Appendix

Table 1

The Definition of the Variables Used in this Study

|  |  |  |
| --- | --- | --- |
| Variable | Registers Used | Definition |
| Drug Abuse | The Swedish Hospital Discharge Register (national coverage 1987-2014 and partial coverage 1969-1986); The Outpatient Care Register (national coverage 2001-2014). The Swedish mortality RegisterThe Swedish Prescription Register containing all prescriptions in Sweden from 2005 to 2014Primary Care Registry (PCR), a research dataset including individual-level information such as diagnoses based on visits to primary health care centers from the following 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). The time periods differ because of the timing of digitalizing patient records. In 2016, these 15 counties (out of 21) contained 87% of the Swedish population. | DA 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 DA; 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). DA 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).  |
| Alcohol use Disorder | The Swedish Hospital Discharge RegisterThe Outpatient Care RegisterThe Primary Care Registry (PCR)The Swedish mortality RegisterThe Swedish Prescription Register | 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). |
| Major Depression | The Swedish Hospital Discharge RegisterThe Outpatient Care RegisterThe Primary Care Registry (PCR)The Swedish Prescription Register | Major depression was identified in the Hospital Discharge, Outpatient (Specialist) Care, and Primary Care Registers (PCR) by ICD code (ICD-8 codes 296.2, 298.0, and 300.4; ICD-9 codes 296.2, 296.4, 298.0, and 300.4; ICD-10 codes F32 and F33). As the PCR did not have national coverage we required that both fathers in a pair had to reside at least 8 years in a county that registered diagnoses in the PCR in order to include a MD-diagnose from the PCR. |
| ADHD | The Swedish Hospital Discharge RegisterThe Outpatient Care RegisterThe Primary Care Registry (PCR)The Swedish Prescription Register | ADHD was identified in the Hospital Discharge, Outpatient (Specialist) Care, and Primary Care Registers (PCR) by ICD code (ICD-8 codes 308,3; ICD-9 314; ICD-10 codes F90) and in the Swedish Prescription register by ATC codes N06BA04, N06BA09, N06BA01, N06BA02. |
| Conduct Disorder | The Swedish Hospital Discharge RegisterThe Outpatient Care RegisterThe Primary Care Registry (PCR)The Swedish Prescription Register | CD was identified in the Hospital Discharge, Outpatient (Specialist) Care, and Primary Care Registers (PCR) by ICD code (ICD-9 309D, 312W; ICD-10 codes F91 |
| Concussion | The Swedish Hospital Discharge RegisterThe Outpatient Care RegisterThe Primary Care Registry (PCR) | Concussion was identified in the Hospital Discharge, Outpatient (Specialist) Care, and Primary Care Registers (PCR) by ICD code (ICD-8 codes 850; ICD-9 850; ICD-10 codes S06) |
| School Achievement | The National School Registry (1988 to 2014) | The National School Registry contained educational achievement (a grade point average) for all students at the end of grade nine (usually at age 16). From 1988 to 1997 the score was expressed on a scale between 1 (lowest) and 5 (overall mean was 3.2). From 1998 and onwards the score was expressed on scale between 10 (lowest) and 320 (overall mean was 207). For each year and by gender we standardized the grade score into a Z-score with mean 0 and SD 1.  |
| Years of Education | The LISA Register (Integrated database for labor market research). 1990-2014 | Maximum number of years of education  |
| Pre-term birth | The Swedish Medical Birth Register (1973-2014). MBR has collected information about births in Sweden since 1973. It is compulsory for every healthcare provider to report to the MBR. Medical and other data on almost all (99%) births in Sweden are listed in the register, which also includes stillbirths | Measured in the Medical Birth Register. Prior to week 37 is defined as pre-term.  |
| Small for gestational age | The Swedish Medical Birth Register | Measured in the Medical Birth Register. Below the 10th percentile for the gestational age. |
| Birth weight | The Swedish Medical Birth Register | Measured in the Medical Birth Register. Measured in grams |
| Gestational age | The Swedish Medical Birth Register | Measured in the Medical Birth Register. Measured in weeks |
| Apgar-Score (1 minute) | The Swedish Medical Birth Register | Measured in the Medical Birth Register. Categorized into 2 groups; below 8 or 8-10.  |
| Birth length | The Swedish Medical Birth Register | Measured in the Medical Birth Register. Measured in cm |

APPENDIX

Table 2

Overlap of the four samples of Maternal Half siblings

S1: sibling pairs who each have lived in the same household as their shared biological mother for at least 15 years while growing up and have resided maximum 1 year in the same household with an affected (AUD/DA or MD) biological father.

S2: Identical to S1, with the exception that we required that the child was registered in the National School Registry.

S3: Identical to sample 1 with the exception that the child had to have the number of years of education registered in the Swedish registers.

S4: both siblings in the pair where registered in the Medical Birth Register. As the outcome variables were measured at birth we made no restrictions on the number of years the siblings had resided with their biological mother or biological father.



APPENDIX

Table 3

Sensitivity analysis of variables from the medical birth register for Maternal Half-Sibling Families with Fathers Discordant for Alcohol Use Disorder.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Outcome | Without control for smoking in Mother  | Controlled for smoking in Mother | Without control for residing with Biological Father  | Controlled for residing with Biological Father |
| Discordant Pairs | 4,801 | 4,801 | 6,983 | 6,983 |
| Pre-term‡ | 1.26(1.06; 1.49) | 1.26(1.07; 1.49) | 1.21(1.05; 1.39) | 1.21(1.05; 1.39) |
| Small for gestational age‡ | 0.85(0.66; 1.10) | 0.87(0.68; 1.13) | 0.86(0.71; 1.06) | 0.87(0.71; 1.06) |
| Apgar\_1 ‡ | 0.91(0.77; 1.08) | 0.91(0.78; 1.07) | 0.93(0.81; 1.06) | 0.92(0.81; 1.06) |
| Birth weight (grams)\*\* | -37.1(-55.0; -19.1) | -32.3(.50.2; -14.4) | -32.5(-47.4; -17.6) | -32.0(-46.9; -17.0) |
| Gestational age (weeks)\*\* | -0.09(-0.16; -0.02) | -0.09(-0.16; -0.02) | -0.08(-0.14; -0.02) | -0.08(-0.14; -0.02) |
| Birth Length (cm)\*\* | -0.13(-0.22; -0.05) | -0.11(-0.20; -0.03) | -0.12(-0.19; -0.05) | -0.12(-0.19; -0.05) |
| ‡ Stratified Logistic Regression Models, controlled for Maternal Age, Sex of child and Birth Order. Numbers are Odds Ratios and 95 % CIs\*\*Stratified Linear Regression Models, controlled for Maternal Age, Sex of child and Birth Order. Numbers are Beta Coefficients and 95 % CIs |

APPENDIX

Table 4

Sensitivity analysis of variables from the Medical Birth Register for Maternal Half-Sibling Families with Fathers Discordant for Drug Abuse.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Outcome | Without control for smoking in Mother  | Controlled for smoking in Mother | Without control for residing with Biological Father  | Controlled for residing with Biological Father |
| Discordant Pairs | 2,306 | 2,306 | 3,047 | 3,047 |
| Pre-term‡ | 1.36(1.07; 1.72) | 1.35(1.07; 1.71) | 1.28(1.05; 1.56) | 1.28(1.05; 1.56) |
| Small for gestational age‡ | 1.26(0.86; 1.84) | 1.24(0.85; 1.83) | 1.17(0.85; 1.60) | 1.17(0.85; 1.61) |
| Apgar\_1 ‡ | 1.13(0.89; 1.43) | 1.13(0.89; 1.43) | 1.20(0.98; 1.46) | 1.20(0.98; 1.46) |
| Birth weight (grams)\*\* | -45.1(-70.9; -19.3) | -41.9(-67.6; -16.2) | -46.7(-69.3; -24.1) | -46.7(-69.2; -24.1) |
| Gestational age (weeks)\*\* | -0.11(-0.21; -0.01) | -0.11(-0.21; -0.01) | -0.14(-0.23; -0.05) | -0.14(-0.23; -0.05) |
| Birth Length (cm)\*\* | -0.09(-0.21; 0.03) | -0.08(-0.20; 0.04) | -0.11(-0.22; -0.01) | -0.11(-0.22; -0.01) |
| ‡ Stratified Logistic Regression Models, controlled for Maternal Age, Sex of child and Birth Order. Numbers are Odds Ratios and 95 % CIs \*\*Stratified Linear Regression Models, controlled for Maternal Age, Sex of child and Birth Order. Numbers are Beta Coefficients and 95 % CIs |

APPENDIX

Table 5

Sensitivity analysis of variables from the medical birth register for Maternal Half-Sibling Families with Fathers Discordant for Major Depression

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Outcome | Without control for smoking in Mother  | Controlled for smoking in Mother | Without control for residing with Biological Father  | Controlled for residing with Biological Father |
| Discordant Pairs | 2,873 | 2,873 | 4,162 | 4,162 |
| Pre-term‡ | 1.14(0.92; 1.40) | 1.13(0.92; 1.40) | 1.10(0.92; 1.31) | 1.10(0.92; 1.30) |
| Small for gestational age‡ | 0.81(0.58; 1.13) | 0.86(0.61; 1.21) | 0.88(0.68; 1.15) | 0.88(0.67; 1.15) |
| Apgar\_1 ‡ | 0.85(0.69; 1.05) | 0.85(0.69; 1.05) | 0.93(0.79; 1.11) | 0.93(0.78; 1.11) |
| Birth weight (grams)\*\* | -22.0(-45-0; 1.12) | -20.0(-43.1; 3.0) | -24.4(-43.7; -5.1) | -24.2(-43.5; -4.9) |
| Gestational age (weeks)\*\* | -0.12(-0.21; -0.03) | -0.12(-0.21; -0.03) | -0.11(-0.19; -0.04) | -0.11(-0.19; -0.04) |
| Birth Length (cm)\*\* | -0.02(-0.13; 0.08) | -0.02(-0.12; 0.09) | -0.09(-0.18; 0.00) | -0.09(-0.18; 0.00) |
| ‡ Stratified Logistic Regression Models, controlled for Maternal Age, Sex of child and Birth Order. Numbers are Odds Ratios and 95 % CIs \*\*Stratified Linear Regression Models, controlled for Maternal Age, Sex of child and Birth Order. Numbers are Beta Coefficients and 95 % CIs |

APPENDIX 6

Sensitivity analysis of Assumptions of our Maternal Half-Sibling Family Model in Sample 1

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Outcome | Results in Main Sample (from Table 2) | Age Difference <=4 years | Affected Father Residing in Same Neighborhood ≤ 1 year | ≤ 1 year in same household in both biological fathers\* | Elimination of Fathers with Registration In 3 Year Period Centered on Conception of Child  |
|  |  | **Alcohol Use Disorder in Biological Father** |
| ***SAMPLE 1 (N Pairs)*** | 15,274 | 6,373 | 12,770 | 15,274 | 14,552 |
| AUD in Child† | 1.72 (1.61; 1.84) | 1.76 (1.60; 1.95) | 1.71 (1.59; 1.84) | 1.65 (1.54; 1.79) | 1.70 (1.59; 1.81) |
|  |  | **Drug Abuse in Biological Father** |
| ***SAMPLE 1 (N Pairs)*** | 4,800 | 2,076 | 4,044 | 4,800 | 4,653 |
| DA in Child† | 1.55 (1.41; 1.70) | 1.34 (1.17; 1.53) | 1.56 (1.41; 1.73) | 1.59 (1.42; 1.78) | 1.53 (1.40; 1.68) |
|  |  | **Major Depression in Biological Father** |
| ***SAMPLE 1 (N Pairs)*** | 6,331 | 2,587 | 5,302 | -- | - |
| MD in Child † | 1.51 (1.40; 1.64) | 1.41 (1.26; 1.59) | 1.50 (1.37; 1.63) | No change | - |
| †Stratified Cox Regression Models, controlled for Year of Birth of Child and Sex of Child. Numbers are Hazard Ratios and 95 % CIs\*These results are derived from fitting an interaction model with the entire sample for years of cohabitation with unaffected father and then estimating the magnitude of transmission in the offspring of the affected vs. unaffected father when the unaffected father resided with the family for ≤ 1 year. No significant interaction was found with MD so results would be the same as those presented in table 2.  |

Table 7

Testing, using the same models as in Table 2, for an Interaction between Sex of Half-Siblings Child and Disorder in Discordant Biological Fathers

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Outcome |  | **Alcohol Use Disorder in Biological Father** | **Drug Abuse in Biological Father** | **Major Depression in Biological Father** |
| AUD in Child† | Male Child | 1.82 (1.68; 1.98) | 1.51 (1.32; 1.73) | 1.09 (0.96; 1.24) |
| Female Child | 1.57 (1.42; 1.74) | 1.87 (1.60; 2.19) | 1.39 (1.18; 1.63) |
| Diff (P-value) | 0.023 | 0.039 | 0.025 |
| DA in Child† | Male Child | 1.58 (1.46; 1.71) | 1.62 (1.43; 1.83) | 1.15 (1.02; 1.29) |
| Female Child | 1.41 (1.29; 1.56) | 1.45 (1.27; 1.67) | 1.15 (0.99; 1.34) |
| Diff (P-value) | 0.076 | 0.238 | 0.952 |
| MD in Child † | Male Child | 1.41 (1.30; 1.53) | 1.43 (1.26; 1.63) | 1.54 (1.37; 1.72) |
| Female Child | 1.23 (1.15; 1.33) | 1.24 (1.10; 1.39) | 1.50 (1.35; 1.66) |
| Diff (P-value) | 0.012 | 0.092 | 0.749 |
|  |  |  |  |  |

Table 8

Table 3 from Main Manuscript Eliminating the Control for Number of Years in the Same Household as the Affected Father

|  |  |  |  |
| --- | --- | --- | --- |
| Outcome | **Alcohol Use Disorder in Biological Father** | **Drug Abuse in Biological Father** | **Major Depression in Biological Father** |
| ***SAMPLE 1*** | N Pairs: 23,830 | N Pairs: 13,664 | N Pairs: 11,321 |
| AUD in Child† | 1.63 (1.54; 1.72) | 1.60(1.46; 1.75) | 1.22(1.13, 1.31) |
| DA in Child† | 1.48(1.41; 1.56) | 1.60(1.47; 1.73) | 1.16(1.08; 1.25) |
| MD in Child † | 1.26(1.21; 1.32) | 1.32(1.22; 1.43) | 1.39 (1.31; 1.47) |
| †Stratified Cox Regression Models, controlled for Year of Birth of Child, Sex of Child. Numbers are Hazard Ratios and 95 % CIs |