finding is that offspring in our sample were more likely to live with their mother, even when she was the affected parent. To formally test whether the stronger influence of maternal AUD was attributable to more contact with mothers, we performed additional logistic regressions stratified by household composition (living with both parents, living with mother only, living with father only). These results are displayed in Supplemental Table 3. Indeed, we found evidence for a strong socialization effect, such that offspring were more likely to develop an externalizing disorder when they lived with the affected parent. Additionally, when offspring lived with both parents, the increased risk for externalizing disorders conferred by affected mothers vs. affected fathers was more equal (on the order of two-fold; with the exception of maternal AUD and risk for daughters' ADHD), providing stronger evidence for a socialization effect.

Thus, mothers with AUD likely exert a stronger influence because offspring are more likely to live with them.

Another explanation is the potential impact of prenatal exposure to alcohol that may increase risk for a variety of disorders [36, 37]. However, for all measures, having two parents with AUD increased risk substantially more than having only one parent with AUD (3.4- to 6.0-fold increased risk vs. 2.3- to 3.9), which is consistent with previous research [16, 21].

Third, the interaction analyses of maternal/paternal AUD by offspring sex further allowed us to ask the question of whether maternal and paternal AUD influence sons vs. daughters differently, while the Wald's tests examined whether the effects of maternal vs. paternal AUD were significantly different. For DA, maternal AUD increased risk of DA more for daughters than sons, while for AUD and CB, paternal AUD increased risk for sons more than daughters. Maternal and paternal AUD did not influence risk for ADHD among sons vs. daughters differently.

These findings are inconsistent with the research that did not find any significant effects of parental or offspring sex [1, 12, 20, 21]. It is possible that part of the explanation for these inconsistencies is due to differences in the outcomes examined, as Belliveau & Stoppard (1995) examined internalizing symptoms. However, the remaining outcomes examined by Saunders et al., Kendler et al., and Mellentin et al. (general maladjustment, alcohol use, and alcohol problems, respectively) are broadly similar to ours. Thus, another possible explanation is that our large sample increased the ability to find small effects that previous studies may not have had the power to detect. Still, these inconsistencies reiterate the need for future research to more rigorously investigate the differential effects of maternal vs. paternal AUD on sons vs. daughters.

Despite the need for more research, the present results shed light on the role of parental and offspring sex. Our finding that maternal AUD increases risk of DA for daughters more than sons, while paternal AUD increases risk of AUD and CB for sons more than daughters, supports the notion of sex-specific transmission of psychopathology within the externalizing spectrum broadly rather than AUD specifically. While previous research has also showed evidence for a general liability accounting for the parent-child transmission of externalizing psychopathology [38–40], we have added to this body of literature by showing that this transmission may be sex-specific. We speculate that this sex-specific transmission of externalizing disorders is due to a combination of genetic and environmental influences. For example, Prescott et al. [41] found that the genetic liability for alcohol use disorder was partially, but not completely overlapping in males and females. Therefore, while some of the genetic liability was common between sexes, a portion was sex-specific, which may reflect other sex-specific genetically influenced factors, such as hormones and metabolism. It is also possible that environmental influences play a major role, such as gender socialization by same-sex parents and social expectations.

These findings can be useful for clinicians delivering prevention interventions and treatment to families with affected parents, as the sex of the affected parent and offspring appear to be informative about risk for specific externalizing psychopathology. For example, clinicians

can focus their attention on the prevention of DA among daughters whose mothers have AUD, while they may be more attentive to the prevention of AUD and CB among sons whose fathers have AUD. Likewise, clinicians treating families may be particularly aware of the signs and symptoms of the respective conditions more likely to affect daughters or sons with maternal and paternal AUD. Moreover, outside of sex-specific effects, clinicians can more generally target prevention and intervention efforts towards individuals with a parental history of AUD, focusing particularly on individuals with two affected parents and children of affected mothers.

Limitations

Despite the present study having clear strengths (e.g., use of a large, nationwide sample), it is not without limitations. First, our sample consisted of Swedish individuals only. It is uncertain if our results will generalize to other populations, although it is likely they are generalizable to other industrialized countries. However, parental SES (indexed by parental education) may not have as much of an impact in a more socialized country like Sweden as it would in the United States.

Second, we relied on medical, legal, and pharmacy registry data for our externalizing measures. While this method has the advantage of not being subject to recall biases, it can produce false negatives and positives. Although the extent to which this occurred could not be estimated, the prevalence of AUD in our sample is lower than estimates from most epidemiologic surveys [42–44]. Accordingly, it may be that registries detect more severe cases of AUD than population-based interview studies. However, a previous study of Swedish adoptees using similar registry variables showed high concordance rates for registration across the different methods, providing support for our externalizing measures [42]. For example, having an AUD registration from the criminal registry increased risk of having a registration from hospital records by 13.5 times, and having a registration from hospital records increases risk of having a registration from an outpatient registry by 74.8 times.

Third, our parental AUD variable was lifetime and it is possible the parent could have received the diagnosis before the proband was born. However, there is considerable evidence that the transmission of externalizing disorders is both genetic and environmental [1, 45]. Thus, in both of these instances, the parent would be conferring genetic risk rather than environmental risk.

Conclusions

Using a large, nationwide Swedish sample, we showed three main findings: (1) Risks for AUD, DA, CB, and ADHD were increased in both sons and daughters of parents with AUD, with significant differences between sons and daughters for CB (regardless of parental sex); (2) maternal AUD conferred greater risk for externalizing psychopathology than paternal AUD overall (regardless of offspring sex), but having two parents with AUD increased risk for externalizing psychopathology substantially more than having one parent; and (3) maternal AUD increased risk of DA for daughters more than sons, while paternal AUD

increased risk of AUD and CB for sons more than daughters, providing evidence for elements of sex-specific transmission of psychopathology within the externalizing spectrum. These findings help to clarify the role of parental and offspring sex in the risk for externalizing psychology among offspring with parental AUD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

This project was supported by grants AA0235341 and K01AA024152 from the US National Institutes of Health, the Swedish Research Council (2014–2517), the Swedish Research Council for Health, Working Life and Welfare (in Swedish: FORTE; Reg. no. 2013–1836), and FORTE (Reg. no. 2014–0804) and the Swedish Research Council (2012–2378 and 2014–10134) as well as ALF funding from Region Skåne.

References

1. Kendler KS, Gardner CO, Edwards A, Hickman M, Heron J, Macleod J, Lewis G, Dick DM (2013) Dimensions of parental alcohol use/problems and offspring temperament, externalizing behaviors, and alcohol use/problems. *Alcohol Clin Exp Res* 37 (12):2118–2127. 10.1111/acer.12196 [PubMed: 23895510]
2. Chassin L, Pitts SC, DeLucia C, Todd M (1999) A longitudinal study of children of alcoholics: Predicting young adult substance use disorders, anxiety, and depression. *J Abnorm Psychol* 108 (1): 106–119. 10.1037/0021-843x.108.1.106 [PubMed: 10066997]
3. Sher KJ, Walitzer KS, Wood PK, Brent EE (1991) Characteristics of children of alcoholics: putative risk factors, substance use and abuse, and psychopathology. *J Abnorm Psychol* 100 (4):427 [PubMed: 1757657]
4. Knopik VS, Heath AC, Jacob T, Slutske WS, Bucholz KK, Madden PA, Waldron M, Martin NG (2006) Maternal alcohol use disorder and offspring ADHD: disentangling genetic and environmental effects using a children-of-twins design. *Psychol Med* 36 (10):1461 [PubMed: 16734942]
5. Campbell KE, Zobeck T, Bertolucci D (1995) Surveillance Report# 38: Trends in alcohol-related fatal traffic crashes, United States: 1977–94. Rockville, MD: National Institute on Alcohol Abuse and Alcoholism, Division of Biometry and Epidemiology.
6. Cases M, Stinson FS, Dufour MC (1995) Surveillance Report# 36: Trends in alcohol-related morbidity among short stay community hospital discharges, United States 1979–1993. Bethesda (MD): National Institute on Alcoholism.
7. Rehm J, Room R, Van Den Brink W, Jacobi F (2005) Alcohol use disorders in EU countries and Norway: An overview of the epidemiology. *Eur Neuropsychopharmacol* 15 (4):377–388. 10.1016/j.euroneuro.2005.04.005 [PubMed: 15925491]
8. Lundin A, Hallgren M, Forsman M, Forsell Y (2015) Comparison of DSM-5 classifications of alcohol use disorders with those of DSM-IV, DSM-III-R, and ICD-10 in a general population sample in Sweden. *J Stud Alcohol Drugs* 76 (5):773–780 [PubMed: 26402358]
9. Kendler KS, Ohlsson H, Sundquist J, Sundquist K (2016) Alcohol Use Disorder and Mortality Across the Lifespan: A Longitudinal Cohort and Co-relative Analysis. *JAMA Psychiatry* 73 (6): 575–581 [PubMed: 27097014]
10. Kessler RC, Aguilar-Gaxiola S, Alonso J, Chatterji S, Lee S, Ormel J, Ustun TB, Wang PS (2009) The global burden of mental disorders: an update from the WHO World Mental Health (WMH) surveys. *Epidemiol Psychiatr Soc* 18 (1):23–33 [PubMed: 19378696]
11. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE (2005) Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 62 (6):617–627. 10.1001/archpsyc.62.6.617 [PubMed: 15939839]

12. Belliveau JM, Stoppard JM (1995) Parental alcohol abuse and gender as predictors of psychopathology in adult children of alcoholics. *Addict Behav* 20 (5):619–625 [PubMed: 8712059]
13. Edwards EP, Eiden RD, Colder C, Leonard KE (2006) The development of aggression in 18 to 48 month old children of alcoholic parents. *J Abnorm Child Psychol* 34 (3):409–423. 10.1007/s10802-006-9021-3 [PubMed: 16649002]
14. Wall TL, Garcia-Andrade C, Wong V, Lau P, Ehlers CL (2000) Parental history of alcoholism and problem behaviors in Native-American children and adolescents. *Alcohol Clin Exp Res* 24 (1):30–34 [PubMed: 10656189]
15. Blazer DG, George LK (1993) Psychiatric disorders in adult children of alcoholics: data from the Epidemiologic Catchment Area project. *Am J Psychiatry* 1 (50):793
16. Yoon G, Westermeyer J, Kuskowski MA, Nesheim L (2013) Impact of the number of parents with alcohol use disorder on alcohol use disorder in offspring: a population-based study. *J Clin Psychiatry* 74 (8):795–801 [PubMed: 24021496]
17. Pollock VE, Schneider LS, Gabrielli WF, Jr., DW Goodwin (1987) Sex of parent and offspring in the transmission of alcoholism. A meta-analysis. *J Nerv Ment Dis* 175 (11):668–673 [PubMed: 3316491]
18. Berkowitz A, Perkins HW (1988) Personality characteristics of children of alcoholics. *J Consult Clin Psychol* 56 (2):206–209 [PubMed: 3372827]
19. Marino EN, Fromme K (2015) Alcohol-induced blackouts and maternal family history of problematic alcohol use. *Addict Behav* 45:201–206 [PubMed: 25705013]
20. Saunders GR, McGue M, Iacono WG, Elkins IJ (2016) Parent–offspring resemblance for drinking behaviors in a longitudinal twin sample. *J Stud Alcohol Drugs* 78 (1):49–58
21. Mellentin AI, Brink M, Andersen L, Erlangsen A, Stenager E, Bjerregaard LB, Christiansen E (2016) The risk of offspring developing substance use disorders when exposed to one versus two parent (s) with alcohol use disorder: A nationwide, register-based cohort study. *Journal Psychiatry Res* 80:52–58 [PubMed: 27295121]
22. Harter SL (2000) Psychosocial adjustment of adult children of alcoholics: a review of the recent empirical literature. *Clin Psychol Rev* 20 (3):311–337 [PubMed: 10779897]
23. Park S, Schepp KG (2015) A systematic review of research on children of alcoholics: Their inherent resilience and vulnerability. *J Child Family Stud* 24 (5):1222–1231. 10.1007/s10826-014-9930-7
24. Ackerman RJ, Gondolf EW (1991) Adult children of alcoholics: the effects of background and treatment on ACOA symptoms. *Int J Addict* 26 (11):1159–1172 [PubMed: 1743816]
25. Jennison KM, Johnson KA (1997) Resilience to drinking vulnerability in women with alcoholic parents: the moderating effects of dyadic cohesion in marital communication. *Subst Use Misuse* 32 (11):1461–1489 [PubMed: 9336860]
26. Long EC, Lönn SL, Ji J, Lichtenstein P, Sundquist J, Sundquist K, Kendler KS (2017) Resilience and risk for alcohol use disorders: A Swedish twin study. *Alcohol Clin Exp Res* 41 (1):149–155 [PubMed: 27918840]
27. Kendler KS, Sundquist K, Ohlsson H, Palmer K, Maes H, Winkleby MA, Sundquist J (2012) Genetic and familial environmental influences on the risk for drug abuse: a national Swedish adoption study. *Arch Gen Psychiatry* 69 (7):690–697. 10.1001/archgenpsychiatry.2011.2112 [PubMed: 22393206]
28. Kendler KS, Lonn SL, Maes HH, Lichtenstein P, Sundquist J, Sundquist K (2016) A Swedish population-based multivariate twin study of externalizing disorders. *Behav Genet* 46 (2):183–192. 10.1007/s10519-015-9741-7 [PubMed: 26494460]
29. SAS Insitiute Inc (2011) Version 9.3. SAS Institute, Cary, NC
30. Kendler KS, Prescott CA, Myers J, Neale MC (2003) The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. *Arch Gen Psychiatry* 60 (9):929–937 [PubMed: 12963675]
31. Kramer MD, Krueger RF, Hicks BM (2008) The role of internalizing and externalizing liability factors in accounting for gender differences in the prevalence of common psychopathological syndromes. *Psychol Med* 38 (1):51–61. 10.1017/S0033291707001572 [PubMed: 17892625]

32. Carle AC, Chassin L (2004) Resilience in a community sample of children of alcoholics: Its prevalence and relation to internalizing symptomatology and positive affect. *J Appl Dev Psychol* 25 (5):577–595. 10.1016/j.appdev.2004.08.005
33. Diaz R, Gual A, Garcia M, Arnau J, Pascual F, Canuelo B, Rubio G, de Dios Y, Fernandez-Eire MC, Valdes R, Garbayo I (2008) Children of alcoholics in Spain: from risk to pathology. Results from the ALFIL program. *Soc Psychiatry Psychiatr Epidemiol* 43 (1):1–10. 10.1007/s00127-007-0264-2 [PubMed: 17932609]
34. Kim HK, Lee MH (2011) Factors influencing resilience of adult children of alcoholics among college students. *J Korean Acad Nurs* 41 (5)
35. King SM, Keyes M, Malone SM, Elkins I, Legrand LN, Iacono WG, McGue M (2009) Parental alcohol dependence and the transmission of adolescent behavioral disinhibition: a study of adoptive and non-adoptive families. *Addiction* 104 (4):578–586. 10.1111/j.1360-0443.2008.02469.x [PubMed: 19215604]
36. Disney ER, Iacono W, McGue M, Tully E, Legrand L (2008) Strengthening the case: prenatal alcohol exposure is associated with increased risk for conduct disorder. *Pediatr* 122 (6):e1225–e1230
37. Fryer SL, McGee CL, Matt GE, Riley EP, Mattson SN (2007) Evaluation of psychopathological conditions in children with heavy prenatal alcohol exposure. *Pediatr* 119 (3):e733–741. 10.1542/peds.2006-1606
38. Bornoalova MA, Hicks BM, Iacono WG, McGue M (2010) Familial transmission and heritability of childhood disruptive disorders. *Am J Psychiatry* 167 (9):1066–1074. 10.1176/appi.ajp.2010.09091272 [PubMed: 20634367]
39. Hicks BM, Foster KT, Iacono WG, McGue M (2013) Genetic and environmental influences on the familial transmission of externalizing disorders in adoptive and twin offspring. *JAMA Psychiatry* 70 (10):1076–1083. 10.1001/jamapsychiatry.2013.258 [PubMed: 23965950]
40. Hicks BM, Krueger RF, Iacono WG, McGue M, Patrick CJ (2004) Family transmission and heritability of externalizing disorders: a twin-family study. *Arch Gen Psychiatry* 61 (9):922–928. 10.1001/archpsyc.61.9.922 [PubMed: 15351771]
41. Prescott CA, Aggen SH, Kendler KS (1999) Sex differences in the sources of genetic liability to alcohol abuse and dependence in a population-based sample of US twins. *Alcohol Clin Exp Res* 23 (7):1136–1144 [PubMed: 10443978]
42. Kendler KS, Ji J, Edwards AC, Ohlsson H, Sundquist J, Sundquist K (2015) An Extended Swedish National Adoption Study of Alcohol Use Disorder. *JAMA Psychiatry* 72 (3):211–218 [PubMed: 25565339]
43. Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS (1994) Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch Gen Psychiatry* 51 (1):8–19 [PubMed: 8279933]
44. Kringlen E, Torgersen S, Cramer V (2001) A Norwegian psychiatric epidemiological study. *Am J Psychiatry* 158 (7):1091–1098 [PubMed: 11431231]
45. Kendler KS, Gardner C, Dick DM (2011) Predicting alcohol consumption in adolescence from alcohol-specific and general externalizing genetic risk factors, key environmental exposures and their interaction. *Psychol Med* 41 (7):1507–1516. 10.1017/S003329171000190x [PubMed: 20942993]

Fig. 1.

Odds ratios for risk of externalizing psychopathology by sex of offspring. All models were adjusted for birth year and parental education. Error bars indicate 95% confidence intervals. Please see Supplementary Table 1 for full parameter estimates

Fig. 2. Odds ratios for risk of externalizing psychopathology by sex of offspring and by sex of affected parent. All models were adjusted for birth year and parental education. Error bars indicate 95% confidence intervals. Please see Supplementary Table 2 for full parameter estimates

Table 1. Descriptive Statistics, *N*(%)

	Sons			
	Parental AUD (Both)	Paternal AUD	Maternal AUD	No Parental AUD
Total	529 (0.10%)	10,376 (1.99%)	3,703 (0.71%)	505,918 (97.2%)
Externalizing psychopathology				
Alcohol use disorder (AUD)	104 (19.7%)	1,144 (11.0%)	461 (12.4%)	20,574 (4.1%)
Drug abuse (DA)	81 (15.3%)	1,219 (11.7%)	462 (12.5%)	21,103 (4.2%)
Criminal behavior (CB)	230 (43.5%)	3,691 (35.6%)	1,312 (35.4%)	83,582 (16.5%)
ADHD	17 (3.2%)	146 (1.4%)	69 (1.9%)	2,763 (0.5%)
Parental Education				
Low	103 (19.5%)	1,390 (13.4%)	572 (15.4%)	49,350 (9.8%)
Mid	260 (49.1%)	5,295 (51.0%)	1,814 (49.0%)	230,698 (45.6%)
High	166 (31.4%)	3,691 (35.6%)	1,317 (35.6%)	225,870 (44.6%)
Household Composition				
Living with no biological parent	65 (12.3%)	362 (3.5%)	287 (7.8%)	5,419 (1.1%)
Living with mother only	159 (29.5%)	4,939 (47.6%)	1,131 (30.5%)	95,045 (18.8%)
Living with father only	59 (11.2%)	468 (4.5%)	759 (20.5%)	25,596 (5.1%)
Living with both parents	71 (13.4%)	2,559 (24.7%)	906 (24.5%)	359,443 (71.0%)
	Daughters			
	Parental AUD (Both)	Paternal AUD	Maternal AUD	No Parental AUD
Total	519 (0.10%)	9,714 (2.0%)	3,394 (0.7%)	473,180 (97.2%)
Externalizing psychopathology				
Alcohol use disorder (AUD)	54 (10.4%)	536 (5.5%)	256 (7.5%)	10,227 (2.2%)
Drug abuse (DA)	55 (10.6%)	459 (4.7%)	200 (5.9%)	7,186 (1.5%)
Criminal behavior (CB)	111 (21.4%)	1,329 (13.7%)	503 (14.8%)	29,543 (6.2%)
ADHD	7 (1.3%)	100 (1.0%)	46 (1.4%)	1,641 (0.3%)
Parental Education				
Low	614 (22.8%)	1,315 (13.5%)	520 (15.3%)	46,448 (9.8%)
Mid	1,290 (47.9%)	4,961 (51.1%)	1,661 (48.9%)	216,670 (45.8%)
High	149 (27.0%)	3,438 (35.4%)	1,213 (35.7%)	210,062 (44.4%)
Household Composition				
Living with no biological parent	83 (16.0%)	496 (5.1%)	324 (9.5%)	9,785 (2.1%)
Living with mother only	141 (27.2%)	4,758 (49.9%)	1,134 (33.4%)	97,542 (20.6%)
Living with father only	47 (9.1%)	254 (2.6%)	559 (16.5%)	15,684 (3.3%)
Living with both parents	53 (10.2%)	2,267 (23.3%)	761 (22.4%)	330,952 (69.9%)