Psychological Medicine

cambridge.org/psm

Cross-generational transmission of genetic risk for alcohol and drug use disorders: the impact of substance availability on the specificity of genetic risk

Kenneth S. Kendler[1,2], Linda Abrahamsson[3], Henrik Ohlsson[3], Jan Sundquist[3,4] and Kristina Sundquist[3,4]

[1]Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, USA; [2]Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, USA; [3]Center for Primary Health Care Research, Lund University, Malmö, Sweden and [4]Department of Family Medicine and Community Health, Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Original Article

Cite this article: Kendler KS, Abrahamsson L, Ohlsson H, Sundquist J, Sundquist K (2023). Cross-generational transmission of genetic risk for alcohol and drug use disorders: the impact of substance availability on the specificity of genetic risk. *Psychological Medicine* **53**, 5109–5118. https://doi.org/10.1017/S0033291722002549

Received: 22 February 2022
Revised: 15 June 2022
Accepted: 21 July 2022
First published online: 22 August 2022

Key words:
Adoption study; alcohol use disorder; drug use disorder; impact of drug availability; parent–offspring transmission

Author for correspondence:
Kenneth S. Kendler,
E-mail: Kenneth.Kendler@vcuhealth.org

Abstract

Background. Among individuals with alcohol use disorder (AUD) and drug use disorder (DUD), is their genetic liability and its specificity moderated by substance availability?

Methods. Offspring (born 1960–1995) and their biological parents from three family types [not-lived-with (NLW) biological father, mother and adoptive] and their AUD and DUD diagnoses were ascertained from Swedish national registers. Parent–offspring resemblance was calculated by tetrachoric correlation.

Results. In Swedes born from 1960 to 1995, prevalence rates of AUD were stable while DUD rates increased substantially. Best-estimate tetrachoric correlations (±95% confidence intervals) between AUD in biological parents and AUD and DUD in their offspring were, respectively, +0.19 (0.18–0.20) and +0.18 (0.17–0.20). Parallel results from DUD in parents to AUD and DUD in children were +0.12 (0.10–0.13) and +0.27 (0.26–0.28). When divided into older and younger cohorts, the specificity of DUD transmission increased substantially over time, while the genetic correlation between AUD and DUD significantly decreased.

Conclusions. Raised when alcohol was the preferred substance of abuse and illicit drugs highly stigmatized, AUD in parents reflected a general liability to substance use disorders, as they transmitted similar genetic risk for AUD and DUD to their children raised when both substances were widely available and relatively acceptable. DUD in parents, by contrast, reflected a more specific liability to DUD and, when transmitted to offspring, produced a considerably stronger risk for DUD than for AUD that increased over time. The magnitude and specificity of the genetic liability to psychoactive substances can be influenced by the availability of that substance.

The transmission of alcohol use disorder (AUD) and drug use disorder (DUD) in families shows evidence both of shared and disorder-specific familial factors (Bierut et al., 1998; Kendler, Ohlsson, Bacanu, Sundquist, & Sundquist, 2020; Merikangas et al., 1998; Rounsaville et al., 1991). Across different substances of abuse, twin studies find evidence both for shared and substance-specific genetic risk factors (Kendler et al., 2011; Kendler, Myers, & Prescott, 2007; Rhee et al., 2003; Tsuang et al., 1998). Twin pairs, being of the same age, are exposed to similar levels of availability of psychoactive substances and social attitudes toward their use. Much less is known about the magnitude and sources of the genetic transmission of AUD and DUD across generations. While a number of classical adoption studies have examined AUD only (Verhulst, Neale, & Kendler, 2015) and a few DUD only (Cadoret, Yates, Troughton, Woodworth, & Stewart, 1995, 1996; Kendler et al., 2012), no adoption study of which we are aware has examined the cross-generational cross-transmission of these two major forms of substance use disorders (SUDs).

In many Western countries, including Sweden, attitudes toward and access to alcohol has been relatively constant over the last several generations, while the diversity, availability and normalization of use of illicit psychoactive substances have increased (Addiction, 2021; Hall & Degenhardt, 2009; Parker, Parker, Aldridge, & Measham, 1998; Sznitman, 2007). Therefore, in a study of current young adults, many grew up in social environments where illicit psychoactive substances were widely available, and their use relatively normalized. By contrast, for many of their parents, access to illicit drugs was restricted and sanctioned when they were young, leaving alcohol the only readily available and acceptable intoxicating substance.

In such a sample, individuals in the parental generation with AUD would likely carry a relatively non-specific genetic risk for substance abuse. By contrast, because of the more limited availability of illicit drugs in the older generation, and the greater deviance associated with their use, individuals in the parental generation with DUD would have a stronger overall liability to substance use and one that was relatively DUD-specific.

To test these hypotheses, we first conducted an expanded National Swedish adoption study of the cross-generational within-disorder and cross-disorder genetic transmission of AUD and DUD through an examination of three informative family types which can assess the degree of genetic parent–offspring transmission within and across SUDs: (i) families with not-lived-with (NLW) biological fathers, (ii) families with NLW biological mothers and (iii) biological parents from an adoption sample. As detailed below, NLW biological parents contributed genes to their offspring but never lived with them nor near them while they were growing up, thus approximating the relationship seen between biological parents and their adopted-away offspring in a classical adoption design.

From these analyses, we examined both the magnitude of genetic cross-generational transmission of (i) DUD → AUD, (ii) AUD → DUD, (iii) DUD → DUD and (iv) AUD → AUD. These analyses also permit us to calculate the genetic correlation for the cross-generational transmission of AUD and DUD.

Second, given evidence of rapid rises in rates of DUD across recent generations, we then divided our sample into older and younger cohorts to explore how the increasing availability and acceptability of drug use might impact on the pattern of cross-generational genetic transmission of risk to AUD and DUD.

In addition to these empirical questions about the cross-generational transmission of AUD and DUD in the historical setting of changes in availability, we are also interested in the broader conceptual issues involved. For genetic studies of traditional medical and psychiatric disorders (e.g. coronary artery disease and schizophrenia) there is nothing analogous to drug exposure which is required from the expression of any genetic risk. These factors are likely to influence the specificity of the emerging genetic risk factors for the abuse of specific substances. We explore these issues further below.

Methods

Information for this study was collected from nationwide Swedish registers (online Supplementary Appendix Table S1). Each person's unique identification number, replaced with serial numbers for confidentiality, was used for linkage between registers. Cases of AUD and DUD were identified in the Hospital Discharge Register, Outpatient Care Register, nationwide primary care data, Prescribed Drug Register, Cause of Death Register, Criminal Register and the Suspicion Register (see online Supplementary Appendix Table S2). The initial study population was individuals born in Sweden 1960–1995, who were alive and resided in Sweden at least until the age of 20.

For the *offspring* in our analyses, we included the number of years, from ages 0 to 15, they resided in the same household and geographic area as their biological mother, biological father, adoptive mother and adoptive father. From 1960 to 1985 (every fifth year), we used household identification numbers from the Population and Housing Census to define family types. The household identification includes all individuals registered at the same residence. From 1986 onward (every year), we defined family type using the family identification from the Total Population Register. The family identification is defined by individuals registered at the same property who are also related, adopted, married or have children in common. For years when there was no information on whether offspring and parents resided together, we used information from the closest year. Geographical areas (as defined by Statistics Sweden, the Swedish government-owned statistics bureau) are called Small Areas for Market Statistics (SAMS). There are approximately 9200 SAMS throughout Sweden, and they are often characterized by homogeneous types of buildings and are limited by 'natural' boundaries.

We defined families with NLW fathers or mothers as those including offspring who never resided in the same household or SAMS area as the biological father/mother. Adoptive families included offspring adopted at younger than 5 years, with information available on both adoptive parents and at least one biological parent. The adoptive parents had to be biologically unrelated to the offspring and the offspring had to reside with each adoptive parent for at least 10 years between the ages 0 and 15. As domestic adoptions are nowadays more unusual, we included offspring born from 1955 to 1995, to increase sample size. The NLW were defined so that their relationships with their offspring resembled those seen between an adoptee and his/her biological parents. For all family types, parents had to be alive throughout 1975 and had to reside in Sweden during some period of time from 1976 and onward.

For reasons of interpretability (Falconer, 1989) and insensitivity to changes in base rates (Babchishin & Helmus, 2016), we assessed parent–offspring transmission of AUD and DUD by tetrachoric correlation which reflects the correlation in relatives of an underlying normally distributed latent liability to illness (Pearson, 1901). To calculate weighted tetrachoric correlations and for testing for heterogeneity across families, we use a meta-analysis fixed effects model (Borenstein, Hedges, Higgins, & Rothstein, 2010). The model is fixed as samples of data come from the same population. For the heterogeneity tests, Bonferroni-corrected significance levels of 0.05 divided by the number of tests were utilized. We also calculated the genetic correlation between AUD and DUD (see online Supplementary Appendix Table S3 for details). Analyses were performed in the complete cohort, as well as stratified on birth year of the offspring, creating an older cohort (born 1960–1970; 1955–1970 for the adopted individuals) and a younger cohort (born 1971–1995). Because both adoptions and the rates of NLW-mother families were declining rapidly over these years compared to the rates of NLW-father families, to roughly balance our power across our three family types, our older cohort covered a shorter time period than our younger cohort.

Cumulative incidence curves of first occurrence of an AUD or a DUD registration were calculated for four different cohorts of individuals born in Sweden: birth years 1960–1969 ($n = 1\,079\,653$), 1970–1979 ($n = 985\,119$), 1980–1989 ($n = 951\,668$) and 1990–1999 ($n = 753\,088$). Follow-up ended on 31 December 2017, death or emigration, whichever came first. Data analyses were performed using R, version 4.0.3 (Team, 2019) (see online Supplementary Appendix Table S4 for details) and SAS, version 9.4 (SAS Institute, 2012).

Results

Descriptive results

Figures 1*a* and *b* present incidence curves for AUD and DUD across the four Swedish birth cohorts which include all

https://doi.org/10.1017/S0033291722002549 Published online by Cambridge University Press

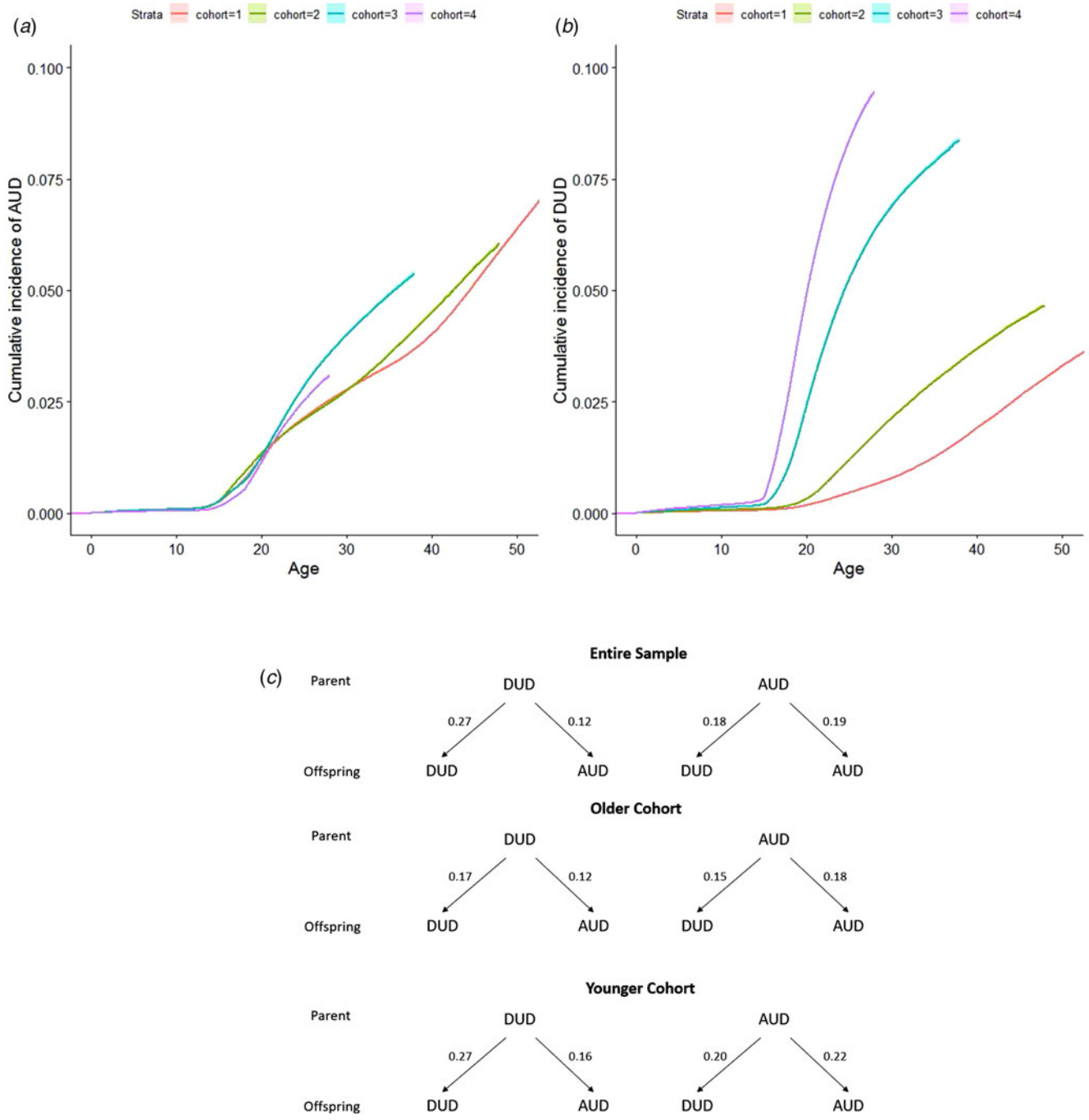

Fig. 1. (*a*) Cumulative incidence curves of first registration for AUD calculated for four different cohorts of individuals born in Sweden: cohort 1 – birth years 1960–1969 ($n = 1\,079\,653$); cohort 2 1970–1979 ($n = 985\,119$); cohort 3 1980–1989 ($n = 951\,668$) and cohort 4 1990–1999 ($n = 753\,088$). Follow-up ended on 31 December 2017, death or emigration, whichever came first. (*b*) Cumulative incidence curves of first registration for DUD calculated for four different cohorts of individuals born in Sweden: cohort 1 – birth years 1960–1969 ($n = 1\,079\,653$); cohort 2 1970–1979 ($n = 985\,119$); cohort 3 1980–1989 ($n = 951\,668$) and cohort 4 1990–1999 ($n = 753\,088$). Follow-up ended on 31 December 2017, death or emigration, whichever came first. (*c*) Weighted estimates of the within-disorder and cross-disorder parent-child tetrachoric correlations for AUD and DUD, that reflect genetic relationships in our entire sample (top), our older cohort (birth years 1960–1970; 1955–1970 for the adopted individuals) (middle) and our younger cohort (birth years 1971–1995) (bottom).

individuals in our study: 1960–1969, 1970–1979, 1980–1989 and 1990–1999. Rates were relatively constant for AUD but increased substantially for DUD.

Descriptive statistics for our three family types in our entire sample are shown in the top section of Table 1. NLW-father families had the largest sample of offspring, followed by adoptive families and NLW-mother families. The mean ages of offspring were over age 40 in all family types, so we have captured a substantial proportion of the DUD and AUD onsets.

The top panel of Table 2 presents the prevalence rates for AUD and DUD in the parents and offspring of our three informative family types. Rates of both disorders were higher in males *v.* females. Rates of AUD and DUD were much higher in biological fathers from NLW-father and adoptive families than in the

https://doi.org/10.1017/S0033291722002549 Published online by Cambridge University Press

Table 1. Sample size, birth year, age and sex distributions across the three family types included in the study

Entire sample			
	NLW-father families	NLW-mother families	Adoptive families
Sample size offspring	122 484	6111	14 714
Sample size biological mother	91 169	6111	14 134
Sample size biological father	122 484	1160	8802
	Offspring		
Year of birth, mean (s.d.)	1975.5 (10.4)	1969.9 (8.8)	1964.2 (7.9)
Age, mean (s.d.)	41.3 (10.8)	46.3 (10.1)	52.0 (9.7)
Male, %	50.8	53.6	52.9
Older cohort			
	NLW-father families	NLW-mother families	Adoptive families
Sample size offspring	45 902	3633	12 302
Sample size biological mother	29 441	3633	11 778
Sample size biological father	45 902	487	7165
	Offspring		
Year of birth, mean (s.d.)	1965.1 (2.9)	1964.2 (2.8)	1961.4 (4.2)
Age, mean (s.d.)	51.1 (6.6)	51.7 (7.1)	54.6 (7.7)
Male, %	50.7	53.6	53.0
Younger cohort			
	NLW-father families	NLW-mother families	Adoptive families
Sample size offspring	76 582	2478	2412
Sample size biological mother	61 728	2478	2356
Sample size biological father	76 582	673	1637
	Offspring		
Year of birth, mean (s.d.)	1981.8 (8.1)	1978.3 (7.8)	1978.7 (6.7)
Age, mean (s.d.)	35.4 (8.3)	38.4 (8.5)	38.5 (7.2)
Male, %	50.9	53.6	52.9

biological fathers from the NLW-mother families who stayed with and raised his own children. A similar pattern is seen for biological mothers.

The ratios of prevalence rates for AUD to DUD were consistently higher in the parental than in the offspring generation of all our families. In all sons, the AUD/DUD prevalence ratio had a mean across family types of 1.5 while in biological fathers, the parallel mean was 4.6. The differences were somewhat less between daughters (1.1) and biological mothers (2.0) but in the same direction.

Analysis of parent–offspring transmission in the entire sample

The top part of Table 3 presents the parent–offspring tetrachoric correlations for DUD → AUD genetic transmission, separately for mothers and fathers in our three family types. The last two columns of the table depict the weighted estimate of those correlations and a heterogeneity test. We had two estimates for each relationship. For example, for the genes only mother–child relationship, we had estimates from the NLW mothers and the biological mothers in the adoptive family.

The three sections of the top part of Table 3 then present parallel analyses for AUD → DUD, DUD → DUD and AUD → AUD transmission. Of the eight heterogeneity tests, only one is significant at Bonferroni-corrected levels.

Table 4 and the top of Fig. 1*c* then compares and combines the results from the mother–offspring and father–offspring analyses, none of which differed at even a nominal p value. The genetic cross-generational transmission [±95% confidence interval (CI)] from AUD to AUD (+0.19, 0.18–0.20) is nearly identical to, and not statistically different from, that from AUD to DUD (+0.18, 0.17–0.20). By contrast, the genetic cross-generational transmission from DUD to DUD (+0.27, 0.26–0.28) is much larger than the parallel transmission from DUD to AUD (+0.12, 0.10–0.13) ($p < 0.001$). The genetic cross-generational correlation for AUD and DUD was estimated at +0.70 (0.67–0.73).

Division of our sample into an older and younger cohorts

As shown in Figs. 1*a* and *b*, over the entire time when our sample was born (1960–1995), rates of DUD were rising rapidly in Sweden while rates of AUD were relatively stable suggesting

https://doi.org/10.1017/S0033291722002549 Published online by Cambridge University Press

Table 2 . Prevalences of AUD (%) and DUD (%) in the relatives and their ratio (AUD/DUD) from the three family types included in this study

Entire sample				
	Disorder	NLW-father families	NLW-mother families	Adoptive families
All offspring	AUD	9.9	12.7	13.3
	DUD	11.3	9.6	7.6
	AUD/DUD	0.9	1.3	1.8
Female offspring	AUD	6.5	8.4	8.3
	DUD	7.4	8.4	6.3
	AUD/DUD	0.9	1.0	1.3
Male offspring	AUD	13.3	16.4	17.7
	DUD	15.0	10.6	8.8
	AUD/DUD	0.9	1.5	2.0
Biological mothers	AUD	7.7	19.5	14.8
	DUD	4.7	9.9	6.2
	AUD/DUD	1.6	2.0	2.4
Biological fathers	AUD	29.1	13.5	31.2
	DUD	9.3	2.3	6.6
	AUD/DUD	3.1	5.9	4.7
Older cohort				
	Disorder	NLW-father families	NLW-mother families	Adoptive families
All offspring	AUD	12.1	15.4	13.9
	DUD	7.5	9.5	7.1
	AUD/DUD	1.6	1.6	2.0
Female offspring	AUD	7.2	9.2	8.4
	DUD	5.8	8.5	5.8
	AUD/DUD	1.2	1.1	1.4
Male offspring	AUD	16.9	20.8	18.7
	DUD	9.2	10.3	8.2
	AUD/DUD	1.8	2.0	2.3
Biological mothers	AUD	6.6	18.3	11.9
	DUD	2.7	7.2	4.0
	AUD/DUD	2.4	2.5	3.0
Biological fathers	AUD	27.8	12.5	27.8
	DUD	4.6	1.6	4.1
	AUD/DUD	6.0	7.8	6.8
Younger cohort				
	Disorder	NLW-father families	NLW-mother families	Adoptive families
All offspring	AUD	8.6	8.7	10.2
	DUD	13.5	9.7	10.2
	AUD/DUD	0.6	0.9	1.0
Female offspring	AUD	6.1	7.1	7.7
	DUD	8.4	8.2	8.6
	AUD/DUD	0.7	0.9	0.9
Male offspring	AUD	11.1	10.0	12.4

(*Continued*)

https://doi.org/10.1017/S0033291722002549 Published online by Cambridge University Press

Table 2 (*Continued.*)

Entire sample				
	Disorder	NLW-father families	NLW-mother families	Adoptive families
	DUD	18.4	11.0	11.7
	AUD/DUD	0.6	0.9	1.1
Biological mothers	AUD	8.2	21.3	29.2
	DUD AUD/DUD	5.7	13.8	17.2
		1.4	1.5	1.7
Biological fathers	AUD	29.8	14.3	46.3
	DUD	12.2	2.8	17.4
	AUD/DUD	2.4	5.1	2.7

that compared to alcohol, we can infer that drugs were becoming both widely accessible with reduced social barriers to use. To further investigate the relationship between cross-generational transmissions of substance availability/stigma, we divided our birth cohort into an older sample born 1960–1970 (for adopted individuals 1955–1970) and a younger sample from 1971 to 1995. As shown in Figs. 1*a* and *b*, in the older sample – cohort 1 in the figures, rates of AUD substantially exceed rates of DUD across the life cycle. However, in the younger sample (depicted by cohorts 2–4 in the figures), rates of DUD are slightly lower than rates of AUD in cohort 2, but then substantially exceed the AUD of AUD in cohort 3 and especially cohort 4.

The sample sizes of our families, age and gender composition are shown in the bottom two sections of Table 1. The prevalences of AUD and DUD in both the offspring and parents are depicted in the bottom two sections of Table 2. In the older cohort, the mean AUD to DUD ratio in biological fathers, mothers and offspring were 6.9, 2.6 and 1.7. In the younger cohort, the parallel results were 3.4, 1.5 and 0.8. As predicted from our general population results in Figs. 1*a* and *b*, relative to AUD, DUD was more common in children than parents in both cohorts, but also considerably more common across both groups of relatives in the younger *v.* older cohorts. The lower two sections of Table 3 present parallel analyses for DUD → AUD, AUD → DUD, DUD → DUD and AUD → AUD transmission in our younger and older samples. None of the 16 heterogeneity tests were significant.

Table 4 and Fig. 1*c* then compares and combines the results from the mother–offspring and father–offspring analyses for our two cohorts. None of the heterogeneity tests across biological mothers and fathers were significant even at a nominal p value. In our older cohort, depicted in the middle third of the table, the genetic cross-generational transmission (±95% CI) from AUD to AUD (0.18, 0.16–0.19) is very similar to, and not statistically different from, that from AUD to DUD (0.15, 0.14–0.17) ($p = 0.24$). The genetic cross-generational transmission from DUD to DUD (0.17, 0.14–0.19) is modestly and significantly larger than the parallel transmission from DUD to AUD (0.12, 0.10–0.15) ($p = 0.01$). The genetic cross-generational correlation for AUD and DUD in this older cohort equaled +0.83 (0.75–0.91).

In our younger cohort – shown in the bottom third of Table 4 – the genetic cross-generational transmission (±95% CI) from AUD to AUD (0.22, 0.21–0.24) is modestly greater than that from AUD to DUD (0.20, 0.18–0.21) ($p < 0.01$). The genetic cross-generational transmission from DUD to DUD (0.27, 0.26–0.29) is, however, substantially larger than the parallel transmission from DUD to AUD (0.16, 0.14–0.17) ($p < 0.001$). The genetic cross-generational correlation for AUD and DUD in this younger cohort equaled +0.73 (0.70–0.77) which was significantly lower than that observed in the older cohort ($p = 0.02$).

Discussion

Over recent decades, twin studies have been a major method used for the assessment of genetic and familial-environmental effects on risk to SUD. This is a powerful approach, which, by studying individuals of the same age, controls for the availability of substances of abuse and their associated stigma during young adulthood when most drug use habits are acquired. However, this becomes a limitation if we want to understand how the liability of individuals with subtypes of SUD differs as a function of the availability and acceptability of various psychoactive substances. We undertook this study to examine this question, taking advantage of a natural experiment in Sweden where, in recent decades, levels of AUD have been relatively stable while rates of DUD have increased substantially.

We were able to show, through an examination of risk for patterns of SUD in their offspring in our entire sample, that individuals in the parental generation with AUD carried a relatively nonspecific genetic vulnerability to SUD while those with DUD had a genetic risk relatively specific for DUD. In interpreting these findings, we propose the following conceptual framework. The familial/genetic risks for AUD and DUD are positively but not perfectly correlated (Bierut et al., 1998; Kendler et al., 2007, 2011, 2020; Merikangas et al., 1998; Rhee et al., 2003; Rounsaville et al., 1991). Therefore, within a population, there will be many people with roughly similar levels of elevated genetic risk for the two disorders. However, there will be others where their risks differ moderately or even in some cases substantially – either being higher for DUD than AUD or the reverse.

We began our analyses examining our entire cohort of children – born from 1960 to 1995 – at time at which rates of AUD were relatively stable and rates of DUD rising rapidly. We expect that for parents of this cohort, on average, alcohol was widely available, and its use relatively normalized while illicit psychoactive drugs were harder to find and much more stigmatized. Therefore, those parents whose genetic risk for AUD was similar to or higher than their risk for DUD would, if they developed SUD, be much more likely to develop AUD than DUD. Among

https://doi.org/10.1017/S0033291722002549 Published online by Cambridge University Press

Table 3 . Parent–offspring tetrachoric correlations and 95% CI, weighted estimates and heterogeneity tests

	NLW father	NLW mother	Adoptive	Weighted estimate	Het test[a]
Entire sample					
DUD → AUD					
Mother–offspring	NA	0.14 (0.08–0.21)	0.05 (0.00–0.10)	0.09 (0.05–0.13)	0.03
Father–offspring	0.13 (0.11–0.14)	NA	0.05 (−0.02 to 0.11)	0.12 (0.11–0.14)	0.02
AUD → DUD					
Mother–offspring	NA	0.20 (0.14–0.26)	0.18 (0.14–0.22)	0.19 (0.15–0.22)	0.59
Father–offspring	0.19 (0.18–0.20)	NA	0.14 (0.09–0.19)	0.18 (0.17–0.20)	0.08
DUD → DUD					
Mother–offspring	NA	0.26 (0.20–0.33)	0.21 (0.16–0.26)	0.23 (0.19–0.27)	0.22
Father–offspring	0.28 (0.27–0.29)	NA	0.19 (0.13–0.26)	0.28 (0.26–0.29)	0.01
AUD → AUD					
Mother–offspring	NA	0.25 (0.20–0.30)	0.16 (0.12–0.20)	0.19 (0.16–0.22)	<0.01
Father–offspring	0.20 (0.19–0.21)	NA	0.12 (0.08–0.16)	0.19 (0.18–0.21)	<0.001*
Older cohort					
DUD → AUD					
Mother–offspring	NA	0.15 (0.06–0.24)	0.08 (0.02–0.14)	0.10 (0.05–0.15)	0.20
Father–offspring	0.14 (0.11–0.17)	NA	0.04 (−0.04 to 0.12)	0.13 (0.10–0.15)	0.02
AUD → DUD					
Mother–offspring	NA	0.19 (0.11–0.26)	0.16 (0.11–0.21)	0.17 (0.13–0.21)	0.57
Father–offspring	0.16 (0.14–0.18)	NA	0.09 (0.03–0.15)	0.15 (0.13–0.17)	0.03
DUD → DUD					
Mother–offspring	NA	0.20 (0.11–0.30)	0.19 (0.13–0.26)	0.20 (0.14–0.25)	0.88
Father–offspring	0.16 (0.13–0.20)	NA	0.10 (0.01–0.20)	0.16 (0.13–0.19)	0.24
AUD → AUD					
Mother–offspring	NA	0.25 (0.18–0.31)	0.18 (0.14–0.22)	0.20 (0.16–0.23)	0.08
Father–offspring	0.18 (0.16–0.20)	NA	0.11 (0.07–0.16)	0.17 (0.15–0.19)	0.01
Younger cohort					
DUD → AUD					
Mother–offspring	NA	0.21 (0.11–0.31)	0.08 (−0.01 to 0.18)	0.15 (0.08–0.22)	0.07
Father–offspring	0.16 (0.14–0.18)	NA	0.14 (0.02–0.25)	0.16 (0.14–0.18)	0.71
AUD → DUD					
Mother–offspring	NA	0.22 (0.13–0.31)	0.18 (0.10–0.27)	0.20 (0.14–0.26)	0.58
Father–offspring	0.19 (0.18–0.21)	NA	0.24 (0.14–0.34)	0.20 (0.18–0.21)	0.36
DUD → DUD					
Mother–offspring	NA	0.33 (0.24–0.42)	0.20 (0.11–0.30)	0.27 (0.20–0.33)	0.06
Father–offspring	0.28 (0.26–0.29)	NA	0.26 (0.15–0.37)	0.28 (0.26–0.29)	0.74
AUD → AUD					
Mother–OFFSPRING	NA	0.29 (0.20–0.38)	0.21 (0.12–0.30)	0.25 (0.19–0.31)	0.20
Father–offspring	0.22 (0.21–0.24)	NA	0.22 (0.12–0.32)	0.22 (0.21–0.24)	0.95

Het test, heterogeneity test with nominal p value.
[a]Significance threshold after Bonferroni correction for 24 tests was $p < 0.002$. Significant tests are marked with*.

those whose genetic risk was higher for DUD than AUD, many, especially when the difference in risk was modest, would also be more prone to develop AUD than DUD because of differences in substance availability and attitudinal barriers. Only those parents with particularly high risk for DUD that substantially exceeded their risk for AUD would, we hypothesize, have been

https://doi.org/10.1017/S0033291722002549 Published online by Cambridge University Press

Table 4. Tests of transmission from mothers and fathers using weighted estimates across all family types

	Mothers	Fathers	Weighted estimate	Nominal *p* value for test of heterogeneity[a]
Entire sample				
DUD → AUD	0.09 (0.05–0.13)	0.12 (0.11–0.14)	0.12 (0.10–0.13)	0.11
AUD → DUD	0.19 (0.15–0.22)	0.18 (0.17–0.20)	0.18 (0.17–0.20)	0.64
DUD → DUD	0.23 (0.19–0.27)	0.28 (0.26–0.29)	0.27 (0.26–0.28)	0.07
AUD → AUD	0.19 (0.16–0.22)	0.19 (0.18–0.21)	0.19 (0.18–0.20)	0.79
Older cohort				
DUD → AUD	0.10 (0.05–0.15)	0.13 (0.10–0.15)	0.12 (0.10–0.15)	0.56
AUD → DUD	0.17 (0.13–0.21)	0.15 (0.13–0.17)	0.15 (0.14–0.17)	0.29
DUD → DUD	0.20 (0.14–0.25)	0.16 (0.13–0.19)	0.17 (0.14–0.19)	0.15
AUD → AUD	0.20 (0.16–0.23)	0.17 (0.15–0.19)	0.18 (0.16–0.19)	0.12
Younger cohort				
DUD → AUD	0.15 (0.08–0.22)	0.16 (0.14–0.18)	0.16 (0.14–0.17)	0.81
AUD → DUD	0.20 (0.14–0.26)	0.20 (0.18–0.21)	0.20 (0.18–0.21)	0.86
DUD → DUD	0.27 (0.20–0.33)	0.28 (0.26–0.29)	0.27 (0.26–0.29)	0.79
AUD → AUD	0.25 (0.19–0.31)	0.22 (0.21–0.24)	0.22 (0.21–0.24)	0.36

[a]Significance threshold after Bonferroni correction for 12 tests was $p < 0.004$. No tests in this table met that threshold. .

likely to seek out and abuse illicit substances leading to a DUD diagnosis.

Given the substantial inter-generational and cross-time changes in availability and normalization of illicit substances, this framework would explain our two sets of genetic findings: the relative non-specificity of the genetic risk for SUD inherited from biological and NLW-parents with AUD, and the specificity and higher potency of the DUD risk inherited from biological and NLW-parents with DUD.

To further investigate and potentially confirm our hypotheses, we then subdivided our sample into an older and younger cohort. As shown in Fig. 1*b*, the offspring in the younger cohort would be exposed to considerably higher levels of DUD than those from the older cohort, likely a result of rising availability and acceptability of illicit drugs over this time period. This expectation is verified by showing that the AUD to DUD ratio was more than twice as high in the offspring of the older than the younger cohort (1.7 *v.* 0.8 respectively). We showed that the specificity of the transmission of AUD in parents to AUD *v.* DUD in their children – that is the ratio of the paths from AUD in parents to AUD *v.* DUD in offspring – actually declined slightly in the older *v.* younger cohort: from a ratio of 1.20 to 1.10. At the same time, the specificity of the transmission of DUD – the ratio of the paths from DUD in parents to DUD *v.* AUD in offspring – increased from 1.42 to 1.69. Finally, as predicted, the genetic correlation between DUD and AUD significantly declined from the older to the younger cohort.

Two prior studies provide some additional empirical support for our explanation of our findings. First, the stability of the prevalence and heritability of AUD in Sweden has been previously demonstrated using registrations from Temperance Boards (Kendler, Prescott, Neale, & Pedersen, 1997). For males born from 1902 to 1950, the proportion registered with the Temperance Boards varied only between 12% and 16% and estimates of the heritability and shared environmental component, estimated at 0.54 and 0.14, were constant across those decades (Kendler et al., 1997). Second, a formal age-period-cohort effect model for DUD hospitalization in Sweden showed substantial cohort effects with rates of DUD declining slightly in both males and females for those born from 1950 to 1970, and then increasing substantially from 1970 to 1990 (Giordano et al., 2013).

Our expanded adoption design assumes that NLW fathers and mothers – who neither lived with nor near their offspring after, respectively, conception or birth – are good proxies for biological parents in an adoption design in that both kinds of parents are, to a first approximation, related to their offspring only through genetic effects. Our results permit us to empirically test these assumptions. Of the 24 tests of these assumptions (some admittedly correlation) in Table 3, only one differed significantly at chance corrected levels. Overall, these findings validate of the assumptions of our expanded adoption design.

Our findings suggest the need for a conceptual framework for interpreting the impact of drug availability, in both genetic epidemiological and molecular genetic studies, on the specificity of genetic risk factors for substances of abuse. We know from several multivariate twin studies that genetic risk factors for psychoactive substances are substantially but not perfectly correlated (Kendler et al., 2007, 2011; Rhee et al., 2003; Tsuang et al., 1998). Our results raise the question of whether the observed genetic correlations between difference substance classes will differ across countries and/or historical cohorts.

If a population is exposed to only one substance of abuse, it seems likely that the genetic risk to that form of DUD will tend to be relatively non-specific. However, as more and more abusable substances become available and easily accessible in that hypothetical population, those at risk have the opportunity to try multiple substances and select the one that is most rewarding and/or produces the fewest adverse effects. This process would likely increase the specificity of the resulting genetic risk factors for the multiple substances of abuse. Thus, the genetic correlation of the same SUD across populations might drop below one, with the decrease a function of the absence or presence of other

https://doi.org/10.1017/S0033291722002549 Published online by Cambridge University Press

competing substances of abuse. Our results and these hypotheses clearly need confirmation from additional empirical studies and also might be well suited for exploration via simulations.

Limitations

These results should be interpreted in the context of six potentially important methodological limitations. First, this study is restricted to Swedish populations, which has rates of DUD and AUD relatively typical of northern European countries (Addiction, 2021). Our results may not extrapolate to other countries within and outside Europe where drinking and drug use cultures may differ (Cook et al., 2021). Second, our findings depend on the overall quality of our diagnoses. In this study, subjects with AUD and DUD were ascertained from medical, criminal or pharmacy registries. Such registry data require neither subject cooperation nor accurate recall. However, it can produce false-negative and false-positive diagnoses, the nature of which is difficult to estimate. Individuals who abuse alcohol or other illicit substances and never come to the attention of the medical or legal system in Sweden for problems related to their substance use will, in particular, escape detection. The validity of the Swedish medical registries in general have been well demonstrated (Ludvigsson et al., 2011) and the validity of our definitions of AUD and DUD are further supported by the high rates of concordance for registration observed across our different ascertainment methods (Kendler et al., 2012, 2015), and the similarity of genetic epidemiological findings for AUD and DUD in Sweden compared to those in other samples (Kendler, Maes, Sundquist, Ohlsson, & Sundquist, 2013; Kendler et al., 2012, 2015, 2016).

Third, an alternative interpretation of our findings is that the liability to DUD and AUD are on the same continuum with DUD reflecting the more severe condition. However, this hypothesis is not consistent with prior evidence that, in AUD cases, the familial genetic risk score (FGRS) for AUD is substantially higher than the FGRS for DUD while the reverse is seen in cases of DUD (Kendler, Ohlsson, Sundquist, & Sundquist, 2021).

Fourth, we refer in this paper to drug availability as measured indirectly in rates of DUD and self-report surveys of illicit drug use (e.g. (Sznitman, 2008)). These are population-level findings and cannot be used to assess the experiences of particular individuals or families in our sample. Furthermore, our indirect measures cannot be equated with more direct measures of availability that are sometimes available for epidemiological surveys, typically for restricted areas and not whole countries, such as 'street-level' cost and access for illicit drugs and density of outlets for alcohol.

Fifth, we have previously examined the cross-generational transmission of DUD → DUD and AUD → AUD in the Swedish population using, respectively, a standard (Kendler et al., 2012) and expanded adoption design (Kendler et al., 2015). As expected, our results in our entire cohort are similar but not identical to those previously reported. Since those analyses were completed, further years of data have become available, and the addition of a primary care registry has expanded our coverage.

Finally, in our main analyses, we made no attempt to apply a diagnostic hierarchy, so that individuals with both AUD and DUD were assigned both diagnoses in our analyses. As expected, comorbidity between these two disorders was common. For example, among our offspring 42.8% of the DUD cases also had a diagnosis of AUD and 44.9% of the AUD cases also had at least one diagnosis with DUD. There is no uniformly accepted way to 'correct' for this in genetic analyses, and some would argue that any correction is counter-productive. While we could apply a 'hard' hierarchy forcing all comorbid cases to have only one of the two disorders, this implies that no individual could have both DUD and AUD as two independent disorders, a conclusion inconsistent with clinical experience.

To obtain a sense of what might result from a 'softer' diagnostic hierarchy, we took all comorbid cases in our sample where the less frequent disorder had 50% or more the number of registrations as did the more common disorder and continued to assign them both diagnoses. But if the rarer disorder had less than 50% of that number, we only give them the more common diagnosis. We then re-analyzed our sample with a substantial reduction in comorbid cases and present these results in online Supplementary Appendix Tables S5–S7.

Comparing the cross-generational correlations with those observed in our original sample (without hierarchy), little change was seen in the within-disorder results (i.e. AUD → AUD and DUD → DUD). But for the two cross-disorder correlations, moderate reductions were seen for AUD → DUD while the DUD → AUD correlations declined substantially. Our hierarchy corrections resulted in a much weaker transmission from DUD in the parental generation to AUD in the offspring generation, thereby further increasing the specificity of DUD *v.* AUD cross-generational transmission. The resulting genetic correlations between AUD and DUD were estimated for the entire sample, the older cohort and the younger cohort, at respectively, +0.48 (0.43–0.52), +0.69 (0.57–0.85) and +0.53 (0.47–0.59), substantially lower than that observed in our sample analyzed without a diagnostic hierarchy. One concern in the interpretation of these results is that they were largely driven by the fact that in the comorbid cases, DUD was more often assigned the final diagnosis because DUD was more frequently registered than was AUD. That might be because DUD was the more 'severe' of the two disorders, but also could have arisen for a range of methodological reasons in the Swedish registries.

Conclusion

This study was motivated by a desire to understand how the availability of psychoactive substances and their degree of normalization can impact on the specificity or non-specificity of the genetic risk of individuals with particular forms of SUD. Our method for addressing this question was the examination of the cross-generational genetic transmission of risk for SUD in an extended adoption design. We showed that, while population rates of AUD in Sweden were relatively constant over the birth years 1960–1999, rates of DUD were rising rapidly. AUD in NLW and biological parents increased the risk for AUD and DUD nearly equally in their offspring. By contrast, DUD in these parents was much more specific in its effect, impacting far more strongly the risk for DUD in their children than risk for AUD. When we divided our sample into an older and younger cohort of parent–offspring pairs, we found that the specificity of the cross-generational transmission of genetic risk for AUD went slightly down across cohorts while the specificity of the cross-generational transmission of genetic risk for DUD increased, providing further support for our theory. Furthermore, the genetic correlation between AUD and DUD significantly decreased from the older to the younger cohort. These results illustrate how the specificity of the genetic liability to individual forms of SUD can change across generations and historical periods due to changes in the availability and

https://doi.org/10.1017/S0033291722002549 Published online by Cambridge University Press

cultural acceptability of various psychoactive substances. These results have potential implications for the analysis of genetic risk to multiple forms of SUD using both genetic-epidemiological and molecular genetic designs.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291722002549.

Financial support. This project was supported by grants R01AA023534 and R01DA030005 from the National Institutes of Health, the Swedish Research Council as well as Avtal om Läkarutbildning och Forskning (ALF) funding from Region Skåne.

Conflict of interest. None of the authors have any conflicts of interest to declare.

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 ethical approval for this study from the Regional Ethical Review Board in Lund (No. 2008/409 with later amendments).

Informed consent. Informed consent was not obtained from individual participants included in the study.

References

Babchishin, K. M., & Helmus, L. M. (2016). The influence of base rates on correlations: An evaluation of proposed alternative effect sizes with real-world data. *Behavior Research Methods*, *48*(3), 1021–1031. doi:10.3758/s13428-015-0627-7.

Bierut, L. J., Dinwiddie, S. H., Begleiter, H., Crowe, R. R., Hesselbrock, V., Nurnberger, J. I., Jr., … Reich, T. (1998). Familial transmission of substance dependence: Alcohol, marijuana, cocaine, and habitual smoking: A report from the Collaborative Study on the Genetics of Alcoholism. *Archives of General Psychiatry*, *55*(11), 982–988. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9819066.

Borenstein, M., Hedges, L. V., Higgins, J. P., & Rothstein, H. R. (2010). A basic introduction to fixed-effect and random-effects models for meta-analysis. *Research Synthesis Methods*, *1*(2), 97–111.

Cadoret, R. J., Yates, W. R., Troughton, E., Woodworth, G., & Stewart, M. A. (1995). Adoption study demonstrating two genetic pathways to drug abuse. *Archives of General Psychiatry*, *52*(1), 42–52. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7811161.

Cadoret, R. J., Yates, W. R., Troughton, E., Woodworth, G., & Stewart, M. A. (1996). An adoption study of drug abuse/dependency in females. *Comprehensive Psychiatry*, *37*(2), 88–94. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8654068.

Cook, W. K., Li, X., Sundquist, K., Kendler, K. S., Sundquist, J., & Karriker-Jaffe, K. J. (2021). Drinking cultures and socioeconomic risk factors for alcohol and drug use disorders among first-and second-generation immigrants: A longitudinal analysis of Swedish population data. *Drug and Alcohol Dependence*, in press.

European Monitoring Centre for Drugs and Drug Addiction (2021). *European Drug report: Trends and development*. Lisbon, Portugal: Praca Europa.

Falconer, D. S. (1989). *Introduction to quantitative genetics* (3rd ed.). New York: Wiley.

Giordano, G. N., Ohlsson, H., Kendler, K. S., Winkleby, M. A., Sundquist, K., & Sundquist, J. (2013). Age, period and cohort trends in drug abuse hospitalizations within the total Swedish population (1975–2010). *Drug and Alcohol Dependence*, *134*(Jan), 355–361. doi:10.1016/j.drugalcdep.2013.11.011.

Hall, W., & Degenhardt, L. (2009). The Australian illicit drug reporting system: Monitoring trends in illicit drug availability, use and drug-related harm in Australia 1996–2006. *Contemporary Drug Problems*, *36*(3–4), 643–661.

Kendler, K. S., Aggen, S. H., Knudsen, G. P., Roysamb, E., Neale, M. C., & Reichborn-Kjennerud, T. (2011). The structure of genetic and environmental risk factors for syndromal and subsyndromal common DSM-IV axis I and all axis II disorders. *American Journal of Psychiatry*, *168*(1), 29–39. doi:10.1176/appi.ajp.2010.10030340.

Kendler, K. S., Ji, J., Edwards, A. C., Ohlsson, H., Sundquist, J., & Sundquist, K. (2015). An extended Swedish national adoption study of alcohol use disorder. *JAMA Psychiatry*, *72*(3), 211–218. doi:10.1001/jamapsychiatry.2014.2138.

Kendler, K. S., Maes, H. H., Sundquist, K., Ohlsson, H., & Sundquist, J. (2013). Genetic and family and community environmental effects on drug abuse in adolescence: A Swedish national twin and sibling study. *American Journal of Psychiatry*, *171*(2), 209–217.

Kendler, K. S., Myers, J., & Prescott, C. A. (2007). Specificity of genetic and environmental risk factors for symptoms of cannabis, cocaine, alcohol, caffeine, and nicotine dependence. *Archives of General Psychiatry*, *64*(11), 1313–1320. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/17984400.

Kendler, K. S., Ohlsson, H., Bacanu, S., Sundquist, J., & Sundquist, K. (2020). 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. *Molecular Psychiatry*, *25*(8), 1777–1786. doi:10.1038/s41380-018-0111-8.

Kendler, K. S., Ohlsson, H., Sundquist, J., & Sundquist, K. (2021). The patterns of family genetic risk scores for eleven major psychiatric and substance use disorders in a Swedish national sample. *Translational Psychiatry*, *11*(1), 1–8.

Kendler, K. S., PirouziFard, M., Lonn, S., Edwards, A. C., Maes, H. H., Lichtenstein, P., … Sundquist, K. (2016). A national Swedish twin-sibling study of alcohol use disorders. *Twin Research and Human Genetics*, *19*(5), 430–437. doi:10.1017/thg.2016.62.

Kendler, K. S., Prescott, C. A., Neale, M. C., & Pedersen, N. L. (1997). Temperance Board registration for alcohol abuse in a national sample of Swedish male twins, born 1902 to 1949. *Archives of General Psychiatry*, *54*(2), 178–184. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9040286.

Kendler, K. S., Sundquist, K., Ohlsson, H., Palmer, K., Maes, H., Winkleby, M. A., & Sundquist, J. (2012). Genetic and familial environmental influences on the risk for drug abuse: A national Swedish adoption study. *Archives of General Psychiatry*, *69*(7), 690–697. doi:10.1001/archgenpsychiatry.2011.2112.

Ludvigsson, J. F., Andersson, E., Ekbom, A., Feychting, M., Kim, J. L., Reuterwall, C., … Olausson, P. O. (2011). External review and validation of the Swedish national inpatient register. *BMC Public Health*, *11*, 450. doi:10.1186/1471-2458-11-450.

Merikangas, K., Stolar, M., Stevens, D. E., Goulet, J., Preisig, M. A., Fenton, B., … Rounsaville, B. J. (1998). Familial transmission of substance use disorders. *Archives of General Psychiatry*, *55*, 973–979.

Parker, H. J., Parker, H., Aldridge, J., & Measham, F. (1998). *Illegal leisure: The normalization of adolescent recreational drug use*. London: Psychology Press.

Pearson, K. (1901). Mathematical contributions to the theory of evolution. VII. On the correlation of characters not quantitatively measurable. *Philosophical Transactions of the Royal Society of London. Series A*, *66*, 241–244.

R Core Team. (2019). *R: A language and environment for statistical computing* (*Version 4.0.3*) *[Computer software]*. Vienna.: R Foundation for Statistical Computing.

Rhee, S. H., Hewitt, J. K., Young, S. E., Corley, R. P., Crowley, T. J., & Stallings, M. C. (2003). Genetic and environmental influences on substance initiation, use, and problem use in adolescents. *Archives of General Psychiatry*, *60*(12), 1256–1264. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/14662558.

Rounsaville, B. J., Kosten, T. R., Weissman, M. M., Prusoff, B., Pauls, D., Anton, S. F., & Merikangas, K. (1991). Psychiatric disorders in relatives of probands with opiate addiction. *Archives of General Psychiatry*, *48*(1), 33–42. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1984760.

SAS Institute, I. (2012). *SAS/STAT® online documentation, version 9.4*. Cary, NC: SAS Institute, Inc. (Reprinted from: not in file).

Sznitman, S. R. (2007). An examination of the normalisation of cannabis use among 9th grade school students in Sweden and Switzerland. *Addiction Research & Theory*, *15*(6), 601–616.

Sznitman, S. R. (2008). Drug normalization and the case of Sweden. *Contemporary Drug Problems*, *35*(2–3), 447–480.

Tsuang, M. T., Lyons, M. J., Meyer, J. M., Doyle, T., Eisen, S. A., Goldberg, J., … Eaves, L. (1998). Co-occurrence of abuse of different drugs in men: The role of drug-specific and shared vulnerabilities. *Archives of General Psychiatry*, *55*(11), 967–972. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9819064.

Verhulst, B., Neale, M. C., & Kendler, K. S. (2015). The heritability of alcohol use disorders: A meta-analysis of twin and adoption studies. *Psychological Medicine*, *45*(5), 1061–1072. doi:10.1017/S0033291714002165.