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Association between phthalate exposure and sleep quality in pregnant women

Results from the Korean Children's Environmental Health Study with repeated assessment of exposure

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Background: Evidence linking environmental toxicants to sleep quality is growing; however, these associations during pregnancy remain unclear. We examined the associations of repeated measures of urinary phthalates in early and late pregnancy with multiple markers of sleep quality among pregnant women.

Methods: The study population included 2324 pregnant women from the Korean Children's Environmental Health Study. We analyzed spot urine samples collected at two time points during pregnancy for exposure biomarkers of eight phthalate metabolites. We investigated associations between four summary phthalates (all phthalates: ∑Phthalates; di-(2-ethylhexyl) phthalate: ∑DEHP; phthalates from plastic sources: ∑Plastic; and antiandrogenic phthalates: ∑AA) and eight individual phthalates and self-reported sleep measures using generalized ordinal logistic regression and generalized estimating equations models that accounted for repeated exposure measurements. The models were adjusted for age, body mass index, education, gestational age, income, physical activity, smoking, occupation, chronic diseases, depression, and urinary cotinine levels.

Results: Multiple individual phthalates and summary measures of phthalate mixtures, including ∑Plastic, ∑DEHP, ∑AA, and ∑Phthalates, were associated with lower sleep efficiency. To illustrate, every 1-unit log increase in ∑AA was associated with a reduction of sleep efficiency by 1.37 % (95% confidence interval [CI] = –2.41, –0.32). ∑AA and ∑Phthalates were also associated with shorter sleep duration and longer sleep latency. Associations between summary phthalate measures and sleep efficiency differed by urinary cotinine levels (*P* for subgroup difference < 0.05).

Conclusions: Findings suggest that higher phthalate exposure may be related to lower sleep efficiency, shorter sleep duration, and prolonged sleep latency during pregnancy.

Keywords: Sleep; Phthalates; Pittsburgh Sleep Quality Index; Pregnant women

Introduction

Poor sleep quality, generally defined as a collection of sleep measures including sleep time, sleep latency, wake time, and sleep efficiency,[1] is very common in pregnant women. According to a recent meta-analysis, 45.7% of pregnant women have reported poor sleep quality, as determined by the Pittsburgh Sleep Quality Index (PSQI).[2] Prevalence estimates of poor sleep quality during pregnancy vary widely, ranging from 17% to 76%.[3,4] Importantly, poor sleep quality during pregnancy adversely affects the mother's well-being and is associated with severe outcomes, including systemic inflammation,[5] longer labor,[6] gestational diabetes,[7] and prenatal or postnatal depression,[3,8] as well as adverse outcomes for offspring, including preterm births,[9] low birth weight,[6] and future developmental and mental health problems.[10] Therefore, identifying modifiable risk factors underlying poor sleep quality in pregnant women is essential to reduce potential health burdens.

Poor sleep quality can be due to genetic,[11] hormonal,[12] sociodemographic,[13] and environmental factors.[14] Specifically, recent studies have hypothesized that exposure to endocrine-disrupting chemicals (EDCs) could induce sleep disruptions.[15,16] Phthalates

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What this study adds

Studies have linked exposure to phthalates to poor sleep quality in adults; however, there is no research on pregnant women. We investigated the association between phthalate exposure and sleep quality in a cohort of pregnant women living in South Korea. This study is the first to report the association between phthalates and lower sleep efficiency, shorter sleep duration, and prolonged sleep latency in pregnant women. We provide evidence that exposure to phthalates may be a risk factor for poor sleep quality in pregnant women.

are a major group of EDCs that humans encounter by multiple routes, such as oral (e.g., phthalate-contaminated food, water, and other liquids), inhalation (e.g., nail polish, hair spray, and other phthalate-containing products), and dermal absorption (e.g., cosmetic and other personal care products).[17] Once absorbed, phthalates rapidly hydrolyze to form the primary metabolites, and some of the metabolites further oxidize and/or glucuronidate to produce secondary metabolites before excreting through urine and feces.[18] Urinary phthalate metabolites are the preferred biomarkers to evaluate in vivo phthalate exposure,[19] and are highly stable in urine samples stored at ≤20 °C.[20]

Recent epidemiological studies have investigated the association between phthalate exposure and sleep health markers in nonpregnant populations.[15,21,22] In a sample of midlife United States women, higher urinary concentrations of phthalate metabolites were associated with reduced sleep quality, increased sleep disturbances, and restless sleep.[15] Another study from the United States found a link between higher phthalate exposure and shorter sleep duration in adolescents.[21] Phthalates can induce toxicity in biological systems, including the reproductive system.[23,24] Changing hormone levels is likely one mechanism underlying the adverse effect of phthalates. Experimental and observational studies have shown that phthalates alter estradiol levels.[25,26] Studies have also associated phthalate mixtures with hormone levels and steroidogenesis in the ovary in animal studies.[25,27] This finding is concerning given pregnant women's wide exposure to phthalates through diet[28] and personal care products.[29] Changes in reproductive hormones during pregnancy likely play some role in sleep disturbances.[30,31]

Phthalates are hypothesized to be associated with poor sleep quality in women by changing the levels of reproductive hormones. One study reported higher urinary concentrations of phthalates and higher levels of estradiol: progesterone in midlife women with insomnia.[15] In our study, we hypothesize that phthalate exposure may contribute to poor sleep quality in pregnant women. To our knowledge, despite the high prevalence and clinical implications of poor sleep quality during pregnancy, no studies have evaluated the impact of phthalate exposure on sleep quality in pregnant women. The purpose of this study was to assess the associations between repeated measures of urinary phthalate metabolites in early and late pregnancy and sleep quality in pregnant women, evaluated at one time point by the PSQI global score and subscales.

Materials and methods

Study population

We conducted this study as part of the Korean Children's Environmental Health Study (Ko-CHENS), an ongoing nationwide community- and hospital-based birth cohort study in South Korea. Researchers previously published the details of Ko-CHENS.[32] Main eligibility criteria included being pregnant by less than 20 gestational weeks at inclusion, being 18 years of age or older, planning to deliver in one of the 12 regional centers, and living in the study area. The present study included pregnant women recruited between 2015 and 2019 who provided urine samples for phthalate metabolites analysis in early pregnancy (before 20 weeks) and late pregnancy (after 30 weeks) (Fig. S1; http://links.lww.com/EE/A295). The study also collected data on prenatal sleep quality. Among the initially recruited pregnant women (n = 5458), we included (n = 2355) those with information on the concentrations of urinary phthalate and creatinine in early (n = 2497) and late pregnancy (n = 3092). We excluded those with missing information on the PSQI scale (n = 2) and gestational age (n = 29), resulting in 2324 pregnant women in the final study population (Fig. S2; http://links.lww.com/EE/A295). The characteristics of participants with phthalate data did not differ significantly from those without phthalate data, except for education and income (Table S1; http://links.lww.com/EE/A295). We conducted this study following the guidelines of the Declaration of Helsinki, and the Institutional Review Board of Inha University Hospital approved the study (approval no. 2021-10-020). The Institutional Review Board of the National Institute of Environmental Research (NIER) approved the Ko-CHENS protocol (approval no. NIER-2015-BR-005-01, 15 May 2015). We obtained informed consent from all subjects involved in the study.

Urinary exposure biomarkers

Spot urine samples from enrolled women were collected at their clinic visits. The collection container was shielded and immediately stored at 2–6 °C, and frozen at –20 °C until analysis. Urine samples were collected in the morning (between 9 AM and 11 AM) at two time points during early and late pregnancy. The average gestational age was 15 weeks (interquartile range [IQR] = 12–18) at the first collection and 32 weeks (IQR = 31–33) at the second collection. We measured phthalate concentrations in early and late pregnancy urine samples at one of the four analytical laboratories assigned for Ko-CHENS. As previously described, we used high-performance liquid chromatography with tandem mass spectrometry.[33,34] Specifically, we measured the following eight phthalate metabolites: mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxo-hexyl) phthalate (MEOHP), mono-(2-ethyl-5-carboxy-pentyl) phthalate (MECPP), mono-n-butyl phthalate (MnBP), mono-benzyl phthalate (MBzP), mono-carboxyoctyl phthalate (MCOP), mono-(3-carboxypropyl) phthalate (MCPP), and mono (carboxynonyl) phthalate (MCNP). The limits of detection (LOD) of phthalate metabolites varied from 0.097 to 0.323 μg/L. For values below the LOD, we assigned LOD/$\sqrt{2}$.[35] Using colorimetry (ADVIA 1800, Siemens, Germany) with the Jaffe reaction method, we measured urinary creatinine to adjust for urinary dilution. For creatinine adjustment, we divided urinary concentrations of phthalate metabolites (μg/L) by urine creatinine levels (g/L) to yield creatinine-adjusted concentrations of phthalates (micrograms per gram creatinine, μg/g creatinine).

To estimate exposure to relevant phthalate mixtures, we quantified individual phthalate metabolites in molar sum groupings based on similar sources and biological activities (Table S2; http://links.lww.com/EE/A295), as previously described.[15] A summary measure of di-(2-ethyl hexyl) phthalate (∑DEHP) exposure was calculated as the molar-converted sum of three urinary metabolites (MEHHP, MECPP, and MEOHP). DEHP is common in consumer products, building materials, and medical equipment.[36] We also calculated a summary measure of urinary phthalate metabolites from parent compounds with known antiandrogenic (∑AA) biological activity in the body[25,37] using ∑DEHP, MnBP, and MBzP. Summary phthalate measure from plastic sources (∑Plastic) was calculated by ∑DEHP, MCPP, and MBzP. Finally, we calculated the molar sum of all phthalates (∑Phthalates) by summing all

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metabolites measured in this study. The molar sum of phthalates was expressed as micromoles per gram creatinine (μmol/g creatinine).

Sleep quality measures

To quantify the quality and patterns of prenatal sleep over 1 month, we used the PSQI scale,[38] a widely used and well-validated indicator of global sleep quality. Research has shown that the PSQI is acceptable for determining global sleep quality during pregnancy.[39] In the present study, we administered the PSQI questionnaire only once during pregnancy, and the timing of administration varied across participants (median gestational age = 15 weeks). Researchers validated the PSQI among patients with sleep disorders in South Korea, finding an internal consistency of 0.84 and a test-retest correlation coefficient of 0.65 for the total score.[40]

The PSQI comprised 19 items grouped into seven domains that reflect usual sleep duration, sleep onset latency, sleep disturbances, sleep medication use, and sleep efficiency, as well as subjective sleep quality and daytime dysfunction. Each domain was measured using an ordinal scale ranging from 0 (no difficulty) to 3 (severe difficulty). The sum of the seven domains provided the global score, which may range from 0 to 21, and a higher global score indicates poorer sleep quality. In the present study, only one participant reported using sleep medication. Therefore, we excluded this component from the PSQI subscale analysis. We also treated the PSQI subscales as continuous measures when possible (i.e., sleep latency in minutes, sleep duration in minutes, sleep efficiency in percentage, and total score of sleep disturbances). The Cronbach's alpha for the Korean version of the PSQI was 0.69.[41] This study's internal consistency for the PSQI was adequate, with a Cronbach's alpha of 0.64.

Covariates

We selected potential confounding variables retained in adjusted models via a directed acyclic graph (DAG) (Fig. S3; http://links.lww.com/EE/A295). We ascertained these variables at enrollment, including mother's age (<30, 30–34, or ≥35), gestational age (weeks), education (high school, college, or graduate school), occupation during pregnancy (yes vs. no), prepregnancy body mass index (BMI) (kg/m^2), the frequency of physical activity (none, 1–2 times per week, 3–4 times per week, 5–6 times per week, or everyday), smoking history (yes or no), household income (<2000, 2000–3999, or ≥4000 USD/month), presence of prenatal depression, and presence of chronic diseases. These variables have been linked to both our exposure and outcomes in our study population and in previous research.[15,22] We categorized prepregnancy BMI into four levels according to Asia-specific standards from the World Health Organization: underweight (BMI <18.5), normal (18.5≤ BMI <23), overweight (23≤ BMI <25), and obese (≥25).[42] Medical records at delivery provided information on gestational age in weeks. We calculated the gestational age at measurement of PSQI from the gestational age at delivery, delivery date, and questionnaire administration date. Urinary cotinine concentration, which was measured using high-performance liquid chromatography-mass spectrometry in the same samples in which phthalates were analyzed, was used as a biomarker for exposure to environmental tobacco (ET). In addition, we assessed prenatal depression using a 20-item Center for Epidemiologic Studies-Depression (CES-D) scale.[43] The summary score of 20 items that uses a four-point Likert scale indicates the potential presence of depression; a score at or above 16 indicates clinically relevant depressive symptoms.[44] We defined chronic diseases by identifying the histories of nine chronic diseases, including stroke, arthritis, osteoporosis, malignant tumor, asthma, chronic bronchitis, chronic hepatitis, diabetes, and chronic nephritis.

Statistical analysis

We reported descriptive statistics for eight phthalate metabolites with creatinine correction, population characteristics, and global PSQI and subscale scores. To verify the normality of continuous variables, the Kolmogorov–Smirnov statistical test was applied. The urinary phthalate metabolites were log-transformed to normalize their distributions. We assessed the distributions of individual and summary phthalate metabolites by computing geometric means (GMs) and IQR and intraclass correlation coefficients to quantify the degree of variation over early and late pregnancies. The correlation coefficients between each phthalate metabolite were determined using Spearman's correlation.

To examine the associations between log-transformed phthalate metabolites and PSQI subscales as ordinal variables, we performed generalized ordinal logistic regression analysis using a user-written Stata command *gologit2*.[45] Before using this analysis, the Brant test was conducted to confirm the parallel regression assumption. We computed cluster-robust standard error to account for repeated exposure measures at two time points in gestation (i.e., early and late pregnancies). In this analysis, the dependent variables (PSQI subscales) were divided into four category levels of sleep quality: 0 = very good, 1 = fairly good, 2 = fairly bad, and 3 = very bad. Hence, we obtained three coefficient sets in terms of odds ratio (OR) and 95% confidence interval (CI) based on the level of sleep quality as follows: Step 1: 1, 2, and 3 levels versus 0 level; Step 2: 2 and 3 levels versus 0 and 1 levels; and Step 3: 3 level versus 0, 1, and 2 levels. An OR greater than 1 indicated that the respondents were more likely to be experiencing poorer sleep quality than better sleep, whereas an OR less than 1 indicated that respondents were more likely to be experiencing better sleep quality than poorer sleep.

To examine the associations of log-transformed phthalate metabolites with continuous outcomes (global PSQI and subscales), we fitted multiple informant models using generalized estimating equation (GEE) models with independent correlation structure and Gaussian link functions.[46,47] Multiple informant models provide a single integrated estimate for the relationship between exposure over time and the outcome, considering repeated exposure measures (in this case, early and late pregnancy) as informants. In addition, we performed restricted cubic splines analysis with three knots placed according to Harrell's recommended percentiles[48] of the log-transformed phthalates distribution to understand the shape of the relationship observed between phthalate metabolites and sleep quality measures as continuous variables. The restricted cubic spline models were adjusted for the same covariates as previously described. We assessed nonlinearity by testing the regression coefficient of the second spline variable, equaled to 0. We also performed stratified analyses to examine potential effect modification by selected maternal characteristics, including age, BMI, education, income, smoking, depression, and urinary cotinine level. The significance of effect modification was evaluated using two-sample z-tests, which examine differences in phthalate-sleep associations between two groups, by comparing point estimates (β) and corresponding standard errors obtained from GEE models. To assess the influence of highly diluted or concentrated samples on our findings, we conducted sensitivity analyses by examining the associations between phthalate metabolites and sleep quality measures as continuous variables among women who had a normal range of urinary creatinine (i.e., >0.3 to <3.0 g/L). We also tested the impact of the urine dilution adjustment approach by using unadjusted phthalate concentrations with urinary creatinine concentration included as a covariate. Furthermore, we assessed the association between phthalate and sleep quality using GEE models without adjustment for gestational age at PSQI sleep questionnaire administration. We used this approach to evaluate the influence of the timing of PSQI administration on sleep quality.

The statistical significance was defined as $P < 0.05$. We did not adjust P values to account for multiple comparisons, following recommendations from the statistical literature.[49] A complete case analysis was performed for all models due to the low percentage of missing data for covariates (1.2%) retained in adjusted models. All analyses were performed using Stata version 17.0 (StataCorp, College Station, TX).

Results

The mean (SD) age of participants was 33.1 (3.8) years; 62.1% of them had poor sleep quality (PSQI >5). Mean (SD) sleep duration was 7.7 (1.4) hours/night, while sleep latency and sleep efficiency were 32.2 (31.8) minutes and 81.7% (22.3%), respectively. Most women were employed (66%), college-educated (75.8%), never smoked (87.4%), and did not meet the criteria for depression based on the CES-D (74.7%). Nearly half of the women had a monthly family income of ≥4000 USD (48.5%), and more than three in four women were underweight or normal weight (83.7%) (Table 1).

Table 1.

Characteristics of the study participants (N = 2,324)

Characteristics	n (%)/mean (standard deviation)
Age (years)	33.1 (3.8)
Age group	
<30	461 (19.8)
30–34	1134 (48.8)
≥35	729 (31.4)
Education	
High school	229 (9.9)
College	1762 (75.8)
Graduate school	333 (14.3)
Gestational age at PSQI sleep questionnaire measurement (weeks)	13.6 (4.1)
Household income (US$/month)	
<2000	114 (4.9)
2000–3999	1084 (46.6)
≥4000	1126 (48.5)
Occupation	
No	789 (34.0)
Yes	1535 (66.0)
Physical activity	
None	1669 (84.7)
1–2/week	118 (5.1)
3–4/week	163 (7.0)
5–6/week	51 (2.2)
Everyday	23 (1.0)
Body mass index (kg/m^2)	
<18.5	249 (10.7)
18.5–22.9	1389 (59.8)
23–24.9	307 (13.2)
≥25	379 (16.3)
Smoking status	
No	2032 (87.4)
Yes	292 (12.6)
Urinary cotinine concentration (μg/g creatinine)	15.4 (118.5)
Chronic diseases	
No	2185 (94.0)
Yes	139 (6.0)
Depressive symptoms	
No (CES-D-20 <16)	1737 (74.7)
Yes (CES-D-20 ≥16)	587 (25.3)
Global PSQI score	6.4 (2.1)
PSQI subscales (continuous variables)	
Sleep latency (minutes)	32.2 (31.8)
Sleep duration (minutes)	459.2 (84.9)
Sleep efficiency (%)	81.7 (22.3)
Sleep disturbances	5.2 (3.4)

We provided the GM concentrations, detection distributions, and limits of eight phthalate metabolites (Table 2). Phthalate metabolites were frequently detected over time (61.9–100% and 60.2–100% in early and late pregnancy, respectively). We observed higher GM concentrations for MECPP and MnBP among phthalate metabolites. The intraclass correlation coefficients of individual and grouped phthalate metabolites varied from 0.29 to 0.65, with most in the range of 0.3–0.5, indicating fair to moderate reproducibility over time (Table 2). Spearman correlations were moderately positive between MEHHP and MnBP ($\rho = 0.48$) and MnBP and MEOHP ($\rho = 0.47$), and the correlation coefficients between MECPP, MEHHP, and MEOHP were 0.9 or above (Table S3; http://links.lww.com/EE/A295).

Table 3 shows the results of the generalized ordinal logistic regressions for the associations between summary measures of phthalates and PSQI subscales; the results for individual phthalates are in the supplementary material (Table S4; http://links.lww.com/EE/A295). Most of the individual and summary measures of phthalate metabolites were associated with increased odds of lower sleep efficiency in adjusted models. In particular, the adjusted ORs for each log-unit increase in MEHHP, MBzP, ∑AA, ∑Plastic, and ∑Phthalates showed significant and positive increases for all steps, and the ORs were different for Steps 1 and 2. We observed similar findings for MEOHP, MECPP, and ∑DEHP in Steps 2 and 3, and ORs were slightly different for each cutoff point. In Step 2, there were positive associations between MCOP and sleep latency, MCNP and sleep disturbances, and MnBP and short sleep duration. The association of phthalate metabolites with daytime dysfunction was not consistent. MCNP was positively associated with daytime dysfunction in Step 3, whereas MEHHP, MEOHP, MECPP, and all summary measures of phthalates were negatively associated with daytime dysfunction in Step 2. We found similar results between adjusted and unadjusted models (Table S5; http://links.lww.com/EE/A295).

Table 4 shows findings from adjusted GEE models of the relationship between urinary phthalate metabolites and continuous measures of sleep quality (i.e., sleep latency, duration, efficiency, and disturbances). We observed significant negative associations of all summary measures of phthalates and five individual phthalates (MEHHP, MEOHP, MECPP, MBzP, and MnBP) with sleep efficiency. For example, each log-unit increase in MBzP and ∑AA was associated with reduced sleep efficiency by 1.42% (95% CI = –2.20, –0.65) and 1.37% (95% CI = –2.41, –0.32), respectively. Sleep latency was positively associated with ∑Phthalates ($\beta = 1.62$; 95% CI = 0.24, 3.01), ∑AA ($\beta = 1.43$; 95% CI = 0.07, 2.78), MCOP ($\beta = 1.65$; 95% CI = 0.54, 2.76), and MCPP ($\beta = 1.72$; 95% CI = 0.40, 3.04), indicating that longer sleep latency was related to higher levels of phthalate concentrations.

We observed negative associations of two summary phthalates (∑AA and ∑Phthalates) and two individual phthalates (MEHHP and MnBP) with sleep duration. To illustrate, each log-unit increase in ∑Phthalates, ∑AA, MEHHP, and MnBP was associated with a 4.17 min (95% CI = –8.28, –0.05), 4.15 min (95% CI = –8.19, –0.10), 2.81 min (95% CI = –5.58, –0.04), and 3.38 min (95% CI = –6.66, –0.09) shorter sleep duration, respectively.

However, none of the phthalate metabolites were associated with global PSQI and sleep disturbances. Both adjusted and unadjusted models produced similar findings in our analysis (Table S6; http://links.lww.com/EE/A295).

The restricted cubic spline with a multivariable GEE model demonstrated that the overall associations of all summary measures of phthalates with sleep efficiency were significant (Figure 1C and S3K–M; http://links.lww.com/EE/A295; $P_{overall} < 0.05$), showing downward relationships with the increasing level of phthalate concentrations. We also found an overall downward relationship between ∑phthalates and ∑AA and sleep duration (Figure 1B and S4I; http://links.lww.com/EE/A295; $P_{overall} < 0.05$). Furthermore, the nonlinearity tests in the associations between all summary measures of phthalates and

Table 2.

Distributions of phthalate metabolites across pregnancy among 2324 study participants

		Early pregnancy (before 20 weeks)			Late pregnancy (over 30 weeks)			
Phthalates	**LOD[a]**	**% ≥ LOD[b]**	**GM[c]**	**IQR[c]**	**% ≥ LOD[b]**	**GM[c]**	**IQR[c]**	**ICC**
Individual chemicals								
MEHHP	0.241	95.4	5.52	6.99	97.5	7.47	8.00	0.36
MEOHP	0.100	95.5	4.78	4.83	100.0	6.26	5.62	0.44
MECPP	0.231	100	10.56	9.17	99.9	12.08	9.73	0.51
MCOP	0.124	90.0	0.88	1.00	90.9	0.78	0.79	0.29
MCPP	0.176	70.4	0.41	0.34	81.3	0.53	0.41	0.36
MBzP	0.197	61.9	0.60	0.83	60.2	0.66	0.90	0.65
MCNP	0.097	70.0	0.23	0.19	78.6	0.28	0.26	0.31
MnBP	0.323	98.1	12.44	12.69	98.0	15.31	14.56	0.50
Phthalate molar-converted sum								
∑DEHP[d]	—	—	0.07	0.07	—	0.09	0.08	0.46
∑AA[e]	—	—	0.14	0.12	—	0.17	0.14	0.49
∑Plastic[f]	—	—	0.08	0.07	—	0.09	0.08	0.46
∑Phthalates[g]	—	—	0.15	0.12	—	0.18	0.15	0.49

[a]µg/L.

[b]Frequency of detection computed using concentrations assessed in each pool of urine samples collected in the early and late pregnancies.

[c]µg/g creatinine.

[d]∑DEHP = (MEHHP/294.34) + (MEOHP/292.33) + (MECPP/308.33).

[e]∑AA = ∑DEHP + (MBzP/256.25) + (MnBP/222.24).

[f]∑Plastic = ∑DEHP + (MCPP/252.22) + (MBzP/256.25).

[g]∑Phthalates = ∑DEHP + (MCOP/322.36) + (MCPP/252.22) + (MBzP/256.25) + (MCNP/336.40) + (MnBP/222.24).

GM, geometric mean; ICC, intraclass correlation coefficient; LOD, limit of detection; MCNP, mono-carboxynonyl phthalate; MBzP, mono-benzyl phthalate; MCOP, mono-carboxyoctyl phthalate; MCPP, mono-(3-carboxypropyl) phthalate; MECPP, mono-(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; MnBP, mono-n-butyl phthalate.

sleep efficiency and sleep duration were insignificant at the 0.05 level, indicating a linear exposure-response function. The spline curves for global PSQI, sleep latency, and sleep disturbances did not have significant overall associations and did not significantly deviate from linearity (Figures 1, A and D, and S4; http://links.lww.com/EE/A295).

Figure 2 compares subgroup-specific associations of sleep efficiency with summary phthalate measures stratified by individual characteristics. We observed significant negative associations only among women with higher cotinine levels (≥0.94 µg/g creatinine), with *P* values of <0.05 for effect difference. Summary phthalate-sleep efficiency associations were more evident among younger women (<35 years), those having a BMI <25, nonsmokers, and higher income groups; however, the effect difference was not significant (*P* values >0.05). Additionally, compared with participants with a CES-D score ≥16, those without depressive symptoms (CES-D >16) showed a more evident association between summary phthalate measures and sleep efficiency, with *P* values of >0.05 for effect difference.

In sensitivity analyses, the associations between urinary phthalates and continuous measures of sleep quality did not materially change when we restricted the analysis to pregnant women with a normal urinary creatinine range (n = 2089) (Table S7; http://links.lww.com/EE/A295). The regression analyses using unadjusted phthalate concentration with urinary creatinine as a covariate revealed the same significant associations reported in the creatinine-adjusted phthalate concentration (Table S8; http://links.lww.com/EE/A295). Furthermore, as per Table S9; http://links.lww.com/EE/A295, the results of GEE models without adjustment for gestational age at PSQI sleep questionnaire measurement were generally consistent with GEE models adjusted for the gestational age (Table 4).

Discussion

This study investigated the associations of eight urinary phthalate metabolites, measured in early (<20 weeks) and late pregnancy (>30 weeks) urine samples, with sleep quality in pregnant women using generalized ordinal logistic and GEE regressions. We found that some individual phthalate metabolites (MEHHP, MECPP, MBzP, and MnBP) and all summary phthalates (∑DEHP, ∑AA, ∑Plastic, and ∑Phthalates) were associated with lower sleep efficiency. Further, MEHHP, MnBP, ∑AA, and ∑Phthalates were associated with shorter sleep duration, and MCOP, MCPP, ∑AA, and ∑Phthalates were associated with prolonged sleep latency. We found stronger associations between summary phthalate measures and sleep efficiency in pregnant women with higher urinary cotinine levels.

Previous research on phthalates and sleep quality in human populations is sparse.[15,21,50] Our findings that urinary phthalate metabolites were associated with short sleep duration are consistent with prior literature linking phthalates to sleep duration in nonpregnant populations. A study using cross-sectional data from the United States National Health and Nutrition Examination Survey (NHANES) (n = 322) found that higher urinary concentrations of phthalate metabolites, including ∑DEHP, were associated with self-reported short sleep duration in adolescents.[21] Another NHANES study (n = 13,634) reported that urinary concentration of DEHP was associated with a higher risk of short sleep duration, measured by a self-report questionnaire, in the general population.[50] However, a recent cross-sectional study (n = 470) in Mexico found that urinary phthalate metabolites were associated with longer sleep duration, which the researchers assessed with wrist-actigraphy among adolescents.[22] The inconsistencies in studies may have arisen from the differences in study populations and the use of sleep measures.[22] Our study found that higher exposure to phthalates was associated with decreased sleep efficiency and prolonged sleep latency, consistent with previous findings in midlife women.[51] Collectively, the current study and previous studies showing the association of phthalates with poor sleep health measures suggest that exposure to phthalates may potentially influence sleep in pregnant women.

Some potential mechanisms may mediate the association between phthalates and poor sleep quality. First, studies have

Table 3.

Associations of log-transformed urinary phthalate summary measures with PSQI subscales using generalized ordinal logistic regression

Step	Phthalates	Sleep quality	Sleep latency	Sleep duration	Sleep efficiency	Sleep disturbances[a]	Daytime dysfunction
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Step 1:	∑DEHP	1.17 (0.84, 1.63)	1.03 (0.93, 1.15)	1.01 (0.92, 1.11)	1.09 (0.99, 1.20)[b]	0.93 (0.84, 1.02)	0.95 (0.85, 1.06)
1,2,3 vs.0	∑AA	1.17 (0.79, 1.74)	1.05 (0.94, 1.18)	1.07 (0.96, 1.18)	1.12 (1.01, 1.25)[c]	0.98 (0.88, 1.09)	0.90 (0.80, 1.01)
	∑Plastic	1.27 (0.83, 1.65)	1.03 (0.92, 1.15)	1.02 (0.93, 1.12)	1.10 (1.00, 1.22)[c]	0.93 (0.84, 1.02)	0.93 (0.84, 1.04)
	∑Phthalates	1.15 (0.77, 1.72)	1.05 (0.93, 1.19)	1.06 (0.96, 1.18)	1.13 (1.01, 1.25)[c]	0.98 (0.88, 1.09)	0.90 (0.79, 1.00)[b]
Step 2:	∑DEHP	0.98 (0.89, 1.09)	0.98 (0.89, 1.08)	1.06 (0.94, 1.19)	1.15 (1.03, 1.28)[c]	0.94 (0.86, 1.04)	0.87 (0.78, 0.97)[c]
2,3 vs. 0,1	∑AA	0.93 (0.83, 1.03)	1.00 (0.90, 1.10)	1.10 (0.97, 1.25)	1.15 (1.03, 1.29)[c]	1.02 (0.92, 1.13)	0.86 (0.77, 0.97)[c]
	∑Plastic	0.99 (0.90, 1.10)	0.97 (0.88, 1.08)	1.06 (0.94, 1.20)	1.17 (1.05, 1.30)[d]	0.94 (0.85, 1.04)	0.88 (0.79, 0.98)[c]
	∑Phthalates	0.93 (0.83, 1.04)	1.00 (0.90, 1.11)	1.10 (0.97, 1.25)	1.16 (1.03, 1.30)[c]	1.02 (0.92, 1.13)	0.86 (0.76, 0.97)[c]
Step 3:	∑DEHP	0.92 (0.71, 1.17)	0.94 (0.82, 1.09)	1.05 (0.70, 1.58)	1.16 (1.04, 1.29)[c]	1.00 (0.89, 1.12)	0.89 (0.71, 1.11)
3 vs. 0,1,2	∑AA	0.86 (0.67, 1.10)	1.02 (0.87, 1.18)	1.11 (0.70, 1.76)	1.15 (1.02, 1.30)[c]	1.05 (0.93, 1.19)	0.93 (0.73, 1.18)
	∑Plastic	0.93 (0.72, 1.19)	0.95 (0.82, 1.09)	1.04 (0.70, 1.56)	1.17 (1.04, 1.31)[d]	1.00 (0.89, 1.13)	0.89 (0.71, 1.12)
	∑Phthalates	0.86 (0.67, 1.11)	1.02 (0.88, 1.19)	1.11 (0.70, 1.75)	1.14 (1.01, 1.29)[c]	1.06 (0.93, 1.20)	0.93 (0.73, 1.19)

[a]Total score divided into quarters. All models adjusted for age, BMI, education, gestational age at PSQI sleep questionnaire measurement, income, physical activity, smoking, maternal cotinine level, maternal occupation, chronic diseases, and depressive symptoms.
[b]*P* value <0.10.
[c]*P* value <0.05.
[d]*P* value <0.01.

found an association between phthalates and altered hormone levels during pregnancy, which may contribute to sleep disturbances.[52–54] Animal studies reported reductions in testosterone concentrations in the pregnant dam following exposure to DEHP, DnBP, and BBzP during gestations.[55,56] DEHP was negatively associated with estradiol concentrations in adult female rodents.[26] In pregnant women, prenatal exposure to DEHP was negatively associated with total and free testosterone concentrations.[54] Observational studies identified associations of altered estradiol, testosterone, and progesterone levels with the risk of poor sleep quality in women.[15,52] Pregnancy can cause changes in maternal hormone levels—progesterone, testosterone, and estradiol concentrations change dramatically during pregnancy[57] and may contribute to sleep disorders in pregnant women. Second, higher urinary DEHP metabolite levels were associated with decreased levels of thyroid hormone in pregnant women,[58] which may be associated with poor sleep quality.[59]

Interestingly, we found that urinary cotinine level modified the association between summary phthalate measures and sleep efficiency in our study population. Cotinine is the principal metabolite of nicotine, which researchers consider an objective marker of the level of exposure to ET.[60] In our study, all summary measures of phthalates were associated with lower sleep efficiency in women with higher cotinine levels but not in women with lower cotinine levels. This finding indicates that exposure to ET may increase urinary phthalate levels in pregnant women. One possible explanation is that women with high cotinine levels already have increased phthalate levels.[61] In our study, the participants with high cotinine levels showed a higher concentration of the molar sum of all phthalates (∑Phthalates) compared to those with low cotinine levels (average levels of 0.220 vs. 0.196 μmol/g creatinine; Wilcoxon rank-sum test, $P < 0.001$). A recent study in Korea showed a significant association between urinary cotinine levels and poor sleep quality in young and middle-aged adults.[62] Whether urinary cotinine levels and phthalates jointly cause the increased risk of poor sleep quality in pregnant women deserves further studies.

This study is the first that we are aware of to examine the relationship between phthalates and sleep quality in pregnant women. Other strengths of this study include the large sample size, multiple confounders adjustment, an exhaustive index for assessing sleep quality, and multiple sensitivity analyses. In addition, this study used the phthalate concentrations measured at two time points during early and late pregnancies to improve the credibility of phthalate measurement. However, this study has several limitations.

First, as part of the participants who completed the PSQI questionnaire did not undergo urinary phthalate measurements, this might cause selection bias. Second, sleep quality was assessed by the self-reported PSQI, and we did not confirm it by clinical examinations, such as polysomnography and actigraphy monitoring, which is the gold standard for diagnosing sleep disorders.[63] Self-reported sleep duration is moderately correlated with estimates from sleep duration measured using actigraphy.[64] Third, we used spot urine samples for exposure assessment. Phthalates are non-persistent and rapidly metabolized. Indeed, research has indicated large within-person variability for phthalates and poor reliability over time.[65] Fourth, as we assessed sleep quality only once during pregnancy, the responses obtained would not have represented changes in sleep patterns throughout pregnancy. Sleep is subject to change during pregnancy, and repeated assessments at different windows of pregnancy would have allowed us to associate repeated measures of phthalates with repeated sleep measures. Fifth, although the analyses included adjustments for several important potential confounders, we cannot discard residual confounding. For example, pregnancy is a period of dramatic hormonal changes, and exposure to phthalates can impact hormonal levels,[23,25] which may confound associations between phthalates and sleep quality. Environmental factors, such as light exposure, electronic screen use, environmental noise, and temperature, can

Table 4.

Associaitons of log-transformed urinary phthalate metabolites with sleep quality measures as continuous variables

	Global PSQI	Sleep latency	Sleep duration	Sleep efficiency	Sleep disturbances
Phthalates	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**
MEHHP	0.01 (–0.06, 0.08)	0.45 (–0.52, 1.41)	–2.81 (–5.58, –0.04)[a]	–1.07 (–1.79, –0.34)[b]	0.01 (–0.11, 0.12)
MEOHP	0.01 (–0.08, 0.09)	0.90 (–0.21, 2.02)	–1.51 (–4.89, 1.87)	–0.88 (–1.75, –0.02)[a]	–0.03 (–0.18, 0.12)
MECPP	–0.002 (–0.11, 0.10)	1.17 (–0.25, 2.59)	–1.87 (–5.85, 2.12)	–1.24 (–2.29, –0.18)[a]	–0.17 (–0.35, 0.01)[c]
MCOP	0.04 (–0.03, 0.11)	1.65 (0.54, 2.76)[b]	–0.06 (–3.02, 2.90)	–0.49 (–1.27, 0.29)	–0.02 (–0.14, 0.10)
MCPP	–0.003 (–0.10, 0.11)	1.72 (0.40, 3.04)[a]	–1.12 (–5.05, 2.82)	–0.93 (–1.96, 0.09)[c]	–0.07 (–0.25, 0.11)
MBzP	0.02 (–0.05, 0.10)	0.27 (–0.66, 1.20)	–0.38 (–3.25, 2.48)	–1.42 (–2.20, –0.65)[d]	0.01 (–0.10, 0.12)
MCNP	0.001 (–0.10, 0.10)	0.45 (–0.88, 1.78)	2.19 (–1.67, 6.06)	–0.89 (–1.86, 0.07)[c]	0.03 (–0.12, 0.18)
MnBP	0.03 (–0.05, 0.11)	0.75 (–0.45, 1.96)	–3.38 (–6.66, –0.09)[a]	–0.94 (–1.78, –0.09)[a]	0.09 (–0.03, 0.21)
∑DEHP	0.003 (–0.09, 0.10)	0.95 (–0.32, 2.22)	–2.46 (–6.13, 1.21)	–1.18 (–2.14, –0.22)[a]	–0.07 (–0.24, 0.09)
∑AA	0.02 (–0.08, 0.12)	1.43 (0.07, 2.78)[a]	–4.15 (–8.19, –0.10)[a]	–1.37 (–2.41, –0.32)[a]	0.04 (–0.12, 0.21)
∑Plastic	0.01 (–0.09, 0.10)	0.99 (–0.31, 2.29)	–2.68 (–6.44, 1.07)	–1.30 (–2.30, –0.31)[a]	–0.08 (–0.25, 0.09)
∑Phthalates	0.02 (–0.09, 0.12)	1.62 (0.24, 3.01)[a]	–4.17 (–8.28, –0.05)[a]	–1.34 (–2.41, –0.27)[a]	0.05 (–0.12, 0.22)

All models adjusted for age, BMI, education, gestational age at PSQI sleep questionnaire measurement, income, physical activity, smoking, maternal cotinine level, maternal occupation, chronic diseases, and depressive symptoms.

[a]*P* value <0.05.

[b]*P* value <0.01.

[c]*P* value <0.1.

[d]*P* value <0.001.

also influence sleep quality and could confound associations between phthalates and sleep quality. Additionally, we cannot exclude reverse causation since sleep disruptions impact food choices.[66] It is possible that pregnant women who have poor sleep may be more likely to have unhealthy dietary habits and, therefore, consume more phthalate-containing foods.[67] Previous research indicates that consuming more ultra-processed food is associated with higher MCNP, MCOP, and MCPP urinary concentrations.[68] Finally, longitudinal studies with repeated measurements over time should further validate the possible causation in the association between urinary phthalate metabolites and sleep quality in pregnant women.

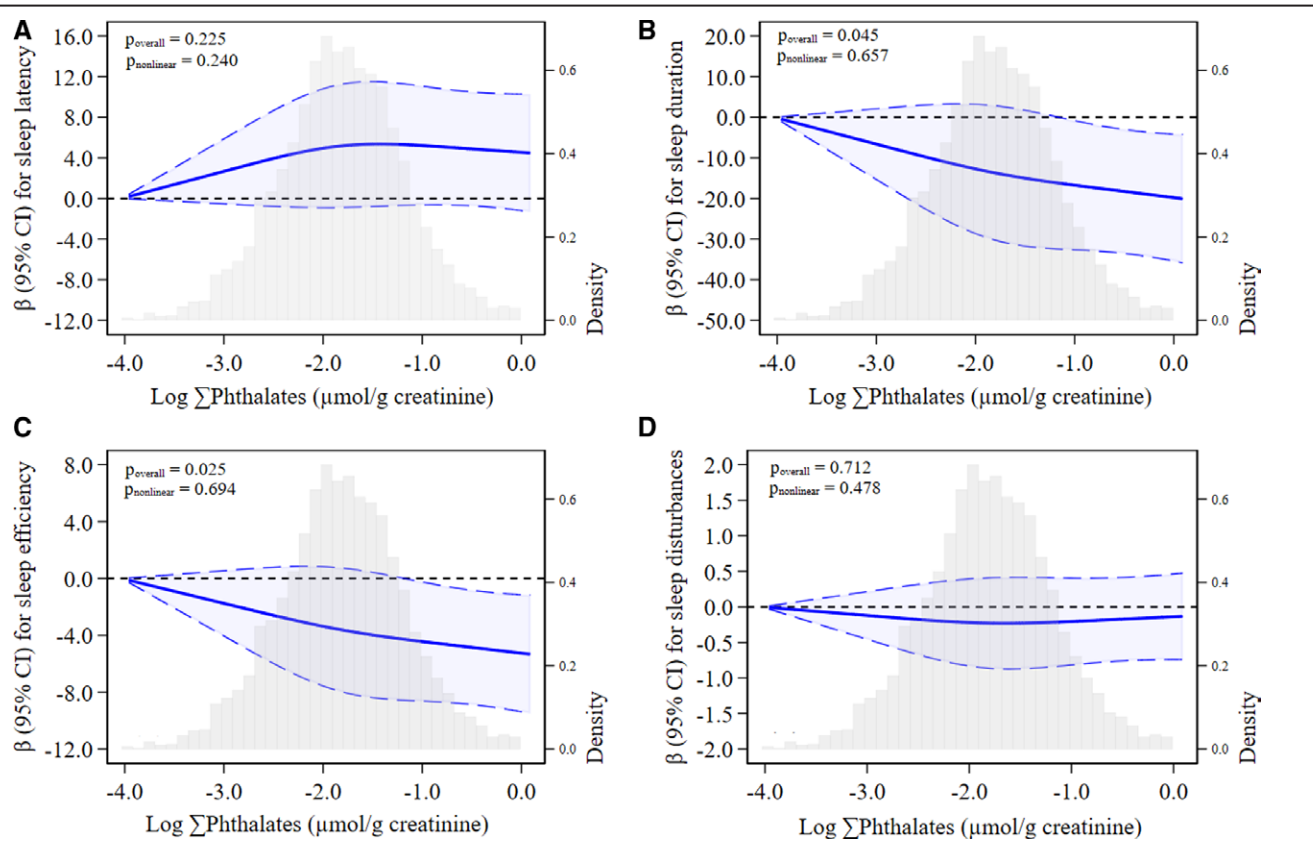

Figure 1. Exposure-response curves for the associations of ∑phthalates with sleep latency, sleep duration, sleep efficiency, and sleep disturbances. A, is the exposure-response curve for sleep latency, (B) for sleep duration, (C) for sleep efficiency, and (D) for sleep disturbances. The solid line represents β, and the long-dashed lines represent the confidence interval. All models adjusted for age, BMI, education, gestational age at PSQI sleep questionnaire measurement, income, physical activity, smoking, maternal cotinine level, maternal occupation, chronic diseases, and depressive symptoms. The histograms show the distribution of log-transformed ∑Phthalates.

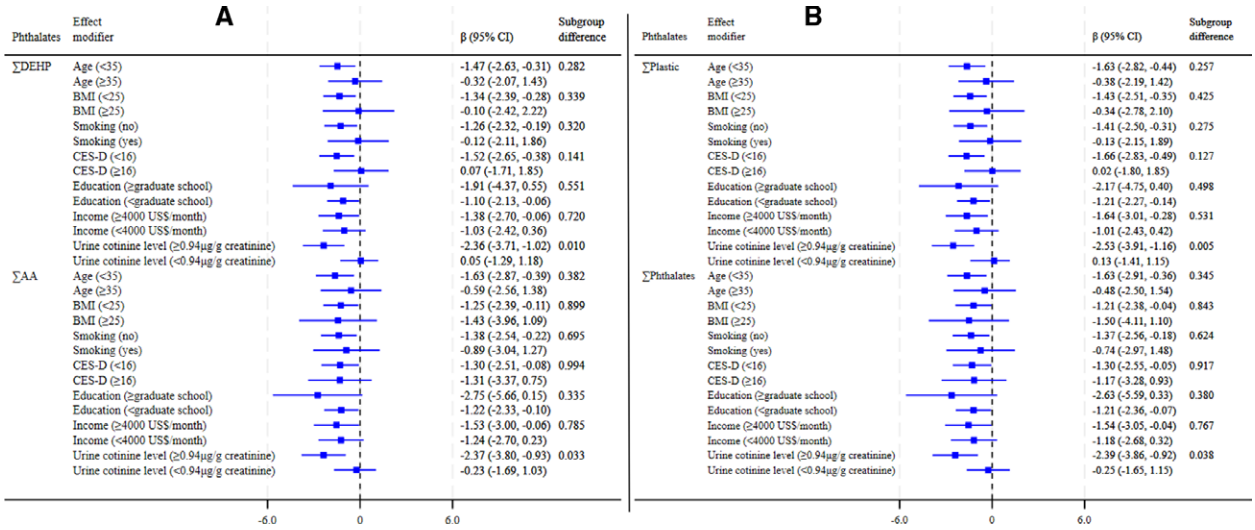

Figure 2. Associations of urinary phthalate metabolite concentrations with sleep efficiency stratified by a modifier (age, BMI, smoking, CES-D score, education, income, and urinary cotinine level). A, displays the associations for ∑DEHP and ∑AA, while (B) displays the associaiton for ∑plastic and ∑phthalates. Analyses were adjusted for age, BMI, education, gestational age at PSQI sleep questionnaire measurement, income, physical activity, smoking, maternal cotinine level, maternal occupation, chronic diseases, and CES-D score. Data are presented as β and 95% confidence interval for every log-unit increase in urinary phthalate metabolite concentrations.

Conclusions

We found evidence that exposure to urinary phthalate metabolites (individual and summary measures) is associated with poor sleep quality, as indicated by low sleep efficiency, short sleep duration, and prolonged sleep latency in pregnant women. Additionally, we found that urinary cotinine levels modify the associations between urinary phthalate metabolites and sleep efficiency. Future studies should explore the present research question with repeated assessments of phthalates, hormones, and sleep quality at different stages of pregnancy to confirm associations and clarify the mechanisms through which phthalates influence sleep in pregnant women.

Conflicts of interest statement

The authors declare that they have no conflicts of interest with regard to the content of this report.

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REFERENCES

1. Krystal AD, Edinger JD. Measuring sleep quality. *Sleep Med*. 2008;9:S10–S17.
2. Sedov ID, Cameron EE, Madigan S, Tomfohr-Madsen LM. Sleep quality during pregnancy: a meta-analysis. *Sleep Med Rev*. 2017;38:168–176.
3. Gelaye B, Addae G, Neway B, et al. Poor sleep quality, antepartum depression and suicidal ideation among pregnant women. *J Affect Disord*. 2017;209:195–200.
4. Mindell JA, Cook RA, Nikolovski J. Sleep patterns and sleep disturbances across pregnancy. *Sleep Med*. 2015;16:483–488.
5. Besedovsky L, Lange T, Haack M. The sleep-immune crosstalk in health and disease. *Physiol Rev*. 2019;99:1325–1380.
6. Zafarghandi N, Hadavand S, Davati A, Mohseni SM, Kimiaiimoghadam F, Torkestani F. The effects of sleep quality and duration in late pregnancy on labor and fetal outcome. *J Matern Fetal Neonatal Med*. 2012;25:535–537.
7. Cai S, Tan S, Gluckman PD, et al; on behalf of the GUSTO study group. Sleep quality and nocturnal sleep duration in pregnancy and risk of gestational diabetes mellitus. *Sleep*. 2017;40:zsw058.
8. Okun ML, Mancuso RA, Hobel CJ, Schetter CD, Coussons-Read M. Poor sleep quality increases symptoms of depression and anxiety in postpartum women. *J Behav Med*. 2018;41:703–710.
9. Wang L, Jin F. Association between maternal sleep duration and quality and the risk of preterm birth: a systematic review and meta-analysis of observational studies. *BMC Pregnancy Childbirth*. 2020;20:125.
10. Vizzini L, Popovic M, Zugna D, et al. Maternal anxiety, depression and sleep disorders before and during pregnancy, and preschool ADHD symptoms in the NINFEA birth cohort study. *Epidemiol Psychiatr Sci*. 2019;28:521–531.
11. Jones SE, van Hees VT, Mazzotti DR, et al. Genetic studies of accelerometer-based sleep measures yield new insights into human sleep behaviour. *Nat Commun*. 2019;10:1585.
12. Sowers MF, Zheng H, Kravitz HM, et al. Sex steroid hormone profiles are related to sleep measures from polysomnography and the Pittsburgh sleep quality index. *Sleep*. 2008;31:1339–1349.
13. Kalmbach DA, Cheng P, Sangha R, et al. Insomnia, short sleep, and snoring in mid-to-late pregnancy: disparities related to poverty, race, and obesity. *Nat Sci Sleep*. 2019;11:301–315.
14. Liu J, Ghastine L, Um P, Rovit E, Wu T. Environmental exposures and sleep outcomes: a review of evidence, potential mechanisms, and implications. *Environ Res*. 2021;196:110406.
15. Hatcher KM, Smith RL, Chiang C, Li Z, Flaws JA, Mahoney MM. Association of phthalate exposure and endogenous hormones with self-reported sleep disruptions: results from the Midlife Women's Health Study. *Menopause*. 2020;27:1251–1264.
16. Shiue I. Urinary arsenic, pesticides, heavy metals, phthalates, polyaromatic hydrocarbons, and polyfluoroalkyl compounds are associated with sleep troubles in adults: USA NHANES, 2005-2006. *Environ Sci Pollut Res Int*. 2017;24:3108–3116.
17. Swan SH. Environmental phthalate exposure in relation to reproductive outcomes and other health endpoints in humans. *Environ Res*. 2008;108:177–184.
18. Frederiksen H, Skakkebaek NE, Andersson AM. Metabolism of phthalates in humans. *Mol Nutr Food Res*. 2007;51:899–911.

19. Calafat AM, Koch HM, Swan SH, et al. Misuse of blood serum to assess exposure to bisphenol A and phthalates. *Breast Cancer Res*. 2013;15:403.
20. Samandar E, Silva MJ, Reidy JA, Needham LL, Calafat AM. Temporal stability of eight phthalate metabolites and their glucuronide conjugates in human urine. *Environ Res*. 2009;109:641–646.
21. Sears CG, Braun JM. Urinary phthalate metabolite concentrations and adolescent sleep duration. *Environ Epidemiol*. 2021;5:e134.
22. Zamora AN, Peterson KE, Tellez-Rojo MM, et al. Urinary phthalates, phenols, and parabens in relation to sleep health markers among a cohort of Mexican adolescents. *Sci Total Environ*. 2023;861:160651.
23. Hannon PR, Brannick KE, Wang W, Flaws JA. Mono(2-Ethylhexyl) phthalate accelerates early folliculogenesis and inhibits steroidogenesis in cultured mouse whole ovaries and antral follicles. *Biol Reprod*. 2015;92:120.
24. Wang W, Craig ZR, Basavarajappa MS, Hafner KS, Flaws JA. Mono-(2-ethylhexyl) phthalate induces oxidative stress and inhibits growth of mouse ovarian antral follicles. *Biol Reprod*. 2012;87:152.
25. Hannon PR, Flaws JA. The effects of phthalates on the ovary. *Front Endocrinol (Lausanne)*. 2015;6:8.
26. Lovekamp-Swan T, Davis BJ. Mechanisms of phthalate ester toxicity in the female reproductive system. *Environ Health Perspect*. 2003;111:139–145.
27. Meling DD, Warner GR, Szumski JR, et al. The effects of a phthalate metabolite mixture on antral follicle growth and sex steroid synthesis in mice. *Toxicol Appl Pharmacol*. 2020;388:114875.
28. Pacyga DC, Sathyanarayana S, Strakovsky RS. Dietary predictors of phthalate and bisphenol exposures in pregnant women. *Adv Nutr*. 2019;10:803–815.
29. Rivera-Nunez Z, Ashrap P, Barret ES, et al. Personal care products: demographic characteristics and maternal hormones in pregnant women from Puerto Rico. *Environ Res*. 2022;206:112376.
30. Deurveilher S, Rusak B, Semba K. Estradiol and progesterone modulate spontaneous sleep patterns and recovery from sleep deprivation in ovariectomized rats. *Sleep*. 2009;32:865–877.
31. Gupta R, Rawat VS. Sleep and sleep disorders in pregnancy. *Handb Clin Neurol*. 2020;172:169–186.
32. Jeong KS, Kim S, Kim WJ, et al; Ko-CHENS Study group. Cohort profile: beyond birth cohort study – the Korean CHildren's ENvironmental health Study (Ko-CHENS). *Environ Res*. 2019;172:358–366.
33. NIER (National Institute of Environmental Research). The 4th Korean National Environmental Health Survey. *Manual for Analysis of Environmental Pollutants in Biological Samples (Organic Chemicals)*. Korea Ministry of Environment; 2022.
34. NIER (National Institute of Environmental Research). The 3rd Korean National Environmental Health Survey. *Manual for Analysis of Environmental Pollutants in Biological Samples (Organic Chemicals)*. Korea Ministry of Environment; 2018.
35. Hornung R, Reed L. Estimation of average concentration in the presence of nondetectable values. *Appl Occup Environ Hyg*. 1990;9:821–827.
36. Serrano SE, Braun J, Trasande L, Dills R, Sathyanarayana S. Phthalates and diet: a review of the food monitoring and epidemiology data. *Environ Health*. 2014;13:43.
37. Marsee K, Woodruff TJ, Axelrad DA, Calafat AM, Swan SH. Estimated daily phthalate exposure in a population of mothers of male infants exhibiting reduced anogenital distance. *Environ Health Perspect*. 2006;114:805–809.
38. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28:193–213.
39. Jomeen J, Martin CR. Assessment and relationship of sleep quality to depression in early pregnancy. *J Reprod Infant Psychol*. 2007;25:87–99.
40. Sohn SI, Kim DH, Lee MY, Cho YW. The reliability and validity of the Korean version of the Pittsburgh sleep quality index. *Sleep Breath*. 2012;16:803–812.
41. Shin S, Kim SH. The reliability and validity testing of Korean version of the Pittsburgh sleep quality index. *J Converg Info Technol*. 2020;10:148–155.
42. Choi SK, Lee G, Kim YH, Park IY, Ko HS, Shin JC. Determining optimal gestational weight gain in the Korean population: a retrospective cohort study. *Reprod Biol Endocrinol*. 2017;15:67.
43. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas*. 1977;1:385–401.
44. Heller HM, Draisma S, Honig A. Construct validity and responsiveness of instruments measuring depression and anxiety in pregnancy: a comparison of EPDS, HADS-A and CES-D. *Int J Environ Res Public Health*. 2022;19:7563.
45. Williams R. Generalized ordered logit/partial proportional odds models for ordinal dependent variables. *Stata J*. 2006;6:58–82.
46. Horton NJ, Laird NM, Zahner GE. Use of multiple informant data as a predictor in psychiatric epidemiology. *Int J Methods Psychiatr Res*. 1999;8:6–18.
47. Sanchez BN, Hu H, Litman HJ, et al. Statistical methods to study timing of vulnerability with sparsely sampled data on environmental toxicants. *Environ Health Perspect*. 2011;19:409–415.
48. Harrell FE. *Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis*. New York, NY, USA: Springer; 2015.
49. Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology*. 1990;1:43–46.
50. Lin J, Cheng S, Zhang J, et al. The relationship between daily dietary intake of fiber and short sleep duration in the presence of Di(2-Ethylhexyl) phthalate: a population-based study. *Front Nutr*. 2022;9:910892.
51. Hatcher KM, Smith RL, Li Z, Flaws JA, Davies CR, Mahoney MM. Preliminary findings reveal that phthalate exposure is associated with both subjective and objective measures of sleep in a small population of midlife women. *Maturitas*. 2022;157:62–65.
52. Kische H, Ewert R, Fietze I, et al. Sex hormones and sleep in men and women from the general population: a cross-sectional observational study. *J Clin Endocrinol Metab*. 2016;101:3968–3977.
53. Morssinkhof MWL, van Wylick DW, Priester-Vink S, et al. Associations between sex hormones, sleep problems and depression: a systematic review. *Neurosci Biobehav Rev*. 2020;118:669–680.
54. Sathyanarayana S, Barret E, Butts S, et al. Phthalate exposure and reproductive hormone concentrations in pregnancy. *Reproduction*. 2014;147:401–409.
55. Kavlock R, Boekelheide K, Chapin R, et al. NTP center for the evaluation of risks to human reproduction: phthalates expert panel report on the reproductive and developmental toxicity of di(2-ethylhexyl) phthalate. *Reprod Toxicol*. 2002;16:529–653.
56. Mylchreest E, Sar M, Wallace DG, Foster PMD. Fetal testosterone insufficiency and abnormal proliferation of Leyding cells and gonocytes in rats exposed to di(n-butyl) phthalate. *Reprod Toxicol*. 2002;16:19–28.
57. O'Leary P, Boyne P, Flett P, Beilby J, James I. Longitudinal assessment of changes in reproductive hormones during normal pregnancy. *Clin Chem*. 1991;37:667–672.
58. Johns LE, Ferguson KK, Soldin OP, et al. Urinary phthalate metabolites in relation to maternal serum thyroid and sex hormone levels during pregnancy: a longitudinal analysis. *Reprod Biol Endocrinol*. 2015;13:4.
59. Song L, Lei J, Jiang K, et al. The association between subclinical hypothyroidism and sleep quality: a population-based study. *Risk Manag Healthc Policy*. 2019;12:369–374.
60. Benowitz NL. Cotinine as a biomarker of environmental tobacco smoke exposure. *Epidemiol Rev*. 1996;18:188–204.
61. Wang L, Zou Y, Wu P, Meng J, Zhang R. Phthalate exposure in pregnant women and the influence of exposure to environmental tobacco smoke. *J Matern Fetal Neonatal Med*. 2020;33:3111–3115.
62. Oh S, Kim S, Sung E, et al. The association between cotinine-measured smoking intensity and sleep quality. *Tob Induc Dis*. 2022;20:77.
63. Malhotra RK, Kirsch DB, Kristo DA, et al; American Academy of Sleep Medicine Board of Directors. American academy of sleep medicine board of directors. polysomnography for obstructive sleep apnea should include arousal-based scoring: an American Academy of Sleep Medicine position statement. *J Clin Sleep Med*. 2018;14:1245–1247.
64. Jackson CL, Patel SR, Jackson WB 2nd, Lutsey PL, Redline S. Agreement between self-reported and objectively measured sleep duration among white, black, Hispanic, and Chinese adults in the United States: multi-ethnic study of atherosclerosis. *Sleep*. 2018;41:zsy057.
65. Townsend MK, Franke AA, Li X, Hu FB, Eliassen AH. Within-person reproducibility of urinary bisphenol A and phthalate metabolites over a 1 to 3 year period among women in the Nurses' Health Studies: a prospective cohort study. *Environ Health*. 2013;12:80.
66. Du C, Almotawa J, Feldpausch CE, Folk SYL, Parag H, Tucker RM. Effects of macronutrient intake on sleep duration and quality: a systematic review. *Nutr Diet*. 2022;79:59–75.
67. Kruger AK, Reither EN, Peppard PE, Krueger PM, Hale L. Do sleep-deprived adolescents make less-healthy food choices? *Br J Nutr*. 2014;111:1898–1904.
68. Buckley JP, Kim H, Wong E, Rebholz CM. Ultra-processed food consumption and exposure to phthalates and bisphenols in the US National Health and Nutrition Examination Survey, 2013-2014. *Environ Int*. 2019;131:105057.