Supplementary Online Content

Kendler KS, Ohlsson H, Sundquist J, Sundquist K. Family genetic risk scores and the genetic architecture of major affective and psychotic disorders in a Swedish national sample. *JAMA Psychiatr*. Published online April 21, 2021. doi:10.1001/jamapsychiatry.2021.0336

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

eMethods 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 (2009-2016), 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).*

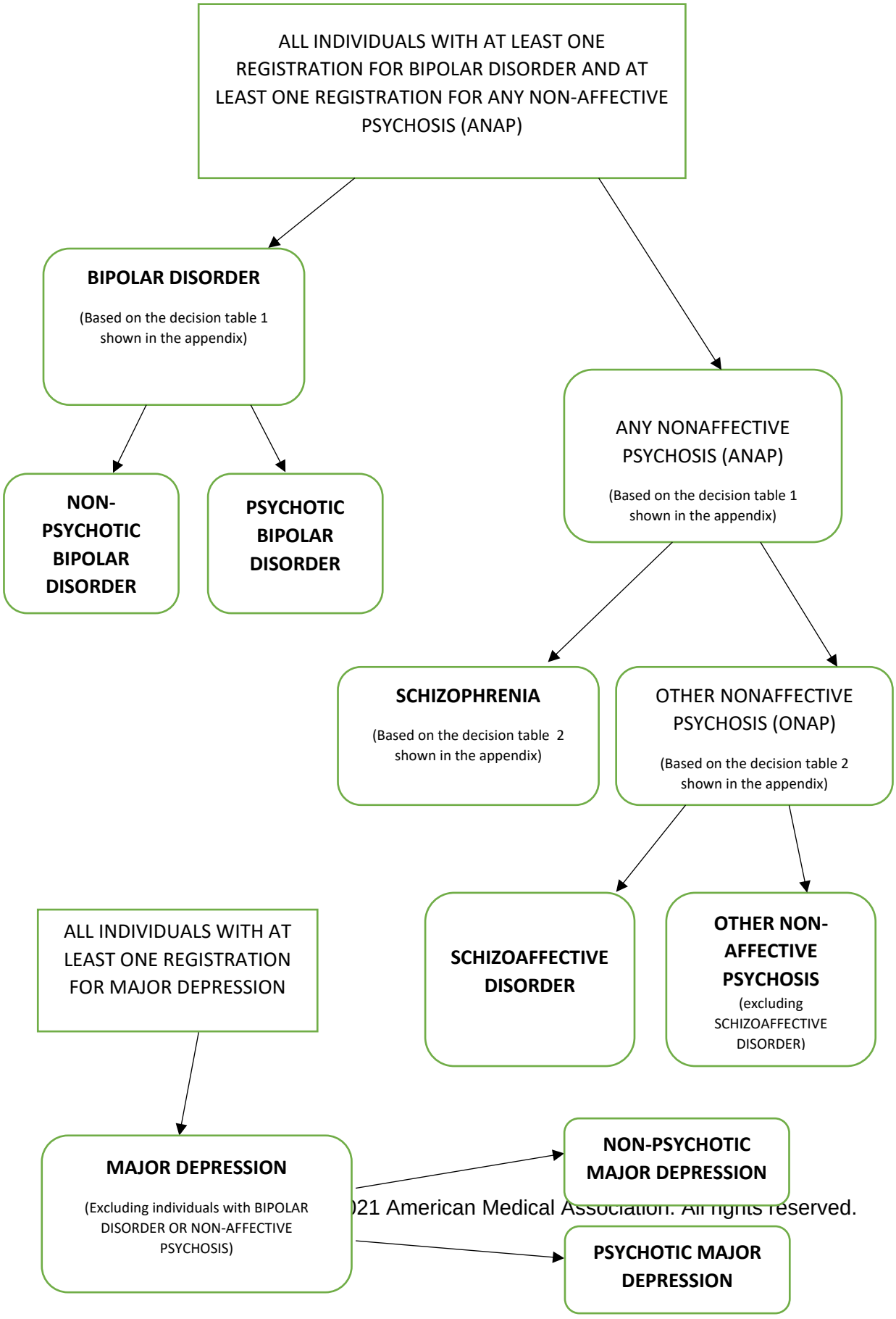
eTable 1. Definition of Phenotypes

The following ICD codes were used to define the traits:

	ICD codes
Major Depression (MD)	ICD-8: 296.2, 298.0, 300.4; ICD-9: 296.2, 296.4, 298.0, 300.4; ICD-10: F32, F33.
Psychotic form of MD	ICD-10: F32.3, F33.3
Non-Psychotic form of MD	ICD-8: 296.2, 298.0, 300.4; ICD-9: 296.2, 296.4, 298.0, 300.4; ICD-10: F32, F33, excluding those used to define Psychotic form of MD
Bipolar Disorder (BD)	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 form of BD	ICD-10: F30.2, F31.2, F31.5
Non-Psychotic form of BD	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 those used to define Psychotic form of BD
Other Non-affective psychosis (ONAP)	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
Schizophrenia (SZ)	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
Non-affective psychosis (ANAP)	ONAP + SZ
Schizoaffective Disorder (SAD)	ICD -10: F25

eFigure 1. **Diagnostic Hierarchy**

We used a hierarchy based on the number of diagnosis in the registers, so that an individual could only be considered as registered with either BP, ONAP, SZ, SAD or MD in our analyses (see flow-chart for a description of the categorization process).



In the first step, we separated individuals who had both registrations for BD and for any nonaffective psychosis (ANAP). The table below illustrates how individuals were categorized as registered either for BP or for ANAP.

eTable 2. First Decision Table

		Number of lifetime ANAP diagnoses in the registers				
		1 (Group 1)	2 (Group 2)	3-5 (Group 3)	6-10 (Group 4)	> 10 (Group 5)
Number of lifetime BP 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
	> 10 (Group 5)	Most common diagnosis	Most common diagnosis	Majority of last 5 diagnoses	Majority of last 5 diagnoses	Majority of last 5 diagnoses

We then applied the same algorithm to categorize individuals as registered either for other nonaffective psychosis (ONAP) or for SZ as outlined in decision table 2.

eTable 3. Second Decision Table						
		Number of lifetime Schizophrenia 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 ONAP 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

To separate out individuals with SAD, we required at least one registration for SAD among individuals registered with ONAP. Finally, individuals registered with MD could not have a registration for BP or ANAP. To separate out individuals with Psychotic form of MD/BP we only required one lifetime registration of Psychotic form of MD/BP.

eMethods 2. Sensitivity Analyses for Diagnostic Hierarchy

Below, we present several sensitivity analyses:

1) *The genetic risk score in different groups based on the algorithm to separate individuals with BD and ANAP*. table 4 show the individuals we categorized as BD. The left column shows the difference between the categorization from the table above (i.e., 5 steps means that the individual had more than 10 registrations for BD (group 5) and no registrations for ANAP (group 0), 4 steps included two combinations: a) More than 10 registrations for BD and 1 registration for ANAP or b) 6-10 registrations for BD and 0 registrations for ANAP. 3, 2, 1 and 0 steps include several combinations each. As seen, the BP FGRS decreases the smaller differences (i.e., cases that we define as BD instead of ANAP despite rather similar registration pattern) while the SZ/MD FGRS are rather stable. *This suggest that if we deleted the group with least separation to be "conservative" (0 steps and 1 step), we would discriminate BD and SZ even more strongly than with the analyses presented in our paper.*

eTable 4. Sensitivity Analysis for Separating Individuals with BD and ONAP				
Difference	% of individuals	Mean MD FGRS (95% CIs)	Mean BD FGRS (95% CIs)	Mean SZ FGRS (95% CIs)
5 steps	26%	0.37 (0.34; 0.39)	0.85 (0.81; 0.90)	0.10 (0.08; 0.13)
4 steps	16%	0.37 (0.34; 0.40)	0.75 (0.70; 0.81)	0.11 (0.08; 0.15)
3 steps	18%	0.38 (0.35; 0.41)	0.55 (0.51; 0.60)	0.12 (0.09; 0.16)
2 steps	12%	0.33 (0.29; 0.36)	0.52 (0.47; 0.58)	0.15 (0.10; 0.19)
1 step	26%	0.30 (0.28; 0.32)	0.36 (0.33; 0.39)	0.09 (0.06; 0.12)
0 steps	2%	0.20 (0.12; 0.29)	0.65 (0.49; 0.80)	0.41 (0.25; 0.56)

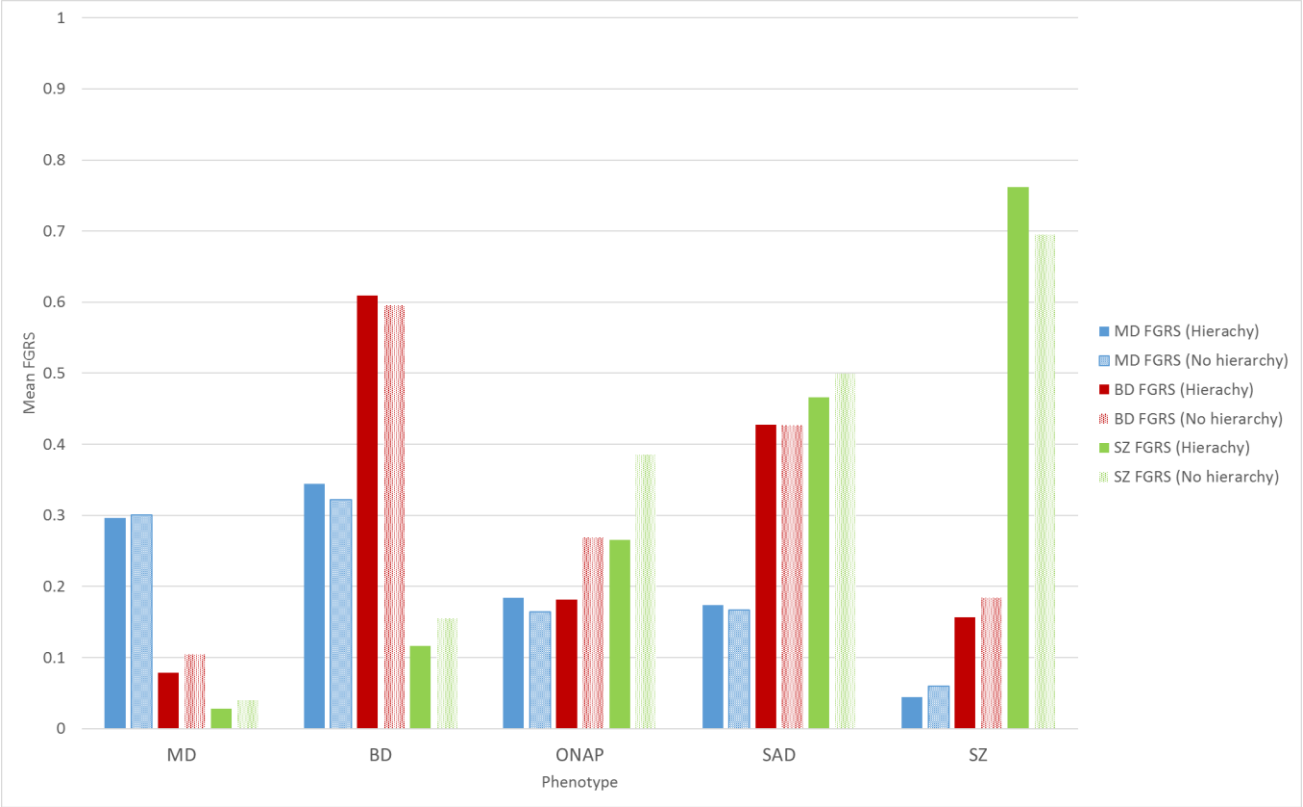
2) *The genetic risk score in different groups based on the algorithm to separate individuals with SZ and ONAP*. Table 5 show the individuals we categorized as SZ. The left column shows the difference between the categorization from the table above (i.e., 5 steps means that the individual had more than 10 registrations for SZ (group 5) and no registrations for ONAP (group 0), 4 steps included two combinations: a) More than 10 registrations for SZ and 1 registration for ONAP or b) 6-10 registrations for SZ and 0 registrations for ONAP. 3, 2, 1 and 0 steps include several combinations each. As seen, the SZ FGRS decreases the smaller differences (i.e., cases that we define as SZ instead of ONAP despite rather similar registration pattern) while the BP FGRS are rather stable. This suggest that, as above, if we deleted the group with least separation (0 steps and 1 step) to be "conservative", we would discriminate SZ more strongly from MD and BP than with the analyses presented in our paper.

eTable 5. Sensitivity Analysis for Separating Individuals with SZ and ONAP				
Difference	% of individuals	MD FGRS	BP FGRS	SZ FGRS
5 steps	21%	0.01 (-0.03; 0.05)	0.14 (0.09; 0.19)	0.89 (0.76; 1.01)
4 steps	15%	-0.02 (-0.06; 0.02)	0.12 (0.07; 0.18)	0.85 (0.71; 0.98)
3 steps	13%	0.05 (0.00; 0.10)	0.15 (0.09; 0.21)	0.74 (0.60; 0.87)
2 steps	16%	0.07 (0.03; 0.12)	0.17 (0.11; 0.22)	0.82 (0.69; 0.95)
1 step	23%	0.07 (0.03; 0.11)	0.18 (0.13; 0.23)	0.58 (0.48; 0.67)
0 steps	12%	0.09 (0.04; 0.14)	0.18 (0.11; 0.25)	0.73 (0.59; 0.87)

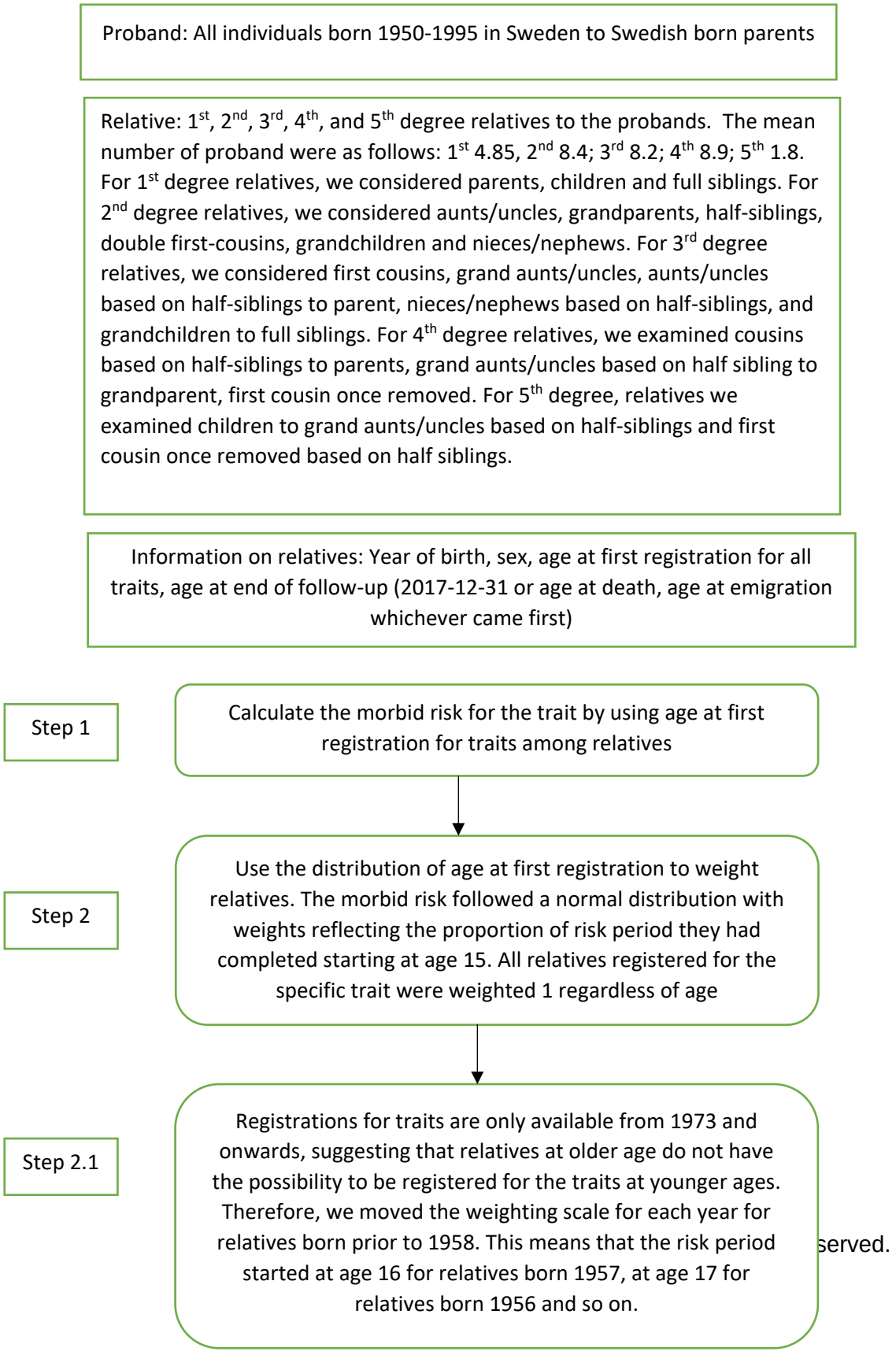
3) In figure 2 below, we show the mean FGRSs comparing the results using the hierarchy we employ in the manuscript and the mean FGRSs *without any diagnostic hierarchy* so that any individual could be registered for several of the different disorders depending on the number of different diagnoses they have in the registries. Note that the differences are relatively modest. Interestingly, for the mean MD FGRS scores for MD and mean BD FGRS scores for BD

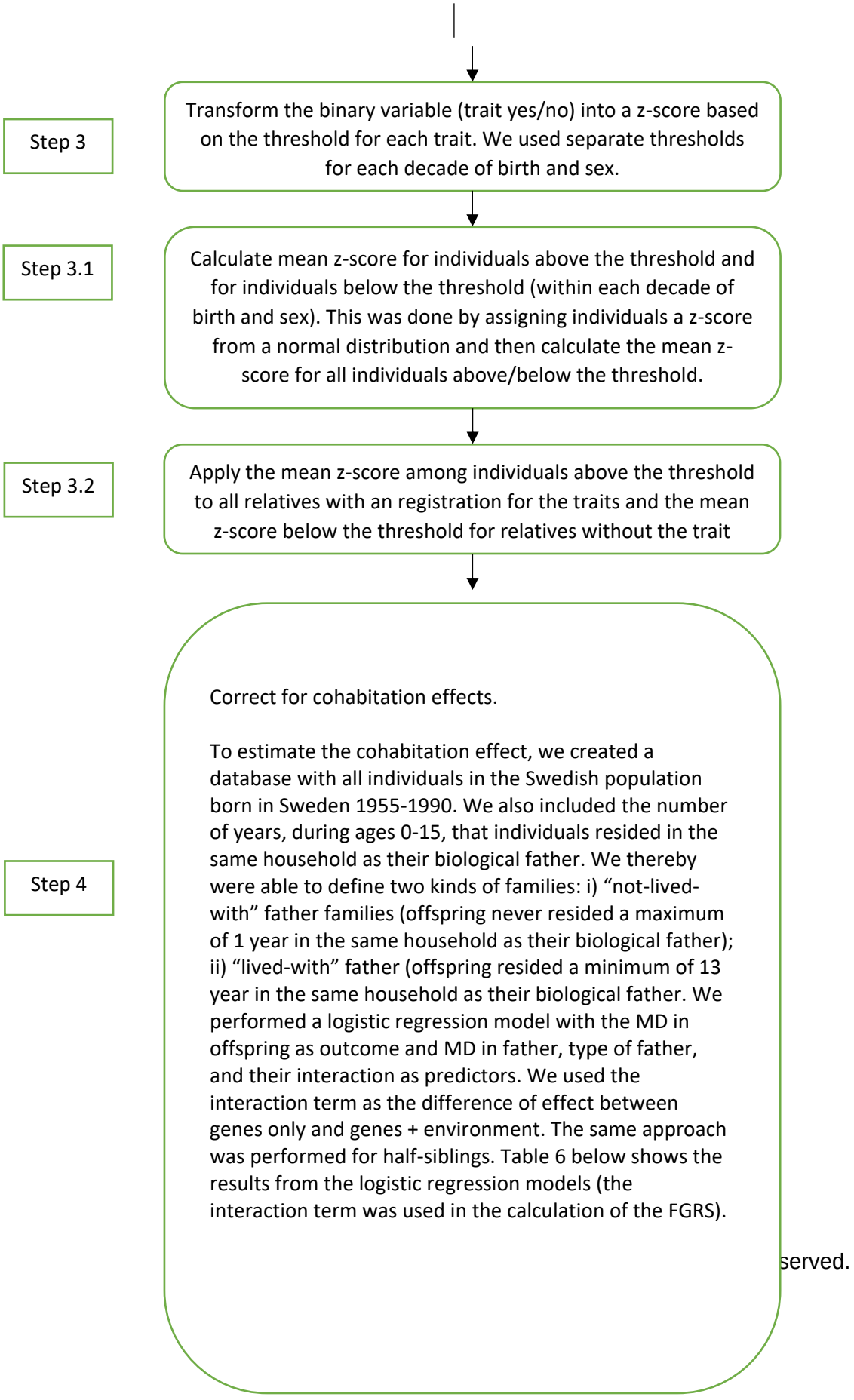
barely change while the SZ FGRS score for SZ declines modestly when the hierarchy is eliminated. The biggest change is that the SZ FGRS in ONAP cases is a fair bit higher in those diagnosed without versus with a hierarchy.

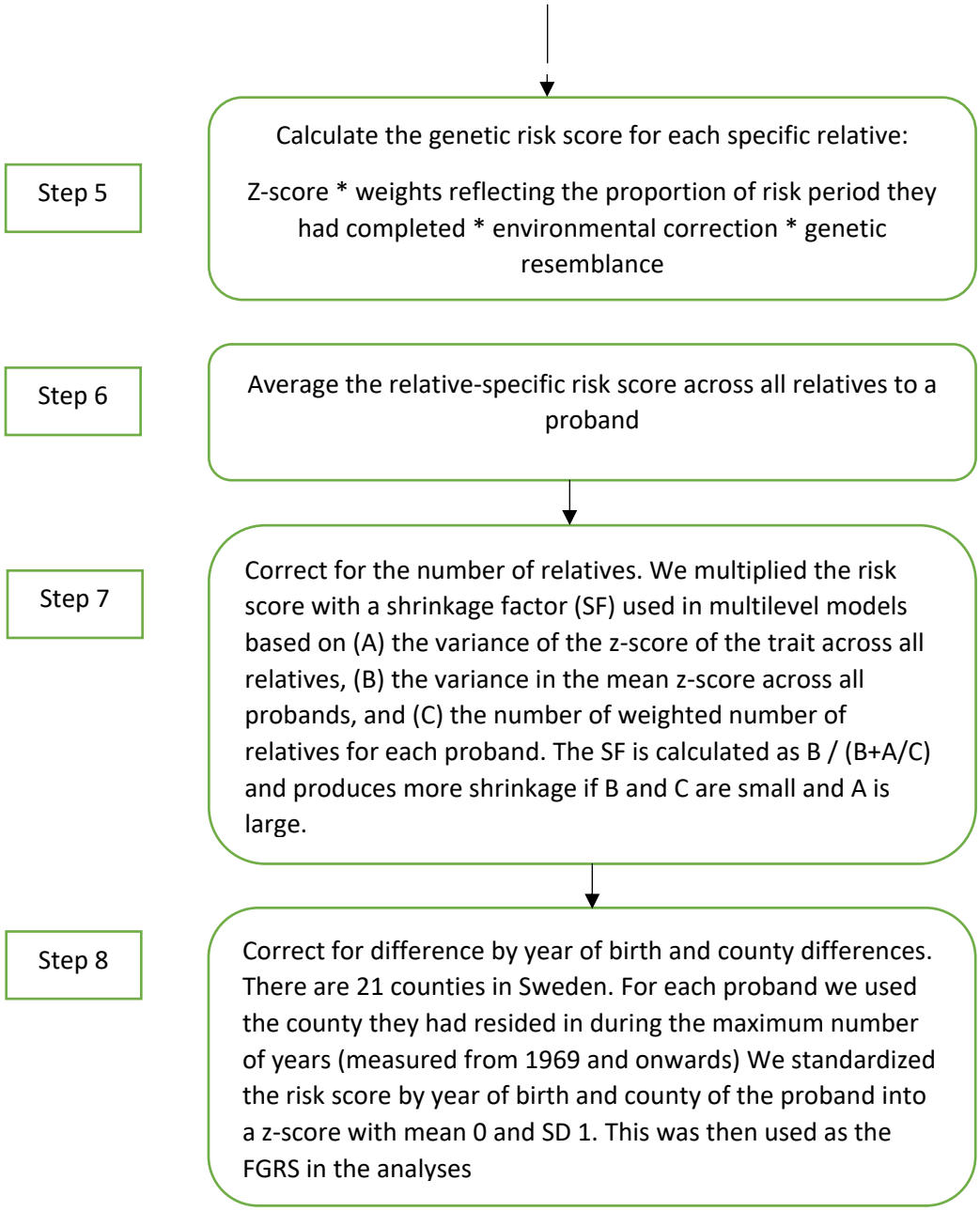
eFigure 2. FGRS Results Depicted in Figure 1 With and Without Diagnostic Hierarchies



eFigure 3. Flowchart for the Calculation of the Family Genetic Risk Score (FGRS)




Step 3
Transform the binary variable (trait yes/no) into a z-score based on the threshold for each trait. We used separate thresholds for each decade of birth and sex.
Step 3.1
Calculate mean z-score for individuals above the threshold and for individuals below the threshold (within each decade of birth and sex). This was done by assigning individuals a z-score from a normal distribution and then calculate the mean z-score for all individuals above/below the threshold.
Step 3.2
Apply the mean z-score among individuals above the threshold to all relatives with an registration for the traits and the mean z-score below the threshold for relatives without the trait
Step 4
Correct for cohabitation effects.
To estimate the cohabitation effect, 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 a maximum of 1 year in the same household 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 MD in offspring as outcome and MD 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. Table 6 below shows the results from the logistic regression models (the interaction term was used in the calculation of the FGRS).



eTable 6. Results From the Logistic Regression Models for the Cohabitation Effects

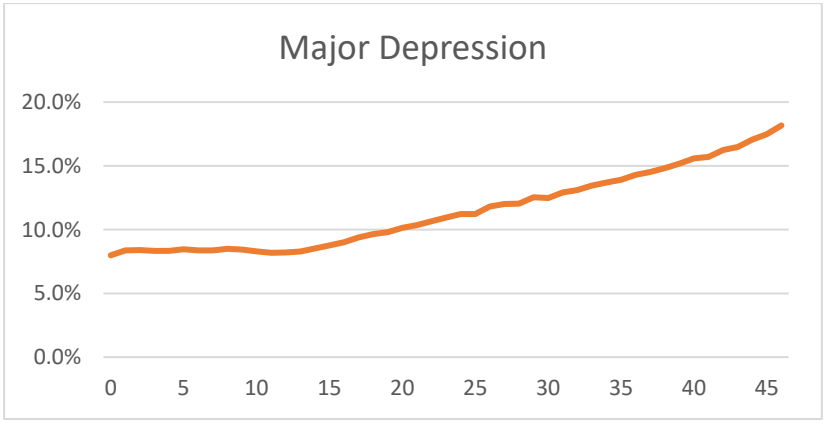
	MD	BD	SZ
PARENTS			
Registration in Parents	1.74 (1.72;1.76)	5.57 (5.17; 6.00)	7.35 (5.84; 9.25)
Not resided in the same household vs resided in the same household	1.40 (1.38; 1.41)	1.48 (1.44; 1.53)	1.83 (1.75; 1.90)
Interaction term	0.93 (0.91; 0.96)	0.76 (0.64; 0.89)	0.66 (0.48; 0.90)
SIBLINGS			
Registration in half-sibling	1.42 (1.39; 1.45)	2.29 (1.95; 2.70)	3.51 (2.59; 4.76)
Not resided in the same household vs resided in the same household	1.02 (1.01; 1.04)	1.04 (1.01; 1.07)	1.08 (1.03; 1.14)
Interaction term	0.86 (0.84; 0.88)	0.80 (0.67; 0.97)	0.60 (0.42; 0.87)

eMethods 3. Sensitivity Analysis for the Genetic Risk Score

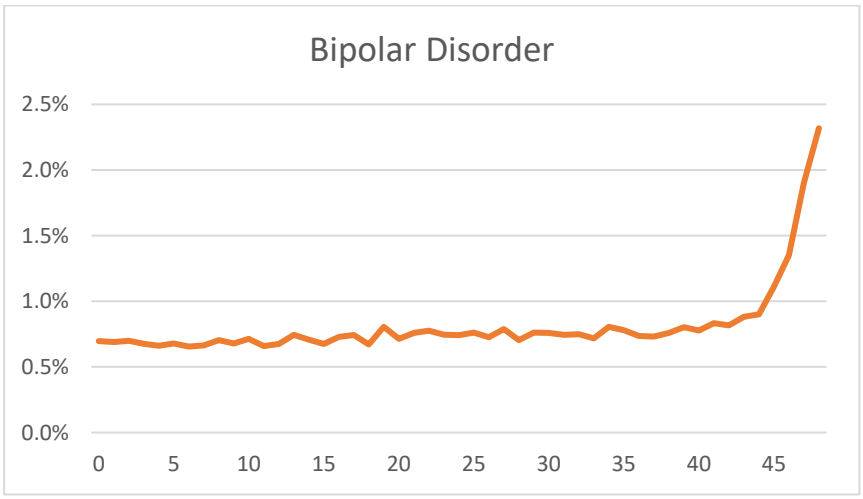
We performed several sensitivity analyses for the calculation of the genetic risk score. Briefly, we aim to show what each step in the original calculation contributes. In table 7 below we present the main results with the 7 additional FGRSs. FGRS(a) included 1st degree relatives only; FGRS(b) applied no age correction so that all relatives were weighted the same regardless of age; FGRS(c) applied no correction for cohabitation effects (i.e., first degree relatives were not down-weighted due to the fact that they resided in the same household as the proband), FGRS(d) applied no shrinking using the shrinkage factor (i.e., families with few relatives were not down-weighted), FGRS(e) final standardization only by year of birth, FGRS(f) final standardization only by county of residence FGRS(g) final standardization without take year of birth and county of residence into account. In table 7 below, we also present the correlation between the FGRS we present in the manuscript and the seven different FGRSs as well as the Area Under the Curve (AUC - an aggregated metric that evaluates how well the logistic regression model classifies positive and negative outcomes at all possible cutoffs). The AUC is measured within each disorder, so MD FGRS predicts MD, BD FGRS predict BD, and SZ FGRS predict SZ. Finally, we present in figures 3-5 the rates of MD in 50 equaled sized groups of the MD FGRS; the rates of BD in 50 equaled sized groups of the BD FGRS; the rates of SZ in 50 equaled sized groups of the SZ FGRS.

eTable 7. Additional Sensitivity Analyses for the Calculation of the Family Genetic Risk Score			
	MD FGRS	BD FGRS	SZ FGRS
Correlation with the FGRS used in the ms			
FGRS(a) - 1st degree relatives	0.76	0.72	0.68
FGRS(b) - no age correction	0.98	0.99	0.99
FGRS(c) - no cohabitation correction	0.99	0.99	0.99
FGRS(d) - no weighting for # relatives	0.96	0.97	0.98
FGRS(e) -std by YoB only	0.97	0.99	0.99
FGRS(f) - std by geography only	0.94	0.95	0.92
FGRS(g) - std only by entire sample	0.92	0.94	0.91
Area Under the Curve			
FGRS used in the manuscript	0.595 (0.594; 0.596)	0.589 (0.582; 0.589)	0.625 (0.620; 0.630)
FGRS(a) - 1st degree relatives	0.582 (0.581; 0.583)	0.543 (0.532; 0.534)	0.454 (0.449; 0.460)
FGRS(b) - no age correction	0.596 (0.595; 0.598)	0.585 (0.581; 0.588)	0.633 (0.628; 0.638)
FGRS(c) - no cohabitation correction	0.596 (0.595; 0.597)	0.585 (0.582; 0.588)	0.618 (0.613; 0.623)
FGRS(d) - no weighting for # relatives	0.592 (0.592; 0.593)	0.585 (0.582; 0.588)	0.607 (0.602; 0.612)
FGRS(e) -std by YoB only	0.608 (0.607; 0.609)	0.601 (0.598; 0.604)	0.651 (0.646; 0.656)
FGRS(f) - std by geography only	0.593 (0.592; 0.594)	0.566 (0.563; 0.570)	0.548 (0.542; 0.554)
FGRS(g) - std only by entire sample	0.605 (0.604; 0.606)	0.588 (0.585; 0.591)	0.568 (0.563; 0.574)

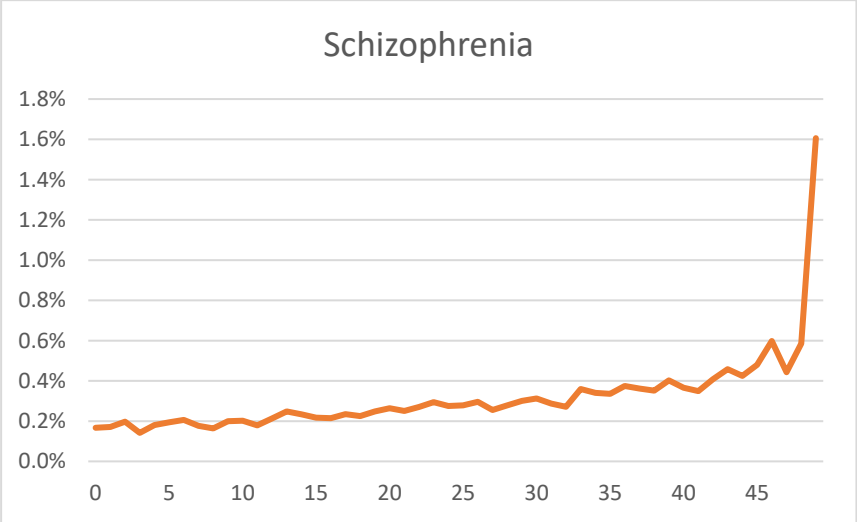
eFigure 4. Rates of MD in 50 Equaled Sized Groups of the MD FGRS



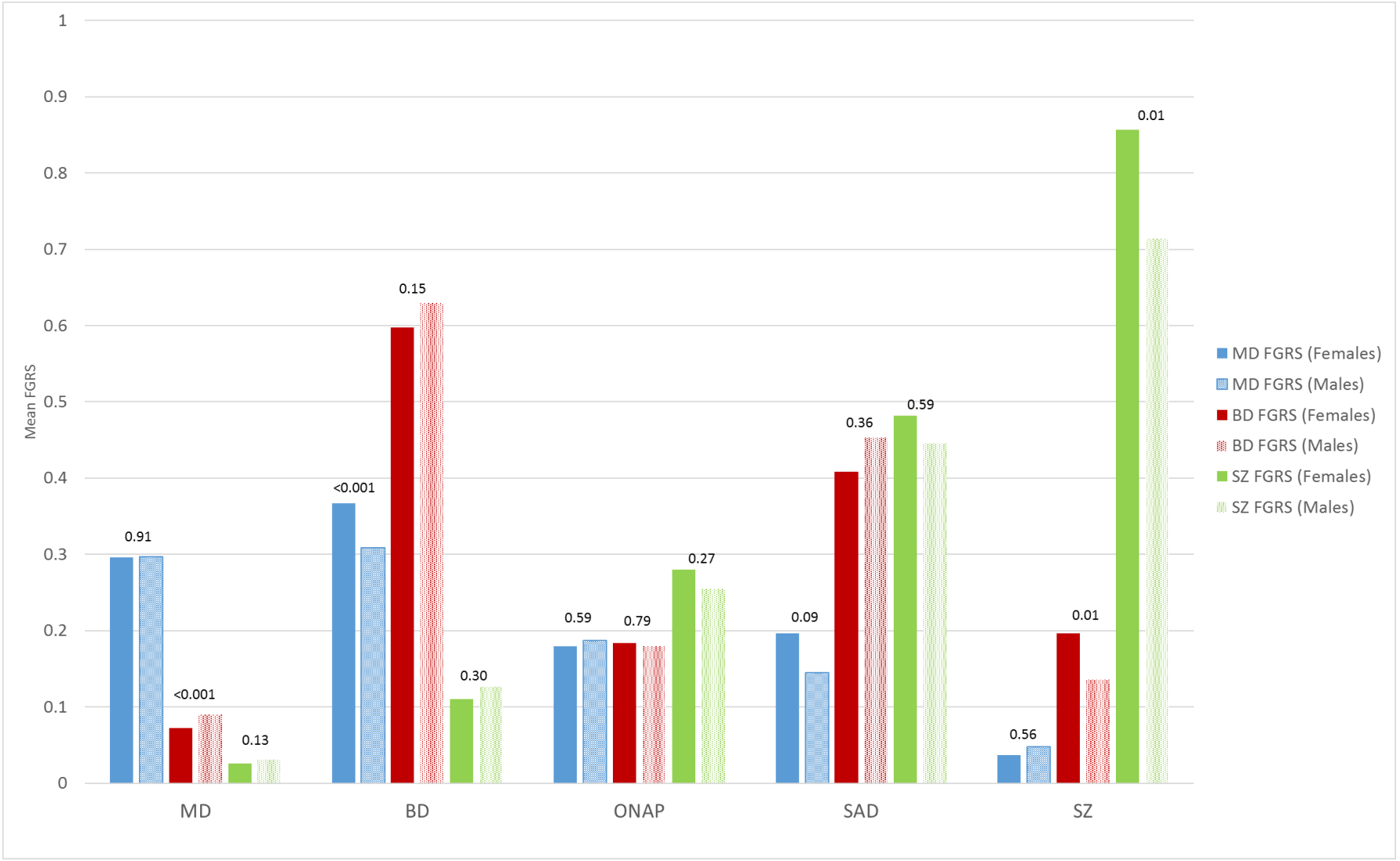
eFigure 5. Rates of BD in 50 Equaled Sized Groups of the BD FGRS



eFigure 6. Rates of SZ in 50 Equaled Sized Groups of the SZ FGRS



eFigure 7. Similarity of FGRSs for MD, BD, and SZ Across Sexes



eFigure 8. Stability of FGRSs for MD, BD and SZ by Median Splits for Cohort and Geographical Region Within Sweden