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Citation for published version:
Tuovinen, S, Lahti-Pulkkinen, M, Girchenko, P, Heinonen, K, Lahti, J, Reynolds, RM, Hämäläinen, E, Villa, PM, Kajantie, E, Laivuori, H & Raikkonen, K 2020, 'Maternal antenatal stress and mental and behavioral disorders in their children', *Journal of Affective Disorders (JAD)*, vol. 278.
https://doi.org/10.1016/j.jad.2020.09.063

Digital Object Identifier (DOI):
10.1016/j.jad.2020.09.063

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Publisher's PDF, also known as Version of record

Published In:
Journal of Affective Disorders (JAD)

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OPEN ACCESS

Download date: 27. Apr. 2024

Journal of Affective Disorders 278 (2021) 57–65

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Maternal antenatal stress and mental and behavioral disorders in their children

Soile Tuovinen[a,*], Marius Lahti-Pulkkinen[a], Polina Girchenko[a], Kati Heinonen[a], Jari Lahti[a], Rebecca M Reynolds[b], Esa Hämäläinen[c], Pia M Villa[d], Eero Kajantie[e,f,g,h], Hannele Laivuori[i,j,k], Katri Raikkonen[a]

[a] Department of Psychology and Logopedics, Faculty of Medicine, University of Helsinki, Finland
[b] Centre for Cardiovascular Science, Queen's Medical Research Institute, University of Edinburgh, Edinburgh, United Kingdom
[c] Department of Clinical Chemistry, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
[d] Obstetrics and Gynecology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
[e] National Institute for Health and Welfare, Helsinki, Finland
[f] PEDEGO Research Unit, MRC Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland
[g] Children's Hospital, Helsinki University Hospital and University of Helsinki, Helsinki, Finland
[h] Department of Clinical and Molecular Medicine, Norwegian University for Science and Technology, Trondheim, Norway
[i] Medical and Clinical Genetics, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
[j] Institute for Molecular Medicine Finland (FIMM), Helsinki Institute of Life Science, University of Helsinki, Helsinki, Finland
[k] Department of Obstetrics and Gynecology, Tampere University Hospital and Tampere University, Faculty of Medicine and Health Technology, Tampere, Finland

ARTICLE INFO

Keywords:
Fetal programming
Mental disorders
Prenatal stress
Depression
Anxiety

ABSTRACT

Background: Maternal antenatal stress, including symptoms of depression, anxiety and perceived stress, is associated with mental and behavioral problems in children. Whether it is associated with child mental and behavioral disorders remains uncertain. We examined if maternal antenatal symptoms of depression, anxiety and perceived stress were associated with mental and behavioral disorders in their children, if the associations varied according to gestational week, stress type, fluctuating or consistently high symptoms, and if they were driven by maternal or paternal lifetime mood or anxiety disorders.

Methods: 3365 mothers participating in the Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction (PREDO) study completed the Center for Epidemiologic Studies Depression Scale, the State Anxiety Inventory and the Perceived Stress Scale up to 14 times throughout pregnancy. The Care Register for Health Care provided data on mental and behavioral (including neurodevelopmental) disorders for their children from birth (11/07/2006–07/24/2010) until 12/31/2016 and for parental lifetime mood and anxiety disorders until 12/31/2016.

Results: The hazard of any childhood mental and behavioral disorder (HR = 1.91, 95% CI: 1.39–2.51) was significantly higher for children whose mothers reported consistently high in comparison to consistently low levels of all types of stress throughout pregnancy. The associations remained significant when adjusted for maternal and paternal lifetime mood and anxiety disorders (and their comorbidity and timing and mood disorder type).

Conclusion: Maternal antenatal stress is associated with higher risk of childhood mental and behavioral disorders. Efforts to reduce maternal antenatal stress should be given a high priority to improve child mental health.

1. Introduction

Maternal antenatal stress, including symptoms of depression, anxiety and perceived stress, is common, complicating 10% to 20% of all pregnancies (Bennett et al., 2004; Gavin et al., 2005; Goodman et al., 2014; Lahti et al., 2017; Molyneaux et al., 2014; Tuovinen et al., 2018; Wallwiener et al., 2019). It hinders maternal well-being and quality of life during pregnancy and has been associated with maternal

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; STAI, State Anxiety Inventory; PPS, Perceived Stress Scale; HILMO, Finnish Care Register for Health Care; ICD-10, International Statistical Classification of Diseases and Related Health Problems-10; LCA, latent class analysis; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion

* Corresponding author.
E-mail address: soile.tuovinen@helsinki.fi (S. Tuovinen).

https://doi.org/10.1016/j.jad.2020.09.063
Received 27 May 2020; Received in revised form 7 September 2020; Accepted 11 September 2020
Available online 15 September 2020
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overweight and obesity (Kumpulainen et al., 2018) and increased risk for obstetric complications (Kurki et al., 2000; Qiu et al., 2009). Maternal antenatal stress has also been associated with child's increased risk of low birth weight (Bussières et al., 2015; Grote et al., 2010) and preterm birth (Bussières et al., 2015; Grigoriadis et al., 2013; Grote et al., 2010; Pesonen et al., 2016).

The risks of children exposed to maternal stress *in utero* are not restricted to the perinatal period. They appear to extend to later life stages and to a number of adverse developmental outcomes, especially to those related to mental, emotional and behavioral problems. Indeed, a number of studies have demonstrated that maternal antenatal stress is associated with increased risk of developmental delay, poorer cognition, difficult temperament, behavioral dysregulation, and internalizing and externalizing behavior problems (Lahti et al., 2017; Madigan et al., 2018; Manzari et al., 2019; O'Donnell et al., 2014; Räikkönen et al., 2011; Toffol et al., 2019; Tuovinen et al., 2018; Van den Bergh et al., 2017; Wolford et al., 2017) in children. These findings support the Developmental Origins of Health and Disease (DOHaD)-framework according to which prenatal exposure to environmental adversity may carry long-lasting effects on brain development and brain developmental sequelae (Barker, 2007).

However, while maternal antenatal stress has been associated with child mental, emotional and behavioral problems, it remains uncertain whether this translates to a risk of more severe problems that meet the criteria of childhood mental and behavioral disorders. We are aware of only one study which has tested if maternal antenatal stress is associated with child mental and behavioral disorders. In the Avon Longitudinal Study of Parents and Children (ALSPAC), maternal depressive symptoms measured at gestational weeks 18 and 32 and maternal anxiety symptoms measured at week 18, but not at week 32, predicted probable borderline personality disorder in the children at age 11–12 years (Winsper et al., 2015). Further, maternal depressive symptoms measured at week 18 predicted depression (Pearson et al., 2013) and anxiety disorders (Capron et al., 2015) and maternal anxiety symptoms measured at week 18 predicted comorbid depression and anxiety disorders in the children at age 18 years (Capron et al., 2015).

As the ALSPAC study focused only on adolescent borderline personality and depression and anxiety disorders, it remains unknown if any potential associations extend to any childhood mental and behavioral disorder. The ALSPAC study also measured maternal depressive and anxiety symptoms only twice during pregnancy. Hence it still remains unknown if there exists a critical window of vulnerability for maternal stress that varies according to the gestational week, and if any fluctuations in maternal antenatal stress or consistently high levels are more critical for brain developmental sequelae than the level of maternal antenatal stress at any one or two time points during pregnancy. It also remains unclear if maternal symptoms of depression, anxiety and stress carry equal harms on child mental and behavioral disorders (Madigan et al., 2018), and whether any associations of maternal antenatal stress with child's disorders are driven by maternal or paternal lifetime mood or anxiety disorder diagnoses.

To address these knowledge gaps, we tested in a large sample of pregnant Finnish women whether maternal antenatal symptoms of depression, anxiety and perceived stress, measured biweekly up to 14 times during pregnancy, are associated with an increased risk of any mental and behavioral disorder in their children followed-up from birth to 6.4–10.8 years of age. The repeated measurements allowed us to study if the predictive significance of maternal antenatal stress varied according to the stage of pregnancy, if any fluctuations or consistently high levels of antenatal stress predicted the risk of any childhood mental and behavioral disorder, if the associations varied according to the type of stress, and if the associations were driven by maternal or paternal lifetime mood or anxiety disorder diagnoses.

2. Methods

2.1. Participants

The Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction (PREDO) study comprises 4777 mothers who gave birth to a singleton liveborn child in Finland between 2006 and 2010 (Girchenko et al., 2017). Recruitment took place at ten study hospitals in Southern/Eastern Finland at the first fetal ultrasound screening in early pregnancy. Three women have since withdrawn from the study. Of the 4774 women, 3365 (70.5%) completed biweekly questionnaires on stress during pregnancy.

Diagnoses on mental and behavioral disorders from childbirth up to 31 December 2016 were available for all 3365 of their children (follow-up data attrition 0%). At the end of the register follow-up the children were 6.4–10.8 years-of-age [median = 8.2, interquartile range: 7.7–8.8].

Compared to the women who did not fill in the antenatal stress questionnaires (n = 1409), those who did (n = 3365) were older (31.9 vs. 30.9 years), more often primiparous (40.9% vs. 33.9%), smoked less often throughout pregnancy (6.7% vs. 13.2%), and had a higher education level (upper tertiary: 34.2% vs. 29.4%) ($p < 0.01$), but did not differ in other study variables (all $p > 0.11$).

All participating women signed an informed consent. The consent enabled linkage of nationwide health register data for the women, their spouses and children using unique personal identification numbers assigned to all Finnish citizens and permanent residents since 1971. The PREDO study protocol was approved by the Ethics Committees of the Helsinki and Uusimaa Hospital District and recruitment was conducted with permission from the participating study hospitals.

2.2. Maternal antenatal stress

The women completed the questionnaire on antenatal stress biweekly up to 14 times throughout pregnancy between 12 and 13 and 38–39 gestational weeks/delivery. Depressive symptoms were measured using the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977). The 20 CES-D items are rated from none (0) to all (3) of the time during the past week, and a sumscore ranges from 0 to 60.

Anxiety symptoms were measured using the State Anxiety Inventory (STAI) (Spielberg et al., 1970). The 20 STAI items are rated from not at all (1) to very much (4) reflecting the present state, and a sumscore ranges from 20 to 80.

Perceived stress was measured using the Perceived Stress Scale (PSS) (Cohen et al., 1983). The five PSS items are rated from never (0) to very often (4), and indicate perceived stress during the past two weeks (Cohen, 1988; Cohen et al., 1983), and a sumscore ranges from 0 to 20.

All three scales have good psychometric properties (Beck et al., 1996; Cohen, 1988; Cohen et al., 1983; Karam et al., 2012; Radloff, 1977). They have also been validated in pregnant populations (Gunning et al., 2010; Karam et al., 2012; Maloni et al., 2005; Tendais et al., 2014). In the present study sample, the Cronbach's alphas for the CES-D varied from 0.89 to 0.92, for the PSS they varied from 0.74 to 0.78, and for the STAI it was 0.95 across all the different measurement points.

2.3. Childhood mental and behavioral disorders

We identified diagnoses of childhood mental and behavioral disorders from the Finnish Care Register for Health Care (HILMO) from the birth of the child between 11/07/2006 and 07/24/2010 to 12/31/2016. The HILMO includes primary and subsidiary diagnoses of all inpatient and outpatient hospital visits and all treatments in specialized medical care coded using the International Statistical Classification of

Diseases and Related Health Problems-10 (ICD-10) (Table S1, available online) during the study period, and is a valid tool for research (Sund, 2012). We studied any mental and behavioral disorder (ICD-10: F00-F99) as the primary outcome. As secondary outcomes we studied disorders of psychological development (F8) and emotional and behavioral disorders of childhood origin (F9) as they were the most frequent.

2.4. Covariates

Covariates included maternal age at childbirth (years), parity (primiparous/multiparous), smoking during pregnancy (no/quit/smoked throughout), early pregnancy body mass index (BMI) (normal weight [BMI < 25 kg/m^2]/overweight [BMI = 25–29 kg/m^2]/obesity [BMI ≥ 30 kg/m^2]), hypertensive disorders (normotension/ chronic hypertension, preeclampsia, gestational hypertension or unspecified hypertension in current pregnancy/ hypertension before current pregnancy; ICD-10: I1, 010-011, O13-O16), diabetes disorders (no/type 1, type 2 or gestational diabetes/ diabetes only in previous pregnancy; ICD-10: E08-E14, O24), and maternal and paternal lifetime mood or anxiety disorder diagnoses (no/ICD-8: 296, 298.00, 300, 301.10, 305, 306.80, 307.99; ICD-9: 296, 300, 301.1, 307.8, 309; ICD-10: F30-F39, F40-F48; Table S1), child's sex, gestational length (weeks), and weight (grams) at birth, with data extracted from hospital records, Medical Birth Register and/ or HILMO; maternal alcohol use during pregnancy (no/yes), and education level (secondary or less/lower tertiary/upper tertiary) were self-reported in early pregnancy. We also conducted additional adjustments for co-morbidity and timing (before / during or after pregnancy) of maternal and paternal mood and anxiety disorders and for type (recurrent / episodic) of maternal and paternal mood disorders (see Table 1 for specific definitions).

2.5. Statistical analyses

Statistical analyses were conducted by using IBM SPSS Statistics software version 24, R version 3.5.2. and Stata MP version 15. Associations between maternal antenatal stress and any mental and behavioral, psychological development and emotional and behavioral disorders in children were tested using Cox proportional hazard models. We first studied the associations of each type of stress separately by averaging depressive, anxiety and stress symptoms across the biweekly measurement points during pregnancy. We then used Student's t-test for dependent samples to study if the hazard ratios differed significantly between the different types of stress. Before applying the Cox regression analyses, we tested if the hazard ratios changed across time, by applying time-dependent Cox regression analysis. No time-dependent effects were found (all $p > 0.05$). The proportionality assumptions were met, there were no outliers, and there was no nonlinearity.

With Cox proportional hazard models, we also tested if maternal depressive, anxiety and perceived stress symptoms showed gestational week -specific effects on child mental and behavioral disorders. To further address gestational-week-specificity of these associations, we conducted reverse temporal mixed random effects regression analyses. In these models, biweekly depressive, anxiety and stress symptoms served as outcomes, each tested in a separate model. Child mental and behavioral disorder diagnoses served as the between-person predictor, gestational week at the time of the biweekly measurement of depressive, anxiety and stress symptoms served as a within-person predictor, and their interaction effect tested if the associations varied by gestational week.

To study if fluctuating or consistently high levels of antenatal stress were more critical in predicting child hazard of mental and behavioral disorders, we applied latent class analysis (LCA) to identify subgroups of women based on their antenatal stress profiles defined by their biweekly depressive, anxiety and perceived stress symptoms simultaneously. At each LCA step, we compared solutions with two to six subgroups. Based on criteria for the optimal number of classes described by Kongsted and Nielsen (Kongsted and Nielsen, 2017), the optimal solution was based on (1) goodness-of-fit criteria: Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), (2) reasonable distribution of participants across subgroups (at least 10% of the sample), (3) high certainty of classification identified by posterior probabilities, and (4) clear clinical characteristics of the participants within each of the subgroups. By using the most optimal LCA solution, we tested with Cox regressions whether the hazard ratios of child mental and behavioral disorders differed between the LCA subgroups.

To study whether any associations between maternal antenatal stress and child mental and behavioral disorders were driven by maternal or paternal lifetime mood or anxiety disorders, we included these variables into the models as covariates, following the other covariates related to the mother and child. Further models adjusted for the co-morbidity of maternal and paternal mood and anxiety disorders, type of mood disorders, and timing of mood and anxiety disorders. In the Cox models, child sex was treated as a stratifying variable.

As effects sizes, we present hazard ratios (HR) and their 95% confidence interval (95% CI) and present *p*-values as two-tailed.

3. Results

Table 1 shows the characteristics of the sample. Table S2 shows the associations of the covariates with maternal depressive, anxiety and perceived stress symptoms, and Table S3 with childhood mental and behavioral disorders in the offspring. Maternal biweekly depressive (r = 0.46–0.80; all $p < 0.001$), anxiety (r = 0.41–0.68; all $p < 0.001$) and perceived stress symptoms (r = 0.43–0.72; all $p < 0.001$) were significantly correlated across time, and they were also significantly intercorrelated (r = 0.71–0.79 for depression and anxiety; r = 0.72–0.78 for depression and perceived stress; r = 0.66–0.73 for anxiety and perceived stress; all $p < 0.001$).

3.1. Maternal antenatal stress, type of stress and gestational-week-specificity

Table 2 shows that higher average levels of maternal antenatal depressive, anxiety and perceived stress symptoms were associated with higher offspring hazards of any childhood mental and behavioral disorder (F00-F99), and psychological development (F8) and emotional and behavioral (F9) disorders. These associations remained significant when adjusted for the covariates and maternal and paternal lifetime mood and anxiety disorders. Further adjustments for comorbidity and timing of maternal and paternal mood and anxiety disorders, and type of mood disorders had little (if any) effects on these associations (Table S4).

Student's *t*-test indicated that the hazard ratios were not significantly different for maternal depressive, anxiety and perceived stress symptoms ($p > 0.15$ for comparing the hazard ratios).

Fig. 1 shows the associations between maternal biweekly depressive, anxiety and perceived stress symptoms during gestation and any mental and behavioral disorder in children. The hazards were significant across all biweekly measurement points, except for one: maternal anxiety symptoms at 22 gestational weeks were not significantly associated with child hazard of any mental and behavioral disorder. Reverse temporal mixed model regressions verified that the associations were not gestation-week specific. Figure S1 shows the associations of biweekly antenatal depressive, anxiety and stress symptoms and child psychological development and emotional and behavioral disorders.

3.2. Fluctuating or persistently high levels of maternal antenatal stress

When we applied the LCA to identify subgroups of women based on their biweekly depressive, anxiety and perceived stress symptoms analyzed simultaneously, the most optimal solution was one which

Table 1
Characteristics of the sample.

	Data available (N)	Mean/ N	SD/%	Range
Maternal characteristics				
Age at delivery (y)	3365	31.8	4.7	17.0–47.4
Education	3360			
Secondary or less		1342	39.9%	
Lower tertiary		869	25.9%	
Upper tertiary		1149	34.2%	
Parity, primiparous	3365	1375	40.9%	
Alcohol consumption during pregnancy, yes	3327	502	15.1%	
Smoking during pregnancy	3364			
No smoking		3139	93.3%	
Quit smoking during 1st trimester		113	3.4%	
Smoked throughout pregnancy		112	3.3%	
Early pregnancy body mass index, kg/m^2	3357			
<24.99		2275	67.8%	
25–29.99		646	19.2%	
>30		436	13.0%	
Diabetes (E08-E14, O24)[a,b]	3365			
No diabetes		2885	85.8%	
Type 1 or type 2 diabetes or gestational diabetes in current pregnancy		425	12.6%	
Diabetes only in previous pregnancy		55	1.6%	
Hypertensive disorders (I1, O10-O11, O13-O16)[a,c]	3365			
Normotension		2680	79.6%	
Chronic hypertension or preeclampsia, gestational or unspecified hypertension in current pregnancy		469	13.9%	
Hypertension before current pregnancy		216	6.4%	
Lifetime mood (F3)[a,d] or anxiety disorder (F4)[a,e] diagnosis, yes	3365	438	13.0%	
Comorbidity of mood and anxiety disorders				
Both mood and anxiety disorder diagnoses, yes		131	3.9%	
Either mood or anxiety disorder diagnosis, yes		307	9.1%	
Type of mood disorder				
Recurrent mood disorder (F33 or F31)[a], yes		152	4.5%	
Mood disorder episode (F32 or F30)[a], yes		140	4.2%	
Timing of mood or anxiety disorder				
Before pregnancy, yes		140	4.2%	
During or after pregnancy, yes		298	8.9%	
Antenatal depressive symptoms (range 0–60)	3365			
Mean of biweekly CES-D scores		11.4	6.4	0–48.3
Antenatal anxiety symptoms (range 20–80)	3365			
Mean of STAI scores		33.4	7.6	20.0–78.3
Antenatal perceived stress symptoms (range 0–20)	3365			
Mean of PSS scores		5.1	2.5	0.1–18.2
Paternal lifetime mood (F3)[a,d] or anxiety disorder (F4)[a,e] diagnosis, yes	1800	106	5.9%	
Comorbidity of mood and anxiety disorders				
Both mood and anxiety disorder diagnoses, yes		15	0.8%	
Either mood or anxiety disorder diagnosis, yes		91	5.1%	
Type of mood disorder				
Recurrent mood disorder (F33 or F31)[a], yes		18	1.0%	
Mood disorder episode (F32 or F30)[a], yes		34	1.9%	
Timing of mood or anxiety disorder				
Before pregnancy, yes		64	3.6%	
During or after pregnancy, yes		42	2.3%	
Maternal and paternal mood (F3)[a,d] or anxiety disorder (F4)[a,e] diagnosis				
Both yes	1800	20	1.1%	
Maternal only, yes		150	8.3%	
Paternal only, yes		86	4.8%	
Child characteristics				
Child's sex, male	3365	1736	51.6%	
Birth weight (g)	3353	3525.7	517.3	580.0–5490.0
Gestational age (weeks)	3365	39.9	1.6	27.7–42.7
Birth year	3365			2006–2010
Any childhood mental and behavioral disorder (F00-F99)[a]	3365	274	8.2%	
Disorders of psychological development (F8)[a]		173	5.1%	
Emotional and behavioral disorders (F9)[a]		139	4.1%	

[a] Diagnostic codes refer to International Statistical Classification of Diseases and Related Health Problems (ICD) 10th revision codes.
[b] Corresponding ICD 9th revision codes are 250, 648.0, 648.8.
[c] Corresponding ICD 9th revision codes are 642, 401–405.
[d] Corresponding ICD 9th revision codes are 296, 3004A, 3011D and corresponding ICD 8th revision codes are 296, 298.00, 300.4, 301.10.
[e] Corresponding ICD 9th revision codes are 3000–3003, 3006–3009, 3078A, 309 and corresponding ICD 8th revision codes are 300.00–300.30, 300.50–300.99, 305, 306.80, 307.99 SD, standard deviation; CES-D, Center for Epidemiological Studies Depression Scale; STAI, State Anxiety Inventory; PPS, Perceived Stress Scale.

identified three groups of women (in comparison to solutions with fewer and larger number of groups; Table S5) who differed from each other in their levels of antenatal symptomatology. In all the groups, stress symptoms showed high stability and lack of fluctuation across pregnancy. The groups showed consistently low (n = 1359, 40.4%), moderate (n = 1475, 43.8%) and high (n = 531, 15.8%) levels of

Table 2
Maternal antenatal depressive, anxiety and stress symptoms and child mental and behavioral disorders.

	Child					
	Any mental or behavioral disorder (F00-F99)		Disorders of psychological development (F8)		Emotional and behavioral disorders (F9)	
	vs. no disorder					
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Maternal						
Depressive symptoms pregnancy mean score (standardized)						
Model 1	1.28 (1.14,1.44)	<0.001	1.34 (1.16,1.55)	<0.001	1.29 (1.10,1.52)	0.002
Model 2	1.26 (1.12,1.43)	<0.001	1.33 (1.14,1.55)	<0.001	1.30 (1.10,1.54)	0.002
Model 3	1.19 (1.05,1.35)	0.006	1.26 (1.08,1.47)	0.004	1.18 (0.99,1.41)	0.057
Anxiety symptoms pregnancy mean score (standardized)						
Model 1	1.25 (1.13,1.40)	<0.001	1.33 (1.17,1.52)	<0.001	1.30 (1.12,1.50)	0.001
Model 2	1.25 (1.12,1.39)	<0.001	1.34 (1.17,1.53)	<0.001	1.30 (1.12,1.52)	0.001
Model 3	1.18 (1.05,1.32)	0.004	1.27 (1.10,1.46)	0.001	1.20 (1.02,1.40)	0.02
Perceived stress symptoms pregnancy mean score (standardized)						
Model 1	1.29 (1.15,1.43)	<0.001	1.36 (1.19,1.55)	<0.001	1.33 (1.15,1.55)	<0.001
Model 2	1.27 (1.14,1.42)	<0.001	1.35 (1.18,1.55)	<0.001	1.33 (1.14,1.55)	<0.001
Model 3	1.20 (1.07,1.35)	0.002	1.29 (1.12,1.49)	0.001	1.23 (1.05,1.44)	0.01

Model 1. Stratified for sex and adjusted for child birth year.
Model 2. Stratified for sex and adjusted for child birth year and further adjusted for maternal age, parity, education, alcohol use and smoking during pregnancy, early pregnancy body mass index, type 1 diabetes or gestational diabetes in current pregnancy, type 2 or other diabetes, chronic hypertension or preeclampsia or gestational or unspecified hypertension in current pregnancy, hypertension before current pregnancy, gestational length, and child's birthweight for gestation.
Model 3. Stratified for sex and adjusted as in Model 2 and further for maternal and paternal lifetime mood or anxiety disorder diagnoses.
HR, hazard ratio; 95% CI, 95% confidence interval
F codes in parenthesis refer to International Statistical Classification of Diseases and Related Health Problems 10th revision codes for mental and behavioral disorders.

depressive, anxiety and perceived stress symptoms throughout pregnancy (Fig. 2).

Compared to the children of mothers with consistently low levels of depressive, anxiety and perceived stress symptoms, the children of mothers with consistently high levels of depressive, anxiety and perceived stress symptoms throughout pregnancy had higher hazard of any childhood mental and behavioral disorder, and psychological development and emotional and behavioral disorders (Fig. 3). These associations remained significant when adjusted for the covariates and maternal and paternal lifetime mood and anxiety disorders.

4. Discussion

Findings from this study showed that higher maternal antenatal depressive, anxiety and stress symptoms were associated with 1.25–1.36 higher hazards of any childhood mental and behavioral disorder in the offspring. This was driven by associations with disorders of psychological development and emotional and behavioral disorders severe enough to require inpatient treatment or outpatient treatment in public specialized medical care in a follow-up from birth to 6.4–10.8 years. We found that maternal stress symptoms were highly stable throughout pregnancy, and that their associations with child mental

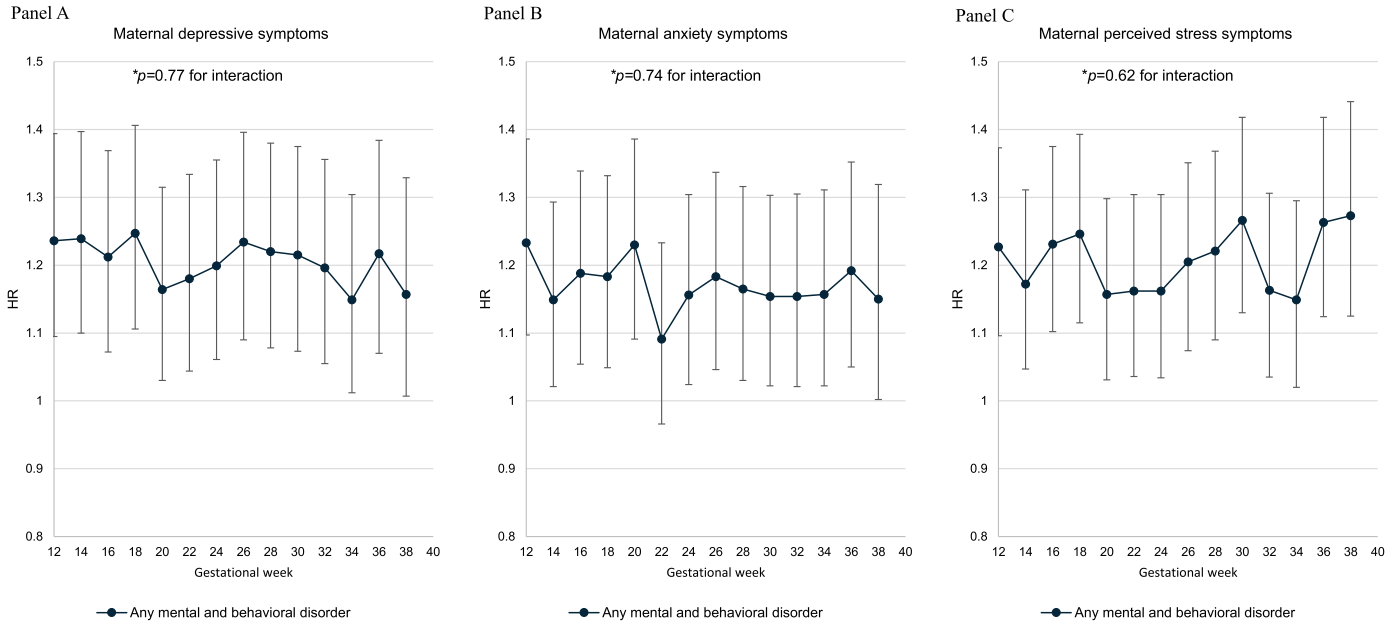

Fig. 1. Associations between maternal biweekly stress symptoms and any childhood mental and behavioral disorder (International Statistical Classification of Diseases and Related Health Problems 10th revision codes F00-F99)
*Interactions between any childhood mental and behavioral disorder and gestational week at the time of antenatal stress measurement in models predicting maternal biweekly symptoms of depressive, anxiety and perceived stress during pregnancy.
HR, Hazard ratio, stratified for sex and adjusted for child birth year (Model 1).

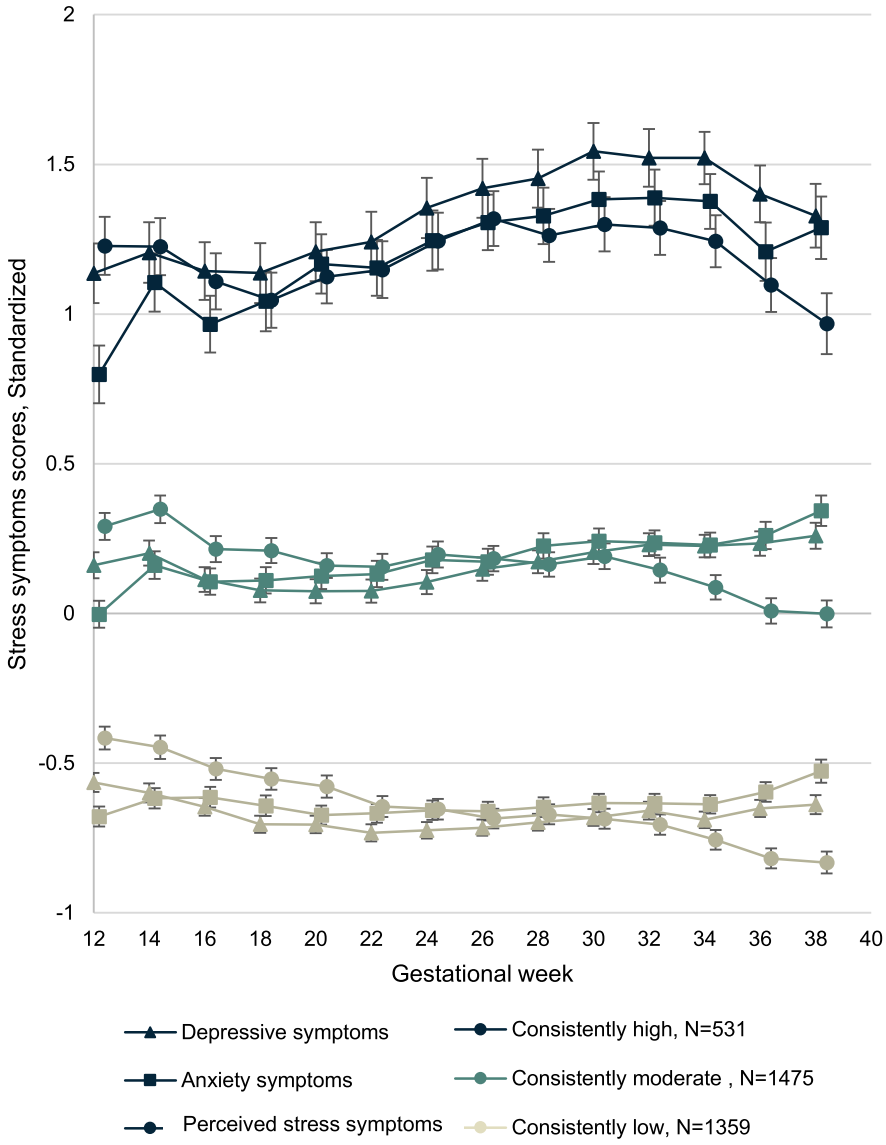

Fig. 2. Latent class analysis (LCA) on the depressive, anxiety and stress symptoms clusters. The figure shows the mean standardized symptom scores across pregnancy in three groups of mothers with low, moderate and high symptoms. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and behavioral disorders were nonspecific to gestation stage.

In addition, the associations were similar regardless of maternal antenatal stress type. This was not surprising as depressive, anxiety and perceived stress symptoms, though being distinct constructs, were highly correlated. However, child hazards of any mental and behavioral, psychological development and emotional and behavioral disorders were the highest, almost 2-fold, for children of mothers who reported consistently high in comparison with low levels of depressive, anxiety as well as perceived stress symptoms throughout pregnancy. Hence, while correlated, depressive, anxiety and perceived stress symptoms may have allowed us to capture a wide range of highly consistent maternal antenatal stress symptomatology.

Our findings correspond well with the findings from ALSPAC showing that maternal depressive and/or anxiety symptoms measured once or twice during pregnancy were associated with child mental disorders (Capron et al., 2015; Pearson et al., 2013; Winsper et al., 2015). However, these ALSPAC studies were restricted to borderline personality disorder, depression and anxiety disorders. Thus, our study extends the previous literature by showing that the effects of maternal antenatal stress symptoms generalize to increased child risk of any childhood mental and behavioral, psychological development and emotional and behavioral disorders. Further, the previous studies have been inconsistent regarding the gestational week at which the effects of antenatal maternal stress on child mental, emotional and behavioral problems and mental disorders are most pronounced (Van den Bergh et al., 2017; Winsper et al., 2015). With repeated measurements of maternal antenatal stress, we were able to show that the associations were non-specific to gestation stage.

These associations were not explained by maternal or paternal lifetime mood and anxiety disorders. They were not either explained by co-morbidity of maternal or paternal mood and anxiety disorders, timing of maternal and paternal mood and anxiety disorders before, during or after pregnancy, or whether maternal or paternal mood disorder was chronic or episodic. Thus, the association between maternal antenatal psychological stress and child mental and behavioral disorders seems not to be explained by maternal or paternal mood or anxiety disorders. These findings thus suggest that even at subclinical levels, maternal antenatal stress is associated with increased child hazard of mental and behavioral disorders. Further, these findings suggest that these effects cannot be attributed to hereditary factors nor

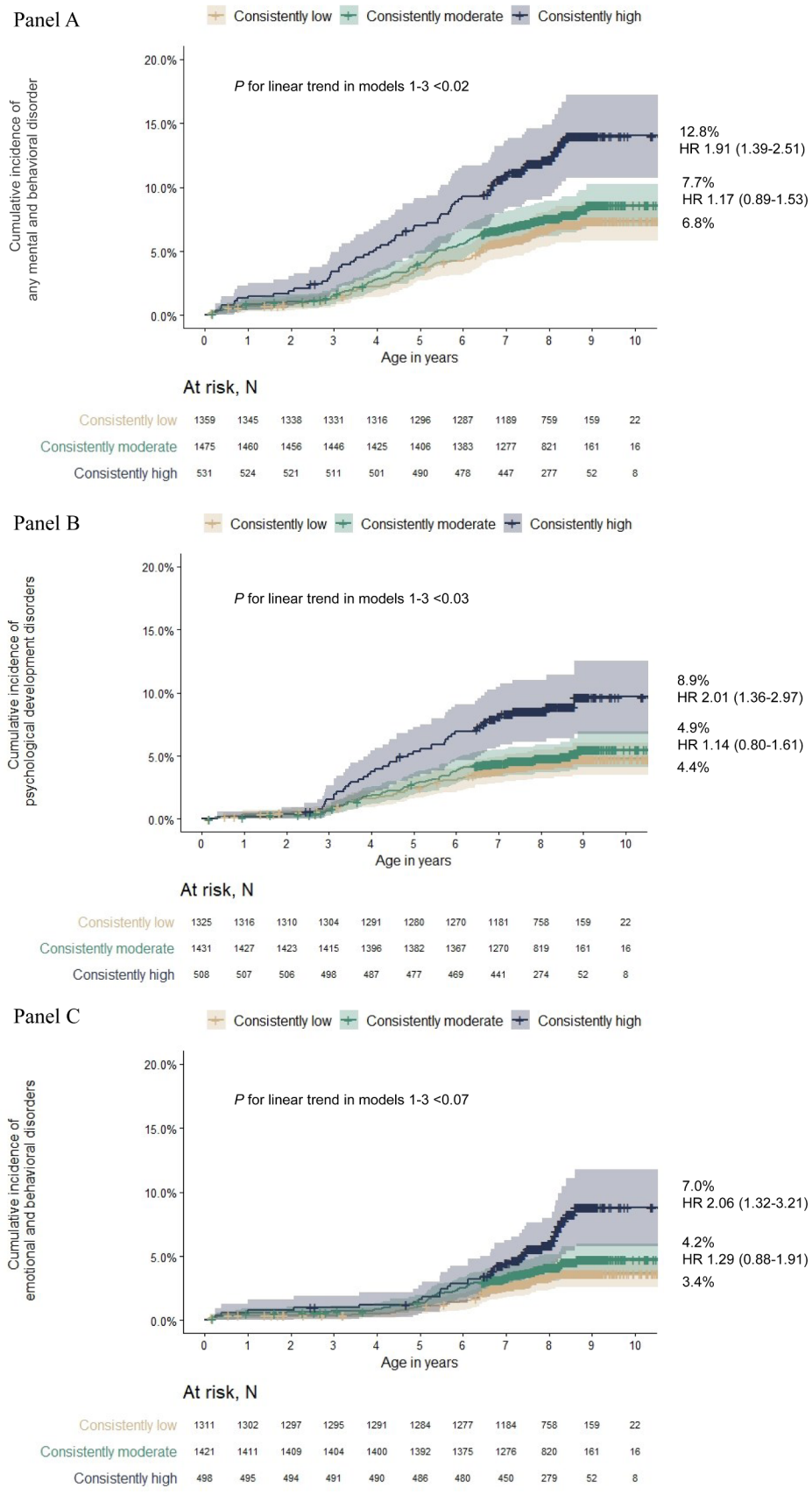

Fig. 3. Cumulative incidences of any childhood mental and behavioral disorder (F00-F99) (Panel A), psychological development (F8) (Panel B) and emotional and behavioral disorders (F9) (Panel C) in children according to their mothers with consistently low, moderate and high levels of antenatal stress symptoms. F codes refer to International Statistical Classification of Diseases and Health Related Problems 10th revision codes.
HR, Hazard ratio compared to the children of mothers with consistently low levels of antenatal stress symptoms, stratified for sex and adjusted for child birth year (Model 1). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

postnatal environmental factors, and they lend credence to the prenatal programming effect (Barker, 2007).

Thus, underlying our findings may be biological mechanisms that include enhanced fetal exposure to glucocorticoids (Räikkönen et al., 2017; Van den Bergh et al., 2017; Wolford et al., 2019), functional and structural changes of related brain areas (Buss et al., 2012; Huizink and

De Rooij, 2018) and inflammatory pathways (Girchenko et al., 2019; Lahti-Pulkkinen et al., 2019). They may also include changes in placental morphology (Lahti-Pulkkinen et al., 2018), and epigenetic modifications in placental glucocorticoid signaling (Raikkonen et al., 2015; Reynolds et al., 2015) and epigenetic immaturity of the child at birth (Suarez et al., 2018). Changes in maternal health behaviors, such as diet and physical activity, cannot either be ruled out (Westerneng et al., 2017), even though the associations were not driven by maternal overweight/obesity, hypertension or diabetes in pregnancy, or smoking or alcohol use during pregnancy. Overall, the underlying mechanisms are likely complex, and may include a possible generic vulnerability (Huizink and De Rooij, 2018). In addition, while maternal antenatal depressive, anxiety and perceived stress symptoms were highly correlated and their associations with child mental and behavioral disorders were not significantly different, it remains possible that the effects of different types of maternal stress during pregnancy are explained by different biological pathways and mechanisms.

Strengths of our study include the prospective design, large and well-characterized sample, which corresponds well to the general population of women who gave birth to a child in Finland in 2006–2017 (Räikkönen et al., 2020), and maternal depressive, anxiety and perceived stress symptoms measured with standardized psychological questionnaires throughout pregnancy. In addition, we focused on mental and behavioral disorder diagnosis derived from a nationwide register which decreases the common-method bias present in studies where both predictor and outcome are reported by the same person (Podsakoff et al., 2003).

The nationwide HILMO register has almost 100% coverage, which resulted in a 0% attrition rate after childbirth in our sample. We were also able to control for several important covariates related to the mother and child as well as maternal and paternal lifetime mood and anxiety disorder diagnoses. However, our study has also limitations. We had no data on paternal stress during pregnancy. Women who did not fill in, in comparison to women who did fill in the antenatal stress questionnaires smoked more frequently throughout pregnancy, were younger and had a lower education level. Thus, the potential effects of selective dropout cannot be ruled out. However, the decrease in sample size reduced statistical power and thus should work against our hypothesis rather than amplify the associations (Nilsen et al., 2009).

To conclude, maternal antenatal depressive, anxiety and perceived stress symptoms are associated with increased hazards of mental and behavioral disorders in their children. These associations pertain in particular to disorders of psychological development and emotional and behavioral disorders. They are not gestational-week-specific, do not differ by the type of maternal antenatal stress and are not driven by maternal or paternal lifetime mood or anxiety disorders. The hazards are the highest for children of women with consistently high depressive, anxiety and perceived stress symptoms throughout pregnancy. Our findings thus suggest that efforts to reduce maternal antenatal stress symptoms should be given a high priority to improve the child mental health outcome.

Author statement

Author contributions: 1. Conception and design, or acquisition of data, or analysis and interpretation of data (Drs. Tuovinen, Lahti-Pulkkinen, Girchenko, Heinonen, Lahti, Reynolds, Hämäläinen, Villa, Kajantie, Laivuori, Räikkönen); 2. Drafting the article or revising it critically for important intellectual content (Drs. Tuovinen, Lahti-Pulkkinen, Girchenko, Heinonen, Lahti, Reynolds, Hämäläinen, Villa, Kajantie, Laivuori, Räikkönen); 3. Final approval of the version to be published (Drs. Tuovinen, Lahti-Pulkkinen, Girchenko, Heinonen, Lahti, Reynolds, Hämäläinen, Villa, Kajantie, Laivuori, Räikkönen).

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgements

The PREDO study is funded by the Academy of Finland, European Union's Horizon 2020 Award SC1–2016-RTD-733280 for Research on European Children and Adults Born Preterm (RECAP), European Commission Dynamics of Inequality Across the Life- course: structures and processes (DIAL) No 724363 for PremLife, EVO (a special state subsidy for health science research), University of Helsinki Research Funds, Signe and Ane Gyllenberg Foundation, Diabetes Research Foundation, Emil Aaltonen Foundation, Finnish Medical Foundation, Foundation for Pediatric Research, Foundation for Cardiovascular Research, Jane and Aatos Erkko Foundation, Novo Nordisk Foundation, Päivikki and Sakari Sohlberg Foundation, Sigrid Juselius Foundation, Sir Jules Thorn Charitable Trust and British Heart Foundation (RE/18/5/34216).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.09.063.

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