Published in final edited form as:

Mol Psychiatry. 2020 August ; 25(8): 1777–1786. doi:10.1038/s41380-018-0111-8.

The risk for drug abuse, alcohol use disorder, and psychosocial dysfunction in offspring from high-density pedigrees: its moderation by personal, family, and community factors

Kenneth S. Kendler^{1,2}, Henrik Ohlsson³, Silviu Bacanu^{1,2}, Jan Sundquist³, Kristina Sundquist³

Kenneth S. Kendler: Kenneth.Kendler@vcuhealth.org

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

²Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, USA

³Center for Primary Health Care Research, Lund University, Malmö, Sweden

Abstract

Previous high-risk family designs in psychiatry have focused largely on offspring of affected parents. We take a pedigree-based approach and examine the social, psychological, and psychiatric features of offspring from extended pedigrees selected for high-densities of alcohol use disorder (AUD) or drug abuse (DA). We identified, from the Swedish population, 665,715 pedigrees containing a mean of 17.9 parents, aunts/uncles, grandparents, and cousins of a core full-sibship we term the *pedigree offspring*. We then derived 13 empirical classes of these pedigrees based on the density of cases of AUD and DA. High rates of AUD or DA in the pedigrees were associated in the offspring with lower levels of school achievement, educational attainment, and resilience, and higher rates of psychiatric illness, neighborhood deprivation, unemployment, social welfare, early retirement, and criminal convictions. Effect sizes were large in the offspring of the highest density pedigrees and were stronger in high-density DA than in high-density AUD pedigrees. Sensitivity to the pathogenic effects of membership in these high-risk sibships was substantially attenuated by high levels of school attainment and resilience, female sex, and absence of parental divorce. Offspring of pedigrees with a high density of AUD or DA are multiply disadvantaged and typically suffer from educational difficulties, social deprivation, socio-economic dysfunction, personality problems, and elevated rates of both psychiatric disorders and externalizing syndromes. Despite these difficulties, personal strengths, including improved school achievement and resilience, and an intact parental marriage can substantially buffer these adverse effects and might form a basis for prevention efforts.

Correspondence to: Kenneth S. Kendler, Kenneth.Kendler@vcuhealth.org.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. We secured approval for this study from the Regional Ethical Review Board of Lund University.

Electronic supplementary material The online version of this article (<https://doi.org/10.1038/s41380-018-0111-8>) contains supplementary material, which is available to authorized users.

Introduction

Alcohol use disorder (AUD) and drug abuse (DA) are both strongly transmitted within families [1, 2]. Twin and adoption studies suggest that both genetic and familial-environmental factors contribute to this transmission [3–6]. Indeed, both of these syndromes likely arise from a complex mixture of genetic, temperamental, and socio-environmental risk factors that act and interact over development [7–9]. Familial high-risk studies have a long tradition in psychiatric research, typically examining offspring of an affected parent as seen, for example, for schizophrenia [10, 11], depression [12], and AUD [13, 14].

We here examine a different high-risk paradigm utilizing pedigrees as the unit of analysis. As seen in Fig. 1, starting from a core set of full-siblings, we define pedigrees to include their biological parents, biological uncles and aunts, grandparents, and full cousins. We select pedigrees from all of Sweden on the basis of the prevalence of men and women in the pedigree who are affected with, respectively, AUD and DA. In this paper, we divide these extended families into what we call *the pedigree* (parents, uncles/ aunts, grandparents, and cousins) and the core set of full-siblings who, for concision, we termed the *offspring* of the pedigree.

We then address the following two questions:

1. What are the diagnostic, cognitive, personality, and socio-economic characteristics of the offspring as a function of the density within their pedigrees of, respectively, AUD and DA?
2. In pedigrees selected for their density for AUD (or DA), is the risk in the offspring for developing AUD (or DA) moderated by sex, neighborhood deprivation, early onset psychiatric disorder, parental divorce, school achievement, and level of resilience?

Methods

This study utilized several different Swedish population-based registers with national coverage, linking them using each person's unique identification number. To preserve confidentiality, this ID number was replaced by a serial number. We secured ethical approval for this study from the Regional Ethical Review Board of Lund University (No. 2008/409).

From the Swedish Multigenerational register, we selected all individuals (who form the offspring of our pedigrees) born in Sweden between 1980 and 1990 who still resided in Sweden at age 16 ($N = 1,207,230$). For each set of offspring (full-siblings of one another), we identified parents, grandparents, aunts, uncles, cousins, half-siblings, and full-siblings. The full-siblings had to be born outside of the period from 1980 to 1990, as individuals born in that decade constitute the offspring sample. Furthermore, we required that the relative should be alive and residing in Sweden in 1973 and not born later than 1995. Note that a relative could be included in several different pedigree families. We identified 780,980 pedigrees but to ensure adequate pedigree size, excluded pedigrees with <7 individuals ($N = 115,265$). We had 665,715 pedigrees for our analyses with a mean (standard deviation [SD]) pedigree size of 16.3 (7.2) individuals and 1,019,590 offspring (mean of 1.53 [0.7] per

pedigree). For each individual within the pedigree, we identified if they had a lifetime registration of DA and AUD. For our definition see Appendix Table 1. Furthermore, we recorded the number of males/females within each pedigree as well as the number of males/females registered with AUD or DA. To stabilize variance of the estimates for further use, we transformed the rates of male and female with AUD/DA using the Freeman and Tukey arcsine transform [15]. Based on the bivariate transformed rates, we used k-means clustering to partition the pedigrees into a pre-specified number of clusters. The purpose of using k-means clustering is to define clusters such that the total intra-cluster variation, or total within-cluster sum of square (WSS), is minimized. The total WSS measures the compactness of the clustering and this should be as small as possible. One of the most common ways to determine the number of clusters is the Elbow method. The Elbow method looks at the total WSS as a function of the number of clusters, i.e., the smallest number of clusters, which account for the largest amount of variation in the data. Appendix Figure 1a, b shows the total WSS as a function of the number of clusters. We chose to work with 13 clusters for both DA and AUD as, at this number, the curves exceed 90% and clearly begin to asymptote. We then calculated the mean genetic resemblance of pedigree members to the offspring. It was important that this not vary substantially across pedigree classes. If genetic resemblance was higher in the denser pedigrees, that could bias upward the rates of illness in offspring.

Next, we investigated how the offspring of the 13 pedigree clusters (representing different densities of DA and AUD) differed in their risk for DA/AUD and their mean rate or level of the following variables: years of education, neighborhood deprivation, unemployment status, early retirement, on social welfare, psychiatric registration, school achievement, resilience-score, criminal behavior, sex, and year of birth. For definitions of these variables, see Appendix Table 1.

We then regressed the mean rates of DA/AUD (across each pedigree cluster) on each of the measured individual variable across all 13 clusters. The corresponding B-coefficients are interpreted as the increase/decrease in the variable under study for each percentage-unit increase in DA/AUD in the pedigree.

Finally, we examined whether the impact of pedigree density on offspring risk for DA or AUD was moderated by six putative predisposing or protective factors: sex, neighborhood deprivation at age 16, early onset psychiatric disorder (prior to age 16), parental divorce prior to age 16, school achievement assessed at age 16, and level of resilience assessed at age 18.

We used a regression model (with DA/AUD in offspring as the dependent variable) with the identity link, and robust standard errors in which each of the clusters were included in a separate interaction term with the variable of interest. The interaction term was then measured on the additive scale. The statistical analysis was performed using SAS 9.4 and R version 3.2.5 [16].

Results

Alcohol use disorder

Pedigrees—The results of the k-means clustering for AUD in the pedigrees are given in Appendix Figure 2a. Table 1a provides key features of the 13 identified classes of pedigrees. They differed substantially in samples size with 59% of all pedigrees containing no individual with AUD and the four highest-density classes constituting only 2% of all pedigrees. Across the 13 pedigree categories, the percentage of individuals affected with AUD increased from 0% in class one to 30% in classes 11–13. The mean genetic relationship among members of these pedigrees to the offspring was stable across the classes, ranging narrowly from +0.24 to +0.27. The intra-class correlation for AUD across this entire population of pedigrees equaled +0.191.

Offspring—We examined a more extensive set of measures in the offspring of these 13 pedigree classes (Table 2a), which includes, in the final column, the linear regression coefficient representing the mean change per percent increased in AUD in the pedigree. Sibship sizes of the pedigree offspring were typical with most clusters having around 1.5 offspring. Sex composition was relatively stable at 51–54% male across the classes. Offspring school achievement was strongly associated with the density of AUD in the pedigrees class, with a mean decline of 0.031 SDs per percent increase of AUD. The difference in school achievement from the lowest to highest density AUD pedigrees was a full SD. The effect was more modest for resilience where the mean score declined 0.013 SDs for each percent increase in AUD in the pedigree. Educational attainment declined in the offspring with increasing rates of AUD in the pedigree at the rate of 0.067 years per percent of AUD. Rates of offspring psychiatric illness increased 0.3% per 1% increased density of AUD in the pedigree.

The level of neighborhood deprivation in which the offspring were residing had a substantial positive relationship with AUD density in the pedigree. With each percent of increasing AUD in the pedigree, the neighborhood deprivation index for the offspring's community increased an average of 0.017 SD units.

We examined three measures of socioeconomic functioning: unemployment, short-term government aid as social welfare, and long-term aid through early retirement/ disability pensions. In the offspring, all three were substantially associated with the density of AUD in the pedigree with the effect being stronger for social welfare and unemployment rates (0.3–0.4% increase per percent increase in rate of AUD in the pedigree) than for early retirement (0.1% increase).

We then explored the rates of AUD, DA, and criminal conviction in the offspring, all of which were strongly associated with the density of AUD in the pedigree (Table 2a). Comparing offspring from the highest to the lowest density pedigrees, rates of AUD, DA, and criminal convictions increased, respectively, 0.23%, 0.45%, and 0.61% per percent increase in AUD in the pedigree. The survival curve for AUD is seen in Appendix Figure 3a. Because of its relatively late age at onset, the survival curves for AUD have not begun to asymptote by the end of our observation period.

Finally, we examined the degree to which the adverse outcomes of offspring from high-density AUD pedigrees could be explained by prior onsets of AUD. In the highest density pedigrees, mean school achievement and neighborhood deprivation scores were, respectively, -0.83 SDs and $+0.79$ SDs. In offspring from that pedigree with no prior AUD registration, the parallel scores were -0.83 SDs and $+0.72$ SDs, respectively. The results for other variables were similar (see Appendix Table 2).

Drug abuse

Pedigrees—Appendix Figure 2b depicts results of the k-means clustering for pedigrees with a variable density of DA. The pattern of pedigrees classes resembled that seen for AUD. The intra-class correlation for DA across this entire population of pedigrees was $+0.287$. In all of our pedigrees, class assignment for the density of AUD and DA was positively correlated: $+0.41$ ($p < 0.0001$).

Key descriptive variables for the 13 identified classes of pedigrees, sorted on their density of DA cases, are shown in Table 1b. The most common two pedigree classes, which contained essentially no case of DA, constituted 70.3% of all pedigrees. The four classes of pedigrees with the highest DA density ($>25\%$), by contrast, made up only 1.0% of all pedigrees. Across the 13 pedigree categories, the percentage of individuals affected with DA ranged from 0% in classes 1 and 2 to 34% and 45% in classes 12 and 13. The mean genetic relationship among members of these pedigrees to the offspring full-sibs was relatively stable across the classes, ranging from $+0.24$ to $+0.29$.

Offspring—Features of the offspring of these 13 pedigree classes, differing in DA density, are shown in Table 2b. Sibship sizes were small and sex composition was stable. Offspring school achievement was strongly associated with increased density of DA in the pedigrees, with a mean decline of 0.035 SDs per percent increase. Offspring from the highest density DA pedigrees had a mean school achievement 1.30 SDs below the mean. The effect was less pronounced for resilience with a mean decline of 0.02 SD units per percent increase in rates of DA in the pedigree. Offspring educational attainment declined 0.08 years and rates of psychiatric illness increased 0.031% for each percent increase in DA pedigree density.

The level of neighborhood deprivation where the offspring resided increased 0.026 SDs per percent of DA pedigree density. In the offspring, all three of our measures of socio-economic functioning increased monotonically with each increasing percent of DA in the pedigree with the change in social welfare being the largest (0.54%), intermediate in unemployment rate (0.46% per class), and least in the receipt of early retirement (0.12%).

Of note, of the eight measures of adverse outcome we examined in our two groups of offspring, the association with pedigree density was stronger with DA than with AUD in all of them.

The rates of DA, AUD, and criminal conviction in offspring were all strongly associated with the density of DA in the pedigree with the rates increasing, respectively, 0.63%, 0.24%, and 0.78% per percent increase in DA in the pedigree. The survival curve for DA is seen in Appendix Figure 3b. Because of its relatively early at onset, the survival curves for DA was

beginning to asymptote by the end of our observation period for all but the highest risk group.

Finally, we examined the degree to which the poor outcomes of offspring from high-density DA pedigrees could be explained by prior onsets of DA. In the highest density pedigrees, mean school achievement and neighborhood deprivation scores were, respectively, -1.30 SDs and $+1.70$ SDs. In offspring from that pedigree with no prior AUD registration, the parallel scores were -1.28 SDs and $+1.58$ SDs, respectively. As seen in Appendix Table 2, the results were similar for other variables.

Moderators of risk

We examined six potential moderators of the risk in offspring of pedigrees with variable densities of illness. These were by design diverse and consisted of sex, resilience, school achievement, early onset psychiatric disorders, parental divorce, and neighborhood deprivation. For all 12 analyses, the model including interactions on an additive scale provided a better fit index (AIC) than the model including only the main effects. We present, in Table 3, the effect sizes as the proportion of variance (i.e., r^2) accounted for by the model with only main effects, main effects + the interaction, and most importantly, the difference between the two. The models with and without interactions always explained more variance for DA than for AUD. The same pattern of results was seen for the interactions themselves.

The strongest interaction effects for AUD were seen for school achievement, early onset psychiatric disorder, and parental divorce. The protective effect of school achievement is shown in Fig. 2a. The density of AUD in an individual's pedigree had a far greater impact on risk for AUD in individuals with poor school achievement than in those who performed well in school.

For DA, the strongest interaction effects were seen for school achievement, resilience, and sex. We illustrate the protective effects of sex and resilience in Fig. 2b, c, respectively. On average, the density of DA in the pedigree of origin had a greater effect on risk for DA in males than in females.

Interestingly, while the slopes were steeper for the three highest density pedigrees, little difference in slope was observed in the high male, high female, and high male–female pedigrees. The interaction between resilience and pedigree class (Fig. 2c) reveals a much stronger impact on the density of DA in the pedigree of origin for individuals with low resilience than with high resilience. The results from the highest risk class 13 pedigrees are particularly noteworthy for the very sharp decline of risk with increasing resilience but could not be defined at the highest levels of resilience as too few subjects from those sibships scores in that range.

Discussion

Using 665,715 pedigrees from the general Swedish population, we examined the traits, patterns of social functioning, and disorders that occurred in offspring from pedigrees with

varying rates of AUD and DA. Then we examined the impact on these outcomes of potential moderators.

We review 11 of our most interesting findings. First, we saw a substantial concentration of cases of AUD and DA in a small number of high-density pedigrees. The densest 10% of pedigrees in Sweden contained 67% of all cases of DA and 65% of all cases of AUD, consistent with our intra-class correlations showing a stronger concentration within pedigrees for DA than AUD. Second, congruent with prior literature [1, 2], risks for AUD and DA in the pedigree offspring were strongly associated with the density of cases in the pedigree. Third, in accord with previous studies [14, 17–19], offspring of high-density pedigrees demonstrated substantially lowered school achievement and educational attainment. Offspring of the highest versus lowest risk AUD pedigrees scored a full SD lower on their school achievement and averaged 2 years less of education. IQ scores at a mean age of 18 were available on nearly all males from the Swedish conscription registry [20] analysis of which showed that offspring from the highest density AUD and DA pedigrees had, respectively, mean IQs 10 and 13 points lower than average. These findings are congruent with evidence that polygenic risk scores for AUD are associated with a reduction in cognitive performance [21].

Fourth, offspring of the highest density AUD and DA pedigrees scored 0.54 and 0.84 SDs below normal on our measure of resilience, consistent with evidence that a range of personality dysfunctions occur in offspring of individuals with AUD and DA [22–25] including lowered levels of resilience [26]. Fifth, in accord with prior evidence of excess rates of both internalizing and externalizing traits and disorders in children of parents with AUD and DA [19, 23], offspring from high-density pedigrees for AUD and DA had elevated rates of other psychiatric disorders. Sixth, in addition to low levels of educational attainment, individuals from high-density AUD and DA pedigrees resided in socially deprived communities, replicating results first noted in one of the classic early studies in psychiatric epidemiology [27] and replicated many times since [28, 29]. The effects were especially strong in offspring of the highest density DA pedigrees, who lived in communities 1.70 SDs below the mean in deprivation scores.

Seventh, the density of AUD and DA in pedigrees was strongly associated with unemployment and various forms of social assistance in the offspring indicating a familial link between substance abuse liability and socio-economic dysfunction [22]. Eighth, consistent with prior evidence of strong familial co-aggregation among externalizing syndromes [30, 31], cases of AUD, DA, and criminal convictions clustered together in the offspring of pedigrees selected for high rates of DA and AUD. Ninth, on all the outcomes examined, performance was poorer for offspring of high-density DA versus AUD pedigrees. Tenth, could the poor cognitive, social and socio-economic outcome of the offspring from the high-density pedigrees arise as a result of developing AUD or DA? Our analyses suggested that this is not a likely explanation for our findings as levels of cognitive, social, and personality dysfunction in offspring of high-density pedigrees with no prior substance use disorder were only slightly less pronounced than that seen in all offspring.

Finally, we examined five putative moderators of the poor outcomes observed in offspring from dense AUD and DA pedigrees. Significant interactions were seen between all putative moderators and density of pedigree substance use in predicting AUD and DA in the offspring. Several of these effects were relatively strong. High rates of AUD and DA in the pedigree had much weaker effects on the offspring at high versus low levels of resilience and education, on women versus men, and on offspring who did not versus did experience parental divorce.

Limitations

These results should be interpreted in the context of four potential methodological limitations. First, our assessments of AUD and DA are based on administrative data from medical, criminal, and pharmacy records and are not equivalent to diagnoses based on personal interview. We are studying individuals whose substance abuse is of sufficient severity to cause medical and/or legal problems. Second, the patterns of psychiatric and social dysfunction concentrated in high-risk pedigrees might differ across countries. Sweden is a relatively egalitarian society. The concentration of psychosocial dysfunction in high-density AUD or DA pedigrees might be more severe in countries with greater social inequalities. Third, the causal relationships between the various traits and disorders concentrated in these high-risk pedigrees are surely complex and involve genetic, psychological, and social factors. Our results are descriptive in nature and these analyses cannot claim to elucidate causal pathways. Finally, our choice of 13 categories for our pedigrees was based on a recognized method but involved subjective judgment. We repeated these analyses extracting 7 and 10 categories, which both produced overall similar results.

Conclusions

While we generally replicate prior results obtained in traditional high-risk designs, in an example of “triangulation” [32], we extend these findings using a different research paradigm in a large, epidemiologically representative national sample, and a broad array of objective outcomes. Specifically, we find that offspring of pedigrees with a high density of AUD or DA are at risk for multiple adverse outcomes including poor cognitive functioning, reduced educational attainment, maladaptive personality traits, lowered occupational functioning, residence in deprived neighborhoods, and high risk for psychiatric and other forms of DA and criminality. Little of these associations can be attributed to prior episodes of substance misuse. The familial vulnerability to AUD and DA is broad and impacts on many key areas of human functioning beyond increasing risk for substance use problems. We can have increased confidence in the validity of these findings because of their detection across various methodologies [32]. Despite the widely distributed and severe dysfunctions seen in offspring from our high-density pedigrees, several moderators of risk—including in particular educational attainment, resilience, female sex, and an intact parental marriage—had substantial protective effects. These findings have broad implications for efforts at primary prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This project was supported by grants R01AA023534 and R01DA030005 from the National Institutes of Health, the Swedish Research Council for Health, Working Life and Welfare (In Swedish: Forte; Reg.nr: 2013-1836), the Swedish Research Council (2012-2378; 2014-10134), and FORTE (2014-0804) as well as ALF funding from Region Skåne.

References

1. Cotton NS. The familial incidence of alcoholism: a review. *J Stud Alcohol*. 1979;40:89–116. [PubMed: 376949]
2. Merikangas KR, Stolar M, Stevens DE, Goulet J, Preisig MA, Fenton B, et al. Familial transmission of substance use disorders. *Arch Gen Psychiatry*. 1998;55:973–9. [PubMed: 9819065]
3. Kendler KS, Ji J, Edwards AC, Ohlsson H, Sundquist J, Sundquist K. An extended Swedish national adoption study of alcohol use disorder. *JAMA Psychiatry*. 2015;72:211–8. [PubMed: 25565339]
4. Kendler KS, Sundquist K, Ohlsson H, Palmer K, Maes H, Winkleby MA, et al. Genetic and familial environmental influences on the risk for drug abuse: a national Swedish adoption study. *Arch Gen Psychiatry*. 2012;69:690–7. [PubMed: 22393206]
5. Tsuang MT, Bar JL, Harley RM, Lyons MJ. The Harvard twin study of substance abuse: what we have learned. *Harv Rev Psychiatry*. 2001;9:267–79. [PubMed: 11600486]
6. Verhulst B, Neale MC, Kendler KS. The heritability of alcohol use disorders: a meta-analysis of twin and adoption studies. *Psychol Med*. 2015;45:1061–72. [PubMed: 25171596]
7. Kendler KS, Gardner CO, Prescott CA. Toward a comprehensive developmental model for alcohol use disorders in men. *Twin Res Hum Genet*. 2011;14:1–15. [PubMed: 21314251]
8. Kendler KS, Ohlsson H, Edwards AC, Sundquist J, Sundquist K. A developmental etiological model for drug abuse in men. *Drug Alcohol Depend*. 2017;179:220–8. [PubMed: 28806639]
9. Blanco C, Rafful C, Wall MM, Ridenour TA, Wang S, Kendler KS. Towards a comprehensive developmental model of cannabis use disorders. *Addiction*. 2013;109:284–94. [PubMed: 24261668]
10. Erlenmeyer-Kimling L, Adamo UH, Rock D, Roberts SA, Bassett AS, Squires-Wheeler E, et al. The New York High-Risk Project. Prevalence and comorbidity of axis I disorders in offspring of schizophrenic parents at 25-year follow-up. *Arch Gen Psychiatry*. 1997;54:1096–102. [PubMed: 9400345]
11. Parnas J, Cannon TD, Jacobsen B, Schulsinger H, Schulsinger F, Mednick SA. Lifetime DSM-III-R diagnostic outcomes in the offspring of schizophrenic mothers. Results from the Copenhagen High-Risk Study. *Arch Gen Psychiatry*. 1993;50:707–14. [PubMed: 8357296]
12. Weissman MM, Gammon GD, John K, Merikangas KR, Warner V, Prusoff BA, et al. Children of depressed parents. Increased psychopathology and early onset of major depression. *Arch Gen Psychiatry*. 1987;44:847–53. [PubMed: 3662741]
13. Sher KJ. *Children of alcoholics: a critical appraisal of theory and research*. Chicago: University of Chicago Press; 1991.
14. Lieberman DZ. Children of alcoholics: an update. *Curr Opin Pediatr*. 2000;12:336–40. [PubMed: 10943813]
15. Freeman MF, Tukey JW. Transformations related to the angular and the square root. *Ann Math Stat*. 1950;21:607–11.
16. R Development Core Team. *The R Project for Statistical Computing: R: a language and environment for statistical computing*, Version 3.2.5. Vienna, Austria: R Foundation for Statistical Computing; 2015 (Online Source).
17. Corral MM, Holguin SR, Cadaveira F. Neuropsychological characteristics in children of alcoholics: familial density. *J Stud Alcohol*. 1999;60:509–13. [PubMed: 10463807]
18. Gabrielli WF Jr, Mednick SA. Intellectual performance in children of alcoholics. *J Nerv Ment Dis*. 1983;171:444–7. [PubMed: 6864203]
19. Moss HB, Vanyukov M, Majumder PP, Kirisci L, Tarter RE. Prepubertal sons of substance abusers: influences of parental and familial substance abuse on behavioral disposition, IQ, and school achievement. *Addict Behav*. 1995;20:345–58. [PubMed: 7653316]

20. Kendler KS, Ohlsson H, Sundquist J, Sundquist K. IQ and schizophrenia in a Swedish national sample: their causal relationship and the interaction of IQ with genetic risk. *Am J Psychiatry*. 2015;172:259–65. [PubMed: 25727538]
21. Clarke TK, Smith AH, Gelernter J, Kranzler HR, Farrer LA, Hall LS, et al. Polygenic risk for alcohol dependence associates with alcohol consumption, cognitive function and social deprivation in a population-based cohort. *Addict Biol*. 2016; 21:469–80. [PubMed: 25865819]
22. Harter SL. Psychosocial adjustment of adult children of alcoholics: a review of the recent empirical literature. *Clin Psychol Rev*. 2000;20:311–37. [PubMed: 10779897]
23. Sher KJ. Psychological characteristics of children of alcoholics. *Alcohol Health Res World*. 1997;21:247–54. [PubMed: 15706777]
24. Vanyukov MM, Tarter RE, Kirisci L, Kirillova GP, Maher BS, Clark DB. Liability to substance use disorders: 1. Common mechanisms and manifestations. *Neurosci Biobehav Rev*. 2003;27:507–15. [PubMed: 14599432]
25. Vanyukov MM, Kirisci L, Tarter RE, Simkevitz HF, Kirillova GP, Maher BS, et al. Liability to substance use disorders: 2. A measurement approach. *Neurosci Biobehav Rev*. 2003;27:517–26. [PubMed: 14599433]
26. Carle AC, Chassin L. Resiliency in a community sample of children of alcoholics: its prevalence and relation to internalizing symptomatology and positive affect. *J Appl Dev Psychol*. 2004;25:577–95.
27. Faris RE, Dunham HW. Mental disorders in urban areas: an ecological study of schizophrenia and other psychoses. Chicago, IL: University of Chicago Press; 1939.
28. Buu A, Mansour M, Wang J, Refior SK, Fitzgerald HE, Zucker RA. Alcoholism effects on social migration and neighborhood effects on alcoholism over the course of 12 years. *Alcohol Clin Exp Res*. 2007;31:1545–51. [PubMed: 17635420]
29. Kendler KS, Ohlsson H, Sundquist K, Sundquist J. The causal nature of the association between neighborhood deprivation and drug abuse: a prospective national Swedish co-relative control study. *Psychol Med*. 2014;44:2537–46. [PubMed: 25055172]
30. Merikangas K, Stolar M, Stevens DE, Goulet J, Preisig MA, Fenton B, et al. Familial transmission of substance use disorders. *Arch Gen Psychiatry*. 1998;55:973–9. [PubMed: 9819065]
31. Kendler KS, Aggen SH, Knudsen GP, Roysamb E, Neale MC, Reichborn-Kjennerud T. The structure of genetic and environmental risk factors for syndromal and subsyndromal common DSM-IV axis I and all axis II disorders. *Am J Psychiatry*. 2011;168:29–39. [PubMed: 20952461]
32. Munafo MR, Davey SG. Robust research needs many lines of evidence. *Nature*. 2018;553:399–401.

Fig. 1.

The overall design of this study. We begin by ascertaining core full sibships born 1980–1990—depicted in blue, which we term the pedigree offspring. We then examine the pedigree—excluding this core sibship—depicted in purple, consisting of the biological parents, grandparents, aunts, uncles, and first cousins of the core sibship. (We do not study the married in aunts and uncles but they are depicted here for completeness.) We then divide the pedigree up into 13 clusters based on the density of alcohol use disorder and drug abuse. From those clusters, we then predict a range of social, psychological, and psychiatric features of pedigree offspring

Fig. 2.

a Risk for alcohol use disorder as a function of school achievement (SA) (measured in standard deviation units) assessed at age 16 in offspring from pedigrees with low to high density of cases of alcohol use disorder. **b** Risk for drug abuse as a function of sex in offspring from pedigrees with low to high density of cases of drug abuse. **c** Risk for drug abuse as a function of levels of resilience (measured in standard deviation units) assessed at age 18 in offspring from low to high risk pedigrees

Table 1a

Characteristics of the ten clusters of pedigrees selected as a function of the density of alcohol use disorder in men and women

	None	Low	Low	Low	Middle	Middle	Middle	Middle	Middle	Middle	High	High	High
	Male 1	Female	Male 2	Male 1	Male 1	Female 1	Male 2	Female 2	Male 1	Female 1	Male 1	Female	Male 2
Class number	1	2	3	4	5	6	7	8	9	10	11	12	13
<i>N</i>	392,756	71,562	40,958	57,227	33,498	20,206	12,015	13,465	10,712	6856	2240	3119	1101
% of Total	59.0	10.7	6.2	8.6	5.0	3.0	1.8	2.0	1.6	1.0	0.3	0.5	0.2
Number of members	15.8	20.3	18.8	15.7	15.3	18.2	13.6	16.8	14.8	14.9	13.3	15.2	14.8
Mean genetic resemblance	0.26	0.24	0.25	0.26	0.27	0.24	0.27	0.26	0.27	0.27	0.27	0.27	0.27
Sex (% males)	0.50	0.53	0.48	0.51	0.48	0.50	0.54	0.50	0.50	0.48	0.53	0.51	0.48
Mean YoB	1958	1961	1960	1959	1958	1961	1958	1960	1959	1959	1959	1960	1960
Mean number of individuals with AUD	0.04	1.06	1.14	1.30	1.88	2.28	1.95	2.93	3.11	3.60	3.84	4.83	5.50
% with AUD	0.00	0.05	0.07	0.09	0.12	0.13	0.14	0.18	0.22	0.25	0.30	0.34	0.40
Mean # AUD males	0.02	1	0.07	1.25	1.76	1.17	0.32	1.67	1.74	3.25	1.12	2.94	4.56
Mean # AUD females	0.02	0.06	1.07	0.04	0.12	1.11	1.63	0.27	1.37	0.36	2.72	1.89	0.93

Mean genetic resemblance—between members of the pedigree and the core sibship

YoB year of birth, AUD alcohol use disorder

Table 1b

Characteristics of the ten clusters of pedigrees selected as a function of the density of drug abuse in men and women

	None	Low Female 1	Low Male 1	Low Female 2	Low Male 2	Middle Female	Middle Male 1	Middle Female	Middle Male 2	High Female	High Male 1	High Female	High Male 2
Class number	1	2	3	4	5	6	7	8	9	10	11	12	13
<i>N</i>	295,375	172,177	59,230	36,020	41,210	13,353	20,632	11,945	9,177	2,184	2096	1895	421
% of Total	44.4	25.9	8.9	5.4	6.2	2.0	3.1	1.8	1.4	0.3	0.3	0.3	0.1
Number of members	18.5	11.3	20.1	17.9	16.1	13.5	16.0	16.0	16.4	14.2	17.1	17.1	20.6
Mean genetic resemblance	0.24	0.29	0.24	0.25	0.26	0.27	0.26	0.26	0.26	0.27	0.26	0.26	0.26
Sex (% males)	0.50	0.51	0.52	0.48	0.51	0.52	0.50	0.50	0.51	0.51	0.52	0.52	0.52
Mean YoB	1960	1954	1962	1961	1960	1958	1961	1962	1963	1962	1965	1964	1969
Mean number of individuals with DA	0.01	0.09	1.04	1.22	1.37	1.58	2.02	2.69	3.18	3.52	4.87	5.39	8.62
% with DA	0.00	0.00	0.05	0.07	0.09	0.12	0.13	0.18	0.20	0.26	0.30	0.34	0.45
Mean # DA males	0.01	0.03	0.98	0.15	1.27	0.15	1.88	1.41	2.81	0.88	4.2	3.01	6.62
Mean # DA females	0.00	0.05	0.06	1.06	0.09	1.44	0.14	1.28	0.36	2.68	0.67	2.39	2.01

Mean genetic resemblance—between members of the pedigree and the core sibship

YoB year of birth, DA drug abuse

Table 2a
 Characteristics of offspring of pedigrees with varying densities of alcohol use disorder

AUD	None	Low Male 1	Low Female	3	4	5	Middle Male 1	Middle Female	7	Middle Male 2	Middle Female	9	Middle Male	High Male 1	High Female	12	High Male 2	Beta (95% CIs)
Class number	1	2	3	4	5	6	6	7	8	8	9	9	9	10	11	12	13	
<i>N</i> subjects	611,725	109,285	62,059	85,729	49,472	29,907	29,907	17,715	19,662	15,196	15,196	15,196	15,196	9767	3125	4392	1556	–
# Individuals/ FAMID	1.56	1.53	1.52	1.50	1.48	1.48	1.48	1.47	1.46	1.42	1.42	1.42	1.42	1.42	1.40	1.41	1.41	–
Sex (% males)	0.51	0.52	0.51	0.51	0.51	0.51	0.51	0.51	0.51	0.51	0.51	0.51	0.51	0.52	0.53	0.51	0.54	–
YoB	1985	1985	1985	1985	1985	1985	1985	1986	1985	1985	1986	1986	1986	1985	1986	1985	1985	–
School achievement ^a	0.17	–0.07	–0.05	–0.10	–0.22	–0.27	–0.27	–0.24	–0.41	–0.45	–0.45	–0.45	–0.45	–0.53	–0.57	–0.70	–0.83	–0.031 (–0.31; –0.030)
Resilience ^{a,b}	0.10	–0.03	–0.02	–0.04	–0.12	–0.16	–0.16	–0.11	–0.23	–0.22	–0.22	–0.22	–0.22	–0.28	–0.34	–0.40	–0.54	–0.013 (–0.015; –0.011)
Years of education	13.5	13.0	13.0	12.9	12.6	12.5	12.5	12.6	12.3	12.2	12.2	12.2	12.2	11.9	11.8	11.6	11.3	–0.067 (–0.068; –0.066)
Psychiatric illness ^c	0.05	0.06	0.07	0.06	0.08	0.08	0.08	0.09	0.10	0.12	0.12	0.12	0.12	0.11	0.14	0.15	0.16	0.0029 (0.0028; 0.0030)
Neighborhood deprivation ^a	–0.01	0.11	0.09	0.13	0.21	0.22	0.22	0.21	0.33	0.36	0.36	0.36	0.36	0.43	0.41	0.51	0.79	0.017 (0.017; 0.018)
On social welfare ^c	0.03	0.05	0.05	0.05	0.08	0.08	0.08	0.08	0.10	0.12	0.12	0.12	0.12	0.13	0.15	0.16	0.20	0.0039 (0.0039; 0.0040)
Unemployed ^c	0.11	0.14	0.14	0.14	0.16	0.16	0.16	0.16	0.18	0.18	0.18	0.18	0.18	0.19	0.21	0.22	0.25	0.0034 (0.0033; 0.0035)
Early retirement ^c	0.02	0.03	0.03	0.03	0.03	0.04	0.04	0.04	0.04	0.05	0.05	0.05	0.05	0.05	0.05	0.06	0.06	0.0011 (0.0009; 0.0011)
AUD ^c	0.02	0.03	0.03	0.03	0.03	0.05	0.05	0.04	0.05	0.07	0.07	0.07	0.07	0.08	0.09	0.11	0.13	0.0023 (0.0023; 0.0024)
Drug abuse ^c	0.04	0.06	0.07	0.07	0.09	0.09	0.09	0.09	0.12	0.14	0.14	0.14	0.14	0.16	0.18	0.19	0.26	0.0045 (0.0044; 0.0046)
Criminal conviction ^c	0.07	0.11	0.11	0.12	0.14	0.15	0.15	0.16	0.19	0.20	0.20	0.20	0.20	0.23	0.25	0.27	0.35	0.0061 (0.0060; 0.0062)

The beta coefficient represents the mean change in the variable per 1% increase in alcohol use disorder in the pedigree. For detailed definitions of the predicted variables, see Appendix Table 1

^aStandardized

^bMales only

Proportion
 Γ_{D_2}

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2b

Characteristics of offspring of pedigrees with varying densities of drug abuse

DA	None	Low Female 1	Low Male 1	Low Female 2	Low Male 2	Middle Female	Middle Male 1	Middle Male 2	High Female	High Male 1	High Female	High Male 2	Beta (95% CIs)
Class number	1	2	3	4	5	6	7	8	9	10	11	12	13
<i>N</i> subjects	460,921	263,033	90,357	54,458	61,541	19,591	30,296	17,040	13,155	3052	2968	2556	622
# Individuals/ FAMID	1.56	1.53	1.53	1.51	1.49	1.47	1.47	1.43	1.43	1.40	1.42	1.35	1.48
Sex (% males)	0.51	0.51	0.51	0.51	0.51	0.51	0.51	0.51	0.52	0.51	0.50	0.54	0.51
YoB	1985	1985	1985	1985	1986	1986	1985	1986	1986	1986	1986	1986	1986
School achievement ^a	0.15	0.13	-0.10	-0.13	-0.18	-0.25	-0.34	-0.49	-0.58	-0.67	-0.82	-0.94	-1.30
Resilience ^{a,b}	0.09	0.06	-0.05	-0.06	-0.09	-0.12	-0.22	-0.33	-0.37	-0.36	-0.55	-0.52	-0.81
Years of education	13.5	13.4	12.9	12.9	12.7	12.6	12.4	12.1	11.9	11.7	11.3	11.1	10.3
Psychiatric illness ^c	0.05	0.05	0.06	0.07	0.07	0.09	0.09	0.11	0.11	0.13	0.14	0.16	0.17
Neighborhood deprivation ^a	-0.02	0.01	0.14	0.15	0.19	0.25	0.33	0.44	0.55	0.60	0.87	0.92	1.70
On social welfare ^c	0.03	0.03	0.05	0.06	0.07	0.08	0.10	0.13	0.15	0.18	0.21	0.25	0.38
Unemployed ^c	0.11	0.12	0.14	0.15	0.16	0.16	0.17	0.19	0.21	0.22	0.25	0.28	0.33
Early retirement ^c	0.02	0.02	0.03	0.03	0.03	0.04	0.04	0.04	0.04	0.05	0.06	0.07	0.10
AUD ^c	0.02	0.02	0.03	0.03	0.04	0.05	0.05	0.06	0.07	0.08	0.09	0.11	0.14
Drug abuse ^c	0.04	0.05	0.07	0.07	0.09	0.10	0.12	0.15	0.18	0.20	0.26	0.31	0.36
Criminal conviction ^c	0.07	0.08	0.12	0.12	0.14	0.15	0.18	0.22	0.24	0.26	0.34	0.37	0.51

The beta coefficient represents the mean change in the variable per 1% increase in drug abuse in the pedigree. For detailed definitions of the predicted variables, see Appendix Table 1

^aStandardized^bMales only^cProportion

Interaction analyses of six putative mediators with the density of alcohol use disorder or drug abuse in pedigrees in the prediction of risk for, respectively, alcohol use disorder or drug abuse in offspring

Table 3

Variable	Outcome	N	AIC without interaction	AIC with interaction	r ² without interaction (95% CIs)	r ² with interaction (95% CIs)	Difference in r ²
Resilience	AUD	184,894	-170,169.4	-170,440.7	1.38% (1.27; 1.49)	1.52% (1.42; 1.64)	0.14%
	DA		-14,470.5	-15,300.8	4.11% (3.93; 4.29)	4.55% (4.36; 4.74)	0.44%
Sex	AUD	1,019,590	-886,231.5	-886,843.1	0.93% (0.89; 0.97)	0.99% (0.95; 1.03)	0.06%
	DA		-144,246.9	-148,157.1	3.37% (3.30; 3.44)	3.74% (3.67; 3.81)	0.37%
School achievement	AUD	973,803	-914,515.6	-916,554.2	1.87% (1.82; 1.92)	2.19% (2.13; 2.25)	0.32%
	DA		-209,213.0	-213,463.6	5.03% (4.95; 5.11)	5.56% (5.47; 5.65)	0.53%
Early onset psychiatric disorder	AUD	1,019,590	-894,547.1	-894,955.5	1.55% (1.50; 1.60)	1.78% (1.73; 1.83)	0.23%
	DA		-137,164.8	-137,455.6	2.43% (2.41; 2.55)	2.73% (2.67; 2.79)	0.24%
Parental divorce	AUD	1,019,590	-889,090.0	-889,577.6	1.04% (1.00; 1.08)	1.26% (1.22; 1.30)	0.22%
	DA		-143,410.6	-144,690.0	3.09% (3.02; 3.16)	3.42% (3.35; 3.49)	0.33%
Neighborhood deprivation	AUD	994,374	-858,536.8	-858,668.4	0.69% (0.66; 0.72)	0.90% (0.86; 0.94)	0.21%
	DA		-128,104.8	-128,713.5	2.25% (2.19; 2.31)	2.50% (2.44; 2.56)	0.25%

For detailed definitions of the predictor variables, see Appendix Table 1

AUD alcohol use disorder; DA drug abuse