Supplemental Material

Contents

Appendix 1. Bivariate analysis of perinatal depression and nonperinatal depression, estimated variance in perinatal depression excluding bipolar disorder and schizophrenia

In order to avoid that the heritability estimate of perinatal depression is artificially increased because of other severe mental disorders, or that the unique additive genetics seen in perinatal depression was in fact unique for bipolar disorder of schizophrenia, we excluded all individuals in the sibling design with at least one hospital admission with a discharge diagnosis code for bipolar disorder (ICD-8 296.00, 296.1, 296.3, 296.88, and 296.99; ICD-9 296.0, 296.1, 296.3, 296.4, 296.8, and 296.9; or ICD-10 F30 and F31) or schizophrenia (ICD-8 295; ICD-9 295; or ICD-10 F25), (N=6,817).

Results

Bivariate analysis of the cohort without individuals ever diagnosed with bipolar disorder or schizophrenia revealed that 17% (95% CI, 13-21%) of the variance explained in perinatal depression was due to genetic factors unique for perinatal depression, while 25% (95% CI, 16-33%) was due to genetic factors shared with nonperinatal depression (Table S1). This indicates that the unique genetic component seen in perinatal depression was not explained by bipolar disorder or schizophrenia.

TABLE S1. Estimated variance in perinatal depression, excluding bipolar disorder and schizophrenia

Estimated variance (95% CI)					
		Environment			
Additive Genetic - unique [a]	Additive Genetic - in common [b]	Shared - unique [a]	Shared - in common [b]	Nonshared - unique [a]	Nonshared - in common [b]
0.17 (0.13-0.21)	0.25 (0.16-0.33)	0.04 (0.01-0.07)	0.00 (0.00-0.00)	0.39 (0.33-0.45)	0.15 (0.11-0.18)

[a] Variance explained in perinatal depression by component unique for perinatal depression.
[b] Variance explained in perinatal depression by component in common with nonperinatal depression.

Appendix 2. Bivariate analysis of perinatal depression and nonperinatal depression, estimated variance in perinatal depression after permutation of perinatal periods

When separating major depressive disorder into perinatal depression and nonperinatal depression, we allow perinatal depression to only occur during perinatal periods while nonperinatal depression can occur at any time of life (excluding perinatal periods). Since pregnancy tends to be clustered around a specific age in women, there is a possibility that the different heritability observed in perinatal depression and nonperinatal depression and the unique genetics observed in perinatal depression are caused by different ages when experiencing the depression, rather than by the actual pregnancy or child birth.

A way to study this is to group the women based on birth year, and randomly assign women born the same year each other's perinatal periods.

Example: Woman 1, born 1955, has been pregnant two times: the first time at age 25 and the second at age 30. After permutation, she has randomly been assigned the perinatal periods of woman 2. Woman 2 is also born 1955 but has been pregnant three times, at age 20, 23 and 28. Now woman 1 has three perinatal periods originally belonging to woman 2, and none of these overlap with her original perinatal periods, but they are still within the age range where most women born that year get pregnant.

Results

After permutation, 84.4% of the women in the cohort had randomly been assigned perinatal periods, belonging to other women born the same year, that did not overlap with their own true perinatal periods. Using these permuted perinatal periods, major depressive disorder was then separated into perinatal depression and nonperinatal depression just like before. But this time, in 84.4% of the women, perinatal depression did not reflect a true pregnancy and postpartum period, but rather a nonperinatal period at the same age range where most women born that year would be pregnant. Bivariate analysis revealed that the variance explained in the permuted perinatal depression was to 34% (95% CI, 30-37%) due to genetic factors in common with nonperinatal depression, and no genetic factors unique for the permuted perinatal depression (Table S2). This signifies the connection between the unique genetic component originally observed in perinatal depression and the actual pregnancy or childbirth.

TABLE S2. Estimated variance in perinatal depression with permuted perinatal periods

Estimated variance (95% CI)					
		Environment			
Additive Genetic - unique [a]	Additive Genetic - in common [b]	Shared - unique [a]	Shared - in common [b]	Nonshared - unique [a]	Nonshared - in common [b]
0.00 (0.00-0.00)	0.34 (0.30-0.37)	0.03 (0.01-0.05)	0.02 (0.00-0.03)	0.47 (0.43-0.51)	0.15 (0.14-0.17)

[a] Variance explained in perinatal depression by component unique for perinatal depression.
[b] Variance explained in perinatal depression by component in common with nonperinatal depression.

Appendix 3. Univariate analyses of perinatal depression using different Edinburgh Postnatal Depression Scale cut-offs.

In the twin design a retrospective Edinburgh Postnatal Depression Scale score is used to create a dichotomous perinatal depression variable, and in the sibling design treatment contacts for depression occurring during pregnancy or within 6 months postpartum was used. No primary care contact information was available and all treatment contacts prior to 2001 were in-patient contacts. This likely make the depression identified using treatment contacts more severe and potentially different from depression identified using the Edinburgh Postnatal Depression Scale.

To further study this, the cut-off on the Edinburgh Postnatal Depression Scale was both increased and decreased from the normal score of ≥12 (≥12 included as reference) and analyzed.

Results

The heritability estimates using different Edinburgh Postnatal Depression Scale cut-offs did only deviate slightly from the estimates used in the main analysis (≥12) and do not support that a more severe depression would be a different disease entity and affect the heritability estimate (Table S3).

TABLE S3. Univariate heritability estimates of perinatal depression with different Edinburgh Postnatal Depression Scale cut-offs using classical twin design (N=3,427)*

			Estimated Variance (95% CI)[a]			Tetrachoric Correlation (SE)	
				Environment			
Model	Cut-off	Observed Outcome Occurrence	Additive Genetic (A)	Shared (C)	Nonshared (E)	Monozygotic Twins	Dizygotic Twins
AE[b]	≥8	13.6%	0.49 (0.34-0.63)	NA	0.51 (0.37-0.66)	0.51 (0.08)	0.19 (0.10)
AE[b]	≥10	10.6%	0.54 (0.38-0.69)	NA	0.46 (0.31-0.62)	0.59 (0.08)	0.11 (0.12)
AE[b]	≥12	7.6%	0.54 (0.35-0.70)	NA	0.46 (0.31-0.65)	0.55 (0.09)	0.22 (0.14)
AE[b]	≥14	5.2%	0.53 (0.32-0.70)	NA	0.47 (0.30-0.68)	0.54 (0.10)	0.29 (0.16)
AE[b]	≥16	3.3%	0.51 (0.20-0.74)	NA	0.49 (0.26-0.80)	0.53 (0.14)	0.15 (0.23)
AE[b]	≥18	1.6%	NA	NA	NA	0.56 (0.18)	Na[c]

* Different cut-offs on the Edinburgh Postnatal Depression Scale was used to define a binary outcome variable of perinatal depression. A score of ≥12 is the widely used cut-off to define a depressive illness.
[a] Profile likelihood confidence intervals.
[b] An AE model, where the C parameter was fixed at zero, was considered as the estimate of the C component was not significant in the initial ACE models.
[c] No concordant dizygotic twins.