Received: 1 April 2019 | Revised: 27 May 2019 | Accepted: 28 May 2019

DOI: 10.1002/bdr2.1536

ORIGINAL ARTICLE

Birth Defects Research | THE TERATOLOGY SOCIETY EST 1967 | WILEY

Exploring associations of maternal sleep during periconceptional period with congenital heart disease in offspring

Anda Zhao[1] | **Kena Zhao**[1] | **Yuanqing Xia**[1] | **Yong Yin**[2] | **Jianzhen Zhu**[3] | **Haifa Hong**[2] | **Shenghui Li**[1]

[1]School of Public Health, Shanghai Jiao Tong University School of Medicine, Shanghai, China

[2]Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China

[3]Shanghai Jiao Tong University School of Medicine, Shanghai, China

Correspondence
Shenghui Li, School of Public Health, Shanghai Jiao Tong University, 227 South Chongqing Road, Huangpu District, Shanghai 200025, China.
Email: lsh9907@163.com, submission9907@163.com

Haifa Hong, Shanghai Children's Medical Center, Shanghai Jiao Tong University, 1678 Dongfang Road, Pudong District, Shanghai 200127, China.
Email: hhfsmallboat@163.com

Funding information
the Key Project from Shanghai Municipal Science and Technology Commission, Grant/Award Number: 18411951600; National Natural Science Foundation of China, Grant/Award Numbers: 81673183, 81874266; the Research Funds from Shanghai Jiao Tong University School of Medicine, Grant/Award Number: 20170509-1; the Science and Technology Funds from Pudong New Area, Shanghai, Grant/Award Number: PKJ2017-Y01; the Scientific Research Development Funds from Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Grant/Award Number: HX0251

Abstract

Background: In general, the existing evidence points to a role for maternal sleep in pregnancy complications and fetal growth, however, little has been focused on birth defects. We aimed to explore the association between periconceptional poor sleep and the risk of congenital heart disease (CHD), and to examine if daytime napping could to some extent change the association.

Methods: A case–control study was conducted in Shanghai Children's Medical Center, in which, a total of 524 cases (262 simple CHD vs. 262 severe CHD), along with 262 controls.

Results: In the multivariable logistic analysis, poor sleep could increase the risk of both simple CHD (OR = 2.486, 95% CI = 1.619–3.818) and severe CHD (OR = 1.950, 95% CI = 1.269–2.997), while routine daytime nap could decrease risk of simple CHD (OR = 0.634, 95% CI = 0.435–0.923). In the stratified analysis, the concurrence with routine daytime nap could weaken the risk of simple CHD caused by poor sleep (OR = 3.183, 95% CI: 1.830–5.537 decreased to OR = 2.236, 95% CI: 1.200–4.165). The examinations were repeated in ventricular septal defect and tetralogy of Fallot, and the established associations can be verified. Moreover, all these findings were also similarly observed in both propensity-score-adjusted and propensity-score-matched analyses.

Conclusions: Poor maternal sleep around periconceptional period seems to be an independent risk factor for CHD. The concurrence with daytime nap could to some extent reduce the risk in simple CHD. The results individually and collectively put forward the importance of maternal sleep in embryonic heart development.

KEYWORDS
case–control study, congenital heart disease, daytime nap, maternal sleep, pregnancy

Anda Zhao and Kena Zhao contributed equally to this work.

1 | INTRODUCTION

Sleep is a major physiological process, which may serve important functions including energy restoration, metabolic regulation, immune enhancement, and so forth (Krueger, Frank, Wisor, & Roy, 2016). Due to the hormone-related physiological changes in immunity and metabolism, poor sleep, characterized by chronic sleep deprivation and sleep disorders, was highly prevalent in pregnant women (Wilkerson & Uhde, 2018; Yang et al., 2018). As suggested by studies, poor sleep has potentially increased the risk of pregnancy complications, such as gestational diabetes mellitus and pregnancy-induced hypertension (Li, Zhao, Hua, & Li, 2018; Palagini et al., 2014; Wilkerson & Uhde, 2018). Meanwhile, a number of studies support that poor sleep, in general, may have negative effect on the fetus resulting in altered gestational length and growth restriction (Abeysena, Jayawardana, & Seneviratne Rde, 2009; Abeysena, Jayawardana, & Seneviratne Rde, 2010; Kajeepeta et al., 2014). Of note is that, up to now, very few studies have focused on birth defects.

To the best of our knowledge, only one epidemiologic study explored the topic (Li et al., 2015). The study evaluated the association of periconceptional poor sleep with risk of neural tube defects (NTDs) based on a case–control design, where it was found that frequent poor sleep (≥4 days/week) could independently increase the risk of NTDs by 3.1 times (Li et al., 2015). The finding encouraged us to do more to probe into the role of maternal sleep in embryonic early development. This is further highlighted by research progress in melatonin. Studies within the last decade suggested that melatonin, a sleep–wake and other circadian rhythm messenger linking mother and fetus, has essential functions in fetal maturation and placenta/uterine homeostasis (Reiter, Tan, Korkmaz, & Rosales-Corral, 2014; Voiculescu, Zygouropoulos, Zahiu, & Zagrean, 2014). Besides, two recent studies jointly revealed that melatonin is involved in embryonic cardiac development (Kudova, Vasicek, Ciz, & Kubala, 2016; Nogueira & Sampaio, 2017). Since it has been confirmed that sleep disturbance during pregnancy could interfere the rhythm and amplitude of melatonin secretion (Shimada, Seki, Samejima, Hayase, & Shirai, 2016; Suzuki et al., 1993), it is now an opportune time to explore the relationship of maternal sleep with heart development and disease. We hypothesized that poor sleep exposure during the key period of embryonic heart development might increase the risk of congenital heart diseases (CHD), cardiovascular malformations caused by abnormal cardiac morphogenesis during early embryonic development (Bouma & Mulder, 2017). Moreover, a recent study suggested that daytime napping could be a beneficial countermeasure to the sleep disruption among pregnant women (Ebert, Wood, & Okun, 2015). We would observe whether daytime napping could weaken or reverse the risk, in which, any significant finding would help better understanding the link of maternal sleep to CHD in offspring.

To extend an insight into the association between maternal sleep and birth defects, a hospital-based case–control study was specifically designed to examine our hypothesis of an association between periconceptional poor sleep and the risk of CHD, and furthermore, to examine if daytime napping could to some extent change the association. The examination would be conducted in both simple CHD and severe CHD, and then repeated in ventricular septal defect (VSD) and tetralogy of Fallot (TOF), the most frequent single type of simple CHD and severe CHD, respectively.

2 | METHODS

2.1 | Ethics statement

The ethical application and consent procedure of this study were approved by the Ethics Committee of Shanghai Jiao Tong University School of Medicine (Approval number: SJUPN-201717).

2.2 | Study design and subjects

A hospital-based case–control study was conducted in Shanghai Children's Medical Center through June 2016 to December 2017. 262 children with severe CHD and 262 children with simple CHD, along with 262 control children without any birth defects, were enrolled in this study. All the children were younger than 2 years old, and those with any of the following conditions were excluded from the study: (a) cases with other congenital deformities except CHD, such as Down syndrome, 22q11.2 microdeletion, Noonan syndrome, Williams syndrome, Marfan syndrome, and etc.; (b) death of mother; (c) mother diagnosed with mental disorder; and (d) inability to locate the mother for interview.

The CHD diagnoses were based on the codes of the International Classification of Diseases, Tenth Revision, Clinical Modification. A team of experts, including pediatric cardiothoracic surgeons and fetal ultrasonologists, made evaluation and ensured the accuracy of the final diagnosis. To discuss the relationship of maternal sleep with the risk of different subgroup of CHD, the CHD cases were divided into simple and severe CHD groups with reference to previous studies (Wu et al., 2010; Yeh et al., 2015). In this study, simple CHD includes VSD, atrial septal defect, congenital pulmonary valve stenosis, congenital stenosis of aortic valve, patent ductus arteriosus, coarctation of aorta, and stenosis of pulmonary artery. To avoid the enrollment of nonsignificant clinical forms or spontaneously resolved defects, only those

children who had a CHD-specific admission were recruited (Chou et al., 2016). Severe CHD in this study includes double outlet right ventricle, transposition of the great arteries, common ventricle, single ventricle, atrioventricular septal defect, TOF, congenital tricuspid stenosis, hypoplastic left heart syndrome, atresia of pulmonary artery, and total anomalous pulmonary venous return. The children in the control group were recruited from the pediatric patients admitted into the same hospital during the same period when the cases were recruited. Among the 262 controls, 132 came from pediatric respiratory medicine, 91 from pediatric general surgery, and 39 from pediatric gastroenterology.

2.3 | Measures

Information on sociodemographic characteristics and health-related behaviors was retrospectively collected through the Periconceptional Behaviors and Environmental Exposure Questionnaire (PBEQ). For both cases and controls, only those mothers who signed informed consent were invited to fill out the questionnaires by themselves while they were in hospital.

2.3.1 | Sleep assessment

Periconceptional Sleep Questionnaire (PSQ), as a part of PBEQ, was specifically designed to evaluate maternal sleep characteristics during periconceptional period. The PSQ was developed on previous literature review (Abeysena et al., 2009; Li et al., 2015; O'Brien et al., 2013; Okun, Luther, Wisniewski, & Wisner, 2013; Okun, Schetter, & Glynn, 2011; Wang, Lin, Lin, Chen, & Lin, 2010), pilot studies and reliability assessment. The Cronbach's alpha coefficient of the PSQ was 0.86, which indicates that the internal consistency is good and acceptable. The PSQ has six questions in total to evaluated maternal sleep characteristics around 1 month before the conception and the whole pregnancy. One is to ask about sleep duration: "how much was your total sleep duration in a typical day?". Four are regarding signs and symptoms of sleep quality: "How often did you have difficulty falling asleep in 30 minutes during a typical week?"; "How often did you have difficulty in maintaining/reinitiating sleep during a typical week?"; "How often did you snore loudly during a typical week?"; and "How often did you take medicine to help sleep during a typical week?". The response was assessed on a 4-point Likert scale ("quite often" if occurred 3 or more nights per week, "sometimes" for 1–2 nights per week, "occasionally" for <1 night per week, and "never"). The last one is about routine daytime nap: "Did you have a daytime nap in general?", and the response was "yes" or "no."

The optimal duration of sleep needed in pregnancy is still unknown. The cut-off of short sleep duration differed in the literature, and <8 hr/d, comparatively, was a common choice (Abeysena et al., 2009; Abeysena et al., 2010; Lee & Gay, 2004; Mizutani, Suzuki, Kondo, & Yamagata, 2007; Yu et al., 2017). In addition, 8 hr/d is close to the bottom 25th centile of the distribution of total sleep duration of our data. Therefore, short sleep duration was defined as sleep duration <8 hr/d in the present study. Each item regarding sleep quality was scored as yes = 1 if responses were "quite often" or "sometimes" and no = 0 if responses were "occasionally" or "never." Based on the scoring system, the index of sleep quality was summed up as 0–4, which was further dichotomized as 0–2 versus 3–4 and the latter was defined as poor sleep quality. Considering the overlap and collinearity existed between short sleep duration and poor sleep quality, we combined them into a single variable named as "poor sleep", defined as sleep duration < 8 hr/d and/or the index of sleep quality being 3–4.

2.4 | Potential confounding variables

2.4.1 | Demographic and obstetric characteristics

Maternal ethnic was categorized as Han ethnicity versus others; maternal age at delivery was grouped as <35 years old versus ≥35 years; maternal educational level was grouped into three categories: middle school and below, high school, and college and above; marital status was categorized as married versus unmarried/divorced/widowed; residence was categorized as urban versus suburban/rural; maternal prepregnancy obesity, was grouped into yes versus no (obesity was defined as body mass index (BMI) ≥ 28 [Zhou, 2002], BMI was calculated as weight in kilograms divided by height in meters squared based on prepregnancy height and weight); multiple birth was grouped as yes versus no; family history of CHD was grouped as yes versus no; and infant gender was categorized as male versus female.

2.4.2 | Maternal health indicators and behaviors

Maternal prepregnancy diabetes (defined as pregestational diabetes, yes vs. no), maternal prepregnancy hypertension (defined as pregestational hypertension, yes vs. no), maternal folic acid supplementation (defined as taking folic acid supplements before and/or during pregnancy, yes vs. no), maternal smoking (defined as smoking before and/or during pregnancy, yes vs. no), and maternal drinking (defined as drinking before and/or during pregnancy, yes vs. no).

2.5 | Statistical analysis

Statistical description was made by use of percentage for categorical variables, and the Chi-square test and Fisher's exact test were employed to compare difference between groups.

To identify the relationship between maternal sleep and CHD, univariate and multivariable logistic regression models were established. Adjustments were made following a two-step procedure: model[a] was adjusted for demographic and obstetric characteristics; and in model[b], maternal health indicators and behaviors were simultaneously controlled. To examine if daytime napping could change the strength of the associations, the likelihood ratio test and stratified analysis were further specifically applied.

The present study adopted a propensity score method for adjustment and matching (Deb et al., 2016; Heinze & Juni, 2011). A multivariable logistic regression model was developed to estimate the propensity score, in which all potential confounding variables related to CHD were included in the model. In propensity-score-adjusted analysis, propensity scores were used as a covariate. The strength of propensity-score-adjusted analysis lies in taking all covariates along with their interactions as one covariate into account, which could reduce potential selection bias between cases and controls, making the regression models more parsimonious and accurate (Deb et al., 2016; Heinze & Juni, 2011). In propensity-score-matched analysis, controls were matched 1:1 to cases based on a greedy nearest neighbor matching algorithm on propensity score with a caliper equaling to 0.1.

We conducted propensity score analyses using R version 3.5.1 (The R Foundation for Statistical Computing). All other analyses were performed with the Statistical Package for the Social Sciences (SPSS) (IBM-SPSS Statistics version 23.0, Inc., Chicago, IL). Statistical significance level was set at p value <.05 (two sided).

3 | RESULTS

3.1 | The characteristics of the sample

Table 1 summarizes the sample information on demographic and obstetric characteristics by CHD cases versus controls. The following variables were significantly different between CHD cases and control group before propensity score matched: residence, maternal education level, and folic acid supplementation (all $p < .05$). In addition, infant gender and family history of CHD were also different, however, only between simple CHD cases and controls (both $p < .05$). After accounting for propensity score matching, no significant differences were observed between cases and controls.

Maternal sleep characteristics were also shown in Table 1. The prevalence of short sleep duration was significantly higher in cases (simple CHD: 33.2%; severe CHD: 30.2%) than in control group (21.0%) before propensity score matched (both $p < .05$). So was the poor sleep (simple CHD: 35.9%; severe CHD: 31.7%; controls: 21.4%, both $p < .05$). The prevalence of poor sleep quality was different in simple CHD versus controls (8.4% vs. 2.3%, $p < .05$), but not in severe CHD versus controls (5.3% vs. 2.3%, $p > .05$). The proportion of mothers who had daytime naps was significantly lower in cases (simple CHD: 50.4%; severe CHD: 50.4%) than in control group (62.2%) (both $p < .05$). After propensity score matching, the significant difference between CHD cases and controls were still kept in most cases.

Information on the characteristics of VSD versus controls and TOF versus controls was also described, as demonstrated in Table S1.

3.2 | The associations of maternal sleep with CHD

3.2.1 | Simple CHD versus controls

As shown in Table 2, the final adjusted model (model[b]) demonstrated that both short sleep duration (OR = 2.289, 95% CI: 1.484–3.532), poor sleep quality (OR = 4.738, 95% CI: 1.691–13.277), poor sleep (OR = 2.486, 95% CI: 1.619–3.818) could increase the risk of simple CHD; while routine daytime nap (OR = 0.634, 95% CI: 0.435–0.923) could decrease the risk. After accounting for propensity score matching, the results were generally kept. When the analyses were repeated in VSD, similar results were obtained in most cases (Table S2).

The likelihood ratio test of the interaction between routine daytime nap and poor sleep did not achieve statistical significance level ($p > .05$). However, in the stratified analysis (Table 3), the concurrence with routine daytime nap could decrease the risk of simple CHD caused by poor sleep (OR = 3.183 with 95% CI: 1.830–5.537 decreased to OR = 2.236 with 95% CI: 1.200–4.165 in the final adjusted model). The trend is similar either after propensity-score-adjusted analysis or after propensity-score-matched analysis. The analysis was also repeated in VSD and the similar results were obtained (Table S3).

3.2.2 | Severe CHD versus controls

After controlling for all possible confounders in model[b], it was indicated that short sleep duration and poor sleep could increase the risk of severe CHD by 86.2% (95% CI: 1.206–2.876) and 95.0% (95% CI: 1.269–2.997), respectively. By contrast to simple CHD, routine daytime nap was not found to be a protective factor for severe CHD. After propensity score analyses, the results were generally kept. In the likelihood ratio test and stratified analysis (Table 3), it

TABLE 1 The description of characteristics by CHD cases versus controls, (*n*, %)

	Simple CHD						Severe CHD					
	Unmatched			Matched			Unmatched			Matched		
	Cases ($n = 262$)	Controls ($n = 262$)	*p*	Cases ($n = 187$)	Controls ($n = 187$)	*p*	Cases ($n = 262$)	Controls ($n = 262$)	*p*	Cases ($n = 186$)	Controls ($n = 186$)	*p*
Demographic and obstetric characteristics												
Maternal ethnic												
Han	250, 95.4	255, 97.3	.243	180, 96.3	180, 96.3	1.000	251, 95.8	255, 97.3	.337	179, 96.2	181, 97.3	.557
Other	12, 4.6	7, 2.7		7, 3.7	7, 3.7		11, 4.2	7, 2.7		7, 3.8	5, 2.7	
Maternal age at delivery												
<35 years old	240, 91.6	240, 91.6	1.000	172, 92.0	172, 92.0	1.000	233, 88.9	240, 91.6	.302	171, 91.9	166, 89.2	.375
≥35 years old	22, 8.4	22, 8.4		15, 8.0	15, 8.0		29, 11.1	22, 8.4		15, 8.1	20, 10.8	
Maternal education												
Middle school and below	83, 31.7	58, 22.1	.014	48, 25.7	51, 27.3	.866	101, 38.5	58, 22.1	<.001	65, 34.9	52, 28.0	.294
High school	55, 21.0	48, 18.3		44, 23.5	40, 21.4		62, 23.7	48, 18.3		33, 17.7	41, 22.0	
College and above	124, 47.3	156, 59.5		95, 50.8	96, 51.3		99, 37.8	156, 59.5		88, 47.3	93, 50.0	
Marital status												
Married	258, 98.5	257, 98.1	1.000[a]	184, 98.4	184, 98.4	1.000[a]	253, 96.6	257, 98.1	.279	182, 97.8	182, 97.8	1.000[a]
Unmarried/divorced/ widowed	4, 1.5	5, 1.9		3, 1.6	3, 1.6		9, 3.4	5, 1.9		4, 2.2	4, 2.2	
Residence												
Urban	110, 42.0	166, 63.4	<.001	87, 46.5	95, 50.8	.408	99, 37.8	166, 63.4	<.001	86, 46.2	91, 48.9	.604
Suburban/rural	152, 58.0	96, 36.6		100, 53.5	92, 49.2		163, 62.2	96, 36.6		100, 53.8	95, 51.1	
Maternal prepregnancy obesity												
Yes	6, 2.3	9, 3.4	.432	6, 3.2	5, 2.7	.760	17, 6.5	9, 3.4	.108	4, 2.2	7, 3.8	.359
No	256, 97.7	253, 96.6		181, 96.8	182, 97.3		245, 93.5	253, 96.6		182, 97.8	179, 96.2	
Multiple births												
Yes	15, 5.7	23, 8.8	.178	13, 7.0	11, 5.9	.673	29, 11.1	23, 8.8	.381	15, 8.1	21, 11.3	.293
No	247, 94.3	239, 91.2		174, 93.0	176, 94.1		233, 88.9	239, 91.2		171, 91.9	165, 88.7	
Infant gender												
Male	128, 48.8	168, 64.1	<.001	98, 52.4	100, 53.5	.836	160, 61.1	168, 64.1	.470	126, 67.7	110, 59.1	.085
Female	134, 51.1	94, 35.9		89, 47.6	87, 46.5		102, 38.9	94, 35.9		60, 32.3	76, 40.9	

(Continues)

TABLE 1 (Continued)

	Simple CHD						Severe CHD					
	Unmatched			Matched			Unmatched			Matched		
	Cases ($n = 262$)	Controls ($n = 262$)	p	Cases ($n = 187$)	Controls ($n = 187$)	p	Cases ($n = 262$)	Controls ($n = 262$)	p	Cases ($n = 186$)	Controls ($n = 186$)	p
Family history of CHD												
Yes	20, 7.6	6, 2.3	.005	3, 1.6	6, 3.2	.502[a]	11, 4.2	6, 2.3	.218	5, 2.7	6, 3.2	.760
No	242, 92.4	256, 97.7		184, 98.4	181, 96.8		251, 95.8	256, 97.7		181, 97.3	180, 96.8	
Maternal health indicators and behaviors												
Diabetes/hypertension												
Yes	2, 0.8	7, 2.7	.176[a]	2, 1.1	1, 0.5	1.000[a]	8, 3.1	7, 2.7	.793	4, 2.2	5, 2.7	1.000[a]
No	260, 99.2	255, 97.3		185, 98.9	186, 99.5		254, 96.9	255, 97.3		182, 97.8	181, 97.3	
Folic acid supplementation												
Yes	204, 77.9	222, 84.7	.044	147, 78.6	152, 81.3	.518	186, 71.0	222, 84.7	<.001	142, 76.3	148, 79.6	.453
No	58, 22.1	40, 15.3		40, 21.4	35, 18.7		76, 29.0	40, 15.3		44, 23.7	38, 20.4	
Smoking/drinking												
Yes	25, 9.5	26, 9.9	.883	18, 9.6	19, 10.2	.863	40, 15.3	26, 9.9	.065	16, 8.6	22, 11.8	.304
No	237, 90.5	236, 90.1		169, 90.4	168, 89.8		222, 84.7	236, 90.1		170, 91.4	164, 88.2	
Sleep characteristics												
Short sleep duration												
Yes	87, 33.2	55, 21.0	.002	63, 33.7	35, 18.7	.001	79, 30.2	55, 21.0	.016	57, 30.6	40, 21.5	.045
No	175, 66.8	207, 79.0		124, 66.3	152, 81.3		183, 69.8	207, 79.0		129, 69.4	146, 78.5	
Poor sleep quality												
Yes	22, 8.4	6, 2.3	.002	17, 9.1	4, 2.1	.004	14, 5.3	6, 2.3	.068	10, 5.4	3, 1.6	.048
No	240, 91.6	256, 97.7		170, 90.9	183,97.9		248, 94.7	256, 97.7		176, 94.6	183, 98.4	
Poor sleep												
Yes	94, 35.9	56, 21.4	<.001	69, 36.9	36, 19.3	<.001	83, 31.7	56, 21.4	.008	60, 32.3	40, 21.5	.019
No	168, 64.1	206, 78.6		118, 63.1	151, 80.7		179, 68.3	206, 78.6		126, 67.7	146, 78.5	
Daytime nap												
Yes	132, 50.4	163, 62.2	.006	93, 49.7	115, 61.5	.022	132, 50.4	163, 62.2	.006	97, 52.2	113, 60.8	.094
No	130, 49.6	99, 37.8		94, 50.3	72, 38.5		130, 49.6	99, 37.8		89, 47.8	73, 39.2	

CHD = congenital heart disease.

[a]The Fisher's exact test was used; in the other cases, the Chi-square test was applied.

TABLE 2 Associations of maternal sleep during periconceptional period with CHD in offspring

	Before propensity score analysis			After propensity score analysis	
		Adjusted OR (95%CI)			
	Crude OR (95% CI)	Model[a]	Model[b]	Propensity-score-adjusted OR (95% CI)	Propensity-score-matched OR (95% CI)
Simple CHD					
Short sleep duration					
Yes vs. no	1.871 (1.263–2.772)**	2.203 (1.439–3.371)***	2.289 (1.484–3.532)***	2.165 (1.425–3.287)***	2.206 (1.370–3.553)**
Poor sleep quality					
Yes vs. no	3.911 (1.559–9.811)**	3.633 (1.404–9.404)**	4.738 (1.691–13.277)**	4.067 (1.570–10.535)**	4.575 (1.509–13.869)**
Poor sleep					
Yes vs. no	2.058 (1.396–3.036)***	2.394 (1.572–3.646)***	2.486 (1.619–3.818)***	2.239 (1.542–3.519)***	2.543 (1.534–3.392)***
Daytime nap					
Yes vs. no	0.617 (0.436–0.873)**	0.640 (0.442–0.929)*	0.634 (0.435–0.923)*	0.646 (0.448–0.931)*	0.619 (0.411–0.934)*
Severe CHD					
Short sleep duration					
Yes vs. no	1.625 (1.092–2.418)*	1.890 (1.229–2.907)**	1.862 (1.206–2.876)**	1.831 (1.197–2.800)**	1.613 (1.009–2.577)*
Poor sleep quality					
Yes vs. no	2.409 (0.911–6.368)	1.925 (0.692–5.352)	2.079 (0.736–5.871)	2.065 (0.741–5.575)	3.466 (0.938–12.803)
Poor sleep					
Yes vs. no	1.706 (1.151–2.529)**	1.964 (1.283–3.004)**	1.950 (1.269–2.997)**	1.918 (1.259–2.921)**	1.738 (1.091–2.769)*
Daytime nap					
Yes vs. no	0.617 (0.436–0.873)**	0.729 (0.504–1.055)	0.759 (0.522–1.103)	0.771 (0.532–1.117)	0.704 (0.467–1.063)

CHD = congenital heart disease.

Model[a]: adjusted for maternal ethic, maternal age at delivery, maternal education, marital status, residence, maternal prepregnancy obesity, multiple births, infant gender, and family history of CHD.

Model[b]: based on model[a], further adjusted for prepegnancy diabetes/hypertension, folic acid use, and smoking/drinking.

*p value <.05; **p value <.01; ***p value <.001.

TABLE 3 Stratified analysis for maternal daytime nap and sleep status during periconceptional period on risk of CHD in offspring

		Simple CHD											
		Before propensity score analysis					After propensity score analysis						
					Adjusted OR (95% CI)		Propensity-score-adjusted			Propensity-score-matched			
Poor sleep	Daytime nap	Cases	Controls	Crude OR (95% CI)	Model[a]	Model[b]	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)	
No	Yes	99	137	1	1	1	99	137	1	72	100	1	
	No	69	69	1.384 (0.907–2.111)	1.309 (0.830–2.064)	1.324 (0.836–2.097)	69	69	1.324 (0.848–2.068)	46	51	1.253 (0.759–2.067)	
Yes	Yes	33	26	1.756 (0.988– 3.122)	**2.139 (1.158–3.952)***	**2.236 (1.200–4.165)***	33	26	**2.121 (1.156–3.892)***	21	15	1.944 (0.938–4.029)	
	No	61	30	**2.814 (1.693–4.676)*****	**3.049 (1.772–5.246)*****	**3.183 (1.830–5.537)*****	61	30	**2.968 (1.737–5.074)*****	48	21	**3.175 (1.750–5.759)*****	
		Severe CHD											
		Before propensity score analysis					**After propensity score analysis**						
					Adjusted OR (95% CI)		**Propensity-score-adjusted**			**Propensity-score-matched**			
Poor sleep	**Daytime nap**	**Cases**	**Controls**	**Crude OR (95%CI)**	**Model[a]**	**Model[b]**	**Cases**	**Controls**	**OR (95% CI)**	**Cases**	**Controls**	**OR (95% CI)**	
No	Yes	96	137	1	1	1	96	137	1	70	95	1	
	No	83	69	**1.717 (1.137–2.593)***	1.309 (0.839–2.041)	1.384 (0.893–2.144)	83	69	1.290 (0.830–2.004)	56	51	1.490 (0.914–2.430)	
Yes	Yes	36	26	**1.976 (1.120–3.487)***	**2.213 (1.179–4.091)***	**2.263 (1.232–4.154)****	36	26	**2.140 (1.176–3.894)***	27	18	**2.036 (1.040–3.985)***	
	No	47	30	**2.236 (1.320–3.787)****	**2.110 (1.203–3.699)****	**2.184 (1.250–3.616)****	47	30	**2.086 (1.193–3.648)***	33	22	**2.036 (1.093–3.790)***	

CHD = congenital heart disease.

Model[a]: adjusted for maternal ethic, maternal age at delivery, maternal education, marital status, residence, maternal prepregnancy obesity, multiple births, infant gender, and family history of CHD.

Model[b]: based on model[a], further adjusted for prepegnancy diabetes/hypertension, folic acid use, and smoking/drinking.

*p value <0.05; **p value <0.01; ***p value <0.001

was demonstrated that the concurrence with routine daytime nap could not decrease the risk of severe CHD caused by poor sleep. When the analyses were repeated in TOF, similar results were obtained in most cases (Table S3).

4 | DISCUSSION

This study, for the first time, explored the associations between maternal poor sleep around periconceptional period and the risk of CHD based on a case–control study. Of particular crucial was that daytime napping might to some extent weaken the association in simple CHD. The findings, in most cases, can be verified in VSD and TOF, the most frequent single type of simple CHD and severe CHD, respectively. We also applied propensity score analysis to confirm the association, the similar results further enforced the evidence that maternal sleep is involved in embryonic heart development. The present study extended our attention on the association between maternal sleep and birth defects, and the findings point to an important area for future research.

As summarized by a systematic review, the global incidence of CHD increased nearly 15 times, from 0.6‰ during 1930–1934 to 9.1‰ in 1995, based on 114 studies all around the world over the past 60 years (van der Linde et al., 2011). In China, the rising trend similarly existed, and the prevalence of CHD among newborns has reached up to 11.1‰ (Qu et al., 2016). Therefore, CHD has been a severe public health challenge worldwide and also in China. Increasing attention should be focused on potential risk factors associated with CHD, especially those factors that can be modified.

As far as we know, to date this is the only one population-based study to explore the association between maternal sleep and CHD in offspring. We found that poor sleep, defined as short sleep duration and/or poor sleep quality, during periconceptional period could increase the risk of CHD. A previous study demonstrated that maternal frequent poor sleep ≥4 days/week, compared to <1day/week, was significantly associated with an increased risk of NTDs by 3.1 times (Li et al., 2015). The study took demographic characteristics and some lifestyle factors into account when examining the associations; therefore, it suggests maternal poor sleep during periconceptional period could be an independent risk factor for NTDs. Similarly, the present study established the relationship between maternal poor sleep and CHD, which is also independent of demographic characteristics, lifestyle factors, and even maternal health indicators as well. Taken together, the only two studies so far consistently suggest poor maternal sleep should be involved in disrupted embryonic development and then birth defects, which points to an important role of maternal sleep in embryonic development, and would probably drive an emerging area of research interest.

More importantly, in the present study, maternal habitual daytime nap during periconceptional period was found to be independently associated with a decreased risk of simple CHD, indicating maternal daytime nap could be a protective factor for simple CHD. To test the association, stratified analysis was further applied to examine the association between poor sleep and daytime nap, in which it suggested that the concurrence with daytime napping might to some extent weaken the risk of simple CHD caused by poor sleep. The significance of the findings lies not only in the verification of the protective impact of daytime nap but also proposing a promising approach to counteract the risk caused by poor sleep on CHD. Meanwhile, the findings provide further support for the role of maternal sleep in CHD.

Presently, limited studies have paid attention to daytime nap in pregnant women and its possible health effect (Ebert et al., 2015; Okun & Coussons-Read, 2007; Tsai, Kuo, Lee, Lee, & Landis, 2013). As demonstrated by a previous study, it seemed that pregnant women need more daytime nap, nearly twice the frequency of nonpregnant women (1.80 vs. 0.94 naps per week) (Okun & Coussons-Read, 2007). Given the substantial degree of sleep deprivation/disruption during pregnancy (Okun & Coussons-Read, 2007; Yang et al., 2018), we speculate that daytime nap among pregnant women may be a compensatory strategy to the poor sleep. As expected, two prospective studies obtained a relatively consistent result that daytime nap during pregnancy was a beneficial action to offset the disturbed sleep, with a minimal negative impact on nocturnal sleep (Ebert et al., 2015; Tsai, Lin, Kuo, Lee, & Landis, 2013). Our finding further extended the understanding that daytime nap during pregnancy may not only be a countermeasure to the sleep disruption, but also even be involved the inversion of the adverse health risk related to gestational poor sleep. Besides these, previous studies suggested that daytime nap participates in the process of emotion regulation, which would exert a positive influence on mood and emotion (Cellini, Lotto, Pletti, & Sarlo, 2017; Peth et al., 2012). It has been reported that maternal exposure to emotional stress and anxiety during pregnancy could increase the risk of CHD and other birth defects (Carmichael et al., 2017; Zhu et al., 2013). Therefore, another possible pathway underlying the implication of daytime nap in a reduced risk of adverse pregnancy outcomes could be through a specific neurophysiological process which helps to relieve maternal stress and anxiety.

Although this is the first epidemiologic study exploring the relationship between maternal sleep and offspring CHD, several potential biological mechanisms are feasible in theory to support the relationship. Accumulating studies demonstrated that short sleep duration and sleep disorders could

increase the risk of impaired glucose metabolism, lead to hyperglycemia, hyperinsulinemia, and gestational diabetes (Wang et al., 2017; Zhong et al., 2018), and meanwhile, it has been generally confirmed that hyperglycemia and hyperinsulinemia have an adverse effect on early embryonic development, could increase the risk of CHD and other congenital anomalies (Bateman et al., 2015; Oyen et al., 2016). Except for this, previous studies have put forward another explanation that disturbed sleep during early pregnancy could contribute to an increased inflammatory response, and then as a result, impaired uterine/placenta blood blow and functioning (Okun et al., 2013; Okun & Coussons-Read, 2007). Furthermore, the research progress in melatonin, a circadian rhythm messenger between mother and fetal, revealed that it played an important role in cardiac differentiation and the maturation of embryonic stem cells, and the formation of the embryo S-shaped heart as well (Ansari, Agathagelidis, Lee, Korf, & von Gall, 2009; Bian et al., 2017; Kudova et al., 2016; Nogueira & Sampaio, 2017).

To the best of our knowledge, this is the first epidemiological study to examine the impacts of maternal sleep on offspring CHD. We established the population-based association between poor maternal sleep around periconceptional period and the risk of CHD, and further found that routine daytime nap might to some extent weaken the associations in simple CHD. In this case–control study, to control recall bias as far as possible, all the children recruited were younger than 2 years old. When we evaluated the associations between maternal sleep and CHD in offspring, a series of factors including demographic characteristics, pregnancy complications, and lifestyle behaviors were taken into accounts. To increase the statistical power and achieve an effect size for the entire population, we included the propensity score as a covariate to adjust the differences in characteristics between cases and controls. Moreover, to reduce potential selection bias and minimize the confounding association caused by differences in characteristics, controls were individually matched to cases by using the propensity score. Further, to verify the stability and reliability of the results, we repeated all analyses in the single type of CHD, including VSD and TOF for comparison. The results of various statistical analyses being prominently consistent give strengthened evidence that maternal sleep plays a key role in CHD of offspring.

Several limitations should be acknowledged in interpreting the results. First, maternal sleep characteristics collected were not detailed enough, compared with most studies using validated sleep questionnaires (Heazell et al., 2018; McCowan et al., 2017). However, the items cover the most important core sleep characteristics, including sleep duration, sleep quality, and daytime nap. A previous study demonstrated that maternal poor sleep was significantly associated with an increased risk of NTDs by 3.1 times (Li et al., 2015). The results of our study similarly established the relationship between maternal poor sleep during periconception and birth defects in offspring. We, even more, also found that daytime napping might be a countermeasure to the adverse effect of maternal poor sleep. Second, the critical period of heart development is the first 8 weeks of pregnancy, however, the sleep parameters in this study were during periconceptional period, which covers 1 month before the conception and the whole pregnancy. Third, sample size was somewhat limited for further stratified analyses. However, all analyses were repeated and almost all the results can be verified in VSD and TOF, the most frequent single type of simple CHD and severe CHD. Fourth, although recall bias is inevitable in a case–control study, we recruited the children were all younger than 2 years old to control recall bias as far as possible. Fifth, the need of sleep duration varies in different individuals, however, we set the only one cut-off point to define short sleep duration. There might be a chance for misclassification bias. Finally, there was potential residual confounding, even though a wide range of confounders has been taken into accounts. However, considering the results were mostly consistent between simple and severe CHD, and can be verified in VSD and TOF, even after accounting for propensity score matching, the evidence regarding association between maternal sleep and CHD has been strengthened to some extent.

5 | CONCLUSIONS

The present study is the first to observe the association between maternal sleep and CHD. The findings provided epidemiological evidence for the relationship of maternal poor sleep with an increased risk of CHD, fortunately, the concurrence with daytime nap might to some extent weaken the risk in simple CHD. They jointly revealed the important role of maternal sleep in embryonic heart development, which extends our understanding on the health effect of maternal sleep. The findings also should be of clinically significance in considering that many aspects of sleep are modifiable.

ACKNOWLEDGMENTS

We gratefully acknowledge the persons who took the time to participate in our study. Collected data: Dr. Qihua Fu, Yimei Ma, Sha Sha, Department of Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine.

ORCID

Anda Zhao https://orcid.org/0000-0002-3284-2531
Shenghui Li https://orcid.org/0000-0002-2687-2697

REFERENCES

Abeysena, C., Jayawardana, P., & Seneviratne Rde, A. (2009). Maternal sleep deprivation is a risk factor for small for gestational age: A cohort study. *The Australian & New Zealand Journal of Obstetrics & Gynaecology*, *49*(4), 382–387.

Abeysena, C., Jayawardana, P., & Seneviratne Rde, A. (2010). Effect of psychosocial stress and physical activity on low birthweight: A cohort study. *The Journal of Obstetrics and Gynaecology Research*, *36*(2), 296–303.

Ansari, N., Agathagelidis, M., Lee, C., Korf, H. W., & von Gall, C. (2009). Differential maturation of circadian rhythms in clock gene proteins in the suprachiasmatic nucleus and the pars tuberalis during mouse ontogeny. *The European Journal of Neuroscience*, *29*(3), 477–489.

Bateman, B. T., Huybrechts, K. F., Fischer, M. A., Seely, E. W., Ecker, J. L., Oberg, A. S., … Hernandez-Diaz, S. (2015). Chronic hypertension in pregnancy and the risk of congenital malformations: A cohort study. *American Journal of Obstetrics and Gynecology*, *212*(3), 337.e331–337.e314.

Bian, S. S., Zheng, X. L., Sun, H. Q., Chen, J. H., Lu, Y. L., Liu, Y. Q., … Ma, Y. X. (2017). Clock1a affects mesoderm development and primitive hematopoiesis by regulating nodal-Smad3 signaling in the zebrafish embryo. *The Journal of Biological Chemistry*, *292*(34), 14165–14175.

Bouma, B. J., & Mulder, B. J. (2017). Changing landscape of congenital heart disease. *Circulation Research*, *120*(6), 908–922.

Carmichael, S. L., Ma, C., Tinker, S., Shaw, G. M., & for the National Birth Defects Prevention Study. (2017). Maternal stressors and social support and risks of delivering babies with gastroschisis or hypospadias. *American Journal of Epidemiology*, *185*(12), 1240–1246.

Cellini, N., Lotto, L., Pletti, C., & Sarlo, M. (2017). Daytime REM sleep affects emotional experience but not decision choices in moral dilemmas. *Scientific Reports*, *7*(1), 11059.

Chou, H. H., Chiou, M. J., Liang, F. W., Chen, L. H., Lu, T. H., & Li, C. Y. (2016). Association of maternal chronic disease with risk of congenital heart disease in offspring. *Canadian Medical Association Journal*, *188*(17–18), E438–E446.

Deb, S., Austin, P. C., Tu, J. V., Ko, D. T., Mazer, C. D., Kiss, A., & Fremes, S. E. (2016). A review of propensity-score methods and their use in cardiovascular research. *The Canadian Journal of Cardiology*, *32*(2), 259–265.

Ebert, R. M., Wood, A., & Okun, M. L. (2015). Minimal effect of daytime napping behavior on nocturnal sleep in pregnant women. *Journal of Clinical Sleep Medicine*, *11*(6), 635–643.

Heazell, A., Li, M., Budd, J., Thompson, J. M. D., Stacey, T., Cronin, R. S., … McCowan, L. (2018). Association between maternal sleep practices and late stillbirth—Findings from a stillbirth case–control study. *BJOG: An International Journal of Obstetrics & Gynaecology*, *125*(2), 254–262.

Heinze, G., & Juni, P. (2011). An overview of the objectives of and the approaches to propensity score analyses. *European Heart Journal*, *32*(14), 1704–1708.

Kajeepeta, S., Sanchez, S. E., Gelaye, B., Qiu, C., Barrios, Y. V., Enquobahrie, D. A., & Williams, M. A. (2014). Sleep duration, vital exhaustion, and odds of spontaneous preterm birth: A case–control study. *BMC Pregnancy and Childbirth*, *14*, 337.

Krueger, J. M., Frank, M. G., Wisor, J. P., & Roy, S. (2016). Sleep function: Toward elucidating an enigma. *Sleep Medicine Reviews*, *28*, 46–54.

Kudova, J., Vasicek, O., Ciz, M., & Kubala, L. (2016). Melatonin promotes cardiomyogenesis of embryonic stem cells via inhibition of HIF-1alpha stabilization. *Journal of Pineal Research*, *61*(4), 493–503.

Lee, K. A., & Gay, C. L. (2004). Sleep in late pregnancy predicts length of labor and type of delivery. *American Journal of Obstetrics and Gynecology*, *191*(6), 2041–2046.

Li, L., Zhao, K., Hua, J., & Li, S. (2018). Association between sleep-disordered breathing during pregnancy and maternal and fetal outcomes: An updated systematic review and meta-analysis. *Frontiers in Neurology*, *9*, 91.

Li, Z., Zhang, L., Jin, L., Ye, R., Raynes-Greenow, C., & Ren, A. (2015). Poor sleep during the periconceptional period increases risk for neural tube defects in offspring. *Birth Defects Research. Part A, Clinical and Molecular Teratology*, *103*(9), 780–786.

McCowan, L. M. E., Thompson, J. M. D., Cronin, R. S., Li, M., Stacey, T., Stone, P. R., … Mitchell, E. A. (2017). Going to sleep in the supine position is a modifiable risk factor for late pregnancy stillbirth: Findings from the New Zealand multicentre stillbirth case–control study. *PLoS One*, *12*(6), e0179396.

Mizutani, T., Suzuki, K., Kondo, N., & Yamagata, Z. (2007). Association of maternal lifestyles including smoking during pregnancy with childhood obesity. *Obesity (Silver Spring)*, *15*(12), 3133–3139.

Nogueira, R. C., & Sampaio, L. F. S. (2017). Eye and heart morphogenesis are dependent on melatonin signaling in chick embryos. *The Journal of Experimental Biology*, *220*(20), 3826–3835.

O'Brien, L. M., Bullough, A. S., Owusu, J. T., Tremblay, K. A., Brincat, C. A., Chames, M. C., … Chervin, R. D. (2013). Snoring during pregnancy and delivery outcomes: A cohort study. *Sleep*, *36*(11), 1625–1632.

Okun, M., Luther, J., Wisniewski, S., & Wisner, K. L. (2013). Disturbed sleep and inflammatory cytokines in depressed and nondepressed pregnant women: An exploratory analysis of pregnancy outcomes. *Psychosomatic Medicine*, *75*(7), 670–681.

Okun, M. L., & Coussons-Read, M. E. (2007). Sleep disruption during pregnancy: How does it influence serum cytokines? *Journal of Reproductive Immunology*, *73*(2), 158–165.

Okun, M. L., Schetter, C. D., & Glynn, L. M. (2011). Poor sleep quality is associated with preterm birth. *Sleep*, *34*(11), 1493–1498.

Oyen, N., Diaz, L. J., Leirgul, E., Boyd, H. A., Priest, J., Mathiesen, E. R., … Melbye, M. (2016). Prepregnancy diabetes and offspring risk of congenital heart disease: A nationwide cohort study. *Circulation*, *133*(23), 2243–2253.

Palagini, L., Gemignani, A., Banti, S., Manconi, M., Mauri, M., & Riemann, D. (2014). Chronic sleep loss during pregnancy as a determinant of stress: Impact on pregnancy outcome. *Sleep Medicine*, *15*(8), 853–859.

Peth, J., Regen, F., Bajbouj, M., Heuser, I., Anghelescu, I., & Hornung, O. P. (2012). The influence of daytime napping versus controlled activity on the subjective well-being of patients with major depression. *Psychiatry Research*, *200*(2–3), 368–373.

Qu, Y., Liu, X., Zhuang, J., Chen, G., Mai, J., Guo, X., … Nie, Z. (2016). Incidence of congenital heart disease: The 9-year experience of the Guangdong registry of congenital heart disease, China. *PLoS One*, *11*(7), e0159257.

Reiter, R. J., Tan, D. X., Korkmaz, A., & Rosales-Corral, S. A. (2014). Melatonin and stable circadian rhythms optimize maternal, placental and fetal physiology. *Human Reproduction Update*, *20*(2), 293–307.

Shimada, M., Seki, H., Samejima, M., Hayase, M., & Shirai, F. (2016). Salivary melatonin levels and sleep-wake rhythms in pregnant women with hypertensive and glucose metabolic disorders: A prospective analysis. *Bioscience Trends*, *10*(1), 34–41.

Suzuki, S., Dennerstein, L., Greenwood, K. M., Armstrong, S. M., Sano, T., & Satohisa, E. (1993). Melatonin and hormonal changes in disturbed sleep during late pregnancy. *Journal of Pineal Research*, *15*(4), 191–198.

Tsai, S. Y., Kuo, L. T., Lee, C. N., Lee, Y. L., & Landis, C. A. (2013). Reduced sleep duration and daytime naps in pregnant women in Taiwan. *Nursing Research*, *62*(2), 99–105.

Tsai, S. Y., Lin, J. W., Kuo, L. T., Lee, C. N., & Landis, C. A. (2013). Nighttime sleep, daytime napping, and labor outcomes in healthy pregnant women in Taiwan. *Research in Nursing & Health*, *36*(6), 612–622.

van der Linde, D., Konings, E. E., Slager, M. A., Witsenburg, M., Helbing, W. A., Takkenberg, J. J., & Roos-Hesselink, J. W. (2011). Birth prevalence of congenital heart disease worldwide: A systematic review and meta-analysis. *Journal of the American College of Cardiology*, *58*(21), 2241–2247.

Voiculescu, S. E., Zygouropoulos, N., Zahiu, C. D., & Zagrean, A. M. (2014). Role of melatonin in embryo fetal development. *Journal of Medicine and Life*, *7*(4), 488–492.

Wang, H., Leng, J., Li, W., Wang, L., Zhang, C., Li, W., … Yang, X. (2017). Sleep duration and quality, and risk of gestational diabetes mellitus in pregnant Chinese women. *Diabetic Medicine*, *34*(1), 44–50.

Wang, L. H., Lin, H. C., Lin, C. C., Chen, Y. H., & Lin, H. C. (2010). Increased risk of adverse pregnancy outcomes in women receiving zolpidem during pregnancy. *Clinical Pharmacology and Therapeutics*, *88*(3), 369–374.

Wilkerson, A., & Uhde, T. (2018). Perinatal sleep problems: Causes, complications, and management. *Obstetrics and Gynecology Clinics of North America*, *45*(3), 483–494.

Wu, M. H., Chen, H. C., Lu, C. W., Wang, J. K., Huang, S. C., & Huang, S. K. (2010). Prevalence of congenital heart disease at live birth in Taiwan. *The Journal of Pediatrics*, *156*(5), 782–785.

Yang, Y., Mao, J., Ye, Z., Zeng, X., Zhao, H., Liu, Y., & Li, J. (2018). Determinants of sleep quality among pregnant women in China: A cross-sectional survey. *The Journal of Maternal-Fetal & Neonatal Medicine*, *31*(22), 2980–2985.

Yeh, S. J., Chen, H. C., Lu, C. W., Wang, J. K., Huang, L. M., Huang, S. C., … Wu, M. H. (2015). National database study of survival of pediatric congenital heart disease patients in Taiwan. *Journal of the Formosan Medical Association*, *114*(2), 159–163.

Yu, Y., Li, M., Pu, L., Wang, S., Wu, J., Ruan, L., … Jiang, W. (2017). Sleep was associated with depression and anxiety status during pregnancy: A prospective longitudinal study. *Archives of Women's Mental Health*, *20*(5), 695–701.

Zhong, C., Chen, R., Zhou, X., Xu, S., Li, Q., Cui, W., … Yang, N. (2018). Poor sleep during early pregnancy increases subsequent risk of gestational diabetes mellitus. *Sleep Medicine*, *46*, 20–25.

Zhou, B., & Cooperative Meta-Analysis Group Of China Obesity Task Force. (2002). Predictive values of body mass index and waist circumference to risk factors of related diseases in Chinese adult population. *Zhonghua Liu Xing Bing Xue Za Zhi*, *23*(1), 5–10.

Zhu, J. L., Olsen, J., Sorensen, H. T., Li, J., Nohr, E. A., Obel, C., … Olsen, M. S. (2013). Prenatal maternal bereavement and congenital heart defects in offspring: A registry-based study. *Pediatrics*, *131*(4), e1225–e1230.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Zhao A, Zhao K, Xia Y, et al. Exploring associations of maternal sleep during periconceptional period with congenital heart disease in offspring. *Birth Defects Research*. 2019;111: 920–931. https://doi.org/10.1002/bdr2.1536