Genetic and environmental factors predict multivariate trajectories of maternal distress after birth

Authors

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Abstract

Background: Maternal distress influences her own wellbeing and shapes her offspring's psychosocial adjustment and neurodevelopment across childhood. The aim of this study was to analyze multivariate trajectories of maternal postpartum distress using a latent class modeling approach and to find genetic and psychosocial factors that predict membership within a given group (latent class).

Methods: Maternal self-reports of depressive symptoms, parenting stress, general stress, and marital stress were measured at regular intervals during the first six years postpartum in 261 mothers participating in the Maternal Adversity, Vulnerability and Neurodevelopment Study. Genetic risk was determined by calculating a polygenic risk score for Major Depressive Disorder (MDD-PRS). Additionally, we assessed maternal history of early life adversity (mELA), educational level, and prenatal symptoms of depression as psychosocial risk factors. Using Latent Gold® Software, we identified latent classes of mothers based on their 1) average levels of distress and 2) change in distress over time.

Results: We identified four latent classes based on average levels of distress and found that class membership probability was influenced by an interaction between MDD-PRS and prenatal depressive symptoms ($\text{Wald}_{\text{Interaction}(3)}=13.19, p=0.004$; $\text{Wald}_{\text{MDD-PRS}(3)}=6.02, p=0.11$; $\text{Wald}_{\text{Depression}(3)}=41.96, p<0.001$), mELA ($\text{Wald}(3)=8.64, p=0.035$), and educational level ($\text{Wald}(3)=11.61, p=0.009$). Furthermore, we found five classes of mothers with distinct across-time trajectories, which were associated with mELA ($\text{Wald}(3)=12.67, p=0.013$).

Conclusions: Our findings might become relevant in the clinical setting, e.g. for identifying pregnant women at risk for distress in the postpartum based on her prenatal symptoms of depression and genetic risk, mELA, and educational level.

Introduction

Maternal emotional wellbeing is an important concern for both women's health as well as the growth and development of their offspring (1, 2). Although maternal mood commonly improves in the postpartum phase (3, 4), onset of mood disturbances during pregnancy or the early postpartum, such as perinatal depression, are estimated to affect 10-20% of mothers in developed countries (4). Moreover, an even higher percentage of mothers experience subclinical levels of depressive symptoms that are sufficient to compromise psychosocial function and parenting (5). These mood disturbances are heterogeneous in their onset, course, and symptomatology (6).

In addition, maternal mood disturbances, such as symptoms of depression, might only be one aspect of maternal emotional wellbeing during pregnancy and the postpartum with impact on child development (7, 8). More severe symptoms of depression are commonly associated with increased levels of distress in different areas of everyday life, including stress related to parenting (9, 10), to the relationship with the romantic partner (11) or general daily life stress. However, it has not been investigated whether the trajectories in these multiple aspects of maternal emotional wellbeing parallel each other or show distinct patterns of change. Furthermore, postpartum emotional wellbeing may be influenced by multiple factors, including genetic predispositions and psychosocial factors, such as childhood adversities, mental disorders existing pre-conception, and/or socioeconomic status (3, 11, 12). While studies on psychosocial risk factors have commonly yielded consistent results, previous findings on a genetic contribution toward peripartum depression are mixed (13). However, a recent study found that the MDD-PRS predicted prenatal and postnatal depressive symptoms, albeit the latter prediction was mediated through prenatal depressive symptoms (14). In addition, latent profile analysis of

14 prenatal and two postnatal (2 weeks after delivery, 6 months after delivery) depressive symptoms scores yielded a consistently low, moderate, and high subgroup. Likewise, a higher PRS predicted greater odds to belong to the consistently moderate or high latent profile groups (14).

The aim of the current study was to analyze multivariate trajectories of maternal distress using a latent class modeling approach. A latent class (LC) is a categorical variable, which distinguishes classes of mothers with similar trajectories in multiple measures of distress. This approach allows us to examine trajectories in multiple variables simultaneously while taking into account individual-level variation in symptom trajectories accounting for relevant covariates and their interaction on these trajectories. Previous studies applying latent class or growth-curve modeling approaches to study trajectories in postpartum emotional wellbeing, mostly in postpartum symptoms of depression, found that the overall level of depressive symptom severity, rather than the change over time, determined the trajectory groups (for a systematic review see 6). Moreover, while research on postpartum depression has examined genetic and psychosocial risk factors, their association and interaction with heterogeneous profiles encompassing multiple aspects of emotional wellbeing is unknown. In the current study, we decomposed each distress trajectory into two components to cover both aspects, an average level of distress across time-points (Average Distress Model, ADM) and the actual change over time – i.e. a mother's distress score at a respective time point in relation to her average distress across time – (Centered Trajectory Model, CTM). We hypothesized that the latent class structure and its relationships with potential genetic and psychosocial risk factors would differ between average levels of distress and changes in distress over time.

The data for this study was derived from the Maternal Adversity, Vulnerability and Neurodevelopment (MAVAN) project, a community cohort study following mother-child dyads from pregnancy to when the child is twelve years old. We focused on four dimensions of maternal distress: depressive symptoms, general daily life stress, parenting stress, and stress in the relationship with the spouse (marital stress), measured at regular intervals over the first six years after birth. The factors examined in this study consisted of a PRS (15) for major depressive disorder (MDD-PRS) (16) – and three psychosocial factors related to postpartum wellbeing: maternal history of early life adversity (mELA) (17-19), levels of maternal education (12), and prenatal symptoms of depression (20). To expand on previous research, we also examined a potential interaction between the MDD-PRS and psychosocial factors considered in previous studies on general depression (21, 22), but not in postpartum mood (23).

Methods and Materials

Participants and Procedure

The study sample was a subsample ($n=261$) of the 496 families originally participating in the MAVAN project. Pregnant women were recruited during the second trimester of pregnancy in Montreal and Hamilton, Canada, between 2003 and 2005; follow-ups occurred at 6, 12, 24, 36, 48, 60 and 72 months after birth. For additional information on recruitment and the MAVAN study design see (24). All mothers provided written informed consent at the time of study enrollment. The protocol was approved by the Research Ethics Board at the Douglas Mental Health University Institute (Montreal cohort) and St-Joseph's Hospital (Hamilton cohort). Our final sample consisted of 261 mothers (age at time of childbirth: $M = 30.60$ years; $SD = 4.88$

years, range: 18 to 43 years) who had (i) measurements at a minimum of three time points (n=375), and (ii) available genotyping data (n=264). The study sample included 10 mothers without partners and thus without observed measures of marital stress; the sensitivity of the results was evaluated by repeating all analyses excluding these 10 mothers. Participant's Characteristics are provided in Table 1.

Table 1
Participant characteristics

	N	%
Recruitment Site		
Montréal	143	54.79
Hamilton	118	45.21
Offspring Gender		
Male	135	51.72
Female	126	48.28
Income Category ¹		
Low Income	54	20.69
Average/High Income	170	65.13
Information Missing	37	14.18
Level of Education	261	
High School Diploma or Less	19	7.28
Attended Community College	19	7.28
Completed Community College	85	32.57
University Degree	126	48.28
Information Missing	12	4.60

¹ according to Statistics Canada

Outcome Variables: Measures of Distress

After delivery, mothers completed questionnaires on symptoms of depression (Centre of Epidemiological Studies Depression Scale, CES-D (25)), parenting stress (Parental Stress Index, PSI (26)), stress in the relationship with the spouse (referred to as marital stress, although not all mothers were married to their partners, Marital Stress Index, MSI (27)), and general perceived

stress (Perceived Stress Scale, PSS (28)) at 6, 12, 24, 36, 48, 60, and 72 months postpartum.

Higher scores on these instruments indicate higher levels of distress. Detailed information on the applied questionnaires can be found in the Supplementary Materials (S1).

Covariates

Investigated covariates consisted of (i) psychosocial factors: mELA, prenatal CES-D score, and maternal level of education, and (ii) a genetic factor: the MDD-PRS (15, 16).

Psychosocial factors. mELA was assessed using a combined measure of the Parental Bonding Instrument (PBI) (29) ‘maternal care’ subscale and the five subscales of the Childhood Trauma Questionnaire (CTQ) (30): ‘physical neglect’, ‘emotional neglect’, ‘physical abuse’, ‘emotional abuse’, and ‘sexual abuse’. The six measures were summarized into a composite score of mELA using principal component analysis (PCA) and retaining the first principal component (as described previously in 31). This first principal component captured 58.41% of the total variation observed in the six mELA measures. A high score indicates high levels of adversity. Prenatal depressive symptoms were measured using the CES-D total score assessed in the third pregnancy trimester. Due to the high proportion of mothers with a university degree in our sample (Table 1), we summarized the maternal educational level with two groups: those with ($n=126$) and those without ($n=123$) a university degree.

Genetic data. Genetic risk was assessed using a polygenic risk score for depression. Genetic Material was collected and extracted from maternal saliva samples using Oragene DNA Collection Kits OG-500 (DNA Genotek Inc., Ottawa, Canada). Genotypes were described using the Illumina PsychChip and PsychArray (Illumina Inc., Victoria, Canada). Data on quality

control (PLINK 1.9, www.cog-genomics.org/plink/1.9/) (32), and missing genotype imputation (Wellcome Trust Sanger Institute, Hinxton, UK(33)), is provided in the Supplementary Materials (S2).

Data Preparation

Polygenic risk score. A polygenic-risk score (PRS) is an aggregate score of risk-associated single nucleotide polymorphisms (SNPs) across the genome. As such, MDD-PRS represents the genetic risk for MDD from additive effects of common genetic variants (34). Here, MDD-PRS was calculated as the summation of risk allele counts multiplied by their effect size (log odds ratio) based on the summary statistics provided by the Psychiatric Genomics Consortium's Genome-Wide Association Study (GWAS) for MDD (16); for more detailed information see Supplementary Materials (S2) and (35). SNP inclusion was based on seven different thresholds of GWAS significance (p-value thresholds < 0.01, 0.05, 0.10, 0.20, 0.30, 0.40, 0.50) to determine the PRS that optimally contributed to the interaction model. The MDD-PRS was generated using PRS-on-Spark (35).

Population Stratification. To account for potential confounding by population structure within our sample (i.e. population stratification)(36, 37), we adjusted the outcome variables using the first two principal components of the genetic data (details in Supplementary Materials S2, and S3 Figure 1). The adjustment was performed using a multivariate linear mixed model, allowing for repeated measures on individuals and for correlations between distinct outcomes.

Adjusted Stress scores. Two adjusted scores were calculated. First, adjusted average distress scores (a mother's distress score averaged across time, Average Distress Model, ADM) and

second, adjusted centered distress trajectory scores (a mother's distress score at a respective time point in relation to her average distress score, Centered Trajectory Model, CTM). A value > 0 indicates that a mother has an adjusted score at the respective time point that is greater than her average score.

Statistical Analyses

Both models for ADM and CTM were fit using Latent Gold®, a software package for LC analysis developed by Statistical Innovations (Belmont, MA). In the Latent Gold® framework, we used the postnatal centered trajectory distress scores (after adjusting for population structure and centering) as the dependent *response variables*, the psychosocial factors and MDD-PRS as *covariates* (exogenous variables influencing the latent class that may vary between, but not within subjects), and months postpartum as *predictors* (exogenous variables that may vary within subjects). The ADM was modeled with class dependent constants, while the CTM was modeled with class dependent intercepts, slopes, and quadratic terms. We chose the regression submodule of Latent Gold®, which allows for the number of responses to vary across subjects. Generally, the latent class models used here followed the structure shown in Figure 1a). This structure implies that maternal genetics and psychosocial background together contribute to determining a latent susceptibility to distress. Models were specified with the following three steps: In step 1, we determined the number of latent classes for each of ADM and CTM models; in step 2, we selected the MDD-PRS at a p-value threshold yielding the greatest R^2 in the given model and the SNPs of the best PRS was analyzed using the gene enrichment analysis tool of the Metacore©

software (Clarivate Analytics); in step 3, we examined the significance of the psychosocial covariates. The details of the respective steps are given in Figure 1 b).

Figure 1. a) General structure of the latent class models used in this study and b) Statistical procedure to specify the ADM and CTM latent class models. Abbreviations: ADM: Average Distress Model; BIC: Baye’s Information Criterion; CTM: Centered Trajectory Model; MDD-PRS: Polygenic Risk Score for Major Depressive Disorder; mELA: maternal history of early life adversities.

Results

Average Distress Models (ADM)

A four-class solution yielded the minimum BIC for ADM LC models without covariates (step 1) (See S3, Figure 2). The distributions of raw distress scores per class are shown in Supplementary Material S3, Figure 3. We identified a significant interaction between MDD-PRS and prenatal CES-D scores (step 2), with an MDD-PRS constructed at a $p < 0.1$ threshold exhibiting the largest effect (S3, Figure 4). After inclusion of this prenatal CES-D by MDD-PRS interaction term in the model, all other psychosocial covariates were significantly associated with class membership (step 3): MDD-PRS and prenatal CES-D score: $\text{Wald}_{\text{Interaction}(3)} = 13.19$, $p = 0.004$; $\text{Wald}_{\text{MDD-PRS}(3)} = 6.02$, $p = 0.11$; $\text{Wald}_{\text{CES-D}(3)} = 41.96$, $p < 0.001$; Maternal Education: $\text{Wald}_{\text{Educ.}(3)} = 11.61$, $p = 0.009$; maternal mELA: $\text{Wald}_{\text{mELA}(3)} = 8.64$, $p = 0.035$. After introducing the covariates, the characteristics of the classes were re-estimated (Figure 2).

Of the four classes, Class 1 ($n=52$) had the highest values of maternal distress (Figure 2). The contour plot in Figure 3A illustrates the effect of the interaction: at a high MDD-PRS (i.e. high genetic risk for MDD), Class 1 membership probability increases with higher scores of CES-D; similarly, at a high score on CES-D, there is an increased membership probability as MDD-PRS increases. Hence Class 1 membership probability was highest for mothers with a high MDD-PRS and high prenatal CES-D scores. Additionally, mothers exposed to high mELA and without a university degree were more likely to belong to this class as compared to mothers with no mELA and with a university degree (Figure 4B). An enrichment analysis of genes included within the MDD-PRS revealed significant enrichment for a number of network processes

including Gonadotropin Releasing Hormone Regulation (see Table 4), which is a system implicated in both reproduction and depression (38).

Levels of distress in Class 2 ($n=97$) were the second highest of the four classes (Figure 2). Again, mothers with high prenatal CES-D scores combined with a high MDD-PRS were more likely to belong to Class 2 than mothers with low prenatal CES-D and MDD-PRS (Figure 3B). In contrast to Class 1, however, mothers holding a university degree were more likely to belong to Class 2 as compared to mothers without a university degree (Figure 4B), and membership probability was independent of mELA.

Class 3 ($n=72$) showed the second lowest levels of distress (Figure 2), and higher levels of mELA were associated with higher membership probability in this class (Figure 4A), suggesting that this was an “environmental risk”-only group. Distress levels in Class 4 ($n=40$) were the lowest of all classes. In contrast to Class 1 and 2, mothers were more likely to belong to Class 4 when they had low levels of prenatal CES-D or low levels of MDD-PRS (Figure 3D) as well as low mELA (Figure 4A) but there was no association with maternal education. Detailed statistical information is provided in Table 2.

Table 2

Four Class Average Distress Model (ADM) with Covariates

Class	Term	Coefficient	SE	Z	p
Class 1	Intercept	-1.829	0.390	-4.695	<.001
	MDD-PRS (p<.1) ¹	-0.413	0.395	-1.045	0.300
	Prenatal CES-D Score	0.187	0.029	6.429	<.001
	Maternal Level of Education ²	-1.065	0.380	-2.806	0.005
	mELA ³	0.486	0.187	2.598	0.009
	MDD-PRS (p<.1) X Prenatal CES-D Score	0.064	0.030	2.134	0.033
Class 2	Intercept	-0.027	0.299	-0.089	0.930
	MDD-PRS (p<.1) ¹	-0.476	0.264	-1.802	0.072
	Prenatal CES-D Score	0.063	0.025	2.472	0.013
	Maternal Level of Education ²	0.692	0.255	2.716	0.007
	mELA ³	-0.016	0.184	-0.085	0.930
	MDD-PRS (p<.1) X Prenatal CES-D Score	0.089	0.026	3.409	<.001
Class 3	Intercept	1.082	0.357	3.031	0.002
	MDD-PRS (p<.1) ¹	0.185	0.314	0.590	0.560
	Prenatal CES-D Score	-0.051	0.031	-1.621	0.100
	Maternal Level of Education ²	0.223	0.300	0.743	0.460
	mELA ³	0.376	0.189	1.985	0.047
	MDD-PRS (p<.1) X Prenatal CES-D Score	0.005	0.034	0.157	0.880
Class 4	Intercept	0.774	0.458	1.690	0.091
	MDD-PRS (p<.1) ¹	0.703	0.338	2.080	0.038
	Prenatal CES-D Score	-0.199	0.052	-3.817	<.001
	Maternal Level of Education ²	0.150	0.366	0.410	0.680
	mELA ³	-0.846	0.396	-2.134	0.033
	MDD-PRS (p<.1) X Prenatal CES-D Score	-0.158	0.050	-3.153	0.002

¹ MDD-PRS was z-transformed; ² 0=no University Degree, 1=with University Degree; ³ First Principal Component Score obtained from five measures on mELA (Childhood Trauma Questionnaire scores: Physical Neglect and Abuse, Emotional Neglect and Abuse, Sexual Abuse, and Parental Bonding Instrument score for Maternal Care).

Figure 2. Estimated mean scores for symptoms of depression (CES-D), parenting stress (PSI), general stress (PSS) and marital stress (MSI) in the Average Distress Model (ADM). Mean scores were normalized using z-transformation ($M=0$ and $SD=1$). Abbreviations: CES-D: Center of Epidemiological Studies Depression Score; MSI: Marital Stress Index; PSI: Parental Stress Index; PSS: Perceived Stress Scale.

Figure 3. The contour plots show the ADM class membership probabilities (on the logit scale) of belonging to Class 1 (A), Class 2 (B), Class 3 (C) and Class 4(D) over differing values of prenatal CES-D and MDD-PRS, and with mother education level at a fixed value of 1 and mELA fixed at the average mELA value. The squares on the plots correspond to a subject (plotted at their value of MDD-PRS and prenatal CES-D). The size of the squares is proportional to the probability of belonging to the respective class, with larger squares indicating greater probability of class membership. Abbreviations: ADM: Average Distress Model; CES-D: Center of Epidemiological Studies Depression Score; mELA: maternal history of early life adversities; MDD-PRS: Polygenic Risk Score for Major Depressive Disorder.

Figure 4. Association between covariates and average class membership probabilities for the Average Distress Model (ADM). A) association with mELA and B) maternal level of education (0 = no university degree; 1 = with university degree). Abbreviations: mELA: maternal history of early life adversities.

Centered Trajectory Model (CTM)

For trajectory scores centered across time, the BIC reached a minimum at seven classes.

However, the more parsimonious and easier to interpret five-class solution yielded a BIC differing only slightly from the minimum (S3, Figure 5); therefore, the five-class solution was selected (step 1). The CTM did not show any evidence of a significant MDD-PRS by psychosocial covariate interaction (step 2), nor a main effect for MDD-PRS on class membership probability. Only mELA showed a significant main effect on the class probabilities of the CTM ($\text{Wald}_{\text{mELA}}(3)=12.67, p=0.013$). As shown in Table 3, increasing values of mELA were

associated with a shift in class assignment from Class 5 to Class 3, but no significant changes in the probabilities of the remaining classes.

Class 1 ($n=27$) was characterized by steeply increasing curves of all measures, rising from lower to higher levels of distress during the observation time window (6 months to 6 years postpartum). Class 2 ($n=63$) trajectories followed a quadratic trend over time: levels of distress increased from 6 months until 3 or 4 years, and then, except for marital stress, decreased towards the 6 month scores until the child reached 6 years of age (Figure 5). Class 3 ($n=28$) consisted of mixed trajectory paths across the different stress measures with depressive symptom and general stress severity following similar quadratic trends, relatively stable levels of parenting stress, and quadratic marital stress trajectory distinct from the other measures (Figure 5). Mothers scoring higher in mELA were more likely to belong to this Class 3 (Figure 6). Class 4 ($n=67$) trajectories were mostly stable over time with all scores showing only a slight decrease in the first 3 years postpartum (Figure 5). Finally, trajectories in depressive symptom severity and general stress of Class 5 ($n=76$) were relatively stable across time (Figure 5A and Figure 5C), while parenting and marital stress levels increased slightly over the six years postpartum (Figure 5B and 5D).

Table 3

Five Class Centered Trajectories Model (CTM) with mELA as Covariate

Class	Term	Coefficient	SE	Z	p
Class 1	Intercept	-0.469	0.217	-2.164	0.030
	mELA ¹	-0.003	0.202	-0.013	0.990
Class 2	Intercept	0.350	0.162	2.156	0.031
	mELA ¹	-0.005	0.162	-0.032	0.970
Class 3	Intercept	-0.659	0.234	-2.815	0.005
	mELA ¹	0.478	0.147	3.263	0.001
Class 4	Intercept	0.360	0.160	2.257	0.024
	mELA ¹	-0.150	0.158	-0.948	0.340
Class 5	Intercept	0.418	0.141	2.963	0.003
	mELA ¹	-0.320	0.171	-1.874	0.061

¹ First Principal Component Score obtained from five measures on mELA (Childhood Trauma Questionnaire scores: Physical Neglect and Abuse, Emotional Neglect and Abuse, Sexual Abuse, and Parental Bonding Instrument score for Maternal Care)

Abbreviations: mELA: maternal history of early life adversity score; SE: Standard Error

Figure 5. Class estimated values for the centered trajectory model (CTM) of A) symptoms of depression (CES-D); B) Parenting Stress (PSI); C) General Stress (PSS); and D) Marital Stress (MSI). Abbreviations: CES-D: Center of Epidemiological Studies Depression Score; MSI: Marital Stress Index; PSI: Parental Stress Index; PSS: Perceived Stress Scale.

Figure 6. Association between mELA and centered class membership probabilities.

Abbreviations: mELA: maternal history of early life adversities.

Table 4

Enrichment Analysis for Process Networks using the curated domains in Metacore

Term	In Data	Total	Ratio	p-value	FDR
Neurophysiological process → Transmission of nerve impulse	87	130	87 / 130	4.2E-07	6.7E-05
Cytoskeleton → Regulation of cytoskeleton rearrangement	77	120	77 / 120	2.1E-05	1.7E-03
Development → Neurogenesis → Synaptogenesis	77	122	77 / 122	5.0E-05	2.7E-03
Cell adhesion → Cell-matrix interactions	91	150	91 / 150	9.6E-05	3.5E-03
Reproduction → Gonadotropin regulation	69	109	69 / 109	1.1E-04	3.5E-03
Cell adhesion → Synaptic contact	75	121	75 / 121	1.5E-04	4.0E-03
Reproduction → GnRH signaling pathway	60	94	60 / 94	2.2E-04	4.8E-03
Cell adhesion → Integrin-mediated cell-matrix adhesion	88	147	88 / 147	2.4E-04	4.8E-03
Neurophysiological process → GABAergic neurotransmission	42	63	42 / 63	5.1E-04	9.0E-03
Transport → Synaptic vesicle exocytosis	58	94	58 / 94	9.9E-04	1.6E-02

Abbreviations: FDR: false discovery rate; GABA: gamma-Aminobutyric acid; GnRH: Gonadotropin releasing hormone

Discussion

Applying a latent class approach for modeling multivariate trajectories in maternal distress – including symptoms of depression, general daily life stress, parental-, and marital stress – during the first six years postpartum yielded four classes of mothers based on average distress (ADM). The probability of belonging to any of the four classes was affected by the interaction between maternal symptoms of prenatal depression and MDD-PRS, as well as mELA and level of education. Furthermore, we identified five classes based on the mothers' centered trajectories of distress (CTM), most of which were associated with mELA.

Average Distress Model (ADM): mean levels of distress

The scores of the four average distress classes were very consistent across all domains of distress (Figure 2), with Class 1 having the highest levels of symptoms of depression, parenting, marital, and general stress, Class 2 having the second highest levels, Class 3 the third highest and Class 4 the lowest levels. The effects of prenatal symptoms of depression, mELA, and maternal level of education are in line with previous findings linking these psychosocial risk factors to impaired wellbeing in the postpartum (12, 17-20, 39, 40). In our data, the PRS that best predicted levels of distress in the presence of psychosocial risk factors was enriched for genes involved in pathways related to neuronal functioning and reproduction. Elegant, functional experimental studies provide compelling evidence of individual differences in mood states associated with variation in hormonal mediators of reproductive (e.g., GnRH)(38, 41), which align well with our findings. An MDD-PRS by psychosocial environment interaction has been shown to predict MDD risk in

adults (21, 22, 42) but findings were mixed with regards to whether individuals with a high MDD-PRS were more or less vulnerable to psychosocial stress. A recent meta-analysis, however, found no significant interaction between MDD-PRS and childhood trauma in predicting MDD status (43). While a study on PRS in a sample of postpartum women found that postpartum depression was not associated with PRS-MDD, but with a PRS for bipolar disorder (23), this might be the first study addressing the interactions between psychosocial risk factors and MDD-PRS to predict postpartum wellbeing. Indeed, we found that the association of a higher MDD-PRS with postpartum distress depended on prenatal symptoms of depression, a more proximal measure as compared to mELA.

The probability of belonging to Class 1 – which had distress scores consistently higher than one standard deviation from the mean (Figure 2) – was increased for mothers with more severe mELA, without a university degree and with both high MDD-PRS and high prenatal symptoms of depression. This combination of risk factors suggests that these mothers were at risk for mood problems even before pregnancy. Class 2 was characterized by medium levels of depressive symptoms, general stress, and marital stress, while parenting stress was in the higher range (Figure 2). Mothers with high MDD-PRS and prenatal symptoms of depression were more likely to belong to Class 2, but compared to Class 1, membership probability was independent of mELA and was higher for mothers with a university degree. We speculate that a higher educational level might have diminished the effects of mELA and thus protected these mothers from clinically high distress scores observed in Class 1 (44). Maternal education, a marker of higher social class, might therefore buffer the effects of mELA (45). However, Class 2 showed relatively high levels of parenting stress, which might be due to reduced social support related to career choices demanding increased geographical mobility (46). Membership probability for

Class 3, which showed distress scores approximately half a standard deviation below the mean, increased with severity of mELA, but was unrelated to all other factors investigated. Class 3 mothers might possess one or more biological or psychosocial factor (e.g. social support) protecting them from the adverse effects related to their childhood environment, independent of genetic risk for MDD, which remains to be identified. Finally, mothers were more likely to belong to Class 4 with the lowest distress levels (approximately one standard deviation below the mean) when they had a low genetic and/or a low psychosocial risk.

Centered Trajectory Model (CTM): Change over time

We identified five classes based on changes in distress after birth. In each class except Class 3, the change over time in one measure was largely paralleled by similar changes in the other measures. Class 1 showed a very steep increase in all measures of postpartum distress. In Class 2, symptoms of depression and general stress increased until 3 years after birth and then returned to baseline levels, while parenting and marital stress peaked at around 4 years. We note that distress in mothers of Class 2 increased when the child gained more autonomy and that the recovery period probably coincided with the beginning of preschool. Class 3 trajectories showed slightly decreasing symptoms of depression and levels of general stress, and membership was increased with higher levels of mELA. This symptom profile observed in mothers assigned to Class 3 may reflect initial concerns about parental roles in individuals exposed to ELA (47). Class 4 showed only a slight decrease in distress, which was mostly limited to the early postpartum. Finally, Class 5 was characterized by very modest increases in all measures of distress and showed the greatest stability compared to the other classes.

Two of the largest trajectory groups in this study (Class 4 and 5) were the ones showing the most stable levels of distress, representing almost 55% of our sample. This result agrees with previous research suggesting that depressive symptom severity is commonly stable in the postpartum (6, 20) and this stability may persist for years after giving birth (48, 49).

Finally, previous research suggests that mothers report higher relationship satisfaction during pregnancy with a decline postpartum (50, 51). This pattern was confirmed in our study, since mothers show a moderate (Classes 2 and 5, until 3 years postpartum Class 3) to strong (Class 1) increase in marital stress after birth. The reasons for increased marital stress might include unmet expectations of paternal involvement, or unbalanced childcare and household chores (52-54).

Clinical Implications

Our findings help identify relevant biological and environmental factors that contribute to individual differences in different domains of maternal distress over time. All of the factors investigated in this study could be assessed even during pregnancy to identify mothers with the highest risk for distress across the postpartum and to offer them additional support. Increased maternal wellbeing could in turn positively affect offspring psychosocial adjustment and neurodevelopment (55). Maternal postpartum distress impacts her personal and psychological parenting resources and is linked to decreased maternal sensitivity towards her child. Indeed, membership probability in the Class with the highest average distress levels (ADM Class 1), was associated to lower maternal sensitivity at 18 and 48 months, decreased school readiness of the child at 60 months, and higher levels of child-reported separation anxiety at 60 months (data not

shown). Consequently, identifying mothers at risk for high levels of distress in the postpartum could support the planning of targeted interventions to prevent mothers and their children from developing psychosocial impairment.

Strengths and Limitations

We used an innovative approach to analyze longitudinal data and to exploit the multivariate assessment of maternal psychosocial stress in the postpartum. The decomposition of the trajectories into average distress and centered trajectory scores allowed us to address the change over time in postpartum distress specifically, which might be interesting in the clinical setting. Additionally, the data were derived from a longitudinal cohort study with multiple assessments in the extended postnatal period until school age, while many studies are restricted to the first three years after childbirth. Last, the inclusion of an interaction term between genetic risk and prenatal symptoms of depression provides information about the degree to which a mother suffered from prenatal symptoms of depression given her genetic risk.

Although promising, the results of this study need to be replicated in an independent cohort with analogous measures of distress, psychosocial, and genetic risk factors, to increase the generalizability of our findings. Moreover, as with many longitudinal studies, we had a high attrition rate due to study dropouts and missing data, resulting in a modest sample size, especially for a genetic study. Finally, we caution against interpreting the factors associated with membership probabilities as being causal. In particular, we did not examine any potentially stressful life events during the post-partum period, which might redirect the trajectory significantly to increased distress levels, thereby also affecting mean distress levels.

Conclusion

We applied an innovative statistical approach accounting for the heterogeneity in the population to identify classes of mothers experiencing distinct longitudinal patterns of distress. Additionally, we assessed genetic and psychosocial factors associated with these classes. Our findings could be relevant in a clinical setting, e.g. for identifying mothers at risk for high levels of distress in the postpartum and thus the planning of targeted interventions supporting mother and child mental wellbeing.

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