CLINICAL ARTICLE

Maternal sleep duration and infant birthweight: A population-based cohort study

Marcella Marinelli[1,2,3], Anne-Elie Carsin[1,2], Michelle C Turner[1,2,4], Ana Fernández-Somoano[2,5], Ana Cristina Rodriguez-Dehli[6], Mikel Basterrechea[2,7,8], Loreto Santa-Marina[2,7,8], Carmen Iñiguez[2,9], Maria-Jose Lopez-Espinosa[2,9], Jordi Sunyer[1,2,4,10], Jordi Julvez[1,2,11,*]

[1]Barcelona Institute for Global Health (ISGlobal), Barcelona, Spain

[2]Spanish Consortium for Research on Epidemiology and Public Health (CIBERESP), Madrid, Spain

[3]Agència de Qualitat i Avaluació en Salut de Catalunya (AQuAS), Barcelona, Catalonia, Spain

[4]McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, Ottawa, Ontario, Canada

[5]University of Oviedo, Oviedo, Asturias, Spain

[6]Servicio de Pediatría, Hospital San Agustín, Avilés, Asturias, Spain

[7]Public Health Division of Gipuzkoa, Basque Government, Spain

[8]Health Research Institute, Biodonostia, San Sebastián, Spain

[9]FISABIO - Universitat Jaume I - Universitat de València Joint Research Unit of Epidemiology and Environmental Health, Valencia, Spain

[10]Universitat Pompeu Fabra (UPF), Barcelona, Catalonia, Spain

[11]Institut d'Investigació Sanitària Pere Virgili (IISPV), Hospital Universitari Sant Joan de Reus, Reus, Catalonia, Spain

***Correspondence**

Jordi Julvez, Institut d'Investigació Sanitària Pere Virgili (IISPV), Hospital Universitari Sant Joan de Reus, Reus, Catalonia, Spain.

Email: jordi.julvez@iispv.cat.

Keywords

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Synopsis

In this study, we found an inverse U-shaped association between maternal sleep duration before and during pregnancy and infant birthweight, using data from a large cohort study.

Abbreviations: g (grams); BCPE (Box-Cox power exponential models); coef. (Coefficient); GAM (Generalized Additive Models); INMA (Infancia y Medio Ambiente [Environment and Childhood] Project); LPM (last menstrual period); MET (metabolic equivalent of task); SCL-90-R (Revised Symptom Checklist).

Abstract

Objective: Sleep duration is an important health indicator. Our aim was to investigate the association between maternal sleep duration and infant birthweight.

Methods: The study included 2,536 mother-infant pairs of a Spanish birth cohort (2004-2006, INMA project). The exposures were questionnaire-based measures of sleep duration before and during pregnancy. The primary outcome was infant birthweight score (g) standardized to 40 weeks of gestation.

Results: In women sleeping less than 7 hours per day before pregnancy, each additional hour of sleep increased birthweight score by 44.7 g ($p = 0.049$) in the minimally-adjusted model, although findings were not statistically significant after considering other potential confounders ($p > 0.05$). However, increasing sleep duration for the group of mothers who slept more than 9 hours per day decreased birthweight score by 39.2 g per additional hour ($p = 0.001$). Findings were similar after adjusting for several socio-demographic confounders and maternal depression-anxiety clinical history as an intermediate factor. Similar but attenuated associations were observed with sleep duration in the second pregnancy trimester.

Conclusion: The relationship between maternal sleep duration before and during pregnancy and infant birthweight is an inverse U-shaped curve. Excessive sleep duration may adversely affect infant health through its impact on birthweight.

1 Introduction

Humans sleep one third of their lives and adequate sleep is an important factor in preventing a variety of metabolic and psychiatric disorders. Sleep disturbances including alterations in sleep duration, poor sleep quality, restless leg syndrome, and breathing sleep disorders caused by hormonal, metabolic, and psychological changes, are common during pregnancy [1, 2]. Alterations in sleep duration in pregnancy may include both longer naps and shorter sleep periods at night [3].

Some studies have considered diverse aspects of the potential association between sleep disturbances during pregnancy and birthweight [4–6]. A cross-sectional study of 457 women of gestational age ≥ 37 weeks in Iran reported a positive correlation between sleep quality (as defined as self-reported refreshing sleep) but not sleep duration and neonatal birthweight [6]. A prospective study of 1,091 women in Greece reported a positive association between being a severe snorer during the third trimester of pregnancy and low birthweight (below 2500 grams) [5]. There was no association with reported sleep length. In a longitudinal study of 885 pregnant mothers in Sri Lanka recruited up to 16 weeks of gestation, sleeping eight hours or less per day during either the second or the third trimester was related to a lower infant birthweight [4].

Other reports have also highlighted the potential role of increased sleep duration in poor health and mortality outcomes among adults [7–10]. A meta-analysis of 16 studies reported a U-shaped association between sleep duration and the risk of all cause-mortality [7]; in particular, shorter sleepers (< 7 hours per night) had a 12% greater mortality risk and longer sleepers (> 8 - 9 hours per night) a 30% greater

mortality risk compared to those sleeping between 7 to 8 hours per night. However, it remains unclear whether oversleeping is a marker for other health issues, such as depression or reduced physical activity. Oversleeping may also be related with the use of alcohol or medications [11].

Further research examining the association pattern between sleep quantity and birth outcomes using data from a large population-based cohort is needed. Additional statistical analyzes of the role of a large range of socio-demographic confounders and mental health intermediate factors is also important, this is in order to better understand the link between two essential health indicators (sleep duration and birthweight).

The aim of this study was to evaluate the association between maternal sleep duration before pregnancy and during the second trimester and infant birthweight using prospective data from four Spanish cohorts with detailed information on important socio-demographic and lifestyle factors, as well as maternal depression-anxiety clinical history.

2 Methods

Design and Study Participants

The Spanish INfancia y Medio Ambiente (Environment and Childhood) Project (INMA) is a mother-and-infant cohort study established in different areas of Spain following a common protocol (recruitment period: 2003-2008) [12]. This study included the INMA cohorts of Asturias (n = 489), Guipuzkoa (n = 574), Sabadell (n = 652) and Valencia (n = 821) with two measures on maternal sleep duration.

Pregnant women agreed to participate and met the inclusion (≥16 years of age, singleton pregnancy, intention to deliver at the reference hospital) and exclusion (no communication difficulties, no fetuses with malformations, no assisted conception) criteria.

In total, 2375 infants with no missing data on birthweight, (463 from Asturias, 533 from Guipuzkoa, 599 from Sabadell, and 780 from Valencia) were included in the present study. The study was approved by the appropriate ethical committees, and written informed consent was obtained from the parents of all infants prior to enrollment into the study.

Assessment of sleep duration

Sleep duration of the mother before pregnancy was assessed by an interviewer-administered questionnaire at the moment of recruitment into the study during the first pregnancy trimester according to the following open-ended question: “How long did you sleep during the day (minutes) and during the night (hours) on average during week-days before getting pregnant?” And again, at the second trimester of pregnancy, but in terms of current sleep duration. Total sleep duration, including both naps and sleep at night, either before pregnancy or during the second trimester, was expressed in hours per day (h/d). These assessments by questionnaires are valid measurements but can generate some recall bias [13].

Assessment of infant birthweight

Infant birthweight was measured in grams by trained midwives. Gestational age was estimated from the date of the last menstrual period (LPM) reported at recruitment

and was confirmed using ultrasound examination in week 12 of gestation. If gestational age (based on reported LMP and ultrasound) differed ≥7 days (12% of newborns), the duration of gestation was recalculated using a formula with crown-rump length from an early ultrasound measurement [14]. We standardized the measure of birthweight at 40 weeks to control for gestational week of pregnancy (birthweight score). Each birthweight score was expressed in terms of birthweight at 40 weeks of gestational age using Box-Cox power exponential models (BCPE) considering the reference study group. This transformation permits to account for differences in gestational age at birth [15].

Covariates

Questionnaires administered to mothers during pregnancy and at delivery collected information on smoking status (yes/no) during pregnancy, alcohol consumption (grams per day) during pregnancy, medical conditions and pregnancy complications, maternal diet and medication use during pregnancy, maternal ethnicity and education (primary or less, secondary school, or university), maternal age at birth, and parity (0, 1, ≥2 infants). Maternal height and weight during pregnancy were measured and pre-pregnancy weight was reported by the mother at the first trimester visit. Both were used to calculate pre-pregnancy BMI (kg/m^2) and weight gain during pregnancy. Mother's social class was obtained according to the UK Registrar General's 1990 classification and according to current ISCO88 parental occupation: Class I-II, Class III and Class IV-V. Maternal marital status (whether the parents were living together or not) and maternal medical history of depression and anxiety was recorded by the interviewer-administered questionnaire during the first trimester of pregnancy. Paternal weight and height were reported by the mother and used to

calculate paternal BMI (kg/m^2). At week 32 of pregnancy, information on whether the mother worked during pregnancy (yes/no) was collected as well as physical activity level during pregnancy as measured by metabolic equivalent of task (MET's hour/day).

Statistical Analysis

Mixed regression models were used to examine the association between selected parental and infant characteristics and birthweight score adjusting for cohort as a random intercept [16, 17].

Generalized additive models (GAM) were used to examine the shape of the relationship between maternal sleep duration and birthweight score. We found evidence of non-linearity in both models and therefore we fitted a piecewise regression model to estimate the slopes of sleep duration <7, 7 to 9, and ≥9 hours per day adjusting for covariates. Cut-off points were chosen based on visual inspection of the GAM plot, considering of the distribution of the variable and in accordance to previous published results [7].

The association between maternal sleep duration both before pregnancy and during the second trimester of pregnancy and birthweight score was examined using piecewise mixed regression models adjusting for cohort as a random intercept.

The main analysis included infant sex, pre-pregnancy maternal BMI, paternal BMI, gestational weight gain, and maternal age as mandatory covariates and adjusted for cohorts as random intercept to account for differences between cohorts. In sensitivity

analyses we also assessed models to account for some other potential confounders: alcohol consumption, smoking status, parity, maternal marital status, social class, education level, total physical activity and working activity during pregnancy. Further the impact of maternal depression and anxiety clinical history reported during the first trimester of pregnancy as potential intermediate variables was also assessed. Other collected variables described above in *Covariates* section were not included in the final models due to no crude statistical relation with either the determinant and/or outcome (data not shown).

The level of Evidence has been classified as II.

3 Results

Median maternal sleep duration was 8 hours in all cohorts both before pregnancy and in the second trimester of pregnancy (Table 1). The distribution of sleep duration is shown in (Figure 1).

Birthweight score (g) decreased with maternal alcohol consumption, smoking status during pregnancy, and lower social class (III, IV-V). Birthweight score increased in male infants, with increasing maternal age, higher pre-pregnancy maternal BMI, higher weight gain during pregnancy, higher paternal BMI, higher maternal education level, and higher parity (Table 2).

We found a significant curvilinear relationship between maternal sleep duration before pregnancy and infant birthweight score (Figure 2) and between sleep duration during the second trimester of pregnancy and infant birthweight score (Figure 3).

In women sleeping less than 7 hours per day before pregnancy, each hour of sleep increased birthweight score by 44.7 g (Table 3). In contrast, in women reporting 9 or more hours of sleep, birthweight score decreased by 39.2 g per additional hour of sleep (p=0.001). The association between sleep duration during the second trimester of pregnancy and birthweight score was similar but attenuated (Table 3).

Associations between maternal sleep duration before pregnancy and infant birthweight score were similar after adjusting for additional confounders including maternal alcohol consumption during pregnancy, smoking during pregnancy, education level, parity, marital status, working activity during pregnancy, social class and physical activity during pregnancy (Table 4).

We also considered the potential intermediate role of maternal anxiety and depression clinical history reported during the first trimester of pregnancy. However, we found similar associations as those observed in the main analysis (Table 5). After excluding 116 women with pregnancy hypertension and/or risk of pregnancy lost, main results were unchanged (data not shown).

4 Discussion

We observed an inverse U-shaped association between maternal sleep duration before pregnancy and infant birthweight. Similar, but weaker associations were observed with maternal sleep duration during the second trimester of pregnancy. Consequently, a background of excessive sleep duration (higher than 9 hours per day) may result in adverse impacts on infant health. This longitudinal study assessed

the association between two different time points of maternal sleep duration (before pregnancy and in 2nd trimester), in terms of both reduced and excessive sleep, and infant birthweight. Further adjustments for important socio-demographic confounders did not alter the findings; neither maternal depression-anxiety clinical history did explain such associations.

In agreement with previous studies, birthweight increases with the age of the mother, a higher maternal BMI, the sex of new born (male) and mothers reporting a higher parity [4]. In addition to this, Abeysena et al.[4] studied whether sleep duration during the second, third or both trimesters together affected birthweight. They observed a reduced infant birthweight (<2500 gr.) among women sleeping less than 8 hours per day and a similar inverse U-shaped association pattern as that observed here. Another small cohort study analyzed maternal sleep duration trajectories and child birthweight, they reported that an increased trajectory of sleep duration was associated with lower birthweight [18]. Furthermore, a recent cohort study observed that pregnant women sleeping less than 7 hours per day had a higher risk of having neonates with lower birthweight [19]. Micheli et al.[5], reported no relationship between sleep duration and infant with low birthweight. Another Japanese study reported no association between maternal sleep duration and small for gestation age children [20]. However, in both studies, they did not examine potential thresholds in the association as we did in the present study.

A range of mechanisms have been proposed to explain the negative health effects of oversleeping: sleep fragmentation, fatigue, immune function (e.g., change in immune function), photoperiodic abnormalities, lack of challenge (e.g., lack of physiological challenge), or an underlying disease process such as sleep apnea, heart disease, or

failing health [21]. Moreover the use of certain substances such as alcohol and drugs may be the cause for fatigue and sleep problems, however in our data set; alcohol use did not affect the findings on oversleeping and birthweight. A possible explanation for the negative association observed between oversleeping and birthweight is pre-pregnancy depression of the mother. Antenatal depressed pregnant women tend to gain less weight[22] and sleep more [23]. Also, maternal stress can be similarly related to sleeping duration in a short term [23]. Stressed women are overly tired at the end of the day and tend to sleep more. However, we could not confirm such pathways in the present data related to these factors. Although it is difficult to evaluate whether increased sleeping duration is related to changes in hormone levels during pregnancy, or a sign of other health problems, in this study, the strongest associations with sleep duration occurred at the beginning, or before pregnancy, rather than in the middle of the pregnancy, suggesting that hormone changes during pregnancy were not the reason for birthweight differences observed here. An alternative explanation could be that mother with excessive sleep duration may show more unhealthy nutritional habits and inadequate caloric intake that may last by affecting newborns with lower birthweight.

One of the main strengths of the present study is its longitudinal design examining sleep duration at two distinct moments: before and during pregnancy. Furthermore, the exhaustive range of potential confounders described above weakens the possibility of residual confounding playing an important role here. Additionally, results were unchanged after adjusting for one of the potential explanatory pathways, maternal mental health status (as a clinical history reported at the first trimester and as a rating scale assessed at 4 years of the child). Finally, since this

study is based on four population-based birth cohorts with a high participation rate;[12] the findings can be considered to imply a certain degree of external validity.

This study also has some limitations: sleep duration before pregnancy and during the second trimester was reported by the mother. As mothers answered the question regarding sleep duration before pregnancy during the first pregnancy trimester, we speculate that current (pregnancy) sleep habits may influence recall of past (pre-pregnancy) sleep habits [13], a phenomenon known as “recall bias”. Consequently, sleep duration before pregnancy could be partly considered as a proxy of sleep duration during the first trimester. Furthermore, while there were no objective measures of sleep duration and sleep quality, the sleep data collected before delivery, may reduce the risk of recall bias associated with delivering preterm or having an SGA infant. Self-reported sleep abnormalities in young adults were highly correlated with objective measurements of sleep status [24]. Little is known about the validity of self-reported survey assessments of sleep duration in pregnancy. A recent study reported no correlation between self-reported and actigraphy measures, though there were no data on validation of actigraphy measures and the sample was small and heterogeneous [25]. However, recent cohort studies with pregnant women used questionnaire-based data as a common measurement for sleep duration, and showed consistent findings with birthweight outcomes [18–19]. Finally, more detailed data on the quality of sleep was not available in order to examine factors beyond duration and their potential association with birthweight.

Further longitudinal studies are needed to confirm the association pattern described here between maternal sleep duration and infant birthweight, studies need to

represent different population samples and use two time-point measurements of sleep duration before and during the entire pregnancy period, and probably include hormone and mental health biomarkers in order to better understand the underlying mechanisms. The use of objective measures of sleep duration and quality such as currently available on many smart watches such as FitBit or Apple are also required in future studies.

5 Conclusion

This longitudinal study showed that excessive maternal sleep before pregnancy and probably during pregnancy is associated with lower birthweight in infants after adjusting for various potential confounding and intermediate factors. Similarly, but as a weaker association pattern, lower sleep duration may reduce infant's birthweight. Further prospective studies are required to confirm these findings and to investigate the mechanisms that may underlie the possible association. Sleep duration is becoming an important health indicator for the general population.

Author contributions

This study was conceived and designed by Marcella Marinelli and Jordi Julvez
The analysis was conducted by Marcella Marinelli and Anne-Elie Carsin.
A first draft of the manuscript was prepared by Marcella Marinelli.
The rest of the co-authors reviewed and edited the MS.

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Conflict of interests

The authors have no conflicts of interest relevant to this article to disclose.

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FIGURE LEGEND

Figure 1. Distribution of sleep duration

Figure 2. Prediction of birthweight score as a function of sleep duration before pregnancy from the main model presented in table 3

Figure 3. Prediction of birthweight score as a function of sleep duration during the 2nd trimester from the model presented in table 3

TABLE 1. Distribution of sleep duration by cohort, INMA Study (2003-2008).

	N	Min	P25	Median	P75	Max
Total Sleep duration (h/d) Before pregnancy						
Sabadell	610	3.00	7.00	8.00	8.33	15.00
Valencia	758	3.00	7.00	8.00	9.00	16.50
Guipuzkoa	534	5.00	7.00	8.00	8.25	15.00
Asturias	439	3.00	7.00	8.00	9.00	14.00
Nap time sleep (h/d) Before pregnancy						
Sabadell	610	0	0	0	0.00	3.00
Valencia	758	0	0	0	0.50	3.00
Guipuzkoa	534	0	0	0	0.17	3.00
Asturias	439	0	0	0	0.50	4.00
Total Sleep duration (h/d) Second Trimester						
Sabadell	610	3	7	8	9	16
Valencia	758	3	7	8	9	14
Guipuzkoa	534	4	8	8	9	12
Asturias	439	3	7	8	9	14
Nap time sleep (h/d) Second Trimester						
Sabadell	606	0	0	0.00	0.50	4.00
Valencia	747	0	0	0.25	1.00	4.00
Guipuzkoa	514	0	0	0.50	1.00	3.00
Asturias	439	0	0	0.00	0.50	3.00

TABLE 2. Association between selected parental and infant characteristics and birthweight score, INMA Study (2003-2008).

Variable	Mean birthweight (g)	Coeff (95% CI)	P	N =2375
Infant sex			<0.001	
Female	3274.39	1 (Reference)		1155
Male	3410.68	136.38 (104.60; 168.16)		1220
Age of the mother (years)		7.52 (3.77; 11.29)	<0.001	2375
Gestational weight gain (grams) #		371.52 (245.03; 498.01)	<0.001	2300
BMI before pregnancy #		12.45 (8.74; 16.16)	<0.001	2374
Paternal BMI #		7.55 (2.84; 12.27)	0.002	2333
Alcohol consumption during pregnancy (grams/day) #		-13.70 (-24.90; -2.49)	0.017	2370
Smoking during pregnancy #			<0.001	
No	3374.05	1 (Reference)		1576
Yes	3282.16	-90.82 (-125.87; -55.78)		738
Maternal education level #			0.067	
≤Primary studies	3329.53	1 (Reference)		586
Secondary studies	3328.58	-3.21 (-44.34; 37.92)		976
University studies	3373.24	38.77 (-4.45; 81.99)		809
Parity #			<0.001	
First infant	3286.13	1 (Reference)		1333
Second infant	3412.36	126.46 (92.80; 160.12)		880
> Second infant	3459.10	175.04 (110.19; 239.89)		160
Marital Status			0.535	
Parents were living together	3345.12	1 (Reference)		2333
Parents were not living together	3304.43	-38.77 (-161.18 ; 83.64)		42
Mother's social class #			0.032	
Class I-II	3387.30	1 (Reference)		503
Class III	3336.32	-48.32 (-95.54; -1.10)		613
Class IV-V	3330.38	-54.54 (-96.14; -12.94)		1258
Working during pregnancy #			0.192	
No	3371.26	1 (Reference)		380
Yes	3339.46	-29.59 (-74.00; 14.82)		1933
Total physical activity (METs hour/day) during pregnancy[a]		2.17 (-2.46;6.80)	0.358	2375
Anxiety history at first trimester (Yes/No) #		-2.10 (-47.96; 43.76)	0.928	2373
Depression history at first trimester (Yes/No) #		-17.76 (-72.14; 36.63)	0.522	2373

Coefficient and 95%CI from mixed regression models including cohort as a random intercept.

Data reflect missing values in some subjects.[a] METs-hour per day (Metabolic Equivalent of Task) reported at 32-weeks of pregnancy.

TABLE 3. Association (β Coeff. and 95 % CI) between sleep duration and birthweight, INMA Study (2003-2008), N=2,165.

Sleep duration	Birthweight (g) □ Coeff (95% CI)	P-values
Sleep before pregnancy		
< 7 hours per day	44.72 (0.28, 89.17)	**0.049**
≥7 and < 9 hours per day	15.75 (-9.37, 40.86)	0.219
≥ 9 hours per day	-39.22 (-61.46, -16.97)	**0.001**
Sleep in 2nd trimester		
< 7 hours per day	16.24 (-13.20, 45.69)	0.280
≥7 and < 9 hours per day	-13.39 (-39.03, 12.26)	0.306
≥ 9 hours per day	-15.97 (-42.55, 10.61)	0.239
Models from piecewise regression where sleep was including as spline with cut-off at 7 and 9 hours per day. Coefficients are the slopes over this given interval adjusted for maternal age, gestational weight gain, maternal pre-pregnancy BMI, paternal BMI, sex of the infant and a random effect for cohort.		

TABLE 4. Association (β Coeff. and 95 % CI) between maternal sleep duration before pregnancy and child birthweight score (g) adjusted for potential confounders

	Sleep before pregnancy			
	≤ 7 hours per day	**> 7 and ≤ 9 hours per day**	**> 9 hours per day**	**N**
	β (95% CI), p-value	β (95% CI), p-value	β (95% CI), p-value	
Model 1: Base model + alcohol	45.27 (0.86, 89.68), p=0.046	15.54 (-9.55, 40.64), p=0.225	-38.82 (-61.05, -16.58), p=0.001	2,165
Model 2: Base model + smoking	39.87(-4.26, 84.01) p=0.077	14.08 (-10.85, 39.02), p=0.268	-33.17 (-55.35, -10.99), p=0.003	2,163
Model 3: Model 2 + maternal education	39.06 (-5.20, 83.32), p=0.084	14.74 (-10.20, 39.68), p=0.247	-31.79 (-54.04, -9.54), p=0.005	2,161
Model 4: Model 2 + parity	35.73 (-7.85, 79.30) p=0.108	18.33 (-6.27, 42.94), p=0.144	-33.29 (-55.15, -11.44), p=0.003	2,161
Model 5: Model 2 + marital status	39.95 (-4.18, 84.09) p=0.076	14.12 (-10.81, 39.05) p=0.267	-33.33 (-55.52, -11.14) p=0.003	2,163
Model 6: Model 2 + working during pregnancy	41.00 (-3.18, 85.19) p=0.069	12.38 (-12.73, 37.49)	-35.06 (-57.45, -12.68) p=0.002	2,159

		p=0.334		
Model 7: Model 2 + mother's social class	38.88 (-5.25, 83.02) p=0.084	14.13 (-10.78, 39.03) p=0.266	-32.61 (-54.82, -10.41) p=0.004	2,162
Model 8: Model 2 + total physical activity	39.89 (-4.24, 84.03) p=0.076	14.09 (-10.84, 39.03) p=0.268	-33.21 (-55.39, -11.02) p=0.003	2,163

β (95% CI) beta, 95% confidence interval from multivariable mixed piecewise regression models.

Base model: adjusting for maternal and paternal BMI, weight-gain, maternal age, sex of the child and cohort as a random intercept.

Physical activity as METs (Metabolic Equivalent of Task)-hour per day reported at 32 weeks gestation

TABLE 5. Association (β Coeff. and 95 % CI) between maternal sleep duration and child birthweight score (g) adjusted for anxiety and depression during pregnancy as potential intermediate factors

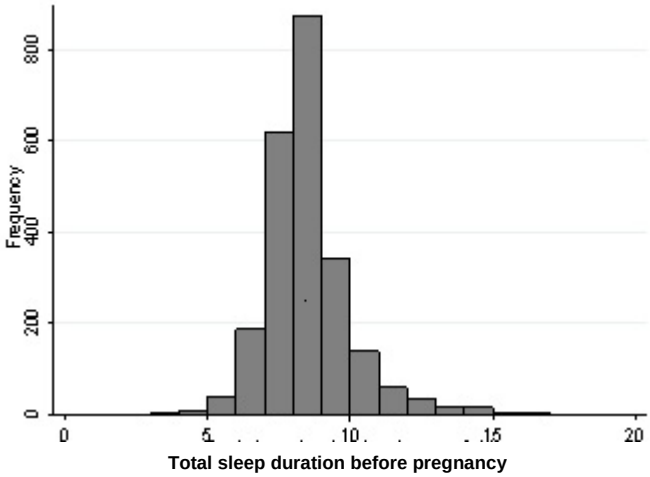
	Sleep before pregnancy			
	≤ 7 hours per day	**> 7 and ≤ 9 hours per day**	**> 9 hours per day**	**N**
	β (95% CI), p-value	β (95% CI), p-value	β (95% CI), p-value	
Model 1 + anxiety clinical history reported at first trimester (Yes/No)	39.97 (-4.23, 84.17), p=0.076	14.02 (-10.94, 38.97), p=0.271	-33.13 (-55.32, -10.93), p=0.003	2,161
Model 1+ depression clinical history reported at first trimester (Yes/No)	39.95 (-4.25, 84.15), p=0.076	14.10 (-10.85, 39.05), p=0.268	-33.30 (-55.51, -11.09), p=0.003	2,161

β (95% CI) beta, 95% confidence interval from multivariable mixed piecewise regression models.
Model 1: adjusting for maternal and paternal BMI, weight-gain, maternal age, sex of the child and cohort as a random intercept.

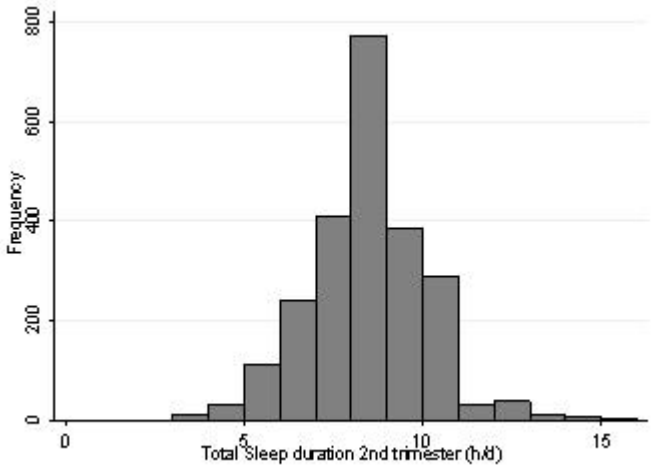
In this study, we found an inverse U-shaped association between maternal sleep duration before and during pregnancy and infant birthweight, using data from a large cohort study.

Figure

Figure 1: Distribution of sleep duration



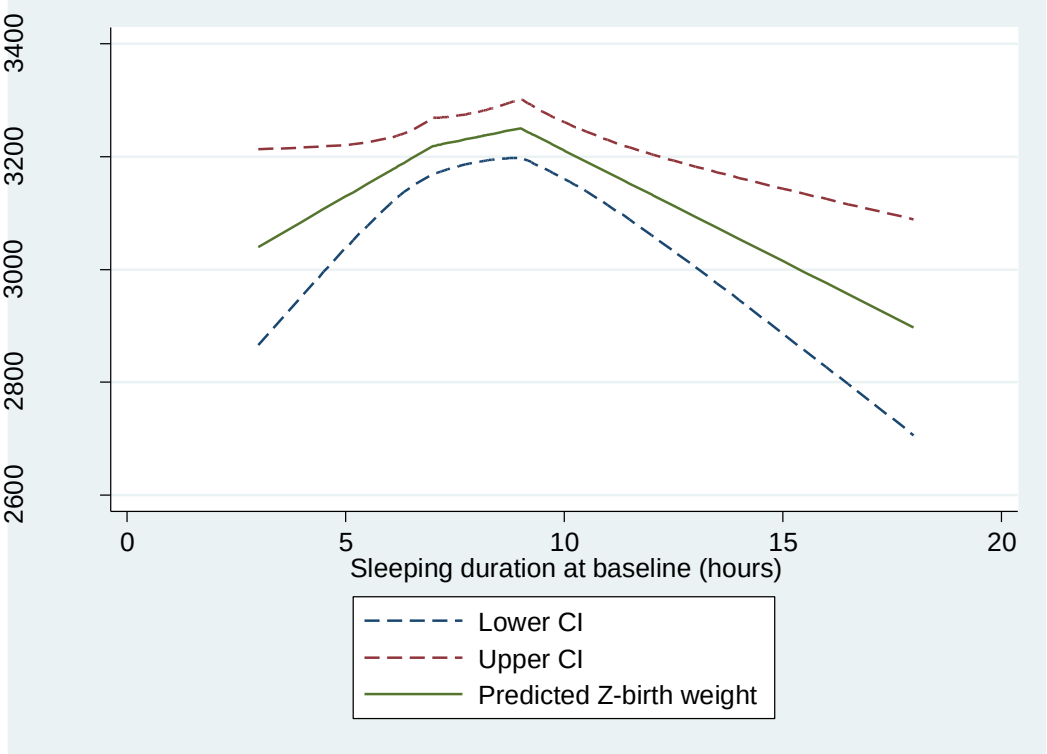
Sleep-duration before pregnancy	n (%)
< 7 h per day	236 (10.1%)
7 to <9 h per day	1491 (63.8%)
9 hours or more per day	608 (26.0%)



Sleep-duration 2nd trimester	n (%)
< 7 h per day	389 (16.7%)
7 to <9 h per day	1181 (50.6%)
9 hours or more per day	765 (32.8%)

Figure

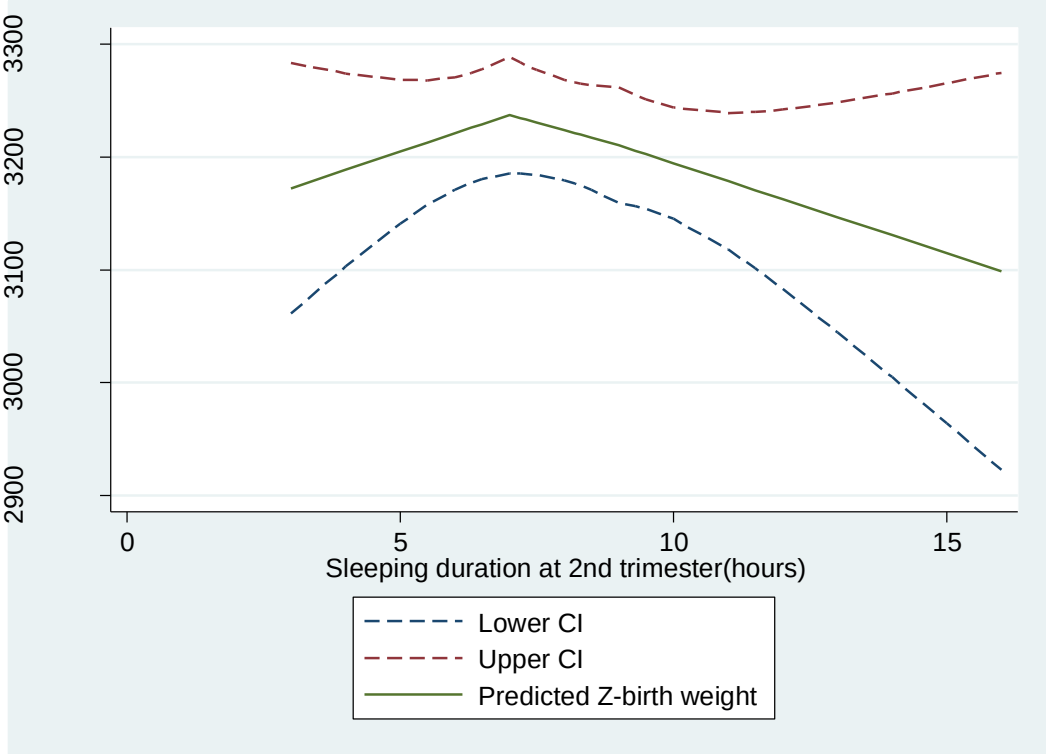
Figure 2: Prediction of birthweight score as a function of sleep duration before pregnancy from the main model presented in table 3



Note: All covariates were set to their mean.

Figure

Figure 3. Prediction of birthweight score as a function of sleep duration during the 2nd trimester from the model presented in table 3



Note: all covariates from the model were set to their mean