APPENDIX

**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/*

*Primary Care Registry*

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 15 of the 21 Swedish counties: Blekinge (2009-2016), Värmland (2005-2015), Kalmar (2007-2016), Sörmland (1997-2017), Uppsala (2005-2015), Västernorrland (2008-2015), Norrbotten (2009-2016), Gävleborg (2010-2016), Halland (2007-2014), Jönköping (2008-2014), Kronoberg (2006-2016), Skåne (1998-2013), Östergötland (1997-2014), Stockholm (2003-2016), and Västergötland (2000-2013). In 2016, these counties included 87% of the Swedish population. 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).*

*The Swedish Crime register*

Includes nationwide almost complete data on all convicted individuals from 1973 and onwards

*The Swedish Suspicion Register*

Includes nationwide data on all individuals suspected of a crime. The Swedish Law regulating the Suspicion Register (1998:621) states that individuals suspected on reasonable grounds for a crime are to be registered in the Suspicion Register (§1), and that they are to be removed from the register if the preliminary inquiry by the police has been dropped (§13, point 1), if an indictment by the prosecutor has been dropped (§13, point 2), if a court of law has passed a sentence convicting or acquitting the accused (§13, point 3), or if an accused is requested to be extradited and this request has been refused or executed by the court of law (§13, point 4).

*The Swedish Prescribed Drug Register*

The Swedish Prescribed Drug Register with personal identity numbers was established in July 2005 and contains all prescribed drugs dispensed at pharmacies. Each row in the register corresponds to one dispensation at a pharmacy.

**Table 1 - Definition of Phenotypes**

The following ICD codes were used to define the traits:

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| --- | --- | --- |
|  | Registers Used | Definition  |
| Alcohol Use Disorder (AUD) | The Swedish Hospital Discharge Register (coverage 1973-2017); Outpatient Care Register (national coverage 2001-2017); Primary Care Registry (Partly coverage from 1999-2017); the Swedish Drug Register (2005-2017); the Swedish Mortality 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: ICD 8: 291, 303, 980, 571.0; 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). |
|  |  |  |
| Major Depression (MD) | The Swedish Hospital Discharge Register (coverage 1973-2017); Outpatient Care Register (national coverage 2001-2017); Primary Care Registry (Partly coverage from 1999-2017) | ICD-8: 296.2, 298.0, 300.4; ICD-9: 296.2, 296.4, 298.0, 300.4; ICD-10: F32, F33.**Note**: all individuals with a registration for Bipolar Disorder (BD) were excluded (see below for a BD definition). |
| Drug Use Disorder (DUD) | The Swedish Hospital Discharge Register (coverage 1973-2017); Outpatient Care Register (national coverage 2001-2017); Primary Care Registry (Partly coverage from 1999-2017); the Swedish Drug Register (2005-2017); the Swedish Mortality Register, and the Swedish Criminal Register (1973-2017) and the Swedish Suspicion Register (1998-2017) | 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). |
| ADHD | The Swedish Hospital Discharge Register (coverage 1973-2017); Outpatient Care Register (national coverage 2001-2017); Primary Care Registry (Partly coverage from 1999-2017) | ICD-9: 314; ICD-10: F90 |
| Anxiety Disorder (AD) | The Swedish Hospital Discharge Register (coverage 1973-2017); Outpatient Care Register (national coverage 2001-2017); Primary Care Registry (Partly coverage from 1999-2017) | ICD-8: 300.0, 300.2 ; ICD-9: 300A, 300C; ICD-10: F40, F41 |
| Bipolar Disorder (BD) | The Swedish Hospital Discharge Register (coverage 1973-2017); Outpatient Care Register (national coverage 2001-2017); Primary Care Registry (Partly coverage from 1999-2017) | ICD-8: 296.1, 296.3, 296.8, 296.9, 298.1; ICD-9: 296A, 296C, 296D, 296E, 296W, 298B; ICD-10: F30, F31 |
| Criminal behavior (CB) | The Swedish Criminal Register (1973-2017) | Criminal behavior (CB) was identified by registration in the Swedish Crime register, which excluded convictions for minor crimes like traffic infractions. CB is measured using all available criminal conviction types. |
| Autism spectrum disorder (ASD) | The Swedish Hospital Discharge Register (coverage 1973-2017); Outpatient Care Register (national coverage 2001-2017); Primary Care Registry (Partly coverage from 1999-2017) | ICD-9: 299; ICD-10: F840, F841, F845, F849 |

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| Table 2 -Steps for the Calculation of the FGRS |
| The dataset for the calculations includes:Column1 = Identification number of the proband (Born 1932-1995)Column2 = Identification number of the relative (1st to 5th degree relatives) Column3 = Proportion of shared additive genetic effects (0.03125 to 0.50) with the probandColumn4 = Year of Birth of relativeColumn5 = Sex of relativeColumn6 = Age at registration for traitColumn7 = Age at end of follow-up (2017-12-31 or age at death, or age at emigration whichever came first) |
| **Step 1:** Using all unique relatives with a registration for the disorder, we non-parametrically estimated the distribution of *Age at first registration*. The empirical distribution is used to obtain weights for relatives without a registration for the disorder, in order to account for the proportion of the time-at-risk period they had completed at the end of follow-up. For example, for relatives at age x at end of follow-up, the weight corresponds to the proportion of relatives registered for the trait that had been registration at age x. For relatives born prior to 1958 we subtracted age at the end of follow-up with the following formula: 1958 - Year of birth of relative. This modification was done in order to control for registration effects (i.e, most registers in Sweden start in 1973 suggesting that relatives from early birth cohorts do not have the possibility to be registered at younger ages). Note that all relatives with the disorder are weighted one. |
| **Step 2:** Transform the binary variable (trait yes/no) into a z-score based on the threshold for each trait. The underlying liability of the individual is not assessable. Instead we estimated the mean of the underlying liability to obtain sex and birth decade specific Z-scores for relatives with the trait registration and relatives without the trait. We generate n random numbers from a N(0, 1) distribution and estimate the mean for relatives registered with the disorder (i.e., mean of the observations above the threshold) and for relatives without a registration (i.e., mean of all observation below the threshold). The thresholds are calculated for each decade of birth and sex. |
| **Step 3**: Correct for cohabitation effects. To estimate the cohabitation effect (i.e. “shared environment”), we created a database with all individuals in the Swedish population born in Sweden 1955-1990. We also included the number of years, during ages 0-15, that individuals resided in the same household as their biological father. We thereby were able to define two kinds of families i) “not-lived-with” father families (offspring never resided for more than 1 year in the same household or in the same community as their biological father); ii) “lived-with” father (offspring resided a minimum of 13 year in the same household as their biological father. We performed a logistic regression model with the binary trait in offspring as outcome and the binary trait in father, type of father, and their interaction as predictors. We used the interaction term as the difference of effect between genes only and genes + environment. The same approach was performed for half-siblings where we compared those who were reared together versus reared apart. The following interaction terms were used in the calculations for each of our 7 main disorders:

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| --- | --- | --- |
|  | Parent/Children  | Siblings |
| MD | .80 | .85 |
| AD | .87 | .81 |
| BD | .67 | .77 |
| AUD | .99 | .69 |
| DUD | .92 | .52 |
| ADHD | .42 | .81 |
| CB | .87 | .81 |

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| **Step 4:** Calculate the product for each relative using the four components:1. Z-score (reflecting sex and year of birth adjusted rates)
2. Weight (reflecting the proportion of risk period they had completed)
3. Cohabitation effects
4. Proportion of shared genetic effects (0.03125 – 0.5) with the proband
 |
| **Step 5:** Average the product calculated in step 4 across all relatives to a proband |
| **Step 6**: Correct for the number of relatives. We multiplied the results from step 5 with a shrinkage factor. Shrinkage factor (SF): B/(B+A/C). It produces more shrinkage if B and C are small and A is large.1. the variance of the z-score of the disorder across all relatives,
2. the variance in the mean z-score across all probands,
3. the weighted number of relatives for each proband (sum of Column 3 across each proband).
 |
| **Step 7:** Correct for difference by year of birth and county differences. There are 21 counties in Sweden. For each proband we used the county they had resided in during the maximum number of years (measured from 1969 and onwards) We standardized the risk score by year of birth and county of the proband into a z-score with mean 0 and SD 1. This was then used as the FGRS in the analyses. |

**Table 3 - Definition of clinical features**

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| **Clinical Feature** | **Definition**  |
| Age at Onset (AAO) | Age at first registration in either of the registers |
| Number of recurrences | Total number of registrations in all registers except from the prescription register. Note that registrations within 90 days from the previous registration is not counted. |
| Source of ascertainment 1 (AUD) | Registration in the criminal registers, the medical registers or the prescriptions register. Here we used a hierarchy – (1) criminal, (2) medical, (3) prescription - for individuals with multiple registrations.Gr 1: N = 104,301 (28.9%)Gr2: N = 234,228 (64.9%)Gr3: N = 22,595 (6.3%) |
| Source of ascertainment medical registers (AUD) | For individuals with a DUD registration in the medical registers we used a hierarchy and categorized individuals into three groups; (1) at least one registration in the inpatient register, (2) registration in the specialist care, and (3) registration in primary care only.Gr 1: 203,509 (73.2%)Gr2: 46,314 (16.7%)Gr3: 28,221 (10.2%) |
| Medical Complications | 202,909 individuals with AUD defined as ICD10: F10, ICD9: 303, 305, ICD8: 303. 7.83% had a Medical Complication defined by ICD codes: ICD 8: 291, 980, 571.0; ICD9: V79B, 357F, 571A-D, 425F, 535D, 291, 980; ICD 10: E244, G312, G621, G721, I426, K292, K70, K852, K860, O354, T51 in the medical registers |
| Comorbidity with Major Depression | MD defined in table above. 99,648 (27.6%) had a lifetime registration of MD. |
| Comorbidity with Drug Use Disorder | DUD defined in table above. 84,380 (23.4%) had a lifetime registration of DUD. |
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**Table 4 - Correlation with the AUD FGRS used in this Manuscript with selected FGRS Missing Certain Features Used in the Final Calculation**

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|  | AUD FGRS |
| FGRS(a) - 1st degree relatives | 0.812 |
| FGRS(b) - no age correction | 0.806 |
| FGRS(c) - no cohabitation correction | 0.992 |
| FGRS(d) - no weighting for # relatives | 0.952 |
| FGRS(e) -std by YoB only | 0.992 |
| FGRS(f) - std by geography only | 0.969 |
| FGRS(g) - std only by entire sample | 0.962 |
| Std – standardized  |  |

Figure 1 - Stability of FGRS Scores for AUD by Geographical Region (North and South) within Sweden and Median split for Cohort (Old: 1932-1963 vs Young: 1964-1995)