Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix 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/*

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 (2009-2018), Värmland (2005-2018), Kalmar (2007-2018), Sörmland (1997-2018), Uppsala (2005-2018), Västernorrland (2008-2018), Norrbotten (2009-2018), Gävleborg (2010-2018), Halland (2007-2018), Jönköping (2008-2018), Kronoberg (2006-2018), Skåne (1998-2018), Östergötland (1997-2018), Stockholm (2003-2018), and Västergötland (2000-2018). 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).*

eTable 1

Definition of phenotypes

	Registers Used	Definition
Major Depression (MD)	The Swedish Hospital Discharge Register (coverage 1973-2018); Outpatient Care Register (national coverage 2001-2018); Primary Care Registry (Partly coverage from 1999-2018)	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 BD were excluded.
Psychotic MD	The Swedish Hospital Discharge Register (coverage 1973-2018); Outpatient Care Register (national coverage 2001-2018); Primary Care Registry (Partly coverage from 1999-2018)	ICD-10: F323, F333. **Note**: all individuals with at least one registration for either SAD or SZ are excluded
Non-Psychotic MD	The Swedish Hospital Discharge Register (coverage 1973-2018); Outpatient Care Register (national coverage 2001-2018); Primary Care Registry (Partly coverage from 1999-2018)	ICD-8: 296.2, 298.0, 300.4; ICD-9: 296.2, 296.4, 298.0, 300.4; ICD-10: F32, F33 (excluding F323, F333) **Note**: all individuals with at least one registration for Psychotic MD are excluded
Bipolar Disorder (BD)	The Swedish Hospital Discharge Register (coverage 1973-2018); Outpatient Care Register (national coverage 2001-2018); Primary Care Registry (Partly coverage from 1999-2018)	ICD-8: 296.1, 296.3, 296.8, 296.9, 298.1; ICD-9: 296A, 296C, 296D, 296E, 296W, 298B; ICD-10: F30, F31
Psychotic BD	The Swedish Hospital Discharge Register (coverage 1973-2018); Outpatient Care Register (national coverage 2001-2018); Primary Care Registry (Partly coverage from 1999-2018)	ICD-10: F312, F315, F302. **Note**: all individuals with at least one registration for either SAD or SZ are excluded
Non-Psychotic BD	Register (coverage 1973-2018); Outpatient Care Register (national coverage 2001-2018); Primary Care Registry (Partly coverage from 1999-2018)	ICD-8: 296.1, 296.3, 296.8, 296.9, 298.1; ICD-9: 296A, 296C, 296D, 296E, 296W, 298B; ICD-10: F30, F31 (excluding F312, F315, F302) **Note**: all individuals with at least one registration for Psychotic BD are excluded
Anxiety Disorder (AD)	The Swedish Hospital Discharge Register (coverage 1973-2018); Outpatient Care Register (national coverage 2001-2018); Primary Care Registry (Partly coverage from 1999-2018)	ICD-8: 300.0, 300.2 ; ICD-9: 300A, 300C; ICD-10: F40, F41
Obsessive-Compulsive Disorder [OCD]	The Swedish Hospital Discharge Register (coverage 1973-2018); Outpatient Care Register (national coverage 2001-2018); Primary Care Registry (Partly coverage from 1999-2018)	ICD-9: 300D; ICD-10: F42
Schizophrenia (SZ)	The Swedish Hospital Discharge Register (coverage 1973-2018); Outpatient Care Register (national coverage 2001-2018); Primary Care Registry (Partly coverage from 1999-2018)	ICD-8: 295.1, 295.2, 2953, 295.9, 295.6; ICD-9: 295B, 295C, 295D, 295G, 295X; ICD-10: F200, F201, F202, F203, F205, F209. **Note**: we use a hierarchy for diagnoses of SZ and SAD (see table below)
Schizoaffective Disorder (SAD)	The Swedish Hospital Discharge Register (coverage 1973-2018); Outpatient Care Register	ICD -10: F25. **Note**: we use a hierarchy for diagnoses of SZ and SAD (see table below)

	(national coverage 2001-2018); Primary Care Registry (Partly coverage from 1999-2018)	
Other Non-affective psychosis (ONAP)	The Swedish Hospital Discharge Register (coverage 1973-2018); Outpatient Care Register (national coverage 2001-2018); Primary Care Registry (Partly coverage from 1999-2018)	ICD-8: 297, 298.3, 298.9, 295.4, 295.7; ICD-9: 298E, 298W, 298X, 295E, 295H, 295W; ICD-10: F22, F23, F24, F25, F26, F27, F28, F29, F208. **Note:** all individuals with at least one registration for SAD are excluded

eTable 2

Decision table for registrations of SAD and SZ

		Number of lifetime SZ diagnoses in the registers				
		1 (Group 1)	2 (Group 2)	3-5 (Group 3)	6-10 (Group 4)	More than 10 (Group 5)
Number of lifetime SAD diagnoses in the registers	1 (Group 1)	Last diagnosis	Last diagnosis	Most common diagnosis	Most common diagnosis	Most common diagnosis
	2 (Group 2)	Last diagnosis	Majority of last 3 diagnoses	Majority of last 3 diagnoses	Most common diagnosis	Most common diagnosis
	3-5 (Group 3)	Most common diagnosis	Majority of last 3 diagnoses	Majority of last 3 diagnoses	Majority of last 3 diagnoses	Majority of last 5 diagnoses
	6-10 (Group 4)	Most common diagnosis	Most common diagnosis	Majority of last 3 diagnoses	Majority of last 5 diagnoses	Majority of last 5 diagnoses
	More than 10 (Group 5)	Most common diagnosis	Most common diagnosis	Majority of last 5 diagnoses	Majority of last 5 diagnoses	Majority of last 5 diagnoses

eAppendix 2

Calculation of the Familial Genetic Risk Score (FGRS)

The dataset for the calculations includes:
Column1 = Identification number of the proband (Born 1960-1990)
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 proband
Column4 = Year of Birth of relative
Column5 = Sex of relative
Column6 = Age at registration for trait
Column7 = Age at end of follow-up (2018-12-31 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 disorders:

	Parent/Children	Siblings
MD	.90	.89
BD	.67	.77

Step 4: Calculate the product for each relative using the four components:

i) Z-score (reflecting sex and year of birth adjusted rates)
ii) Weight (reflecting the proportion of risk period they had completed)
iii) Cohabitation effects
iv) 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.

(A) the variance of the z-score of the disorder across all relatives,
(B) the variance in the mean z-score across all probands,
(C) 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.

eAppendix 3

Simulation Methods

To get realistic (Swedish population-like) simulations, after unsuccessful attempts to utilize the *R* pedigree simulating packages *pedSimulate* and *synbreed,* we implemented a de-novo pedigree simulation using Julia script because of its greater speed. For increased generality, the script was built to have numerous adjustable parameters:

1) Additive heritability of the trait [setting for this manuscript (SFTM) h^2= {20%, 40%, 60%, 80%}],
2) variance of siblings' trait that is explained by the common or shared environment (SFTM c^2= {2.5%, 5%, 10%, 20%}) which was applied only for full siblings,
3) k=number of generations (SFTM: k=5, i.e., founder generation gen=0 and gen=1- 4 for subsequent generations),
4) vector of average number of children per couple in generations 0 to k-2 (SFTM: μ ={2.1, 2.2, 1.7, 1.7}, as estimated from Swedish registries assuming average generation time is 25 years),
5) number of founders (SFTM: n=500K),
6) number of independent breeding groups (SFTM m=500, rather similar to villages),
7) (to avoid inbreeding) number of subgroups=k-1 for mothers in a subgroup to breed circularly with fathers from the next subgroup. (Children inherit the subgroup of mothers.)

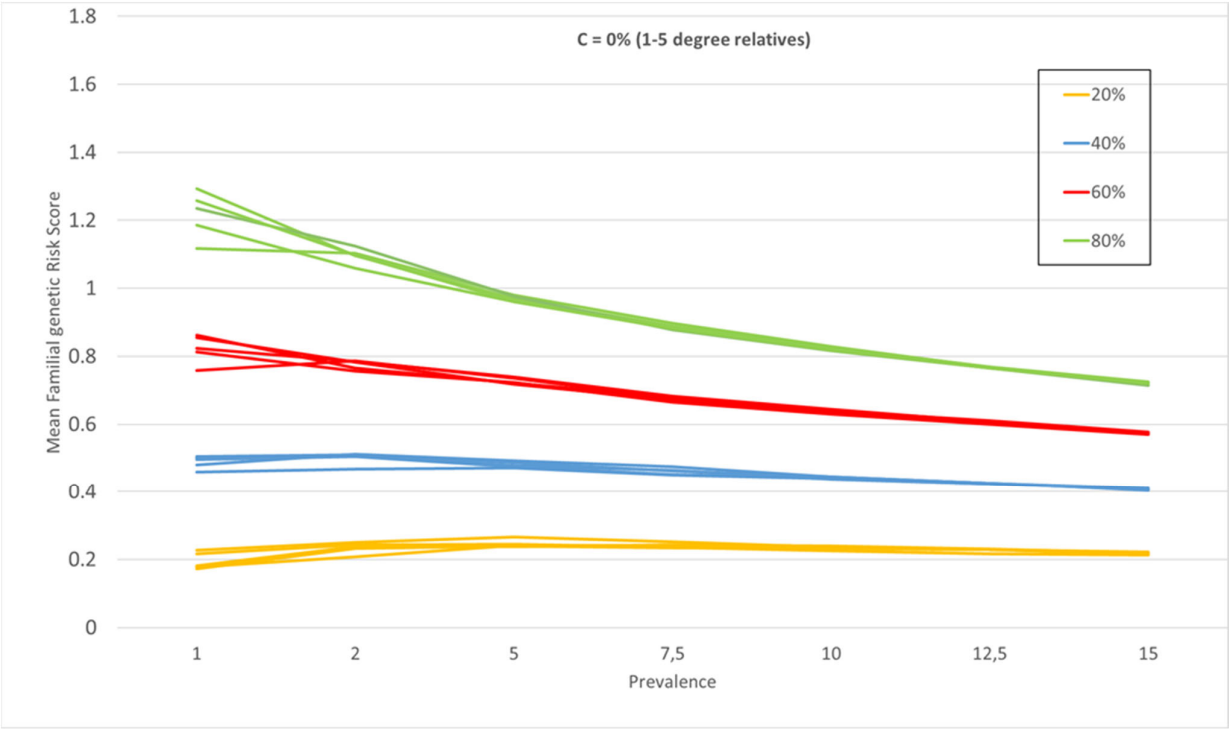
The theoretical algorithm simulations were as follows:

1) Simulate independent True Breeding Values (TBV) for founder generation (gen=0), i.e. $TBV_j = \sqrt{h^2} * Z_j$, where Z_j are independent standard normal (Gaussian) variates (j=1,…n),
2) For subsequent generations (gen=i>0)
    a. Within each group
        i. Permute mothers from one subgroups and fathers from the next,
        ii. Pair mothers and fathers with the same rank,
        iii. For each pair, simulate number of sibs m~ Poisson (μ_i),
        iv. If m>0, within each sibship
            1. Simulate sib's j TBV_j as the sum of parent' average and mendelian sampling, i.e., sib $TBV_j = \frac{TBV_{mother}+TBV_{father}}{2} + \sqrt{\frac{h^2}{2}}\, Z_j$, where Z_j are independent standard normal (Gaussian) variates (j=1,…m),
            2. Simulate the common environment for all sibs within family as, $C = \sqrt{c^2}\ Z$, with Z a single Gaussian variant for entire sibship,
            3. Simulate the independent environment for each sib within family as, $E_j = \sqrt{1 - h^2 - c^2}\, Z_j$, where Z_j are independent standard normal (Gaussian) variates (j=1,…m),
            4. Compute liability for each sib as $L_j = TBV_j + C + E_j$
            5. Compute the affected status for each sib using the liability using a liability threshold model (for computational efficiency, computing affected status for multiple prevalences in a single pass).

Our simulations contained a mean (SD) of 324,656 (1,105) probands, each proband having a mean number of 3.7 (SD: 1.3) 1st degree relatives, 7.4 (SD: 1.8) 2nd degree relatives, 13.7 (SD: 4.3) 3rd degree relatives, and 23.3 (5.2) 4th degree relatives for a total mean number of relatives: 48.1 (SD:8.7).

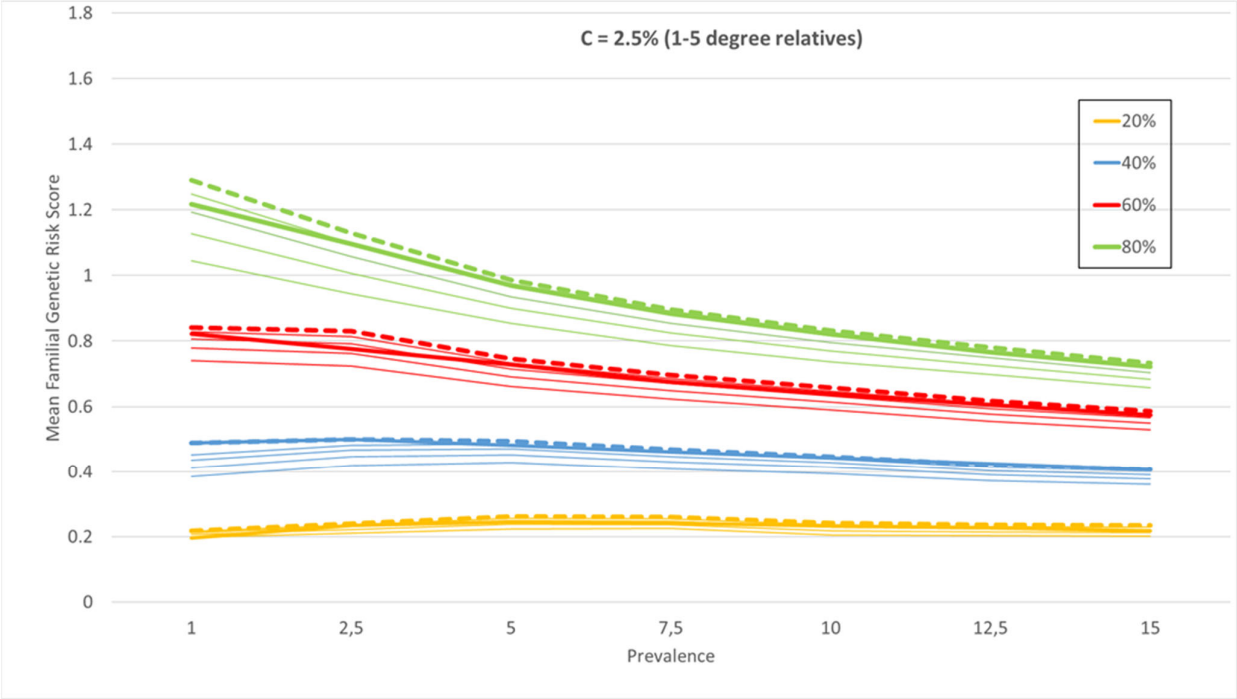
eFigure 1. Results of Simulations of Pedigrees Containing 1st-5th Degree Relatives Analyzed by FGRS as a Function of Heritability and Prevalence

(For eFigures 1-4 – see above for simulation methods.)

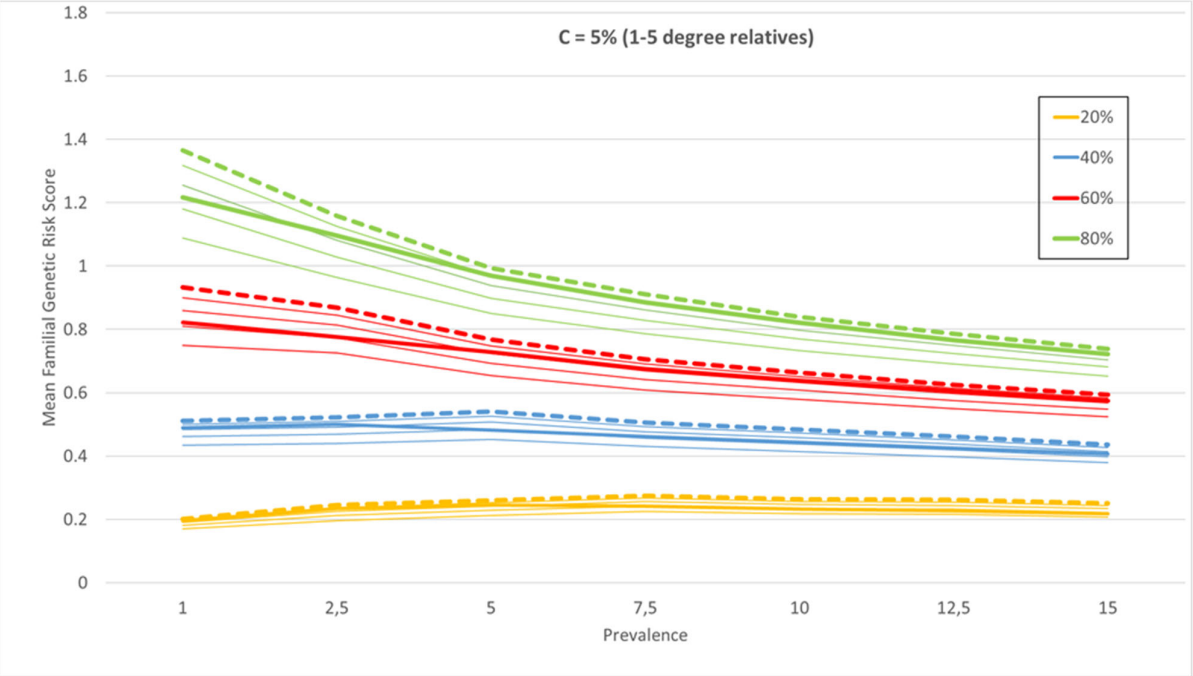


eFigure 2

We included in our simulations estimates of shared environment for siblings with c2 equal to, respectively, 2.5, 5 and 10%. The thick colored lines are the estimates with the addition of the shared environment. The dotted lines are those calculated with the c2 parameter added. We then correct for that sibling effect with 4 values of ”down-weighting”: 0.8, 0.6, 0.4, 0.2, which are represented by the thinner lines in the figures. The down-weighting values used in this paper are seen above in table 4 step 3.



eFigure 3



eFigure 4