TABLE S1. Definitions of Our Putative Indices of Familial Risk Assessed in Probands With Major Depression

1. Age at first registration: was centered at the mean value (age 29) and inverted so that lower ages represent positive values.
2. Number of episodes: a new episode was defined as a major depression (MD) registration that was preceded by at least a 3-month period without any registration for MD. The variable was included as a categorical variable in the models (1, 2, 3-4 and 5 or more episodes), using 1 episode as reference.
3. History of anxiety disorder (AD): AD was identified in the Hospital Discharge, Outpatient (Specialist) Care and Primary Care Registries by the following ICD codes: ICD-9: 300.0, 300.2; ICD-10: F40, F41. The AD diagnose could be registered at any time.
4. History of Antidepressants (AnD): AnD was based on Anatomical Therapeutic Chemical (ATC) codes N06A in the Prescribed Drug Register (containing all prescriptions in Sweden picked up by patients from 2005 to 2014).
5. Psychiatric registration (PR): PR was categorized into three groups based on were the MD diagnose was registered; (1) psychiatric clinic from the Hospital Discharge register; (2) psychiatric clinic from the Outpatient (Specialist) Care register; (3) other type of registration. In the models, we used other type of registration as the reference group.
6. History of electroconvulsive therapy (ECT): ECT was identified in the Hospital Discharge, Outpatient (Specialist) Care and by the following codes (procedure codes): DA006, DA024, and DA025. The ECT could be registered at any time.
7. Sick-leave registration (SL): SL is categorized into a binary variable based on whether or not the proband has received any income compensation for illness during the same year as the MD registration.
8. Early retirement registration (ER): ER is categorized into a binary variable based on whether or not the proband has received any early retirement within four years of the MD registration. Early Retirement Pension was paid to people aged 16- 64 and granted when their working capability was deemed to be permanently reduced by at least one quarter due to medical reasons.

TABLE S2. Hazard Ratios (and % MD in Relative) Based on Deciles of the Sum of the Standardized (Mean 0 and std 1) Variable

Z-Score	MZ-Twins	% MD	Full Siblings	% MD	Half Siblings	% MD	Cousins	% MD	P- value for interaction term between genetic resemblance and Z-score group
1	Ref	23.5	Ref	16.9	Ref	19.6	Ref	15.0	
2	1.28 (1.14; 1.43)	24.4	1.10 (1.05; 1.15)	18.5	1.01 (0.99; 1.04)	19.3	0.98 (0.95; 1.00)	14.6	0.0016
3	1.36 (1.21; 1.52)	32.1	1.13 (1.08; 1.18)	18.4	1.03 (1.00; 1.05)	20.2	0.98 (0.95; 1.01)	14.7	0.0009
4	1.51 (1.34; 1.69)	22.6	1.19 (1.13; 1.24)	19.2	1.05 (1.03; 1.08)	21.1	0.99 (0.97; 1.02)	14.8	0.0013
5	1.50 (1.34; 1.68)	29.7	1.18 (1.12; 1.23)	19.0	1.04 (1.02; 1.07)	20.8	0.98 (0.96; 1.01)	14.6	0.0001
6	1.87 (1.67; 2.09)	35.7	1.28 (1.22; 1.34)	20.0	1.06 (1.03; 1.09)	21.6	0.96 (0.94; 0.99)	14.4	<0.0001
7	1.96 (1.75; 2.19)	42.9	1.32 (1.26; 1.38)	20.8	1.08 (1.06; 1.11)	20.2	0.98 (0.96; 1.01)	14.7	<0.0001
8	2.29 (2.05; 2.57)	46.2	1.39 (1.33; 1.48)	21.5	1.09 (1.06; 1.11)	20.5	0.96 (0.93; 0.99)	14.3	<0.0001
9	2.57 (2.30; 2.87)	50.8	1.48 (1.41; 1.54)	22.4	1.12 (1.09; 1.15)	21.2	0.97 (0.95; 1.00)	14.4	<0.0001
10	2.82 (2.52; 3.15)	53.0	1.53 (1.47; 1.60)	22.8	1.13 (1.10; 1.16)	21.9	0.97 (0.94; 1.00)	14.4	<0.0001

TABLE S3. Tetrachoric Correlations for Major Depression in Maternal and Paternal Half-Siblings Reared Apart

Sex	N Pairs	% MD	Correlation
All			
Male-Male	26,596	9.6%	0.083 (0.018)
Female-Female	23,811	17.1%	0.145 (0.014)
Male-Female	49,634	9.6%/16.8%	0.126 (0.011)
Maternal			
Male-Male	3,877	10.5%	0.079 (0.044)
Female-Female	2,967	18.4%	0.138 (0.038)
Male-Female	6,698	10.1%/17.7%	0.152 (0.029)
Paternal			
Male-Male	22,719	9.4%	0.083 (0.019)
Female-Female	20,844	16.9%	0.146 (0.015)
Male-Female	42,936	9.5%/16.7%	0.122 (0.012)

TABLE S4. Different Definitions of Reared-Together and Reared-Apart Half-Siblings and Their Impact on Estimates of Genetic, Shared Environmental, and Individual-Specific Environmental Effects for Major Depression

Half-Sibs Reared Together and Apart≤	≥90%/≤10%	≥80%/≤20%	≥70%/≤30%
r	0.87 (0.84; 0.87)	0.89 (0.87; 0.91)	0.86 (0.86; 0.87)
a^2m	0.40 (0.39; 0.40)	0.36 (0.31; 0.38)	0.38 (0.37; 0.38)
c^2m	0.03 (0.03; 0.03)	0.05 (0.05; 0.05)	0.04 (0.03; 0.04)
e^2m	0.58 (0.56; 0.58)	0.59 (0.58; 0.61)	0.58 (0.56; 0.59)
a^2f	0.49 (0.48; 0.51)	0.51 (0.51; 0.53)	0.47 (0.47; 0.48)
c^2f	0.03 (0.03; 0.03)	0.02 (0.02; 0.02)	0.04 (0.03; 0.04)
e^2f	0.49 (0.47; 0.49)	0.47 (0.46; 0.49)	0.49 (0.48; 0.49)

TABLE S5. Sample Size, Lifetime Prevalence and Tetrachoric Correlations for Treated Major Depression in Swedish Twin, Full Sibling, and Half-Sibling Pairs, With Exclusion Criteria (for cases of BPI and SZ) Eliminated

	Sex	N Pairs	Lifetime Prevalence of MD (%)	Tetrachoric Correlation (SE)
Monozygotic Twins	Male-Male	3,660	7.6	0.436 (0.042)
	Female-Female	4,338	13.1	0.508 (0.028)
Dizygotic Twins	Male-Male	3,938	7.1	0.198 (0.051)
	Female-Female	4,030	12.9	0.266 (0.036)
	Male-Female	11,004	7.2/12.9	0.229 (0.026)
Full-Siblings Reared Together	Male-Male	418,200	7.2	0.227 (0.005)
	Female-Female	371,352	13.4	0.275 (0.004)
	Male-Female	781,793	7.4/13.3	0.218 (0.003)
Full-Siblings Reared Apart	Male-Male	3,730	11.1	0.136 (0.043)
	Female-Female	2,891	19.0	0.214 (0.037)
	Male-Female	6,891	11.7/18.2	0.127 (0.028)
Half-Siblings Reared Together	Male-Male	13,618	10.4	0.159 (0.023)
	Female-Female	13,040	18.9	0.171 (0.018)
	Male-Female	26,026	10.8/18.5	0.142 (0.014)
Half-Siblings Reared Apart	Male-Male	27,558	10.2	0.088 (0.017)
	Female-Female	24,890	18.1	0.142 (0.013)
	Male-Female	51,774	10.3/17.9	0.126 (0.011)

TABLE S6. Parameter Estimates (and 95% Confidence Intervals) From the Full Models Applied to the Twins and Reared-Together and Reared-Apart Full and Half-Siblings With Exclusion Criteria (for cases of BPI and SZ) Eliminated

	a^2_m	c^2_m	e^2_m	a^2_f	c^2_f	e^2_f	r
Twins	0.43 (0.20-0.50)	0.00 (0.00-0.18)	0.57 (0.50-0.64)	0.48 (0.31-0.56)	0.02 (0.00-0.17)	0.49 (0.44-0.55)	1.00 (0.80-1.00)
Full and Half-Siblings	0.36 (0.34-0.37)	0.05 (0.05-0.06)	0.59 (0.57-0.60)	0.51 (0.51-0.52)	0.02 (0.02-0.02)	0.47 (0.46-0.48)	0.87 (0.86-0.89)

TABLE S7. Sample Size, Sex Composition, and Clinical Features in Affected Probands in Pairs of Relatives Used in the Analyses to Examine the Clinical Features of Major Depression Which Predict Risk of Illness in Relatives With Exclusion Criteria (for cases of BPI and SZ) Eliminated

	MZ-Twins	Full Siblings	Half Siblings	Cousins
N Pairs	759	191,982	73,011	686,138
% MD in Relative	36.9%	21.1%	21.8%	15.2%
Mean age at Reg	29.4 (5.7)	28.0 (5.8)	28.2 (6.1)	28.3 (6.0)
Mean # episodes	2.40 (2.0)	2.33 (2.0)	2.34 (1.9)	2.32 (2.0)
Mean YoB	1979	1980	1980	1980
AD Registration	388 (41%)	100,114 (52%)	40,810 (56%)	357,558 (52%)
Antidepressants	599 (79%)	150,686 (78%)	58,359 (80%)	543,265 (79%)
ECT	10 (1.3%)	1,628 (0.9%)	567 (0.8%)	5,581 (0.8%)
Sick leave	260 (34%)	66,976 (35%)	27,671 (38%)	250,300 (36%)
Early Retirement	82 (11%)	18,301 (10%)	8,961 (11%)	70,874 (10%)
No Psychiatric Registration	464 (61%)	112,590 (59%)	39,283 (54%)	389,428 (57%)
Psychiatric Registration in Specialist Care	193 (25%)	56,945 (30%)	23,442 (32%)	212,397 (31%)
Psychiatric Registration in patient Care	102 (13%)	22,447 (12%)	10,286 (14%)	84,313 (12%)

TABLE S8. Analyses of Individual Clinical Features of Major Depression and Their Association with Risk for Major Depression in Monozygotic Co-twins, full siblings, half-siblings and cousins. With Exclusion Criteria (for cases of BPI and SZ) Eliminated

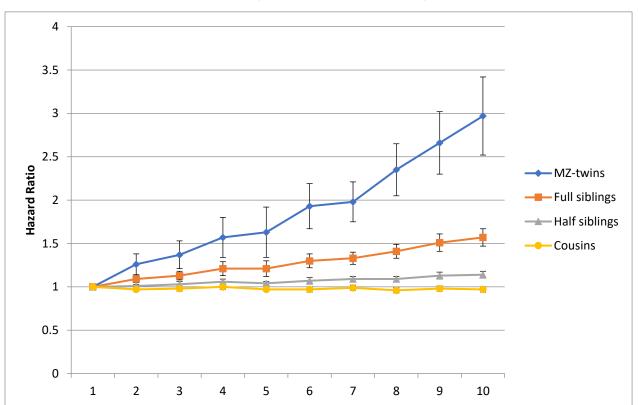|	MZ-Twins	Full Siblings	Half Siblings	Cousins	P value, interaction between genetic resemblance and predictor
Number of Episodes					
1	Reference	Reference	Reference	Reference	
2	1.23 (1.16; 1.31)	1.12 (1.10; 1.15)	1.07 (1.06; 1.09)	1.05 (1.03; 1.07)	<0.0001
3-4	1.44 (1.36; 1.53)	1.22 (1.19; 1.25)	1.12 (1.10; 1.13)	1.07 (1.05; 1.09)	<0.0001
5+	1.88 (1.75; 2.02)	1.38 (1.34; 1.41)	1.18 (1.16; 1.19)	1.09 (1.07; 1.11)	<0.0001
Age At Diagnosis					
1 Year decrease	1.05 (1.04; 1.05)	1.02 (1.02; 1.02)	1.01 (1.00; 1.01)	1.00 (1.00; 1.00)	<0.0001
Antidepressants					
Yes	1.52 (1.43; 1.61)	1.19 (1.17; 1.22)	1.06 (1.04; 1.07)	1.00 (0.98; 1.01)	<0.0001
ECT					
Yes	1.22 (0.95; 1.57)	1.03 (0.93; 1.14)	0.95 (0.90; 1.01)	0.91 (0.85; 0.97)	0.09
Specialist or In-Patient Care					
None	Reference	Reference	Reference	Reference	
Specialist Care	1.23 (1.17; 1.30)	1.01 (0.97; 1.94)	0.91 (0.90; 0.93)	0.87 (0.86; 0.88)	<0.0001
In-patient Care	1.28 (1.19; 1.37)	1.03 (1.00; 1.06)	0.93 (0.91; 0.94)	0.88 (0.86; 0.90)	<0.0001
Anxiety Disorder					
AD	1.49 (1.42; 1.56)	1.23 (1.20; 1.25)	1.11 (1.10; 1.13)	1.06 (1.05; 1.07)	<0.0001
Sick leave					
Yes	0.91 (0.87; 0.96)	0.98 (0.96; 1.00)	1.01 (1.00; 1.02)	1.03 (1.02; 1.04)	<0.0001
Early Retirement					
Yes	1.39 (1.29; 1.50)	1.16 (1.12; 1.19)	1.06 (1.04; 1.07)	1.01 (0.99; 1.03)	<0.0001
Analyses control for Year of Birth, Gender and Age Difference in relative pairs. Results presented are from a model applied to all four groups of relatives					

FIGURE S1. With Exclusion Criteria (for cases of BPI and SZ) Eliminated