APPENDIX

**Table 1 - Description of Registers**

*Multi-Generation Register*

The Multi-Generation Register is a register made up of persons who have been registered in Sweden at some time since 1961 and those who were born in 1932 or later. These are called index persons. The register contains connections between index persons and their biological parents. There are about 11 million index persons in the register. The Multi-Generation Register is a part of the register system for Total Population Register, where information comes from the National Tax Board. Every year, a new version of the register is created, including new index persons who immigrated or were born during the year. Information from the Multi-Generation Register may be disclosed for research and statistical purposes. For more information, see *Statistics Sweden, Background Facts, Population and Welfare Statistics 2017:2, Multi-generation register 2016. A description of contents and quality*

*National Patient Register*

In the 1960's the National Board of Health and Welfare started to collect information regarding in-patients at public hospitals, the National Patient Register (NPR). Initially it contained information about all patients treated in psychiatric care and approximately 16 percent of patients in somatic care. The register at that time covered six of the 26 county councils in Sweden. In 1984, the Ministry of Health and Welfare together with the Federation of County Councils decided a mandatory participation for all county councils. From 1987, NPR includes all in-patient care in Sweden. Since 2001, the register also covers outpatient doctor visits including day surgery and psychiatric care from both private and public caregivers. For more information, see *https://www.socialstyrelsen.se/en/statistics-and-data/registers/register-information/the-national-patient-register/*

*Nationwide Primary Care Data*

We also used information from our new Primary Care Registry (PCR), a research dataset including individual-level information on clinical diagnoses from primary health care centers from the following Swedish counties: Blekinge (2009-2018), Dalarna (2005-2018), Gotland (2011-2018), Gävleborg (2010-2018), Halland (2007-2018), Jönköping (2008-2018), Kalmar (2007-2018), Kronoberg (2006-2018), Norrbotten (2001-2018), Skåne (1989-2018), Stockholm (2003-2018), Södermanland (1992-2018), Uppsala (2005-2018), Västra Götaland (2000-2018), Värmland (2005-2018), Västerbotten (1991-2018), Västernorrland (2008-2018), Västmanland (2014-2018), Östergötland (1990-2018), and Örebro (2006-2018). The retrieval of data differs due to timing of digitalization of patient records. In 2018, 99% of the Swedish population lived in these 20 counties. For more information see *Sundquist, J., Ohlsson, H., Sundquist, K. et al. Common adult psychiatric disorders in Swedish primary care where most mental health patients are treated. BMC Psychiatry 17, 235 (2017).*

*Prescribed Drug Register*

The Swedish Prescribed Drug Register started in July 2005 and includes all prescribed drugs being fetched at pharmacies, linked to personal numbers. For more information, see *https://www.socialstyrelsen.se/en/statistics-and-data/registers/register-information/the-swedish-prescribed-drug-register/*

*Cause of Death Register*

The Cause of Death Register includes all deaths occurring in Sweden from 1961 (including for Swedish citizens dying abroad) and is updated yearly. There is also a historical register between the years 1952 to 1960. For more information, see *https://www.socialstyrelsen.se/statistik-och-data/register/alla-register/dodsorsaksregistret/*

*Criminal and Suspicion Register*

The Swedish Criminal Register and the Swedish Suspicion Register includes individual-level information on all committed crimes from 1973 and all suspicions of crimes related to an individual from 1998. For more information, see *https://polisen.se/lagar-och-regler/behandling-av-personuppgifter/polisens-register/*

*Population and Housing Censuses*

Every fifth year between 1960 and 1990 Sweden conducted censuses. These register includes among other things, the population's employment, the composition of households and housing. For more information, see *https://www.scb.se/hitta-statistik/statistik-efter-amne/befolkning/befolkningens-storlek-och-forandringar/hushalls-och-bostadsrakning-census/*

**Table 2 - Definition of Alcohol Use Disorder and Drug Use Disorder**

|  |  |  |
| --- | --- | --- |
|  | Registers Used | Definition  |
| Alcohol Use Disorder (AUD) | The Swedish Hospital Discharge Register (coverage 1973-2018); Outpatient Care Register (national coverage 2001-2018); Primary Care Registry (Partly coverage from 1999-2018); the Swedish Prescribed Drug Register (2005-2018); the Swedish Cause of Death Register, and the Swedish Criminal Register (1973-2017) and the Swedish Suspicion Register (1998-2017) | Alcohol Use Disorder (AUD) was identified in the Swedish medical and mortality registries by ICD codes: ICD9: V79B, 305A, 357F, 571A-D, 425F, 535D, 291, 303, 980; ICD 10: E244, G312, G621, G721, I426, K292, K70, K852, K860, O354, T51, F10); in the Crime Register by codes 3005, 3201, which reflect crimes related to alcohol abuse; in the Suspicion Register by codes 0004, 0005 (Only those individuals with at least two alcohol-related crimes or suspicion of crimes from both Crime Register and Suspicion Register were included); in the Prescribed Drug Register by the drugs disulfiram (Anatomical Therapeutic Chemical (ATC) Classification System N07BB01), acamprosate (N07BB03), and naltrexone (N07BB04). |
| Drug Use Disorder (DUD) | The Swedish Hospital Discharge Register (coverage 1973-2018); Outpatient Care Register (national coverage 2001-2018); Primary Care Registry (Partly coverage from 1999-2018); the Swedish Prescribed Drug Register (2005-2018); the Swedish Cause of Death Register, and the Swedish Criminal Register (1973-2017) and the Swedish Suspicion Register (1998-2017) | Drug Use Disorder (DUD) was identified in the Swedish medical and mortality registries by ICD codes (ICD8: Drug dependence (304); ICD9: Drug psychoses (292) and Drug dependence (304); ICD10: Mental and behavioral disorders due to psychoactive substance use (F10-F19), except those due to alcohol (F10) or tobacco (F17)); in the Suspicion Register by codes 3070, 5010, 5011, and 5012, that reflect crimes related to DUD; and in the Crime Register by references to laws covering narcotics (law 1968:64, paragraph 1, point 6) and drug-related driving offences (law 1951:649, paragraph 4, subsection 2 and paragraph 4A, subsection 2). DUD was identified in individuals (excluding those suffering from cancer) in the Prescribed Drug Register who had retrieved (in average) more than four defined daily doses a day for 12 months from either of Hypnotics and Sedatives (Anatomical Therapeutic Chemical (ATC) Classification System N05C and N05BA) or Opioids (ATC: N02A). |

**Table 3 - Calculation of the genetic correlations and rearing correlation**

We calculated the genetic correlation, $r\_{g}$, between AUD and DUD, using

$$r\_{g}=\frac{Cov(AUD,DUD)}{\sqrt{V\left(AUD\right),V(DUD)}}=\frac{r(AUD,DUD)}{\sqrt{r\left(AUD,AUD\right),r(DUD,DUD)}}.$$

For the correlation $r(AUD,DUD)$ we made use of a weighted tetrachoric correlation explaining parent-offspring cross-transmissions from AUD to DUD as well as from DUD to AUD. For the correlations $r(AUD,AUD)$ and $r(DUD,DUD)$ we used the weighted tetrachoric correlations explaining parent-offspring transmissions from AUD to AUD and DUD to DUD, respectively. We made use of 151 531 parent-offspring pairs (based on 140 601 offspring) reflecting a genes only relationship. These pairs were found in the families NLW father (biological father), NLW mother (biological mother) and adoptive (biological fathers and biological mothers). For the 95% confidence intervals we used non-parametric bootstrap sampling along with the percentile method. We produced 10 000 samples of the same size as used for the calculation of the point estimate, by resampling from the individuals in the offspring population.

**Table 4 – Details on R-packages used in statistical analyses**

1. Fox J. polycor: Polychoric and Polyserial Correlations. R package. 2019.

2. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw. 2010;36(3):1-48

3. Kassambra A, Kosinski M, Biecek P. survminer: Drawing Survival Curves using ‘ggplot2’. R package. 2021.

4. Therneau T. survival: A Package for Survival Analysis in R. R package. 2020.

5. Wickham H, Miller E. haven: Import and Export 'SPSS', 'Stata' and 'SAS' Files. R package. 2021.

6. Wickham H, François R, Henry L, Müller K. dplyr: A Grammar of Data Manipulation. R package. 2021.

7. Dowle M, Srinivasan A. data.table: Extension of `data.frame`. R package. 2021.

Table 5

|  |
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| **Entire sample** |
|  | Disorder | NLW Father Families | NLW Mother Families | Adoptive Families |
| All offspring | AUDDUDAUD/DUD | 8.210.40.8 | 11.28.21.4 | 12.26.02.0 |
| Female offspring | AUDDUDAUD/DUD | 5.56.80.8 | 7.37.41.0 | 7.45.31.4 |
| Male offspring | AUDDUDAUD/DUD | 10.813.80.8 | 14.68.91.6 | 16.56.52.5 |
| Biological mothers | AUDDUDAUD/DUD | 7.44.01.8 | 18.27.42.4 | 14.04.82.9 |
| Biological fathers | AUDDUDAUD/DUD | 27.86.04.6 | 13.41.68.2 | 30.53.68.5 |
| **Older cohort** |
|  | Disorder | NLW Father Families | NLW Mother Families | Adoptive Families |
| All offspring | AUDDUDAUD/DUD | 10.96.21.8 | 13.97.81.8 | 13.05.32.4 |
| Female offspring | AUDDUDAUD/DUD | 6.45.01.3 | 8.17.51.1 | 7.64.81.6 |
| Male offspring | AUDDUDAUD/DUD | 15.47.32.1 | 18.88.12.3 | 17.85.83.1 |
| Biological mothers | AUDDUDAUD/DUD | 6.52.22.9 | 17.55.23.3 | 11.63.23.7 |
| Biological fathers | AUDDUDAUD/DUD | 27.52.411.6 | 12.51.48.7 | 27.52.113.0 |
| **Younger cohort** |
|  | Disorder | NLW Father Families | NLW Mother Families | Adoptive Families |
| All offspring | AUDDUDAUD/DUD | 6.512.90.5 | 7.38.60.9 | 8.19.10.9 |
| Female offspring | AUDDUDAUD/DUD | 5.08.00.6 | 6.27.10.9 | 6.37.60.8 |
| Male offspring | AUDDUDAUD/DUD | 8.017.60.5 | 8.49.90.8 | 9.710.40.9 |
| Biological mothers | AUDDUD AUD/DUD | 7.84.91.6 | 19.210.71.8 | 26.112.92.0 |
| Biological fathers | AUDDUDAUD/DUD | 28.08.23.4 | 14.11.87.9 | 43.710.04.4 |

Prevalences of AUD (%) and DUD (%) in the Relatives and their Ratio (AUD/DUD) from the Three Family Types With a “Soft” Diagnostic Hierarchy

|  |
| --- |
| Table 6 Parent-offspring tetrachoric correlations and 95% CI, Weighted Estimates and Heterogeneity Tests With a “Soft” Diagnostic Hierarchy Imposed |
|  | NLW Father | NLW Mother | Adoptive | Weighted Estimate | Het Test a  |
| **Entire sample** |
| **DUD→AUD** |  |  |  |  |  |
| *Mother-Offspring* | NA | 0.06 (-0.01-0.14) | -0.01 (-0.07-0.05) | 0.02 (-0.03-0.06) | 0.11 |
| *Father-Offspring* | 0.01 (-0.01-0.03) | NA | -0.12 (-0.20-(-0.03)) | 0.01 (-0.01-0.03) | <.01 |
| **AUD→DUD** |  |  |  |  |  |
| *Mother-Offspring* | NA | 0.14 (0.07-0.20) | 0.15 (0.10-0.19) | 0.14 (0.11-0.18) | 0.81 |
| *Father-Offspring* | 0.14 (0.13-0.15) | NA | 0.10 (0.05-0.15) | 0.14 (0.13-0.15) | 0.13 |
| **DUD→DUD** |  |  |  |  |  |
| *Mother-Offspring* | NA | 0.28 (0.21-0.35) | 0.22 (0.16-0.28) | 0.24 (0.20-0.29) | 0.20 |
| *Father-Offspring* | 0.27 (0.26-0.29) | NA | 0.16 (0.08-0.25) | 0.27 (0.25-0.29) | 0.01  |
| **AUD→AUD** |  |  |  |  |  |
| *Mother-Offspring* | NA | 0.23 (0.17-0.28) | 0.15 (0.11-0.19) | 0.18 (0.15-0.21) | 0.04 |
| *Father-Offspring* | 0.18 (0.16-0.19) | NA | 0.11 (0.07-0.16) | 0.17 (0.16-0.18) | <.01 |
| **Older cohort** |
| **DUD→AUD** |  |  |  |  |  |
| *Mother-Offspring* | NA | 0.09 (-0.01-0.19) | 0.02 (-0.05-0.09) | 0.04 (-0.02-0.10) | 0.24 |
| *Father-Offspring* | 0.07 (0.03-0.11) | NA | -0.12 (-0.23-(-0.00)) | 0.05 (0.01-0.08) | <.01 |
| **AUD→DUD** |  |  |  |  |  |
| *Mother-Offspring* | NA | 0.12 (0.03-0.20) | 0.13 (0.07-0.18) | 0.12 (0.08-0.17) | 0.87 |
| *Father-Offspring* | 0.13 (0.11-0.16) | NA | 0.06 (-0.00-0.12) | 0.12 (0.10-0.15) | 0.03 |
| **DUD→DUD** |  |  |  |  |  |
| *Mother-Offspring* | NA | 0.20 (0.09-0.31) | 0.16 (0.08-0.24) | 0.17 (0.11-0.24) | 0.53 |
| *Father-Offspring* | 0.12 (0.07-0.16) | NA | 0.06 (-0.06-0.19) | 0.11 (0.07-0.15) | 0.43 |
| **AUD→AUD** |  |  |  |  |  |
| *Mother-Offspring* | NA | 0.22 (0.16-0.29) | 0.17 (0.12-0.21) | 0.18 (0.15-0.22) | 0.17 |
| *Father-Offspring* | 0.17 (0.15-0.19) | NA | 0.11 (0.06-0.16) | 0.16 (0.14-0.18) | 0.02 |
| **Younger cohort** |
| **DUD→AUD** |  |  |  |  |  |
| *Mother-Offspring* | NA | 0.11 (-0.01-0.23) | 0.03 (-0.09-0.14) | 0.07 (-0.02-0.15) | 0.32 |
| *Father-Offspring* | 0.05 (0.02-0.07) | NA | -0.05 (-0.20-0.11) | 0.04 (0.02-0.07) | 0.25 |
| **AUD→DUD** |  |  |  |  |  |
| *Mother-Offspring* | NA | 0.16 (0.07-0.26) | 0.13 (0.03-0.22) | 0.14 (0.08-0.21) | 0.61 |
| *Father-Offspring* | 0.15 (0.13-0.16) | NA | 0.14 (0.03-0.25) | 0.15 (0.13-0.16) | 0.89 |
| **DUD→DUD** |  |  |  |  |  |
| *Mother-Offspring* | NA | 0.34 (0.25-0.44) | 0.24 (0.14-0.34) | 0.30 (0.23-0.37) | 0.16 |
| *Father-Offspring* | 0.26 (0.24-0.28) | NA | 0.20 (0.06-0.33) | 0.26 (0.24-0.28) | 0.35 |
| **AUD→AUD** |  |  |  |  |  |
| *Mother-Offspring* | NA | 0.26 (0.16-0.35) | 0.24 (0.15-0.33) | 0.25 (0.18-0.31) | 0.77 |
| *Father-Offspring* | 0.19 (0.17-0.21) | NA | 0.24 (0.14-0.35) | 0.19 (0.17-0.21) | 0.33 |

a) Significance threshold after Bonferroni correction for 24 tests was P < 0.002. Significant tests are marked with \*. Het test – Heterogeneity test with nominal p value.

Table 7

Tests of Transmission from Mothers and Fathers using Weighted Estimates across all Family Types With a “Soft” Diagnostic Hierarchy

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Mothers | Fathers | Weighted estimate | Nominal P value for test of heterogeneity a |
| **Entire sample** |
| DUD→AUD | 0.02 (-0.03-0.06) | 0.01 (-0.01-0.03) | 0.01 (-0.01-0.03) | 0.66 |
| AUD→DUD | 0.14 (0.11-0.18) | 0.14 (0.13-0.15) | 0.14 (0.13-0.15) | 0.64 |
| DUD→DUD | 0.24 (0.20-0.29) | 0.27 (0.25-0.29) | 0.27 (0.25-0.28) | 0.36 |
| AUD→AUD | 0.18 (0.15-0.21) | 0.17 (0.16-0.18) | 0.17 (0.16-0.18) | 0.87 |
| **Older cohort** |
| DUD→AUD | 0.04 (-0.02-0.10) | 0.05 (0.01-0.08) | 0.05 (0.01-0.08) | 0.96 |
| AUD→DUD | 0.12 (0.08-0.17) | 0.12 (0.10-0.15) | 0.12 (0.10-0.14) | 0.82 |
| DUD→DUD | 0.17 (0.11-0.24) | 0.11 (0.07-0.15) | 0.13 (0.09-0.16) | 0.08 |
| AUD→AUD | 0.18 (0.15-0.22) | 0.16 (0.14-0.18) | 0.17 (0.15-0.18) | 0.26 |
| **Younger cohort** |
| DUD→AUD | 0.07 (-0.02-0.15) | 0.04 (0.02-0.07) | 0.04 (0.02-0.07) | 0.59 |
| AUD→DUD | 0.14 (0.08-0.21) | 0.15 (0.13-0.16) | 0.15 (0.13-0.16) | 0.97 |
| DUD→DUD | 0.30 (0.23-0.37) | 0.26 (0.24-0.28) | 0.26 (0.24-0.28) | 0.34 |
| AUD→AUD | 0.25 (0.18-0.31) | 0.19 (0.17-0.21) | 0.19 (0.18-0.21) | 0.10 |

a) Significance threshold after Bonferroni correction for 12 tests was P < 0.004. Significant tests are marked with \*.