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Original Article

ORIGINAL ARTICLE

Gestational sleep deprivation is associated with higher offspring body mass index and blood pressure

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Abstract

Study Objectives: The objective of this study was to evaluate the association between gestational sleep deprivation and childhood adiposity and cardiometabolic profile.

Methods: Data were used from two population-based birth cohorts (Rhea study and Amsterdam Born Children and their Development study). A total of 3,608 pregnant women and their children were followed up until the age of 11 years. Gestational sleep deprivation was defined as 6 or fewer hours of sleep per day, reported by questionnaire. The primary outcomes included repeated measures of body mass index (BMI), waist circumference, body fat, serum lipids, systolic and diastolic blood pressure (DBP) levels in childhood. We performed a pooled analysis with adjusted linear mixed effect and Cox proportional hazards models. We tested for mediation by birthweight, gestational age, and gestational diabetes.

Results: Gestational sleep deprivation was associated with higher BMI (beta; 95% CI: 0.7; 0.4, 1.0 kg/m^2) and waist circumference (beta; 95% CI: 0.9; 0.1, 1.6 cm) in childhood, and increased risk for overweight or obesity (HR; 95% CI: 1.4; 1.1, 2.0). Gestational sleep deprivation was also associated with higher offspring DBP (beta; 95% CI: 1.6; 0.5, 2.7 mmHg). The observed associations were modified by sex (all p-values for interaction < 0.05); and were more pronounced in girls. Gestational diabetes and shorter gestational age partly mediated the seen associations.

Conclusions: This is the first study showing that gestational sleep deprivation may increase offspring's adiposity and blood pressure, while exploring possible mechanisms. Attention to glucose metabolism and preterm birth might be extra warranted in mothers with gestational sleep deprivation.

Statement of Significance

A suboptimal intrauterine environment is now a recognized risk factor to overweight/obesity and higher blood pressure during later life during later life. The vast majority of pregnant women experience significant sleep disruption. However, whether gestational sleep deprivation affects offspring adiposity and blood pressure in childhood remains unclear. This is the first study showing that gestational sleep deprivation may increase offspring's adiposity and blood pressure. By exploring possible mechanisms with formal mediation analysis, we recognize that attention to glucose metabolism and preterm birth might be extra warranted in mothers with gestational sleep deprivation. Besides sleep duration, future studies should also investigate the role of sleep quality during pregnancy.

Key words: gestational sleep deprivation; DOHaD; child; BMI; obesity; blood pressure; adiposity

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Introduction

A suboptimal intrauterine environment is now a recognized risk factor to overweight/obesity and higher blood pressure during later life [1, 2]. Pregnancy is a period when lifestyle interventions are encouraged, and parents are aware of their choices. Current interventions are mainly focused on maternal physical activity and/or a healthful diet, and appear effective in decreasing gestational weight gain and diabetes, with some evidence for positive maternal and child outcomes [3–6].

During pregnancy, the great majority of women experience significant sleep disorders including increased rates of inadequate sleep [7, 8]. Sleep disorders in pregnancy have been associated with increased gestational weight gain and pregnancy complications such as hypertension, pre-eclampsia, and gestational diabetes mellitus [9, 10], as well as with adverse perinatal outcomes including intrauterine growth restriction, low birthweight and preterm birth [11–16], longer labor, more pain during labor, and cesarean sections [12, 16]. Some of these factors, such as gestational diabetes, pre-term delivery, and birthweight [11–16], have also been associated with child's risk of overweight/obesity and cardiometabolic status [17–21], suggesting a plausible link between the two. Yet there is a lack of human studies linking gestational sleep disruption with child's cardiometabolic health or exploring potential mediating pathways.

Current evidence to support the hypothesis that sleep disorders during pregnancy has long-term cardiometabolic effects on offspring comes solely from mice studies. Sex dimorphism has been found in a mice study on metabolic dysfunction due to late gestational sleep fragmentation; male offspring had higher food intake, body weight, visceral fat mass, and insulin resistance and lower adiponectin levels, but not female offspring. Dyslipidemia was apparent in both male and female offspring after gestational sleep deprivation [22]. Two other mice studies found that gestational sleep deprivation increases blood pressure in offspring via alterations in cardiovascular autonomic regulation and renal morphofunctional changes [23, 24]. The effects of gestational sleep deprivation were similar between male and female mice, but in females, the effects were bigger in mice that underwent an ovariectomy and lacked female hormones.

In epidemiologic studies, poorer sleep in children has been associated with metabolic risk, adiposity, and altered lipid profile [25–30], and these effects in children have been more prominent in girls compared with boys [25, 31, 32]. As far as we know, there is no published human-based research on the role of sleep during pregnancy on childhood obesity and metabolic health. Our aim was to evaluate the association between gestational sleep deprivation and childhood adiposity and cardiometabolic profile in a pooled analysis of mother–child pairs from two European birth cohorts, with attention to possible interaction by sex and plausible factors mediating these associations.

Methods

Study population

This study utilized data from two European birth cohorts, the Greek "Rhea" birth cohort [33] (n = 1,363) and the Dutch Amsterdam Born Children and their Development (ABCD) study [34] (n=12,379). Both studies are population-based birth cohorts that started during pregnancy. Children from the Rhea cohort were examined at ages 4 (n = 879) and 6 (n = 606) years, while children from the ABCD study were examined at ages 5 (n = 3,260), 10 (n = 2,162), and 11 years (n = 935).

Gestational sleep deprivation

Information on sleeping habits of the participating mothers of the Rhea cohort was collected through a computer-assisted interview in the third trimester of pregnancy (median (25th–75th) gestational week: 32 (31–35) week) [13]. Sleep duration was obtained by the following close-ended question: "During the past month, how many hours did you sleep per day?" The mother reported sleep duration as 5 or fewer hours, 6–7 h, 8–9 h, and 10 or more hours [13]. Sleep deprivation was defined as five or fewer hours of sleep. Information on gestational sleep duration was available in 685 children with available outcome data at age 4 years and in 436 children with data available at age 6 years.

Pregnant women in the ABCD-study received a written questionnaire (median: [25th–75th] gestational week: 16 [14–18] week) and were asked an open-ended question: "How many hours did you sleep or rest lying down per day (of 24 h) on average in the past week." Sleep deprivation was defined as 6 or fewer hours of sleep, compared with 5 for Rhea, in order to account for the extra daytime resting hours that were reported. Information on gestational sleep duration during pregnancy was available in 3,191, 2,112, and 917 children with available outcome data at age 5, 10, and 11 years old, respectively.

Gestational sleep deprivation was used as a binary variable to assess the associations of extremely short gestational sleep with the outcomes of interest instead of sleep duration differences in hours. The cutoff was set at 5 hours of sleep for Rhea and at 6 hours for ABCD due to differences in the sleep questionnaires administered in the two cohorts. We decided on this as extremely short sleep is generally considered as unhealthy, whereas sleep duration needs may vary from person to person and differ across cultures. However, as sensitivity analysis we also used two additional cutoffs at 5 and 7 h of sleep in both cohorts.

Child outcome measurements

Details of child anthropometry, blood pressure, and serum lipids outcomes are given in the online supplement. In summary, children's weight and height, waist circumferences, percentage of body fat, diastolic (DBP) and systolic (SBP) blood pressure, and lipid profile were measured in the two cohorts at health clinic visits and/or planned follow-up study assessments. For both cohorts we defined overweight using the same procedure. First, we calculated BMI (weight/height^2) [35] and then categorized children into normal, overweight, or obese according to the cutoff points for sex and age proposed by the International Obesity Task Force (IOTF) definitions [36]. As a sensitivity analysis we also used age and gender specific z-scores for the outcomes BMI and blood pressure. Serum lipids included: fasting plasma, total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C).

Statistical analysis

We conducted descriptive analysis using standard univariate statistic procedures (chi-square, t-test). We compared mother–child pairs with normal sleep duration or gestational sleep deprivation for baseline characteristics between cohorts. Additionally,

we compared the mother–child pairs with follow-up and complete data on covariates (participants) to mothers that participated in the study during pregnancy but missed information on one or more covariates on follow-up after pregnancy (non-participants) per cohort.

Our main analysis was a pooled analysis of the Rhea and ABCD cohorts. For continuous outcomes, we used linear mixed models and for overweight/obesity, we used Cox proportional hazards models. Linear mixed models included random effects for cohort and child and a random slope for child age. Mixed models also included an interaction term between the exposure and child age at examination. Child age at examination in the interaction term was used categorically (4, 5, 6, 10, and 11 years in the models for BMI; 4, 5, 6, and 11 years in the models for all other outcomes). The overall effect of the exposure was evaluated using the marginal effects and the difference between the two groups was tested using Wald's test. The associations are reported in terms of beta coefficients and their corresponding 95% CIs. In Cox proportional hazards models, shared frailties for cohort were introduced in order to account for the shared risk within each cohort and hazard ratios (HR) and 95% CIs were reported. Birth was considered as the time of study entry and age at study visit as the time scale in our analysis. The exact age at the visit during which the child first became overweight/obese was used as the time of event. Children who did not become overweight/obese during follow-up were censored at the end of study follow-up or when lost to follow-up. The proportional hazards assumption was tested using both graphical inspection methods and Schoenfeld residuals.

We constructed a directed acyclic graph (DAG) based on previous knowledge and selected the set of confounders using DAGitty version 3.0 (Supplementary Figure S1) [37]. The confounders included in all models were maternal age at conception, parity (nulliparous and multiparous), maternal smoking early in pregnancy (yes/no), pre-pregnancy BMI (normal weight/overweight/obese), maternal education (low/middle/high), and maternal origin (country of cohort/other). Child sex and age at assessment (years) were also included. Models with blood pressure as an outcome were further adjusted for child height and BMI and models with lipids as an outcome were further adjusted for child BMI. In order to evaluate potential effect modification by sex, we included a multiplicative exposure-sex interaction term in each model.

As a sensitivity analysis, we performed a random effects meta-analysis. For this, we obtained cohort specific estimates using mixed effects models with child random effects and a random slope for child age for continuous outcomes and Cox proportional hazards models for binary outcomes. Consequently, we combined these estimates using random effects meta-analysis, in order to check the consistency with the pooled analysis and for quantifying heterogeneity among included studies with chi-square test from Cochran's Q and I^2 statistics.

We tested if there was significant mediation by three plausible mediators (gestational diabetes; gestational age; and birthweight) on the association between gestational sleep deprivation and childhood BMI and other outcomes (Figure 1). We made two separate mediator models with structural equation modeling (SEM); the first one with the continuous mediators gestational age and birthweight as parallel mediators; the second one with gestational diabetes as a single binary mediator. The second model included only mother–child pairs from the ABCD study, as gestational sleep deprivation was measured in early pregnancy, before the diagnosis of gestational diabetes would be made. The a-path of a mediator reports the association between gestational sleep deprivation and the mediator and the b-path reports the association between the mediator and offspring BMI at age four to five years. The indirect effect is a product of the a- and b-path. A 95 percentile bootstrap CI was calculated based on 1,000 bootstrap resamples for the indirect effect (ab), in order to test for significance. The total indirect effect is a sum of both indirect effects in a parallel model. The total direct effect (c′-path) refers to the association between gestational sleep deprivation and offspring BMI, corrected for the b-path. The total effect (c-path) is the association between gestational sleep deprivation and offspring BMI. The following confounders were added to the simple adjustment model: child sex, age at assessment (years). Considering the small numbers in each group, we did not perform a mediation analysis with full adjustment for all confounders.

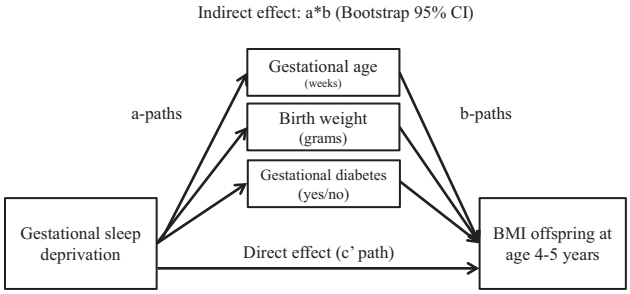

Figure 1. Mediation models. Theoretical model for mediation: the a-path reports the change in gestational age or birthweight (continuous mediators) or the odds ratio for gestational diabetes (binary mediator) if the mother had gestational sleep deprivation; and the b-path reports the increase in offspring BMI at age 4–5 years associated with a one point increase of each mediator. The c′ path reports the direct effect of gestational sleep deprivation on offspring BMI.

All analyses were conducted using Stata version 13 and 15 and significance level for all two-sided tests was set at the 5% level. We used capture program for mediation analysis.

Results

Participant characteristics

In the present analyses complete data on exposure, outcome, and covariates were available in a total of 661 and 453 Rhea mother–child pairs at ages 4 and 6 years, respectively and in a total of 2,947, 1,957, and 874 ABCD mother–child pairs at ages 5, 10, and 11 years, respectively. Table 1 shows maternal and infant characteristics. In total, 144 (4.0%) mothers were sleep deprived during the index pregnancy (5.6% in Rhea and 3.6% in ABCD). Cardiometabolic characteristics of the children are presented in Supplementary Table S1. In the Rhea-cohort, 21.4% of the children was overweight at age 6 years and 11.0% was obese; whereas in the ABCD-cohort 7.1% of the children was overweight at age 5 years and 1.5% was obese. In the ABCD, sociodemographic characteristics of the mothers with gestational sleep deprivation varied significantly from mothers with adequate gestational sleep; they had higher rates of gestational diabetes (6.5% vs. 1.5%); and children were born at lower gestational age (39.1 vs. 39.5 weeks) and with a lower birthweight (3,364 vs. 3,477 g). Besides parity, we did not see these differences

Table 1. Maternal and infant characteristics

	Overall, *N* = 3,608	Rhea, *N* = 661	ABCD, *N* = 2,947	
	No. (%) or mean ± *SD*	No. (%) or mean ± *SD*	No. (%) or mean ± *SD*	*P*-value*
Maternal characteristics				
Maternal age at conception (years)	31.6 (4.6)	29.8 (4.9)	32.0 (4.5)	<0.001
Maternal education				<0.001
Low	181 (5.0)	103 (15.6)	78 (2.6)	
Middle	805 (22.3)	337 (51.0)	468 (15.9)	
High	2,622 (72.7)	221 (33.4)	2,401 (81.5)	
Maternal origin-non native	717 (19.9)	31 (4.7)	686 (23.3)	<0.001
Parity-Nulliparous	1,965 (54.5)	305 (46.1)	1,660 (56.3)	<0.001
Smoking in early pregnancy-yes	487 (13.5)	223 (33.7)	264 (9.0)	<0.001
Pre-pregnancy BMI (kg/m^2)	23.3 (4.1)	24.7 (4.8)	22.9 (3.8)	<0.001
Underweight and normal weight (BMI < 25 kg/m^2)	2,764 (76.6)	426 (64.4)	2,338 (79.3)	<0.001
Overweight (BMI 25–30 kg/m^2)	606 (16.8)	147 (22.2)	459 (15.6)	
Obese (BMI ≥ 30 kg/m^2)	238 (6.6)	88 (13.3)	150 (5.1)	
Gestational characteristics				
Gestational diabetes	110 (3.1)	60 (9.2)	50 (1.7)	<0.001
Gestational age at delivery (weeks)	39.2 (1.8)	38.2 (1.5)	39.5 (1.7)	<0.001
Cesarean section	739 (20.5)	330 (49.9)	409 (13.9)	<0.001
Gestational sleep deprivation	144 (4.0)	37 (5.6)	107 (3.6)	0.020
Infant characteristics				
Female	1,785 (49.5)	309 (46.7)	1,476 (50.1)	0.121
Birth weight (g)	3,424.7 (542.2)	3,208.8 (448.6)	3,473.1 (549.6)	<0.001
Ever breastfed	2,929 (82.0)	558 (86.9)	2,371 (80.9)	<0.001

*Univariate analysis with chi-square or t-test.
BMI, body mass index.

in the Rhea cohort (Supplementary Table S2). Nonresponse analysis revealed that participants were of higher education and lower BMI-pregnancy in both cohorts compared to lost to follow-up mother–child pairs (Supplementary Table S3).

Gestational sleep deprivation and childhood cardiometabolic health

Table 2 shows the association of gestational sleep deprivation with child BMI, waist circumference, body fat, blood pressure, and the risk of overweight/obesity after adjusting for covariates. Gestational sleep deprivation was associated with higher child BMI (beta 0.7 kg/m^2 [95% CI: 0.4, 1.0]), waist circumference (beta 0.9 cm [95% CI: 0.1, 1.6]) and DBP (beta 1.6 mmHg [95% CI: 0.5, 2.7]) but not with per cent body fat (beta 0.7% [95% CI: −0.3, 1.7]). Children born to mothers with sleep deprivation in pregnancy had 40% increased risk of overweight and obesity (HR 1.4 [95% CI:1.1, 2.0]). There were no significant associations with child lipid profile (Supplementary Table S4).

There was significant effect modification by sex on the observed associations (*p*-values for interaction < 0.05; Table 2). When stratified by sex, short sleep duration in pregnancy was significantly associated with higher DBP, BMI and risk for overweight/obesity in girls only, whereas these associations in boys were smaller and not significant. The adverse associations of short maternal sleep with child's waist circumference and SBP was also stronger in girls compared to boys, however the interactions did not reach statistical significance (Table 2).

Sensitivity analysis

When using age and sex specific z values for BMI and blood pressure, we also found BMI and DBP to be associated with gestational sleep deprivation in girls (Supplementary Table S5).

The second sensitivity analysis showed us that using the same cutoff of ≤5 h of sleep/day for gestational sleep deprivation in both cohorts made the associations stronger and still significant, even with a prevalence of gestational sleep deprivation of 2%. When we used ≤7 h as a cutoff in both cohorts, the prevalence of gestational sleep deprivation was 19% and associations remained significant for overweight/obesity and blood pressure in girls (Supplementary Table S6).

The random effects meta-analysis of the cohort specific estimates from the mixed models confirmed the girl-specific associations of short maternal sleep during pregnancy with BMI, waist circumferences, and blood pressure (Figure 2 and Supplementary Table S7). The associations were stronger and only significant in the ABCD-cohort, compared to the Rhea-cohort. There was significant interaction by age for the association with BMI, waist circumference, total cholesterol, and LDL as the effects of gestational sleep deprivation became stronger with age (Supplementary Table S8). The I^2 statistic for BMI was suggestive for heterogeneity of the effect in the two studies (I^2 = 71.6, *p*-value = 0.061) but the stratification according to child sex, revealed evidence for heterogeneity among boys (I^2 = 71.6, *p*-value = 0.115) and not among girls (I^2 = 0.0%, *p*-value = 0.323). No heterogeneity was observed for the other outcomes (I^2 = 0.0%, *p*-values < 0.1; Figure 2).

Mediation by gestational diabetes, gestational age, and birthweight

Table 3 presents results for the mediation analysis on BMI. The total direct effect (c′ path) was 0.5, meaning that children of mothers with gestational sleep deprivation had a 0.5 kg/m^2 higher mean childhood BMI. Gestational diabetes was a significant mediator in the association between gestational sleep deprivation and offspring BMI. Mothers with gestational sleep deprivation during early pregnancy had 4.5 times higher odds of gestational diabetes (a-path), and gestational diabetes was

Table 2. A longitudinal pooled analysis of associations between gestational sleep deprivation and adiposity and blood pressure during childhood adjusting for potential confounders and testing for sex interaction

	Rhea and ABCD (*n* = 3,608)								
	Overall			Boys			Girls		
Outcomes	*N*	Estimate (95% CI)	*P*-value	*N*	Estimate (95% CI)	*P*-value	*N*	Estimate (95% CI)	*P*-value	*P*-interaction with sex
BMI (kg/m²)[§,‖]	3,607	**0.7 (0.4, 1.0)**	**<0.001**	1,823	0.5 (0.0, 1.0)	0.050	1,784	**0.9 (0.4, 1.3)**	**<0.001**	**0.046**
Overweight or obese[‡,*]	3,607	**1.4 (1.1, 2.0)**	**0.019**	1,823	0.9 (0.5, 1.5)	0.663	1,784	**2.2 (1.5, 3.3)**	**<0.001**	**0.004**
Waist circ. (cm)[*,‖]	3,601	**0.9 (0.1, 1.6)**	**0.031**	1,818	0.4 (–0.8, 1.6)	0.498	1,783	**1.3 (0.2, 2.3)**	**0.018**	0.167
Body fat (%)[*,‖]	3,590	0.7 (–0.3, 1.7)	0.164	1,816	0.7 (–0.7, 2.1)	0.332	1,774	0.7 (–0.7,2.1)	0.319	0.957
SBP (mmHg)[*,†,‖]	3,491	0.5 (–0.8, 1.8)	0.416	1,758	–0.4 (–2.2, 1.5)	0.687	1,733	1.8 (–0.1, 3.6)	0.063	0.135
DBP (mmHg)[*,†,‖]	3,485	**1.6 (0.5, 2.7)**	**0.006**	1,753	0.3 (–1.3, 1.9)	0.726	1,732	**2.8 (1.2, 4.3)**	**0.001**	**0.045**

Gestational sleep deprivation was defined as at least 5 and 6 h for Rhea and ABCD cohort, respectively. All models are adjusted for child sex, age at assessment (years), parity (nulliparous and multiparous), maternal smoking early in pregnancy (yes/no) maternal age at conception, pre-pregnancy BMI (normal weight/overweight/obese), maternal origin (country of cohort/other), and maternal education (low/middle/high). Bold-faced text indicated significant associations (p-value < 0.05).

*Point for sex and age that was proposed by the IOTF.

†Additionally adjusted for child height and BMI at assessment.

‡Hazard ratios and 95% CIs obtained by Cox proportional hazard models with shared cohort frailties.

§Defined with use of the BMI cutoff point for sex and age that was proposed by the IOTF.

‖Beta coefficient and 95% CIs as marginal effect estimates obtained by mixed effects models with cohort and child random effect and age interaction.

BMI, body mass index; BP, blood pressure.

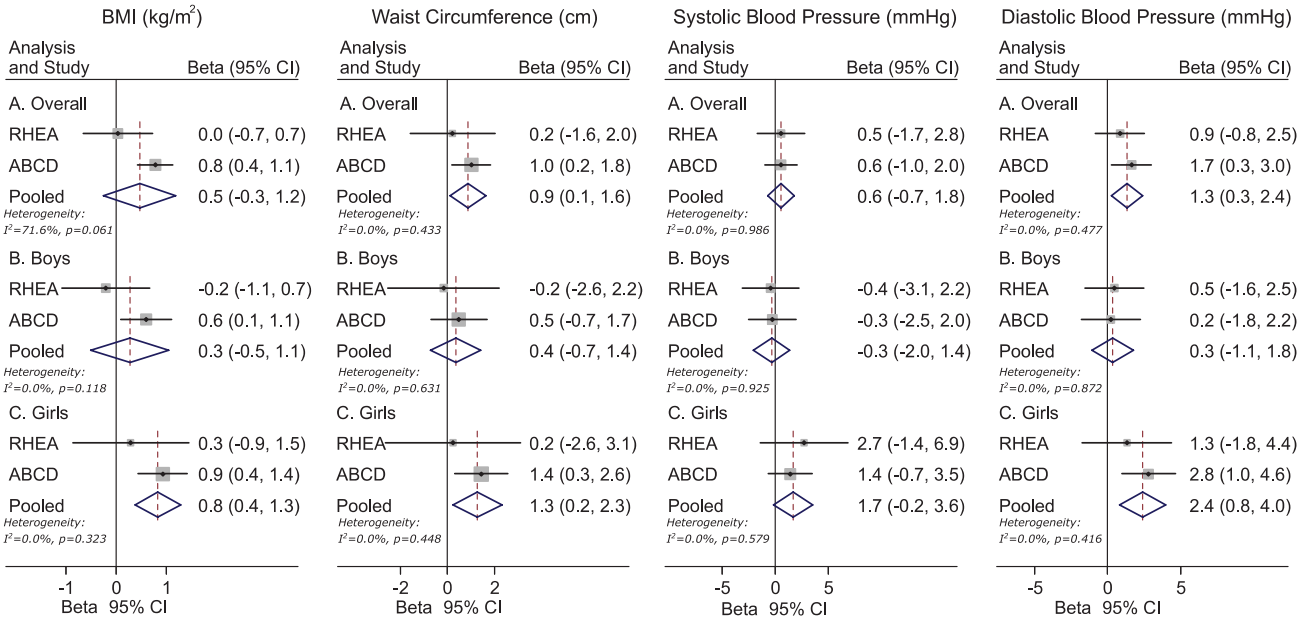

Figure 2. A random effects meta-analysis of adjusted associations between gestational sleep deprivation and adiposity and blood pressure in childhood. Gestational sleep deprivation was defined as at least 5 and 6 h for Rhea (*n* = 661) and ABCD cohort (*n* = 2,947), respectively. Cohort specific estimates were obtained by mixed effects models with child random effects and a random slope for child age. Cohort-specific estimates were adjusted for child sex, age at assessment (years), parity (nulliparous and multiparous), maternal smoking early in pregnancy (yes/no) maternal age at conception, pre-pregnancy BMI (normal weight/overweight/obese), maternal origin (country of cohort/other), and maternal education (low/middle/high). Models for blood pressure were additionally adjusted for child height and BMI at assessment.

associated with a mean increase of 1.1 kg/m² in offspring BMI. The confidence interval of the indirect effect was wide, due to small numbers. Gestational age was also a significant mediator in the association between gestational sleep deprivation and offspring BMI, leading to on average a 0.06 point higher BMI. We found that children of mothers with gestational sleep deprivation were born with half a week shorter gestational age (a-path), and that a shorter gestational age was associated with a higher offspring BMI (b-path). Both indirect effects were found significant as the bootstrap confidence interval of the indirect effects did not contain zero, even though the numbers for gestational diabetes were small resulting in a wide confidence interval.

Low birthweight was not a significant mediator. The effect of gestational sleep deprivation on birthweight was not significant (a-path), but a higher birthweight was associated with a higher offspring BMI (b-path).

Apart from the BMI outcome, we also tested mediation for the other metabolic outcomes of interest. Gestational diabetes was a mediator for overweight/obesity, waist circumference,

Table 3. Mediation by gestational age, birthweight, and gestational diabetes in the association between gestational sleep deprivation and offspring BMI at ages 4–5 years

		Sleep → Mediator (a-path) measure of association	Mediator → BMI (b-path) measure of association	Mediation (a × b)
Single mediator model with binary mediator (ABCD *n* = 2,947)	Gestational diabetes at delivery (yes/no)	**OR 4.51**	**β 1.10**	**5.25 (1.35, 21.28)**
	Total direct effect (c′ path)			**0.52 (0.24, 0.80)**
Multiple paralell mediator model with continuous mediators (ABCD and Rhea, *n* = 3,607)	Gestational age (weeks)	**β –0.48**	**β –0.12**	**0.06 (0.02, 0.10)**
	Birthweight (g)	β –77	**β 0.001**	–0.04 (–0.09, 0.01)
	Total indirect effect			0.02 (–0.02, 0.057)
	Total direct effect (c′ path)			**0.49 (0.23, 0.75)**

Gestational sleep deprivation was defined as at least 5 and 6 h for Rhea and ABCD cohort, respectively. Mediation model based on SEM, adjusted for child sex and age at assessment (years). Bold-faced text indicates significant associations (p-value < 0.05).
OR, odds ratio.

and per cent body fat, but not for DBP and SBP. Gestational age was a mediator for overweight/obesity and waist circumference. Low birthweight was not a mediator for the outcomes of interest (Supplementary Table S9).

Discussion

This is the first human epidemiological study showing that gestational sleep deprivation could be associated with offspring cardiometabolic profile. Children born to mothers with short sleep duration during pregnancy had higher adiposity and blood pressure levels with associations being more pronounced in girls than in boys and the effects becoming stronger with age. The effect estimates for each cohort separately were in the same direction, but stronger and significant in the ABCD cohort. The associations with adiposity were partly mediated by gestational diabetes and shorter gestational age.

Both sleep duration and sleep quality are known to change during pregnancy [38]. A recent meta-analysis found that about half of pregnant women experience poor sleep quality and that median sleep quality decreases from the second to third trimester [39]. Studies in the general population, as well as in pregnant women, suggest that sleep disturbances may alter the neuroendocrine homeostasis of the body, with an increased activity of the sympathetic nervous system and hypothalamic–pituitary system, as well as the stress and pro-inflammatory responses which are associated with numerous health consequences [40, 41]. Syntheses of findings from epidemiological studies in general populations suggest that lack of sleep is associated with obesity and a wide range of adverse cardiometabolic outcomes affecting both adults and children [42–45].

Importantly, during pregnancy the adverse physiologic response to sleep deprivation may lead to a suboptimal intrauterine environment, with subsequent effects on the placenta function, direct maternal, and fetal effects, but also with long-term consequences [2, 40]. Gestational sleep disruption has been associated with gestational diabetes, pre-term delivery, and birthweight [11–16], factors also being associated with child's risk of overweight/obesity and cardiometabolic status [17–21], thus may be involved in the causal pathway. In agreement with that, for the association between gestational sleep deprivation and offspring BMI, overweight, waist circumference, and per cent body fat, we found partly mediation by gestational diabetes. Mothers with gestational sleep deprivation during early pregnancy had higher odds of gestational diabetes during later pregnancy and consequently gestational diabetes was associated with higher offspring BMI. The underlying pathogenic mechanisms behind gestational diabetes and the abnormal metabolic risk profile in offspring are unknown, but epigenetic changes induced by exposure to maternal hyperglycemia during fetal life may be implicated in impaired insulin sensitivity in the offspring [46].

We also found that part of the association between gestational sleep deprivation and offspring adiposity in our cohort was mediated by gestational age; children of mothers with gestational sleep deprivation were born on average half a week earlier, and that was associated with a small increase in offspring BMI. Studies suggest the balance between pro- and anti-inflammatory cytokines may vary in each trimester, and sleep deprivation can adversely affect pro-inflammatory response with endothelial dysfunction in the placenta, which along with impaired glucose metabolism and can lead to preterm labor [14, 47, 48]. This causal pathway is further supported by another cohort study showing that obesity at the age of 2 years among children who were born extremely preterm was associated with perinatal systemic inflammation [49].

We found interaction by sex in our associations, with associations being more pronounced in girls than in boys. A sex-specific effect of poor sleep has also been observed by epidemiological studies in children, where sleep disruption was associated with more prominent effects on metabolic risk, adiposity, and altered lipid profile in girls compared with boys [25, 31, 32]. Also, during pregnancy sexual dimorphisms have been observed in the effects of maternal obesity on childhood growth [17]. A possible mechanism could be differences in placenta function between boys and girls, which are caused by differences in gene expression in response to maternal health [50]. The differences in adaptation between males and females may be context, species and stage specific, and therefore it is difficult to say whether one sex copes better than the other [50]. Our findings in human are not in line with studies in mice, where associations between sleep fragmentation were stronger in male offspring [22] and sleep deprivation had similar associations with blood pressure in both sexes [23, 24]. In a mouse study with female offspring the effects of gestational sleep deprivation were bigger in females that underwent an ovariectomy and lacked female hormones [24]. Future research could investigate if there is still interaction by sex when the children reach adolescence.

Strengths and limitations

Our study has several strengths. We were able to test longitudinal mediation in a large number of mother–infant pairs from different

countries. By doing this, we were able to test potential mechanisms for the association between gestational sleep deprivation and adiposity. In the mediation analysis, the number of mothers with gestational sleep deprivation and gestational diabetes was low, but we still found a significant mediation effect with the minimal adjustment set. However, these results should be interpreted with caution due to the small sample size. Although our data are observational, the sequence of events and associations over time might implicate causal relationships. All data were collected prospectively and outcome measurements during childhood were all performed by research staff. Third, we tested the association in a pooled analysis from two cohorts, but we do also provide cohort specific estimations for the benefit of quantifying the heterogeneity between cohorts and plotting the associations.

There were several limitations, mostly inherent to the cohorts' study design. Our exposure variable of gestational sleep deprivation was composed from a self-administered questionnaire and therefore recall bias and possible under- or overreporting may occur. We measured sleep at two different points during pregnancy, during the third (Rhea) and second (ABCD) trimester, capturing two stages of pregnancy. Effects of sleep duration, as well as sleep duration itself, may vary during pregnancy, and that may, besides other unknown factors, explain the different associations between the two cohorts. Also, the phrasing of the sleep question differed between both cohorts. Therefore, we used different cutoffs in the main analysis, correcting for resting time during the day that was included in the ABCD-study. However, our sensitivity analysis where two different common cutoffs in both cohorts were used, showed the same associations. We have no details about the timing of sleep during the daytime and nighttime, for example, the effects of nocturnal sleep might be different from daytime naps, and we have no information about gestational weight gain in the ABCD-cohort. Moreover, there are important differences in demographics between the two cohorts, causing some heterogeneity in our analysis. There are higher rates of maternal smoking; obesity; gestational diabetes; and cesarean section in the Rhea cohort. The smaller numbers in the RHEA cohort (for the random effects meta-analysis $n = 661$ vs. $n = 2,947$ for ABCD cohort) resulted in limited power which might be one of the reasons for the non-significant findings in this cohort. However, effect estimates were in the same direction, specifically with regard to stronger associations in girls. Nevertheless, the random effects meta-analysis indicates low to moderate heterogeneity for most of the outcomes, and pooled analysis was adjusted for cohort and other relevant covariates. Due to numerical difficulties we were not able to provide a measure of risk (OR or RR) for overweight/obesity, instead we calculated Hazard Ratios assuming that the development of overweight/obesity happened at the exact time of the follow-up visit. SEMs allowed us to assess multiple potential mediators but it makes strong assumptions that the relations between all variables are unconfounded. For this reason, we consider the mediation analysis an explorative study and do not claim causality. Lastly, loss to follow-up over the years of childhood caused our analysis to have a lower rate of mothers with short sleep duration in the participant group versus non-participants. We hypothesize that this difference was most likely attributed to higher loss to follow-up rates in non-Greek or non-Dutch origins, as ethnicity was previously shown to be associated with shorter sleep duration in a Dutch population [51], and we corrected our analyses for that.

Gestational sleep deprivation and clinical implications

Pregnancy is a period where lifestyle interventions are encouraged and parents are more aware of their choices [52]. Healthy gestational sleep has several perinatal benefits, whereas based on our findings, it probably also has positive long-term effects on childhood cardiometabolic health. Primary prevention may be limited to few socioeconomic factors previously related to sleep deprivation, for example, ethnicity and occupation [53]. But also secondary prevention could have a great impact for mothers with sleep disturbances already in early pregnancy. Closer monitoring for glucose metabolism and preterm birth might be extra warranted in mothers with sleep deprivation during pregnancy. Although sleep needs may vary by age and gender, both the National Sleep Foundation and American Academy of Sleep Medicine and Sleep Research Society have recommended 7–9 h of sleep per 24 h for adults [54, 55]. In a sensitivity analysis, we found that the associations are stronger for more severe sleep deprivation (≤5 compared to ≤7 h). During some circumstances sleeping more than 9 h per night might be appropriate too and for other it is uncertain if this is associated with health risk. There are no official sleep recommendations for pregnant women, but we postulate based on our findings that sleep deprivation (meaning a sleep duration of less than 6 h) should be avoided at any stage during pregnancy.

Future perspectives

Future studies should be done to replicate our findings in other populations, different stages of pregnancy, and to further study the underlying mechanism. Also, the associations we found for gestational sleep deprivation with child adiposity and blood pressure should be further explored in relation not only to sleep deprivation, but also in relation to sleep quality during pregnancy. We tested potential mechanisms with an explorative mediation analysis. Further research on the effects of gestational sleep deprivation on gestational diabetes and shorter gestational age and subsequent childhood metabolic health are needed to investigate causality and opportunities for prevention. We tested for three potential perinatal mediators, however other potential mediators (e.g. childhood lifestyle and sleep) could exist during gestation and early life which may warrant further study. There is one published research protocol of a prospective cohort study that investigates the effects of circadian rhythm on birth and infant outcomes, which can replicate the studied associations [56].

Conclusion

Our study is the first analysis on the association between maternal sleep duration during pregnancy and later childhood health. We used data from two ethnical and demographical diverse European cohorts and found that gestational sleep deprivation may be associated with increased risk for overweight and higher blood pressure in offspring, up until the age of 11 years, with more pronounced significant effects in girls than boys. Gestational diabetes and gestational age partly mediated these effects, pointing to altered glucose metabolism

and inflammatory pathways as possible biological mechanisms underlying the observed associations.

Supplementary material

Supplementary material is available at SLEEP online.

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