



Original Article

Maternal depressive symptoms during and after pregnancy are associated with poorer sleep quantity and quality and sleep disorders in 3.5-year-old offspring



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ARTICLE INFO

Article history:

Received 5 June 2018

Received in revised form

25 September 2018

Accepted 11 October 2018

Available online 14 December 2018

Keywords:

Sleep quality

Sleep quantity

Sleep disorders

Maternal antenatal depression

Longitudinal study

Early childhood

ABSTRACT

Objective: Maternal depressive symptoms during pregnancy have been associated with poor offspring sleep. Yet, it remains unknown whether depressive symptoms throughout pregnancy are more harmful to the child than depressive symptoms only during certain time periods in pregnancy, whether associations are specific to pregnancy stage, whether maternal symptomatology after pregnancy mediates or adds to the prenatal effects, and whether any effects are specific to some child sleep characteristics.

Methods: A total of 2321 mothers from the Prediction and Prevention of Pre-eclampsia and Intrauterine Growth Restriction (PREDO) study completed the Center for Epidemiological Studies Depression Scale biweekly between gestational weeks + days 12 + 0/13 + 6 and 38 + 0/39 + 6. At child's mean age of 3.5 (standard deviation = 0.7) years, mothers completed the Beck Depression Inventory–II and answered questions on child sleep quantity and quality using the Brief Infant Sleep Questionnaire (BISQ) and sleep disorders using the Sleep Disturbance Scale for Children.

Results: Maternal depressive symptoms showed high stability throughout pregnancy. Children of mothers with clinically significant symptomatology throughout pregnancy had shorter mother-rated sleep duration, longer sleep latency, higher odds for waking up two or more times during the night and for total and several specific sleep disorders. These associations were robust to covariates. However, maternal depressive symptoms at the child follow-up fully mediated the associations with sleep duration and awakenings, partially mediated those with sleep latency and disorders, and added to the effects on sleep disorders.

Conclusion: Maternal depressive symptoms throughout pregnancy are associated with mother-rated child sleep quantity, quality, and disorders. Maternal depressive symptoms at child follow-up mediate and add to the prenatal adverse effects on child sleep characteristics.

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1. Introduction

Insufficient sleep quantity, poor sleep quality, and sleep disorders, such as difficulty initiating and maintaining sleep, sleep breathing disorders, and nightmares, are common concerns in children. It has been estimated that such concerns affect up to 76% of school-aged children, with 4% of children aged 0–18 years with a diagnosed sleep disorder [1–4]. These problems tend to persist into adolescence [5] and even into adulthood [6,7]. Because insufficient sleep quantity, poor sleep quality, and sleep disorders not only increase an individual's obesity and insulin resistance [8–13] and risk for a variety of physical and mental disorders [14], but also hinder one's quality of life, cognitive, emotional, and social functioning and academic performance [15–17], it is especially important to identify factors, as early in life as possible, that may render an individual vulnerable to sleep problems.

One key early life risk factor is maternal depressive symptoms during pregnancy. Emerging evidence suggests that although pregnancy in itself induces alterations in physiological homeostasis, these alterations may be aggravated in depressive states. The alterations include changes in the hypothalamic–pituitary–adrenocortical axis, inflammatory and autonomic nervous system functioning, and in oxidative stress and nutrition levels [18–25]. These depression-related changes may alter the development of fetal cells, tissues and organs, their structure and functioning, the set points of body's chrono-biological systems, and increase the risk for adverse programmed phenotypes in the offspring that will persist throughout the lifespan [24,26]. Indeed, a series of studies have shown that maternal depressive symptoms during pregnancy are associated with sleep quantity and quality and sleep disorders of the offspring in childhood [27–33]. In one of the largest of these studies that reported findings from both the Avon Longitudinal Study of Parents and Children (ALSPAC) and the Generation R, maternal depressive symptoms measured at 32 gestational weeks in the ALSPAC and at 20 gestational weeks in the Generation R, were associated with shorter sleep duration and higher number of nighttime awakenings in children at the age of 18 and 20 months [30]. In another large-scale study reporting findings from the project Viva, maternal depressive symptoms during pregnancy were associated with the child's shorter sleep duration at ages one and two years [31]. Yet, another study using the ALSPAC data demonstrated that maternal depressive symptoms measured at 18 and 32 weeks of gestation were not associated with sleep duration or number of nighttime awakenings when the child was 6, 18, or 30 months of age but were associated with a total sleep problems score when the child was 18 and 30 months of age [32].

The existing studies have, however, typically relied on one or two measurements of maternal depressive symptoms during pregnancy. Hence, it remains unclear whether depressive symptoms throughout pregnancy carry more harmful effects to the child than depressive symptoms only during specific time periods. Moreover, the studies have not accounted for maternal depressive symptoms at the time of rating the child sleep, which in fact may bias the mother's report of child sleep. Thus, it remains unclear whether any potential associations between maternal depressive symptoms and child sleep are specific to the prenatal stage, and whether maternal depressive symptoms at the time of rating the child add to the prenatal effects. Finally, it remains unclear whether maternal depressive symptoms during pregnancy are associated with specific sleep problems or whether the associations generalize to all domains of sleep. Further specificity into these associations may afford the development of more targeted and personalized preventive interventions.

To address these caveats in the literature, we tested, in a large prospective pregnancy cohort of 2321 Finnish women and their children, whether maternal depressive symptoms measured biweekly during pregnancy starting from gestational week 12–13 were associated with their 3.5-year-old child's mother-rated nocturnal sleep duration, nighttime awakenings and sleep latency, and disorders of initiating and maintaining sleep, sleep breathing disorders, arousal disorders, sleep–wake transition disorders, disorders of excessive somnolence, and sleep hyperhidrosis. Our repeated-measures study design allowed us to test whether maternal depressive symptoms at some stages or throughout pregnancy carried harmful effects on child sleep. Finally, we also tested whether maternal depressive symptoms at the time of rating the child's sleep accounted for, mediated, or added to the effects of maternal depressive symptoms during pregnancy.

2. Methods

2.1. Participants

The participants come from the Prediction and Prevention of Pre-eclampsia and Intrauterine Growth Restriction (PREDO) study. The study design is described in the cohort profile [34]. A total of 4785 pregnant women were recruited in arrival order when they attended the first ultrasound screening at 12 + 0–13 + 6 weeks + days of gestation in one of the 10 hospital maternity clinics in southern and eastern Finland. Of them, 4777 gave birth to a singleton live child between 2006 and 2010. Of these women, 3400 (71.2% of those with live-born offspring) filled in the biweekly depressive symptoms questionnaire during pregnancy.

In 2011–2012, a total of 4585 women and their children of the original sample were invited for a follow-up (three children had died after birth or before the follow-up, 33 did not have data in Finnish nationwide Medical Birth Register, 56 women had declined participation in a follow-up, and for 100 women, addresses were not traceable), which included a survey on maternal depressive symptoms and child sleep. Of the invited women and children, 2667 (58.2%) participated.

Of the 2667 women and children with follow-up data, 2620 had data available on mother-rated child sleep at the follow-up, and 2321 had data available on both antenatal depression and child sleep. The current study sample thus comprises these 2321 women and their on-average 3.5-year-old children ($SD = 0.7$, range 1.9–5.9) (1177 boys, 1144 girls; 68.3% of those with data on depressive symptoms during pregnancy).

Compared to the women who were invited but did not participate to the follow-up study, those who participated were older (mean age 31.9 vs 31.1 years, $SD = 4.6$ vs 5.1, $p < 0.001$), had lower early-pregnancy BMI (mean 24.3 vs 24.8 kg/m^2 , $SD = 4.8$ vs 5.2, $p = 0.001$), were less likely to smoke throughout pregnancy (2.8% vs 7.5%, $p < 0.001$), were less likely to have a primary or secondary education only (37.3% vs 46.0%, $p < 0.001$), were more likely to have an upper tertiary education (35.7% vs 29.3%, $p < 0.001$), and were more likely to be primiparous (42.0% vs 35.5%, $p < 0.001$), and their children were more likely to be girls (49.3% vs 46.4%, $p = 0.049$). They did not differ in hypertensive or diabetic pregnancy disorders or depressive symptom scores during pregnancy, and their children did not differ in length of gestation, birth anthropometry, or other perinatal characteristics.

The PREDO study protocol was approved by the Ethics Committee of Obstetrics and Gynecology and Women, Children and Psychiatry of the Helsinki and Uusimaa Hospital District and by the participating hospitals. All participants provided written informed consent. Consent of participating children was provided by parent(s) or guardian(s).

2.2. Maternal depressive symptoms

Starting from gestation weeks + days 12 + 0–13 + 6, and at 2-week intervals up to delivery or gestation weeks + days 38 + 0–39 + 6, the women filled in the Center for Epidemiological Studies Depression Scale (CES-D) [35]. The scale comprises 20 questions on frequency of depressive symptoms during the past seven days, rated on a scale from none of the time (0) to all of the time (3). The total CES-D sum score is calculated as the sum of responses to all 20 questions (range 0–60), with the higher score indicating more frequent depressive symptomatology. The cutoff score of 16 or greater identifies individuals at risk for clinically relevant depression.

In addition, at the time of rating the child sleep, the mothers completed the Beck Depression Inventory–II (BDI-II), which comprises 21 questions assessing depressive symptoms during the previous two weeks. Each item contains four statements, rated from 0 to 3, reflecting increasing degrees of symptom severity [36]. The total BDI-II sum score is calculated as the sum of the responses to all 21 questions (range 0–63), with higher scores indicating more severe depressive symptomatology.

Both the CES-D and the BDI-II have good psychometric properties [35–39] and the CES-D has been used extensively and validated also in pregnant populations [38]. In our sample, the CES-D (Cronbach's $\alpha = 0.88$ – 0.92 in the 14 biweekly measurement points) and the BDI-II ($\alpha = 0.90$) showed high internal consistency.

2.3. Child sleep quantity, quality, and disorders

We used three questions from the mother-rated Brief Infant Sleep Questionnaire (BISQ) to measure child's nocturnal sleep duration (hours), latency to falling asleep for the night (minutes), and number of nighttime awakenings (categorized as none, one, two or more times) during the previous week. These questions have good test–retest reliability and discriminant validity between clinical and nonclinical groups [40].

The Sleep Disturbance Scale for Children (SDSC) [41] comprises 26 items measuring child sleep-related behaviors and disturbances during the previous six months. The items are rated on a scale ranging from 1 (never) to 5 (always–daily). In addition to a total sleep disorders score, the SDSC yields scores for six sleep disorder subscales, namely disorders of initiating and maintaining sleep, sleep breathing disorders, disorders of arousal (sleepwalking, sleep terrors, nightmares), sleep–wake transition disorders (hypnic jerks, rhythmic movement disorders, hypnagogic hallucinations, nocturnal hyperkinesia, bruxism), disorders of excessive somnolence, and sleep hyperhidrosis. Those reporting the closest score to the 85th percentile cut-off score for a given subscale were identified as having sleep disorders. The SDSC scale has good internal consistency and validity [42–44].

2.4. Covariates

These included the following maternal characteristics: age at delivery (years), early-pregnancy body mass index (BMI; kg/m²), parity (primiparous/multiparous) and smoking during pregnancy (no/quit during first trimester/smoked throughout pregnancy), and hypertensive (gestational hypertension, preeclampsia, chronic hypertension) and diabetic (gestational diabetes, type 1 diabetes; no women had type 2 diabetes) pregnancy disorders derived from the Finnish Medical Birth Register (MBR). For a subsample, diabetic and hypertensive disorders were verified by a clinical jury. Maternal education (primary or secondary/lower tertiary/upper tertiary) and alcohol use during pregnancy (yes/no) were self-reported in early pregnancy. Child characteristics included as covariates were child's

sex (girl/boy), gestational age (weeks), and weight (kg) at birth, and at the follow-up child's age and weight-for-height Standard Deviation (SD) unit score specific for the child's age and sex according to Finnish growth charts [45] derived from the child's welfare clinic records. We also accounted for the child's psychiatric symptoms rated by the mothers using the Child Behavior Checklist 1½–5 (CBCL 1½–5) [46] parallel to rating the child sleep.

2.5. Statistical analyses

We first examined maternal depressive symptoms profiles during pregnancy with a latent profile analysis. Latent profile analysis is a technique to identify a number of distinct, fully comprehensive, and nonoverlapping latent classes of individuals based on individual responses to a set of continuous indicators [47]. In our case, these classes will describe women based on their distributions of depressive symptoms across pregnancy. Our study with 14 assessments of maternal antenatal depressive symptoms among more than 2000 participants is well suited for latent profile analyses [47]. We compared solutions with one to nine clusters, and identified the most optimal one by using Akaike Information Criterion, sample size–adjusted Bayesian Information Criterion, and Vuong–Lo–Mendell–Rubin likelihood ratio test and Lo–Mendell–Rubin–adjusted likelihood ratio tests. By using linear (sleep duration and latency), multinomial (nighttime awakenings) and logistic regression analyses (sleep disorders), we then compared child sleep characteristics between the maternal latent profile groups. These group differences are presented as mean differences (MD) and odds ratios (OR) and their 95% confidence intervals (CI).

All the analyses were adjusted for child's age and sex. We thereafter made adjustments for maternal age, education, parity, early pregnancy BMI, pregnancy and pre-pregnancy disorders, smoking and alcohol use, and child's gestational age and birth weight (model b).

Because child anthropometric measures at the time of rating the sleep were available only for a subsample of participants ($n = 1869$), child weight-for-height SD score specific for the child's age and sex according to Finnish growth charts [45] was added to the covariates in a separate model (model c).

To account for maternal depressive symptoms at the time of rating the child sleep, maternal symptoms variable at the child follow-up was added into the regression models, together with maternal depressive symptoms during pregnancy and model b covariates.

To account for child's psychiatric symptoms at the time of child sleep assessment, we conducted sensitivity analyses by excluding children who displayed borderline significant total behavior problems (T-score at or above 65) in the CBCL from the analyses.

To test whether the associations between maternal depressive symptoms during pregnancy and child sleep were trimester-specific, we conducted additional regression analyses in which we used maternal trimester-specific mean depressive symptoms scores (only one value at first trimester, mean of values between 14 and 24 and between 26 and 40 gestational weeks for the second and third trimesters, respectively) as predictor variables.

Next, to study whether maternal depressive symptoms at the time of rating the child sleep mediated the effects of maternal depressive symptoms during pregnancy, we used mediation analysis using the PROCESS Macro 2.16.3 (www.processmacro.org) [48] for SPSS with 5000 bootstrapped samples. In these interaction and mediation analyses, we used maternal trimester-weighted (mean of trimester-specific values) mean depressive symptoms score as the pregnancy stage variable. Finally, an interaction term of maternal depressive symptoms during pregnancy \times maternal

depressive symptoms at child follow-up entered together with their main effects tested whether maternal depressive symptoms at the time of rating child sleep added to the effects of maternal depressive symptoms during pregnancy.

To facilitate the interpretation, continuous outcome variables, predictors, and covariates were standardized to the mean of 0 and standard deviation (SD) of 1. In all the analyses, two-tailed *p* values of <0.05 were considered significant. The analyses were conducted using IBM SPSS statistics software version 24.0 (IBM Corp., Armonk, NY) and the R program (R Team Core 2016).

3. Results

Characteristics of the sample are shown in Table 1. Maternal biweekly, trimester-specific, and trimester-weighted mean values of depressive symptoms during pregnancy were significantly

Table 1
Characteristics of the participants.

Pregnancy and birth (<i>n</i> = 2321)	
Maternal characteristics	
Educational attainment	
Primary or secondary	866 (37.3)
Lower tertiary	626 (27.0)
Upper tertiary	829 (35.7)
Age at delivery (y)	31.9 (4.6)
Early-pregnancy body mass index (kg/m ²)	24.3 (4.9)
Primiparous (yes) (<i>n</i> = 2316)	972 (42.0%)
Alcohol use during pregnancy (yes) (<i>n</i> = 2300)	379 (16.5%)
Smoking during pregnancy	
No	2181 (94.0%)
Quit during first trimester	75 (3.2%)
Smoking throughout pregnancy	65 (2.8%)
Any diabetic (gestational diabetes, type 1 diabetes) or hypertensive (chronic hypertension, gestational hypertension, preeclampsia)	455 (19.6%)
Pregnancy and pre-pregnancy disorders (yes)	
Center for Epidemiological Studies	
Depression Scale score	
Trimester 1 (<i>n</i> = 2217)	11.4 (7.9)
Trimester 2 (<i>n</i> = 2313)	11.0 (6.5)
Trimester 3 (<i>n</i> = 2255)	11.8 (7.2)
Trimester-weighted mean	11.4 (6.4)
Sex (male)	1177 (50.7%)
Birth weight (g)	3521 (512.2)
Gestational age (wk)	39.9 (1.6)
Follow-up at 3.5 y	
Maternal characteristics	
Beck Depression Inventory–II score (<i>n</i> = 2289)	6.4 (6.3)
Child characteristics	
Age (y)	3.5 (0.7)
Weight for height SD (<i>n</i> = 1869)	0.01 (1.0)
Total psychiatric problems (<i>n</i> = 2296)	
Borderline	183 (8.0%)
Child sleep characteristics	
Sleep duration/night (h) (<i>n</i> = 2276)	10.2 (0.8)
Sleep latency (min) (<i>n</i> = 2274)	21.6 (15.1)
Number of awakenings (<i>n</i> = 2247)	
None	883 (39.3%)
1	1059 (47.1%)
≥2	305 (13.6%)
Sleep disorders (yes; ≥85th percentile)	
Total sleep disorders (<i>n</i> = 2320)	353 (15.2%)
Disorders of initiating and maintaining sleep (<i>n</i> = 2306)	510 (22.1%)
Arousal disorders (<i>n</i> = 2313)	624 (27.0%)
Sleep breathing disorder (<i>n</i> = 2303)	373 (16.2%)
Sleep–wake transition disorder (<i>n</i> = 2306)	411 (17.8%)
Daytime excessive somnolence (<i>n</i> = 2313)	466 (20.2%)
Sleep hyperhidrosis (<i>n</i> = 2306)	508 (22.0%)

Means and standard deviations are given for continuous variables, and frequencies and percentages are given for groups of categorical variables. SD, standard deviation.

correlated (Pearson $r = 0.45$ – 0.96 , all $p < 0.001$) and were also significantly correlated with depressive symptoms after pregnancy (Pearson $r = 0.32$ – 0.44 , all $p < 0.001$). The median number of consecutive depressive symptom measurements during pregnancy in the entire sample was 13 and the interquartile range was 12–14. There were altogether 1131 women (48.7%) with data on all 14 measurement points during pregnancy, and only 472 women (20.3%) had more than two missing values during pregnancy.

Of the 1463 (63.1%) children with any of the sleep disorders, 675 (46.1%) had one, 389 (26.6%) had two, 221 (15.1%) had three, and 178 (12.2%) had four to six sleep disorders. The six sleep disorder scores were moderately intercorrelated (Pearson $r = 0.11$ – 0.37 , all $p < 0.001$); Pearson r between disorders of initiating and maintaining sleep, sleep breathing disorders, arousal disorders, sleep–wake transition disorders, disorders of excessive somnolence and sleep hyperhidrosis with total sleep problems score were 0.76, 0.39, 0.52, 0.74, 0.62, and 0.46, respectively (all $p < 0.001$).

Table S1 shows associations between covariates and child sleep quantity, quality, and sleep disorders.

3.1. Associations between maternal depressive symptoms during pregnancy and child sleep quantity, sleep quality, and sleep disorders

Latent profile analysis shows that the most optimal latent profile solution (in comparison to solutions with one to nine groups) identified three groups of women with consistently low ($n = 1075$), subthreshold ($n = 963$), and clinically significant ($n = 283$) levels of depressive symptoms throughout pregnancy (Akaike Information Criterion = 186,577.7, sample-size-adjusted Bayesian Information Criterion = 186,911.2, Vuong–Lo–Mendell–Rubin likelihood ratio test, and Lo–Mendell–Rubin-adjusted likelihood ratio test p values = 0.02 and 0.03, respectively) (Fig. 1).

Compared to children of women with consistently low depressive symptoms during pregnancy, children of women with clinically significant symptomatology throughout pregnancy had shorter sleep duration (Table 2), longer sleep latency (Table 2), and higher odds of waking up two or more times during the night (Fig. 2). All of these associations survived covariate adjustment, including adjustment for child weight-for-height SD score. In contrast to the other associations that were also independent of maternal depressive symptoms concurrently with child sleep ratings (Table 2, Fig. 2), the association with sleep duration did not survive adjustments for maternal depressive symptoms parallel to rating the child sleep (Fig. 2). Children of women with subthreshold symptomatology also had longer sleep latency across all adjustment models, including adjustment for maternal depressive symptoms parallel to rating the child sleep (Table 2). Fig. 3 shows that in comparison to children of women with low depressive symptoms during pregnancy, children of women with clinically significant symptomatology had higher odds for having total sleep disorders, and disorders of initiating and maintaining sleep, sleep breathing disorders, arousal disorders, sleep–wake transition disorders, excessive somnolence disorders, and sleep hyperhidrosis disorders. All of these associations survived for covariate adjustments, and when adjusted for child weight-for-height SD score or maternal depressive symptoms parallel to rating the child sleep only, the association with sleep breathing disorders was rendered nonsignificant. In addition, children of women with subthreshold depressive symptoms during pregnancy had higher odds for total sleep disorders and for all the subscale disorders (Fig. 3). These associations also survived for covariate adjustments and adjustments for maternal depressive symptoms parallel to rating the child sleep, except when adjusted for maternal depressive symptoms parallel to rating the child sleep the odds for arousal,

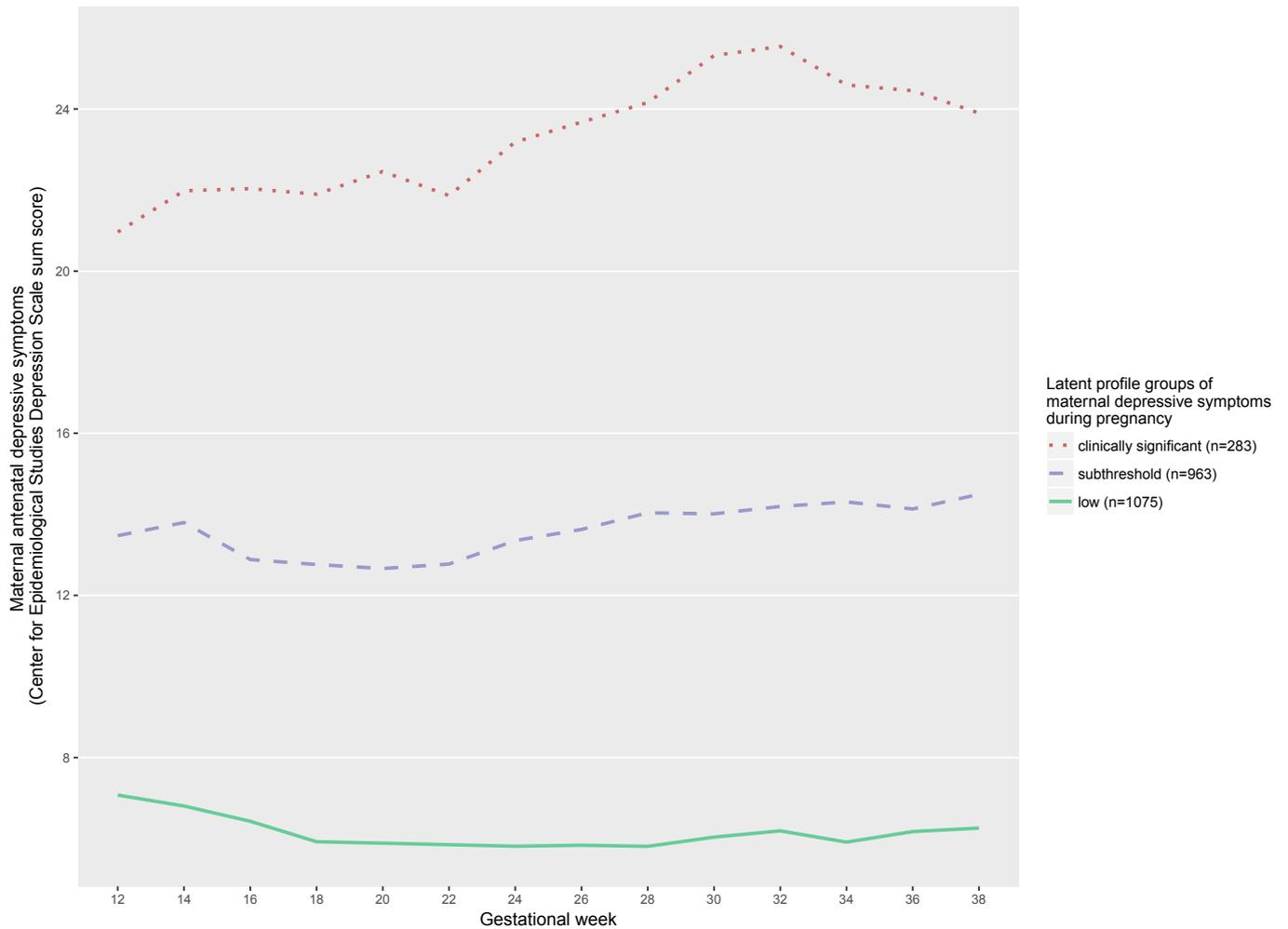


Fig. 1. Latent profiles of maternal depressive symptoms during pregnancy.

Table 2

Child sleep duration and sleep latency according to maternal depressive symptoms latent profile groups during pregnancy.

Subthreshold vs low maternal depressive symptoms during pregnancy	Sleep duration	Sleep latency
	B (95% CI)	B (95% CI)
Model a ^a	-0.03 (-0.12 to 0.05)	0.39 (0.26–0.52)
Model b ^b	-0.04 (-0.13 to 0.05)	0.38 (0.25–0.52)
Model c ^c	-0.01 (-0.10 to 0.09)	0.43 (0.28–0.58)
Model d ^d	0.00 (-0.09 to 0.09)	0.29 (0.15–0.43)
Clinically significant vs low maternal depressive symptoms during pregnancy	B (95% CI) ^a	B (95% CI) ^a
Model a ^a	-0.20 (-0.33 to -0.07)	0.14 (0.06–0.23)
Model b ^b	-0.22 (-0.36 to -0.09)	0.15 (0.06–0.24)
Model c ^c	-0.19 (-0.34 to -0.04)	0.15 (0.05–0.24)
Model d ^d	-0.14 (-0.28 to 0.00)	0.10 (0.01–0.19)

Unstandardized regression coefficients (B) and 95% confidence intervals (CI), indicating adjusted mean differences in standard deviation units in sleep duration and sleep latency between children of mothers with subthreshold vs low and clinically significant vs low depressive symptoms during pregnancy. All dependent variables are expressed in standard deviation units.

^a Model a is adjusted for child's age and sex.

^b Model b is adjusted for model a covariates + maternal age, educational attainment, parity, early pregnancy body mass index, hypertensive and diabetic pregnancy and pre-pregnancy disorders, smoking and alcohol use during pregnancy, and child's gestational age and birth weight.

^c Model c is adjusted for model b covariates + child's weight-for-height standard deviation unit score specific for the child's age and sex according to Finnish growth charts.

^d Model d is adjusted for model b covariates and maternal depressive symptoms at the time of rating the child sleep.

sleep–wake transition and sleep hyperhidrosis disorders were rendered nonsignificant (Fig. 3).

None of the findings changed when we conducted sensitivity analyses and excluded the 183 children with borderline clinically

significant total behavior problems from the analyses (all $p < 0.05$).

Table S2 shows that when we used maternal trimester-specific depressive symptoms values as predictor variables, all the

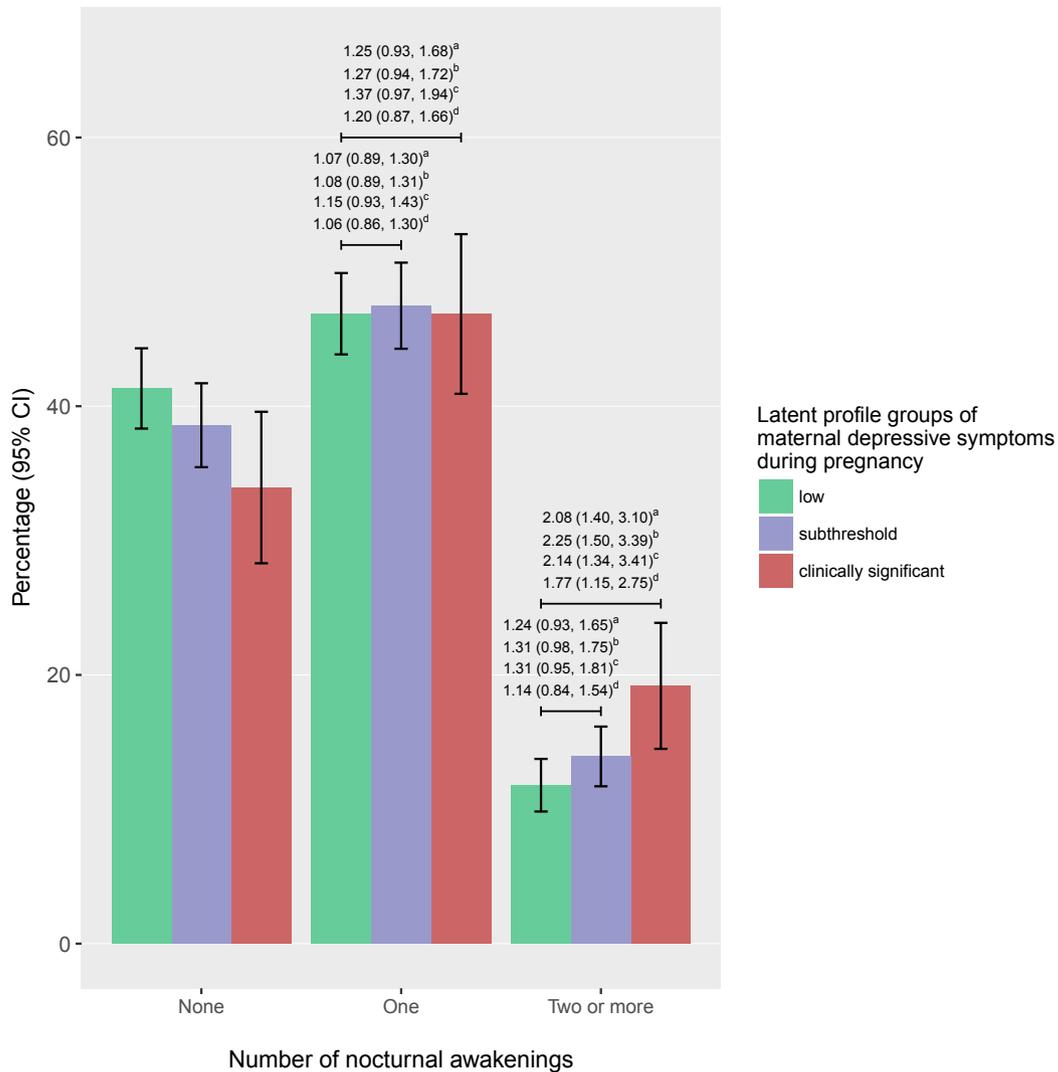


Fig. 2. Proportion of children with no, one, and two or more nocturnal awakenings according to maternal depressive symptoms latent profile groups during pregnancy. Numbers represent odds ratios (95% confidence interval) of having one and two or more nocturnal awakenings for children of mothers with subthreshold vs low and clinically significant vs low depressive symptoms during pregnancy. Model a refers to adjustments for child's age and sex. Model b refers to model a adjustments + maternal age, educational attainment, parity, early-pregnancy body mass index, hypertensive and diabetic pregnancy and pre-pregnancy disorders, smoking and alcohol use during pregnancy, and child's gestational age and birth weight. Model c refers to model b adjustments + child's weight-for-height standard deviation unit score specific for the child's age and sex according to Finnish growth charts. Model d refers to model b adjustments + maternal depressive symptoms at the time of rating the child sleep.

significant associations identified in the latent profile analyses were significant regardless of the pregnancy trimester.

3.2. Mediating effects of maternal depressive symptoms at the time of rating the child sleep

Figure S1 shows that although maternal depressive symptoms during pregnancy had a direct effect on child sleep latency (panel B) and total sleep disorders (panel D), maternal depressive symptoms at the time of rating the child sleep partially mediated these associations, and fully mediated the associations with nocturnal sleep duration (panel A) and nighttime awakenings (panel C).

3.3. Additive effects of maternal depressive symptoms at the time of rating the child sleep

Interactions between maternal depressive symptoms during pregnancy × maternal depressive symptoms at the time of rating the child sleep were significant in the analyses of child sleep duration (p for interaction = 0.001 in model adjusted for covariates)

and total sleep disorders (p for interaction < 0.001 in model adjusted for covariates). Fig. 4 shows that maternal depressive symptoms parallel to rating the child did not add to the prenatal depressive symptoms effects on child sleep duration (panel A), but rather entirely accounted for the prenatal effects as sleep duration of children of mothers with clinically relevant symptoms at the time of rating the child sleep ($\text{BDI-II} \geq 14$) and both during pregnancy ($\text{CES-D} \geq 16$) and at the time of rating the child sleep ($\text{BDI-II} \geq 14$) were the shortest. Maternal depressive symptoms parallel to rating the child, however, added to the maternal prenatal depression effects on child sleep disorders. Fig. 4 (panel B) shows that the proportion with sleep disorders was the highest for children of mothers with clinically significant depressive symptoms both during pregnancy and at the time of rating the child sleep.

4. Discussion

Our study shows that maternal depressive symptoms throughout pregnancy are associated with shorter nocturnal sleep duration, longer sleep latency, higher odds of more frequent

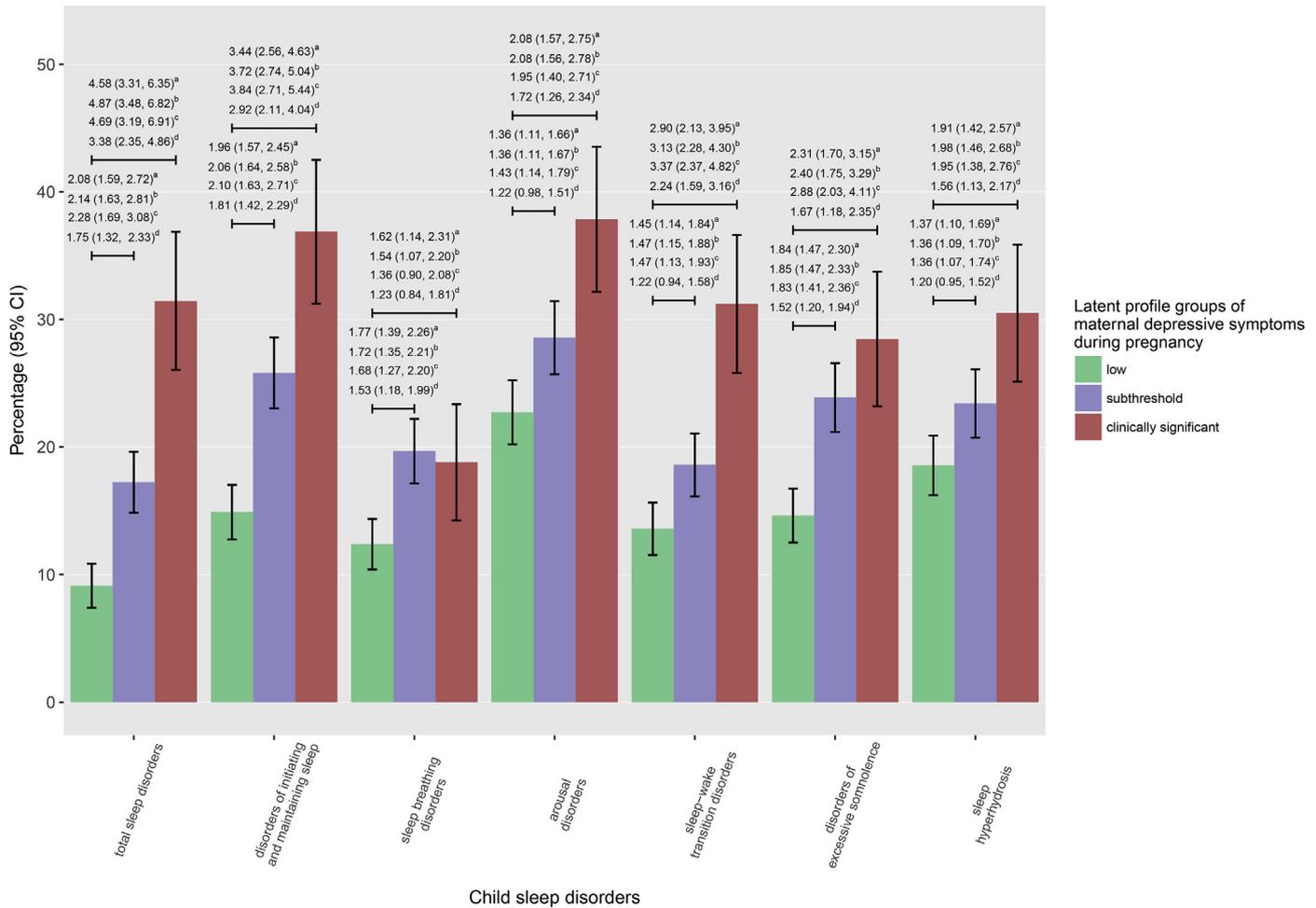


Fig. 3. Proportion of children with sleep disorders according to maternal depressive symptoms latent profile groups during pregnancy. Numbers represent odds ratios (95% confidence interval) of having a sleep disorder (≥ 85 th percentile) for children of mothers with subthreshold vs low and clinically significant vs low depressive symptoms during pregnancy. Model a refers to adjustments for child's age and sex. Model b refers to model a adjustments + maternal age, educational attainment, parity, early-pregnancy body mass index, hypertensive and diabetic pregnancy and pre-pregnancy disorders, smoking and alcohol use during pregnancy, and child's gestational age and birth weight. Model c refers to model b adjustments + child's weight-for-height SD score specific for the child's age and sex according to Finnish growth charts. Model d refers to model b adjustments + maternal depressive symptoms at the time of rating the child sleep.

nighttime awakenings, and higher odds of total sleep disorders and disorders across all the measured sleep domains in the 3.5-year-old offspring. These associations were not pregnancy stage specific, as maternal depressive symptoms showed high stability throughout pregnancy, a finding that we have demonstrated in the PREDO study previously [49], and as the associations were significant when we used trimester-specific values of maternal depressive symptoms as predictors of child sleep characteristics. These associations were not accounted for by important covariates, including both maternal pregnancy and child perinatal characteristics, and not by child borderline clinically significant psychiatric problems either.

Our study also shows that the prenatal depression effect on child sleep latency was not accounted for but partially mediated by maternal depressive symptoms parallel to rating the child sleep, that maternal depressive symptoms parallel to rating the child sleep partially mediated and added to the prenatal depression effects on child sleep disorders, and that the prenatal depression effect on child nocturnal sleep duration and awakenings were accounted for by maternal depressive symptoms measured parallel to rating the child.

Although our findings agree with the previous literature [27–29,31–33], they augment the literature also by showing that

maternal depressive symptoms during and after pregnancy indicate widespread harms on child sleep characteristics. As maternal clinically relevant depressive symptoms both during and after pregnancy are common, with a 10%–20% prevalence [50,51], and show high continuity across pregnancy and from the pregnancy to the child's early childhood stage [52], our findings carry an important public health message: if the associations are causal, at least part of the sleep problems that concern a large pediatric population could be potentially prevented by effective treatment interventions that aim at alleviating maternal depression symptoms during pregnancy and preventing clinically significant symptoms. This is particularly important, because child sleep problems show high developmental stability and relate to psychological and physical health concerns. Moreover, poor child sleep was not limited to children of mothers with clinically relevant symptomatology, but also those with subthreshold symptomatology. This emphasizes the need of such preventive interventions even further.

Our findings are also in agreement with the Developmental Origins of Health and Disease-concept [26]. However, the mechanisms underlying these associations remain to be elucidated. For example, fetal overexposure to maternal glucocorticoids and inflammatory cytokines may underlie these prenatal programming

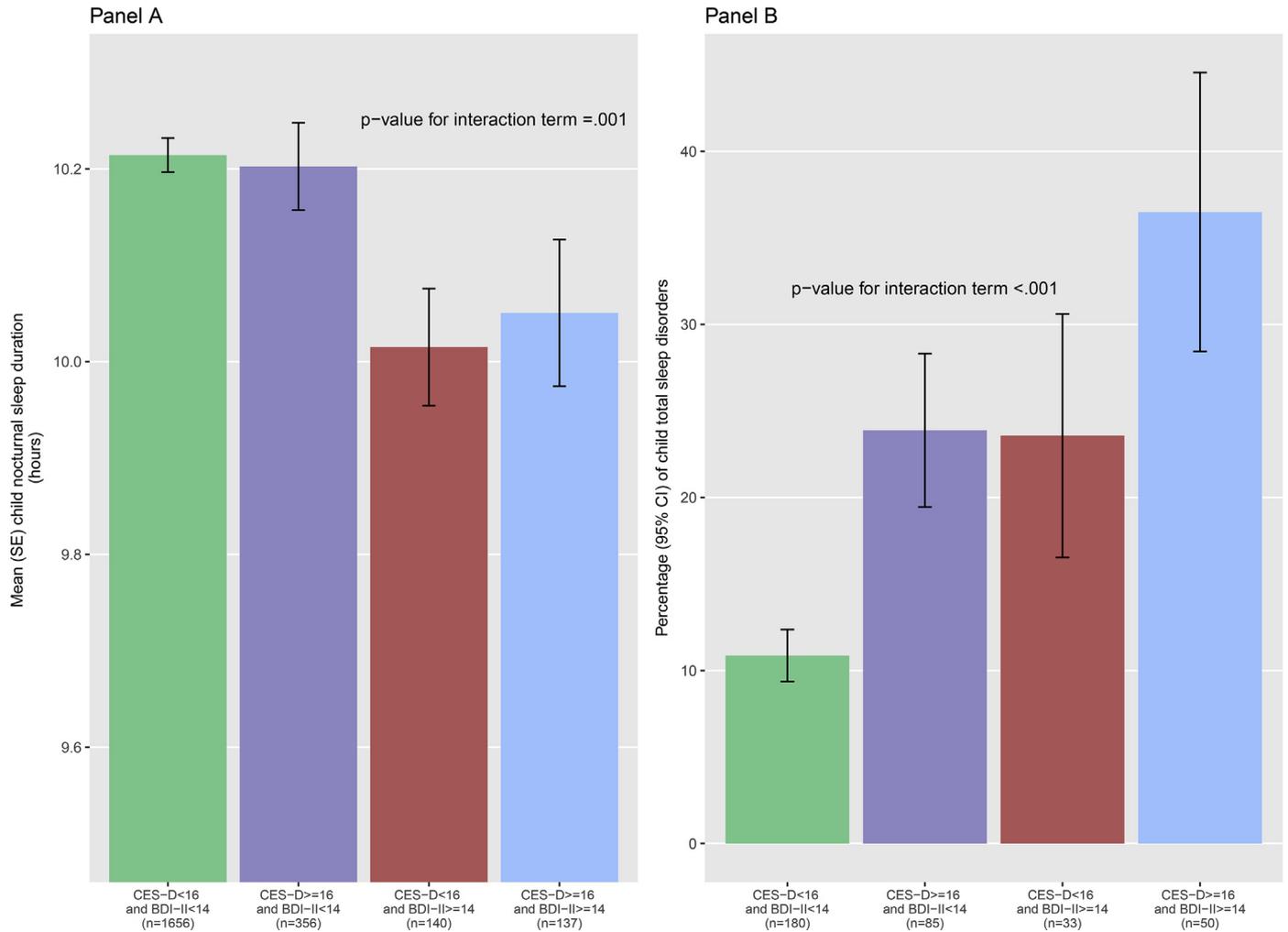


Fig. 4. Means and standard errors of child nocturnal sleep duration (panel A) and proportions and 95% confidence intervals of child sleep disorders (panel B) according to maternal depressive symptoms during pregnancy (mean score above and below the clinical cutoff of 16 on the Center for Epidemiologic Studies Depression Scale [CES-D]) and after pregnancy (mean score above and below the clinical cutoff of 14 on the Beck Depression Inventory–II [BDI-II]). *p* Values for the interaction term are from fully adjusted models (controlled for child's age and sex, maternal age, educational attainment, parity, early pregnancy body mass index, pregnancy conditions, smoking, alcohol, child's gestational age and birth weight, and maternal depression at follow-up).

effects. Maternal depression and stress during pregnancy are associated with higher mRNA placenta levels of the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) [53], as well as raised plasma levels of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol [54]. High placental GR has been found to mediate the effects of maternal depressive symptoms on infant regulatory behavior, including sleeping behavior [22]. Animal studies have shown that prenatal stress induces a phase-shift in the offspring circadian rhythm for corticosterone secretion and a slower rhythm resynchronization. Altered circadian corticosterone activity and corticosterone levels in response to stress are in turn associated with disturbed circadian behavioral cycles, including sleep abnormalities (increased rapid eye movement [REM] sleep and sleep fragmentation, decreased REM sleep latency, prolongation of the first REM sleep episode, diminished slow-wave sleep, and increased amount of paradoxical sleep [55–58]). These observations suggest that prenatal stress may be associated, among other, with an underlying dysfunction of the circadian clock, which results in abnormal circadian and sleep functions.

Alternative mechanisms to explain these associations include epigenetic and inflammatory mechanisms [59,60], along with a shared genetic background between the examined traits (given

that altered sleep is a well-known symptom of depression). For example, maternal depression during pregnancy is associated with epigenetic modifications of the GR gene in the placenta and fetal cord blood DNA [61], and recent studies have found altered methylation of inflammatory and androgen receptor genes in children and adults with obstructive sleep apnea [62,63], as well as different DNA methylation of genes related to cell adhesion processes and calcium ion binding in relation to different diurnal preference in monozygotic twins [64]. On the other hand, maternal depressive symptoms are associated with inflammation and oxidative stress biomarkers in animal and human studies [65,66] and in utero exposure to inflammatory state is related to impaired circadian rhythms, altered sleep architecture, and sleep problems in the offspring [59,67]. It is likewise possible that socio-cultural factors contribute to our findings. Mothers who are depressed during and after pregnancy may themselves have disturbed sleep–wake rhythms, or may experience dysfunctional cognitions and perceptions about both infant sleep and their own capacity to answering the child's needs, including sleep-related ones [28,68]. Further studies are needed to elucidate these possible mechanisms.

Strengths of our study include a large sample size and the prospective study design with repeated measures of maternal

depressive symptoms during pregnancy and at the child follow-up, and the use of different instruments to assess children's sleep quantity, quality, and disorders from multiple perspectives. We were also able to account for a number of important covariates in our analyses, including maternal age at delivery, early pregnancy obesity, hypertensive and diabetic pregnancy and pre-pregnancy disorders, smoking and alcohol use during pregnancy, parity, child gestational age, birth weight, age at follow-up, and weight-for-height SD score based on Finnish growth charts. We were also able to account for child's psychiatric problems by conducting sensitivity analyses in which children with borderline clinically significant psychiatric problems were excluded. Finally, we were also able to account for depression-related bias in mother-reported child sleep. Although this is a strength, the fact that both maternal depressive symptoms and child sleep were rated by the mothers means that we cannot entirely rule out shared method variance and that child sleep problems may also be a stress factor that increases maternal depression. The latter, however, pertains to maternal depressive symptoms only after pregnancy.

This study also has a number of other limitations. Child sleep characteristics were all mother-rated. Even though these characteristics were measured using well-validated surveys, generalizations to objectively measured sleep duration, latency, and diagnosed sleep disorders cannot be made. Furthermore, even though we studied sleep characteristics in two to six year-old children, that is, when the sleep pattern is already fairly well consolidated, generalizations to younger and older study populations cannot be made either, and neither do these study findings generalize to other ethnic groups or cultures in which child sleep practices may differ. Importantly, we lacked data on paternal characteristics, including depressive symptoms, age, and education level and occupation. Paternal depressive symptoms also predict child psychosocial development [69], and future studies are needed to compare the risks set forth on child sleep problems by maternal and paternal depressive symptoms, and to assess possible confounding by socioeconomic adversity more thoroughly, also taking paternal characteristics into account. Follow-up sample attrition was selective: the participating women were more educated, older, leaner in early pregnancy, and smoked less often during pregnancy. Our findings do not generalize to study populations that differ in these population characteristics. Because maternal depression after pregnancy was measured concurrently to rating the child sleep, a reverse causality (ie, child sleep characteristics contributing to maternal depressive symptoms) cannot be ruled out; thus, the results of our mediation analysis should be interpreted with caution. Finally, even though we could account for a number of maternal and child characteristics as covariates, we cannot rule out residual confounding. It is possible that maternal characteristics, including maternal depression, account for a tendency of the mothers to report depressive and sleep symptoms in their children. However, this seemed not to introduce any major bias in our study, as the six sleep domain scores were only moderately intercorrelated, and as only about one-fourth of the children were reported as having three or more co-occurring sleep disorders. Also, as depressed mothers by diagnostic definition suffer from sleep difficulties including insomnia [70], they may also be more aware of how their child sleeps and hence of the child's sleep problems. Yet, also in this regard, it is important to note that maternal antenatal depressive symptoms also showed effects on child sleep that were independent of maternal concurrent depressive symptoms.

5. Conclusion

Maternal depressive symptoms throughout pregnancy, regardless of pregnancy stage, are associated with shorter sleep duration,

longer latency, more frequent nocturnal awakenings, and increased risk for sleep disorders in children. Associations with child sleep duration and nocturnal awakenings are not specific to the prenatal period, whereas those with child sleep latency and disorders are. Maternal depressive symptoms at child follow-up partially mediated and added to the adverse effects of prenatal depressive symptoms on child sleep disorders. Interventions for preventing and alleviating depressive symptoms already during pregnancy may have long-term beneficial impact on the offspring's sleep health.

Acknowledgements

The PREDO study is funded by the Academy of Finland, Era-NetNeuron, European Commission (RECAP H2020-SC1-2016-RTD award 733280), EVO, University of Helsinki Research Funds; the Signe and Ane Gyllenberg Foundation, Emil Aaltonen Foundation, Jane and Aatos Erkko Foundation, Juho Vainio Foundation, Novo Nordisk Foundation, Päivikki and Sakari Sohlberg Foundation, Sigrid Juselius Foundation and Yrjö Jahnsson Foundation; the Finnish Medical Foundation.

Conflict of interest

The sponsors had no role in the conduct or design of the study, and no conflict of interest is declared.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: <https://doi.org/10.1016/j.sleep.2018.10.042>.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.sleep.2018.10.042>.

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