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# Prospective assessment of sleep health and reproductive outcomes

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BOSTON UNIVERSITY  
SCHOOL OF PUBLIC HEALTH

Dissertation

**PROSPECTIVE ASSESSMENT OF SLEEP HEALTH  
AND REPRODUCTIVE OUTCOMES**

by

**CHAD MATTHEW COLEMAN**

B.S., Wayne State University, 2015  
M.P.H., Boston University, 2017

Submitted in partial fulfillment of the  
requirements for the degree of  
Doctor of Philosophy

2025

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Approved by

First Reader

---

Lauren A. Wise, Sc.D.  
Professor of Epidemiology

Second Reader

---

Traci N. Bethea, Ph.D.  
Assistant Professor of Oncology  
Georgetown University Lombardi Comprehensive Cancer Center

Third Reader

---

Amelia K. Wesselink, Ph.D.  
Research Assistant Professor of Epidemiology

## **DEDICATION**

This dissertation is dedicated to my parents, Steven and Kimberley Coleman, for their continuous and unwavering support of my aspirations. I would not be where I am today without their endless love, encouragement, and sacrifices. Thank you for always believing in me and my dreams.

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**PROSPECTIVE ASSESSMENT OF SLEEP HEALTH  
AND REPRODUCTIVE OUTCOMES**

**CHAD MATTHEW COLEMAN**

Boston University School of Public Health, 2025

Major Professor: Lauren A. Wise, Sc.D., Professor of Epidemiology

**ABSTRACT**

Sleep disturbances and disorders are prevalent in the United States and continue to increase over time. Women often report worse sleep outcomes than men, and these disparities can likely be attributed to both gender and biologic sex. While poor sleep has been associated with many adverse health outcomes, few prospective studies have examined the influence of sleep on reproductive health. Therefore, the goal of this dissertation is to prospectively assess the relationship between sleep health, evaluated through self-reported and objective measures, and three reproductive outcomes: uterine leiomyomata (UL), menstrual cycle disturbances, and fecundability.

In the first study, we estimated prospectively the association of self-reported sleep health, including duration and quality, with ultrasound-detected UL incidence and growth. We performed this analysis in the Study of Environment, Lifestyle, and Fibroids (SELF), a prospective ultrasound-based cohort study of reproductive-aged Black individuals from metropolitan Detroit, Michigan. We found that increased frequency of sleep trouble was associated with increased UL incidence rate over 10 years of follow-up. Conversely, short and long sleep durations and feeling well-rested less than half the week were associated with decreased UL incidence rates. Sleep health was not appreciably

associated with 18-month standardized UL growth.

In the second study, we examined prospectively the association of self-reported sleep health, including duration and quality, and menstrual cycle disturbances. We leveraged data from Pregnancy Study Online (PRESTO), an Internet-based preconception cohort study of non-contracepting pregnancy planners from the United States and Canada. We found that short sleep duration and poor sleep quality increased the risk of several menstrual cycle disturbances, including short and long cycle lengths, prolonged bleed length, heavy menstrual flow volume, and dysmenorrhea. Also, poor sleep quality was associated with greater risk of cycle irregularity.

In the third study, we estimated prospectively the association of objective preconception sleep health, including duration, continuity, and irregularity, with fecundability, the per-menstrual cycle probability of conception. For this study, we utilized Fitbit wrist actigraphy data collected in PRESTO to measure sleep health. We observed that short and long sleep durations, increased wake after sleep onset and midpoint variability, and decreased sleep maintenance efficiency were associated with reduced fecundability. Additionally, we found that even if participants slept the recommended duration (7–8.9 hours/day), the association between poor sleep health and reduced fecundability persisted.

In summary, we identified associations between sleep health and uterine leiomyomata, menstrual cycle disturbances, and fecundability. We leveraged novel analytic and data collection methods to address our research questions. Given that Healthy People 2030 has highlighted sleep as a priority area for research and

intervention, our findings offer valuable insights for developing effective public health strategies. This dissertation underscores the importance of addressing sleep health to potentially improve reproductive outcomes.

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## LIST OF ABBREVIATIONS

25(OH)D	25-hydroxyvitamin D
AUB	abnormal uterine bleeding
BMI	body mass index
CI	confidence interval
DMPA	depot medroxyprogesterone acetate
FIGO	International Federation of Gynecology and Obstetrics
FR	fecundability ratio
GED	General Educational Development
HPA	hypothalamic-pituitary-adrenal
HPG	hypothalamic-pituitary-gonadal
HR	hazard ratio
LH	luteinizing hormone
LMP	last menstrual period
MDI	Major Depression Inventory
MET	Metabolic Equivalent of Task
PCOS	polycystic ovary syndrome
PRESTO	Pregnancy Study Online
PSG	polysomnography
PSQI	Pittsburgh Sleep Quality Index
PSS	Perceived Stress Scale
RR	risk ratio

SELF ..... Study of Environment, Lifestyle, and Fibroids  
TTP ..... time-to-pregnancy  
UL ..... uterine leiomyomata  
U.S. .... United States  
USD..... United States dollars  
WASO..... wake after sleep onset  
%D ..... percent difference

## 1. INTRODUCTION

Sleep health, defined as the “multidimensional pattern of sleep-wakefulness, adapted to individual, social, and environmental demands, that promotes physical and mental well-being,” is a strong determinant of overall health.<sup>1-3</sup> Sleep health is influenced by many factors, including life course events, environmental exposures, and behaviors.<sup>2,4,5</sup> In turn, sleep health affects body physiology and functioning through properly-maintained circadian rhythms, which control body temperature, appetite and digestion, locomotion, and hormone production and secretion.<sup>6-8</sup> Thus, optimal sleep is essential to maintenance of physical and mental health.<sup>4</sup>

One-third of United States (U.S.) adults report insufficient sleep duration (<7 hours/day)<sup>9,10</sup> and the prevalence of sleep problems (*e.g.*, short sleep duration, insomnia, and excessive daytime sleepiness) has increased over the past 20 years.<sup>7,11,12</sup> Sequelae of poor sleep health include increased risks of cardiometabolic diseases, obesity, cancer, and premature mortality.<sup>2,7</sup> For these reasons, Healthy People 2030 identifies sleep as a priority area for public health research and intervention.<sup>13</sup>

Subjective assessments of sleep consist of self-reported sleep health captured through standalone survey questions or validated questionnaires.<sup>2</sup> These measures provide insight into the lived sleep experience that objective measures may be unable to assess.<sup>2,14</sup> Objective sleep assessments are home- and clinic-based measurements and include polysomnography (PSG) and actigraphy.<sup>2,15</sup> PSG is the gold standard for assessing sleep health and involves overnight assessments of neurophysiology during sleep through the detection of electrical signals.<sup>2,15</sup> As PSG requires extensive time

involvement for participants, is costly, and is infeasible to perform over multiple nights for large populations, researchers have sought other valid methods of objective sleep measurement.<sup>2</sup> Actigraphy measures accelerometry via wearable devices often worn on the wrist<sup>2,16</sup> and produces metrics of sleep health through passive measurement.<sup>16,17</sup> There is strong concordance between actigraphy and PSG,<sup>15,16,18–20</sup> and actigraphy is identified as a valid tool for sleep measurement by the American Academy of Sleep Medicine.<sup>21</sup> Objective assessments of sleep mitigate recall and reporting biases that may affect self-reported measures.<sup>2,22–24</sup>

On average, women report greater sleep difficulties, worse subjective sleep quality, and more daytime sleepiness than men.<sup>25–28</sup> Insomnia and restless leg syndrome, two of the most common sleep disorders in the U.S.,<sup>2</sup> are more prevalent in women.<sup>29</sup> Both gendered experiences and biologic sex may contribute to these sleep disparities. Women tend to experience more gender-related stressors (*e.g.*, housework and childcare responsibilities that result in greater unpaid labor,<sup>30,31</sup> caregiving expectations,<sup>29</sup> job discrimination,<sup>32</sup> reduced wealth due to the gender income gap,<sup>33</sup> and gender-based discrimination<sup>34</sup>) that may result in poor sleep health. The higher prevalence of sleep problems among women may also be due to the menstrual cycle, which produces fluctuations in reproductive hormones and circadian rhythms.<sup>26,35–38</sup> Additionally, the pregnancy and postpartum periods are associated with shifts in sleep patterns and increased sleep disturbances.<sup>39–43</sup> Still, there are few prospective studies of sleep health and reproductive outcomes.<sup>27</sup> This dissertation aims to address gaps in the literature by prospectively investigating the influence of sleep health, using self-reported and objective

measures, on three reproductive outcomes: uterine leiomyomata, menstrual cycle disturbances, and fecundability.

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## **2. SELF-REPORTED SLEEP HEALTH AND UTERINE LEIOMYOMATA INCIDENCE AND GROWTH: A PROSPECTIVE ULTRASOUND STUDY**

### **2.1 INTRODUCTION**

Uterine leiomyomata (UL; fibroids) are hormone-dependent neoplasms of the myometrium.<sup>1-4</sup> Although UL are diagnosed in approximately 25% of individuals with a uterus,<sup>4</sup> ultrasound-based studies suggest that the cumulative lifetime incidence exceeds 70%.<sup>5</sup> While many UL are asymptomatic,<sup>3</sup> commonly-reported symptoms and sequelae include heavy menstrual bleeding, pelvic pain, anemia, obstetric complications, and infertility.<sup>5</sup> UL are the most common benign gynecologic neoplasm and the leading diagnosis in gynecologic inpatient hospitalizations.<sup>3,4</sup> As such, UL are the leading indication for hysterectomy.<sup>2-4</sup> Direct and indirect annual healthcare costs associated with UL are approximately \$5.9–34.4 billion.<sup>6</sup> Black individuals have 2- to 3-times the incidence rate compared to White individuals,<sup>3,4,7</sup> earlier onset of disease (by approximately 3–10 years),<sup>3,7,8</sup> and greater disease severity (*e.g.*, more UL tumors, larger UL size, faster UL growth rates and greater risk of rapid growth, and worse symptomatology).<sup>7-10</sup> However, reasons for this racial disparity have not been fully documented.

Poor sleep health is a plausible risk factor for UL – and potential explanation for racial disparities in UL – that has not been well studied. Multiple biological pathways may link poor sleep health with increased UL incidence and growth. The hypothalamic-pituitary-adrenal (HPA) axis, a neuroendocrine system, regulates physiologic responses to stress and maintains homeostasis.<sup>11-14</sup> Properly regulated circadian rhythms maintain

the HPA axis, while poor sleep activates stress responses. Prolonged and repeated stress responses due to sleep disturbances may deteriorate HPA axis function, which can result in endocrine imbalance.<sup>15,16</sup> Stress responses by the HPA axis may promote fluctuations in ovarian hormonal levels, which in turn may promote UL development and growth.<sup>3,17,18</sup> Inflammation is another mechanism by which sleep could influence UL incidence and growth. In both animal and human studies, sleep deprivation stimulates production of proinflammatory cytokines, including interleukin-6 and tumor necrosis factor alpha, and promotes imbalance in inflammatory homeostasis.<sup>14,19</sup> In turn, inflammatory cytokines may be expressed by leiomyomata progenitor cells.<sup>20</sup> However, less is known about inflammatory pathways and UL pathogenesis. Furthermore, Black individuals report worse sleep health, including shorter sleep duration,<sup>21–28</sup> worse sleep quality,<sup>23,25,29,30</sup> increased sleep latency,<sup>22,23,31</sup> greater daytime sleepiness,<sup>23,25,29,32,33</sup> and more sleep complaints<sup>22–25,31,32</sup> than non-Black individuals. In objective assessments, Black individuals are more likely to experience shorter sleep duration,<sup>29,30,32–34</sup> increased sleep fragmentation,<sup>29,32</sup> wake after sleep onset,<sup>29,32</sup> and sleep latency;<sup>32,34</sup> and decreased sleep maintenance efficiency<sup>32–34</sup> and slow wave sleep percentage.<sup>30,32</sup> With respect to sleep disorders, there is an elevated prevalence of sleep-disordered breathing,<sup>22,26</sup> sleep apnea syndrome,<sup>33</sup> and obstructive sleep apnea<sup>35,36</sup> in Black individuals.

No study has investigated sleep health as a risk factor for UL incidence and growth. Given the dearth of literature in this area and the biologic plausibility, we examined the association between poor sleep health and UL incidence and growth in an ultrasound-based prospective cohort study. We hypothesize that shorter sleep duration,

greater frequency of sleep trouble, and worse sleep quality during 10 years of follow-up will increase rates of incident UL and hasten growth of UL.

## **2.2 METHODS**

### *2.2.1 Study population*

We leveraged data from the Study of Environment, Lifestyle, and Fibroids (SELF), a prospective cohort study of reproductive-aged Black individuals from the Detroit, Michigan metropolitan area.<sup>37,38</sup> The primary goal of SELF is to identify risk factors associated with UL development.<sup>3,37,38</sup> Recruitment occurred between 2010 and 2012 and eligibility was restricted to individuals who self-identified as “Black” or “African American” given the greater incidence rate and higher burden of UL in this population. Additional eligibility criteria included: aged 23–35 years, had an intact uterus, and had no history of clinical diagnosis of UL and autoimmune or cancer diagnoses that required medication. Participants attended a clinic visit at baseline and at approximately 20 months, 40 months, 60 months, and 10 years after enrollment. At each clinic visit, participants completed computer-assisted web and telephone interviews and underwent ultrasonography to detect and measure UL. The prospective study design mitigated potential for reverse causation bias. SELF was approved by the Institutional Review Boards of Boston University Medical Campus, Henry Ford Health, and the National Institute of Environmental Health Sciences, and all participants provided informed consent.

### *2.2.2 Exposure assessment: Sleep health*

At baseline and all follow-up clinic visits, participants reported three measures of sleep: duration, frequency of trouble, and quality. All sleep questions were developed from the National Health and Nutrition Examination Survey and the National Health Interview Survey.<sup>39,40</sup> To assess sleep duration, we asked participants to report the number of hours of sleep they received before a workday, with response options of <4, 4, 5, 6, 7, 8, 9, 10, and >10 hours. For frequency of sleep trouble, participants were asked “About how many days per month do you have trouble falling asleep or going back to sleep?” with response options of 0, 1, 2, 3, 4, 5–9, 10–14, and  $\geq 15$  days. Finally, to assess sleep quality, participants were asked “How many days per week do you wake up feeling well-rested?” with response options from 0 to 7 days/week.

We categorized sleep duration as <6, 6, 7, 8, and  $\geq 9$  hours/day, according to American Academy of Sleep Medicine and Sleep Research Society guidelines.<sup>41</sup> Similar to previous research investigating sleep and reproductive health, we defined frequency of sleep trouble as 0, 1–14, and  $\geq 15$  days/month.<sup>42</sup> We dichotomized frequency of feeling well-rested as <4 and  $\geq 4$  days/week, which has been used in previous literature.<sup>40</sup>

### *2.2.3 Outcome assessment: UL incidence and growth*

At each study visit, participants underwent a transvaginal ultrasound to screen for UL. Transvaginal ultrasonography is the clinical standard for detecting UL, with 91% sensitivity and 99% specificity relative to the gold standard of histologic confirmation.<sup>43</sup> Study sonographers were trained in gynecologic ultrasonography for consistency in

differential diagnoses and measurement<sup>37</sup> and identified UL  $\geq 0.5$  centimeters in diameter according to extended Muram criteria.<sup>44</sup> A lead study sonographer reviewed a sample of ultrasounds to ensure validity in measurement and documentation. Uterus and, when identified, UL size were measured in triplicate across three perpendicular planes (*i.e.*, longitudinal, anterior-posterior, transverse). Sonographers identified the type (*i.e.*, submucosal, intramural, subserosal, pedunculated serosal) and uterine location (*i.e.*, fundus, corpus, lower uterine segment/cervix) of each UL at all visits. Clinic visits for participants who were pregnant at their scheduled visit date were delayed until at least three months postpartum in order to properly visualize the uterus.

Among non-cases who reported undergoing a hysterectomy procedure and who consented to share their medical records, a physician (Q.H.) reviewed their operative and/or pathologic reports to identify UL. Non-cases whose operative or pathologic reports indicated UL were reassigned as cases.

#### *2.2.4 Covariate assessment*

We collected data on covariates at baseline and follow-up visits. Time-varying covariates were updated at each follow-up visit. Participants reported information on socio-demographics; lifestyle factors; medical history; reproductive and menstrual history; mental health; stress and quality of life; and diet. We calculated body mass index (BMI) as weight (kilograms) divided by height (meters) squared, which were measured by trained study staff. We defined exercise intensity using a combination of Metabolic Equivalent of Task (MET) score for physical activities,<sup>45</sup> duration of activities, and

frequency of activities per week. Participants provided blood samples at each clinic visit, and we performed liquid chromatography-tandem mass spectrometry to estimate season-adjusted serum 25-hydroxyvitamin D (25(OH)D), defined as the sum of serum 25-hydroxyvitamin D<sub>2</sub> and 25-hydroxyvitamin D<sub>3</sub>.<sup>46</sup>

### 2.2.5 Exclusions

During the recruitment period (2010–2012), 1,693 participants enrolled in SELF (Figure 2.1). We excluded 385 (22.7%) participants with prevalent UL at baseline. Additionally, we censored participants at their first missed clinic visit in order to accurately build inverse probability weights. First, if a participant skipped a visit, we would have to carry forward their last reported exposure and covariate values, which would require the assumption that there were no changes in their responses across visits. Additionally, we would have to further assume the participant did not develop UL during the period of their skipped visits. Therefore, we excluded 171 (13.1%) participants who did not complete their first follow-up. As such, we examined UL incidence among 1,137 participants.

To assess UL growth, we identified 736 prevalent and incident UL cases from baseline through 60 months of follow-up. Among prevalent and incident UL cases at baseline, we attempted to match UL across ultrasounds (*i.e.*, identify the same UL across ultrasounds based on location). We were able to match at least one UL among 434 (59.0%) participants; we included these participants, who contributed 734 matched UL and 1,359 growth intervals, in the growth analyses. Attempts to match UL observed at the

10-year follow-up visit are ongoing.

### 2.2.6 Statistical analysis: UL incidence

To assess UL incidence, we calculated person-time (in months) contributed to the study as the time between the baseline visit and UL detection or a censoring event, including hysterectomy, first missed clinic visit, or the end of the study period, whichever occurred first. For those participants whose UL were detected via hysterectomy operative and/or pathologic report, we ended their follow-up time at the midpoint between their last clinic visit and the date of their hysterectomy procedure. We used Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for each exposure and UL incidence through 10 years of follow-up, using age (years) and follow-up time (months) as time scales. We used time-varying exposure and covariate data, which were updated at each follow-up visit. We used an Andersen-Gill data structure with one observation per month contributed to the study to update time-varying exposures and covariates.<sup>47</sup> We examined Kaplan-Meier curves to evaluate the proportional hazards assumption. We used the Efron approximation method for tied events, as this method allowed for use of inverse probability weights.<sup>48</sup>

We constructed a directed acyclic graph to identify potential confounders (Figure 2.2). Because past exposure may affect future covariates (*e.g.*, past or present sleep health may affect future perceived stress), we used marginal structural models to apply inverse probability of treatment weights.<sup>49,50</sup> We fitted logistic and multinomial<sup>51</sup> logistic regression models for each sleep health exposure, conditional upon hypothesized

confounders, to estimate the probability of reporting the exposure value the participant reported. For each clinic visit  $j$  completed by participant  $i$ , we estimated stabilized weights using the following equation:

$$sw_{ij} = \Pr[A_k | A_{k-1}] / \Pr[A_k | A_{k-1}, L_k]$$

where  $A$  represents treatment,  $k$  represents time, and  $L$  represents a series of hypothesized confounders. We identified the following confounders, some of which were time-varying: age; education ( $\leq$ high school diploma or General Educational Development certificate, some college or Associate degree,  $\geq$ Bachelor degree); household income ( $<20,000$ ,  $20,000-50,000$ ,  $>50,000$  U.S. dollars); job hours/week; employment status; night work in the past month; current rotating shift work; BMI ( $<25$ ,  $25-29$ ,  $30-34$ ,  $35-39$ ,  $\geq 40$  kg/m<sup>2</sup>); cigarette smoking; alcohol intake (low [ $<10$  drinks/year], moderate [ $1-5$  drinks/day on days when the participant drinks and only drinks  $\geq 4$  drinks once/month or less], heavy [ $\geq 6$  drinks/day on days the participant drinks or  $\geq 4$  drinks at a single sitting at least twice per month]); exercise intensity (low [ $<1$  hour/week of vigorous physical activity, 2 hours/week of moderate physical activity, and 14 hours/week of walking], low to moderate [MET score below 72 but not low activity], moderate [MET score above 72 but not high or very high], high [ $2.5-5$  hours/week of vigorous physical activity or  $7-10$  hours/week of moderate physical activity], very high [ $\geq 5$  hours/week of vigorous physical activity or  $\geq 10$  hours/week of moderate physical activity]); history of diagnosed diabetes, hypertension, anxiety, or depression (all modeled individually); perceived stress (Perceived Stress Scale [PSS]-4 score); hormonal contraceptive use; parity; years since last birth; breastfeeding duration; and 25(OH)D level ( $<20$  ng/mL,  $\geq 20$  ng/mL).

We also constructed inverse probability of continuation weights to account for loss to follow-up (Figure 2.3).<sup>49,52</sup> We fitted logistic regression models to estimate the probability of continuation, conditional upon exposure history and hypothesized predictors of loss to follow-up. For each participant  $i$ , we constructed stabilized continuation weights for each completed visit  $j$  using the following equation:

$$sw_{ij}^c = \Pr[C_{ik}=0 | C_{i(k-1)}=0, A_{i(k-1)}] / \Pr[C_{ik}=0 | C_{i(k-1)}=0, A_{i(k-1)}, L_{i(k-1)}]$$

where  $C$  represents censoring status,  $A$  represents treatment,  $k$  represents time, and  $L$  represents a series of hypothesized predictors of follow-up. We included the following predictors, some of which were time-varying: age; education ( $\leq$ high school diploma or General Educational Development certificate, some college or Associate degree,  $\geq$ Bachelor degree); household income ( $<20,000$ ,  $20,000-50,000$ ,  $>50,000$  U.S. dollars); job hours/week; employment status; night work in the past month; current rotating shift work; BMI ( $<25$ ,  $25-29$ ,  $30-34$ ,  $35-39$ ,  $\geq 40$  kg/m<sup>2</sup>); cigarette smoking; alcohol intake (low [ $<10$  drinks/year], moderate [ $1-5$  drinks/day on days when the participant drinks and only drinks  $\geq 4$  drinks once/month or less], heavy [ $\geq 6$  drinks/day on days the participant drinks or  $\geq 4$  drinks at a single sitting at least twice per month]); exercise intensity (low [ $<1$  hour/week of vigorous physical activity, 2 hours/week of moderate physical activity, and 14 hours/week of walking], low to moderate [MET score below 72 but not low activity], moderate [MET score above 72 but not high or very high], high [ $2.5- <5$  hours/week of vigorous physical activity or  $7- <10$  hours/week of moderate physical activity], very high [ $\geq 5$  hours/week of vigorous physical activity or  $\geq 10$  hours/week of moderate physical activity]); history of diagnosed diabetes, hypertension,

anxiety, or depression (all modeled individually); perceived stress (PSS-4 score); hormonal contraceptive use; parity; years since last birth; marital status (never married or lived as married, previously married or lived as married, currently married or lived as married); intensity of menstrual bleed (light, moderate, heavy); frequency of daily life stress (very stressful, moderate, mild, not at all); age at menarche (<11, 11, 12, 13, >13 years); frequency of difficulty paying for basic life expenses (very difficult, moderate, slightly or occasionally, not at all); multivitamin use in the past four weeks; and use of government health insurance.

We multiplied treatment and loss to follow-up weights from each completed visit to create one final weight per participant. We trimmed the final weight at the 99<sup>th</sup> percentile to avoid influence of extreme weights.<sup>53</sup> We applied the weight to each Cox regression model to estimate weighted HRs and 95% CIs.

Missingness of sleep health data ranged from 0–0.2% across clinic visits. Covariate missingness ranged from 0% (*e.g.*, age) to 8.4% (*i.e.*, intensity of menstrual bleed [at 60-month follow-up visit]). We used a combination of simple and multiple imputation to impute missing exposure and covariate data. For missing education and household income at an individual study visit, we used available participant-reported responses on education, income, employment status, and job hours/week at previous, current, and future clinic visits to simply impute values. For all remaining variables, we used multiple imputation with fully conditional specification methods at each clinic visit to generate 20 imputed datasets.<sup>54,55</sup> We statistically combined regression estimates using Rubin's rules.<sup>54</sup> We included all baseline covariates, as well as covariates with missing

data in follow-up visits, in imputation models.

### 2.2.7 Statistical analysis: UL growth

To assess UL growth, we calculated the change in natural logarithmic volume of each UL matched across successive clinic visits.<sup>38</sup> We standardized the change in volume to 18 months to account for varying length in time across matched intervals. We fitted linear mixed models to generate regression coefficients ( $\beta$ ) for the association between sleep health and UL growth, which accounted for correlated growth of multiple UL within the same participant and the same UL across intervals. We used random intercepts with variance components covariance structure and repeated subjects at the UL level. We calculated percent differences (%D; positive or negative) for each sleep health exposure using the following formula:

$$\%D = (\exp(\beta) - 1) * 100$$

We defined exposure as self-reported sleep health at the start of each growth interval. Because we examined growth using a matched interval and were not concerned about treatment-confounder feedback, we accounted for confounding using a traditional adjustment approach. We adjusted for the following confounders, reported at the start of each interval: age; education ( $\leq$ high school diploma or General Educational Development certificate, some college or Associate degree,  $\geq$ Bachelor degree); household income (<20,000, 20,000–50,000, >50,000 U.S. dollars); job hours/week; employment status; night work in the past month; current rotating shift work; BMI (<25, 25–29, 30–34, 35–39,  $\geq$ 40 kg/m<sup>2</sup>); cigarette smoking; alcohol intake (low [ $<10$  drinks/year], moderate [1–5

drinks/day on days when the participant drinks and only drinks  $\geq 4$  drinks once/month or less], heavy [ $\geq 6$  drinks/day on days the participant drinks or  $\geq 4$  drinks at a single sitting at least twice per month]); exercise intensity (low [ $< 1$  hour/week of vigorous physical activity, 2 hours/week of moderate physical activity, and 14 hours/week of walking], low to moderate [MET score below 72 but not low activity], moderate [MET score above 72 but not high or very high], high [2.5– $< 5$  hours/week of vigorous physical activity or 7– $< 10$  hours/week of moderate physical activity], very high [ $\geq 5$  hours/week of vigorous physical activity or  $\geq 10$  hours/week of moderate physical activity]); history of diagnosed diabetes or hypertension (modeled individually); hormonal contraceptive use; parity; years since last birth; breastfeeding duration; 25(OH)D level ( $< 20$  ng/mL,  $\geq 20$  ng/mL); number of UL ( $< 2$ ,  $\geq 2$ ); and UL volume ( $< 4.19$ ,  $\geq 4.19$  centimeters<sup>3</sup>). Because mental health<sup>56</sup> and perceived stress<sup>57</sup> could act as either confounders or mediators of the association with UL growth, we further adjusted for history of diagnosed depression or anxiety (modeled individually) and PSS-4 score in secondary models.

For those participants not included in incidence analyses and with missing exposure or covariate data, we performed simple imputation and assigned missing values to the median or modal value of the cohort. Among these participants, exposure missingness ranged from 0–0.4% and covariate missingness ranged from 0% to 2.7% (*i.e.*, history of diagnosed anxiety). We performed all analyses using SAS version 9.4 (SAS Institute, Cary, NC).

## 2.3 RESULTS

At baseline, 654 participants (57.5%) reported <7 hours/day and 57 (5.0%) reported  $\geq 9$  hours/day of sleep before a workday, 107 participants (9.4%) had trouble falling asleep or going back to sleep  $\geq 15$  days/month, and 695 participants (61.1%) felt well-rested less than half of the week (Table 2.1).

Participants who slept <6 or  $\geq 9$  hours/day were less likely to have a Bachelor degree and to have a household income of >50,000 U.S. dollars, and were more likely to be current users of depot medroxyprogesterone acetate and have a history of depression or hypertension diagnoses, compared to participants who reported 7–8 hours/day (Table 2.1). Those with shorter sleep durations were more likely to have worked a night job in the past month or in a current rotating shift position, have been diagnosed with anxiety, be parous, and report longer breastfeeding durations, but were less likely to have low exercise intensity. Participants who reported  $\geq 9$  hours/day of sleep were more likely to have a BMI  $\geq 40$  kg/m<sup>2</sup>, have a history of diagnosed diabetes, smoke cigarettes, and be unemployed.

Patterns of baseline characteristics were mostly similar for frequency of sleep trouble (Table 2.1), with the exception of educational attainment, hypertension and diabetes diagnoses, night work in the past month, current work in a rotating shift position, and BMI. We also observed similar patterns for frequency of feeling well-rested less than half of the week relative to sleep duration, but these participants were more likely to be employed for  $\geq 30$  hours/week. Participants consistently reported sleep health across measures, such that those who reported worse sleep in one domain (*e.g.*, sleep duration)

consistently reported worse sleep in the other domains (*i.e.*, frequency of sleep trouble, frequency of feeling well-rested).

Among the 1,137 participants included in analyses, we identified 349 incident cases of UL via SELF ultrasound and 2 via hysterectomy (10-year cumulative incidence:  $351/1,137 = 30.9\%$ ; Table 2.2). There were 10 participants (0.9%) who were censored for hysterectomy procedures for non-UL indications. We censored 211 participants (18.6%) at their first missed clinic visit and 565 participants (49.7%) were censored after 10 years of follow-up.

We observed an inverted U-shaped relationship for sleep duration, such that short and long sleep durations were associated with lower UL incidence rates (Table 2.3). Weighted HRs were 0.30 (95% CI: 0.17, 0.55) for <6 hours/day, 0.56 (95% CI: 0.34, 0.94) for 6 hours/day, 0.71 (95% CI: 0.39, 1.30) for 7 hours/day, and 0.59 (95% CI: 0.09, 3.67) for  $\geq 9$  hours/day, relative to 8 hours/day.

Conversely, increased frequency of sleep trouble was associated with increased UL incidence rate (Table 2.3). Relative to participants who reported no sleep trouble, weighted HRs were 1.32 (95% CI: 0.82, 2.13) for 1–14 days/month and 1.96 (0.76, 5.09) for  $\geq 15$  days/month. We observed a large change in effect estimates after weighting in analyses for frequency of sleep trouble (*e.g.*, for  $\geq 15$  days/month: unweighted HR=1.08, 95% CI: 0.67–1.76, weighted HR=1.96, 95% CI: 0.76–5.09).

Compared with feeling well-rested  $\geq 4$  days/week, feeling well-rested less than half of the week was associated with 0.78 times the incidence rate of UL (95% CI: 0.56, 1.08; Table 2.3).

Of the 1,359 matched UL growth intervals, 1,320 (97.1%) were from immediately successive clinic visits (*e.g.*, baseline to first follow-up, first to second follow-up, or second to third follow-up; Table 2.4). Short sleep duration and feeling well-rested less than half of the week were not meaningfully associated with UL growth (Table 2.5). Adjusted %Ds were -2% (95% CI: -14%, 13%) for <6 hours/day of sleep, 1% (95% CI: -11%, 15%) for 6 hours/day, and -4% (95% CI: -15%, 9%) for 7 hours/day, relative to 8 hours/day. Compared to  $\geq 4$  days/week, the adjusted %D for feeling well-rested <4 days/week and UL growth was 1% (95% CI: -8%, 10%). We observed a decreased rate of UL growth among participants who slept  $\geq 9$  hours/day (%D=-12%, 95% CI: -32%, 14%) compared with 8 hours/day, and for any report of sleep trouble (1–14 days/month: %D=-9%, 95% CI: -17%, 0%;  $\geq 15$  days/month: %D=-6%, 95% CI: -19%, 9%, vs. 0 days/month), although results were imprecise. We did not observe an appreciable change in estimates with additional adjustment for mental health and perceived stress variables (Table 2.5).

## 2.4 DISCUSSION

In this prospective ultrasound-based cohort study of reproductive-aged Black individuals, short and long sleep durations and feeling well-rested less than half of the week were associated with decreased UL incidence rates, while frequency of sleep trouble was associated with greater UL incidence rates. The sleep health measures that we evaluated were not substantially associated with UL growth.

We report the first findings of the prospective relationship between sleep health and UL incidence and growth. UL and associated symptomatology (*e.g.*, heavy menstrual bleeding) are known to be associated with poor sleep health.<sup>58,59</sup> Several systematic reviews have identified relationships between sleep health and benign gynecologic conditions (*e.g.*, endometriosis,<sup>60</sup> polycystic ovary syndrome [PCOS]<sup>61–64</sup>), with a notable increase in sleep-disordered breathing and obstructive sleep apnea among individuals with PCOS.<sup>65</sup> However, none of these studies have examined sleep as a risk factor for these conditions.

Our findings of an association between short sleep duration, decreased frequency of feeling well-rested, and lower UL incidence and growth are contradictory to our hypothesis. These findings could be attributed to several different explanations. First, exposure misclassification is possible, as we utilized self-reported sleep health measures.<sup>66–68</sup> Second, there may be misspecification of the relevant exposure definition. It may be possible that more extreme values of sleep duration and frequency of feeling well-rested are associated with increased UL incidence rates. However, we were unable to examine this association due to available sample size. Finally, we did not collect data on some important covariates, including depressive symptoms and treatment, throughout follow-up. As mental health is strongly related to sleep,<sup>56</sup> unmeasured confounding is possible.

These unexpected findings warrant exploration of alternative biologic mechanisms. UL are hormone-dependent neoplasms, and UL pathogenesis and growth are promoted by increased estrogen and progesterone levels.<sup>3,69,70</sup> Estrogen upregulates

gene expression of growth factors and estrogen and progesterone receptors,<sup>69</sup> and progesterone stimulates growth and maintenance of UL tumors.<sup>69,71</sup> Markers of tumor proliferation<sup>72</sup> and mitotic count<sup>73</sup> in leiomyoma tissue are highest during the luteal phase,<sup>69</sup> which also corresponds to when progesterone concentrations peak during the menstrual cycle. Conversely, short sleep duration has been associated with decreased serum concentrations of estradiol and luteal phase progesterone.<sup>74</sup> Ovarian hormones regulate and maintain the sleep-wake cycle,<sup>75</sup> and higher estrogen<sup>76-78</sup> and progesterone<sup>79</sup> levels are protective against worse sleep health, although findings are inconsistent.<sup>15</sup> During perimenopause, individuals are more likely to report poor sleep quality as their ovarian hormone levels deplete.<sup>75</sup> Thus, reproductive hormones may exert antagonistic effects on sleep and UL incidence and growth (*i.e.*, higher levels may promote UL incidence and growth but protect against poor sleep health), which may explain our findings in part.

These findings may also be attributed to allostatic load and physiologic responses to chronic stress. Allostasis, or the process of achieving homeostasis through compensatory physiologic change, is the body's response to internal and external stressors.<sup>80,81</sup> The long-term, cumulative physiologic response to chronic stress results in greater allostatic load, which is detrimental to health due to greater breakdown of body systems.<sup>80,81</sup> Poor sleep health has been shown to be a chronic stressor and can produce greater allostatic load.<sup>82,83</sup> In turn, allostatic overload and lack of adaptation can disrupt or blunt normal HPA axis responses to stress and increase glucocorticoid levels.<sup>80,81,84,85</sup> These responses can dysregulate the hypothalamic-pituitary-ovarian axis and inhibit

reproductive hormone production, including estrogen and progesterone,<sup>16,86</sup> and, ultimately, protect against UL pathogenesis. Black individuals have been found to have greater allostatic load than White individuals, which supports the weathering hypothesis of earlier health deterioration in Black individuals due to stigmatization and disadvantages,<sup>87,88</sup> and could possibly explain these unexpected findings.

Frequency of sleep trouble was positively associated with UL incidence rates, which contradicts the association among other exposures. There are several potential explanations for this finding. First, these findings may support our initially proposed biologic mechanism, where increased frequency of sleep trouble produces stress, which in turn promotes UL incidence through HPA axis deterioration.<sup>3,17,18</sup> Second, it is possible that confounding effects for frequency of sleep trouble are different than those for sleep duration and frequency of feeling well-rested. We observed null effects prior to weighting, while there was minimal difference between unweighted and weighted estimates for other exposures. We also identified different patterns in some covariates relative to frequency of sleep trouble compared to sleep duration and frequency of feeling well-rested. However, we used a directed acyclic graph and inverse probability weighting to identify confounding and avoid overadjustment. Finally, we observed wide confidence intervals for this exposure. As such, our positive findings may be attributable to chance.

Many of our study strengths come from its design: we performed prospective, serial screening for UL using transvaginal ultrasonography,<sup>37</sup> which has high sensitivity and specificity relative to histologic evidence.<sup>43</sup> We were able to identify asymptomatic cases, which account for a large proportion of UL tumors,<sup>3</sup> thereby reducing potential for

outcome misclassification. Most studies examining UL rely on self-report, which may only capture symptomatic cases and individuals with access to a clinical diagnosis. We followed a large cohort of reproductive-aged Black individuals for approximately 10 years. This long follow-up period allowed us to update exposure and covariate information over time. Cohort retention exceeded 80% for each clinic visit and we utilized inverse probability of continuation weights, which mitigated potential selection biases due to loss to follow-up. Finally, our analytic methods were guided by directed acyclic graphs and we utilized inverse probability of treatment weights to account for confounders,<sup>49,50</sup> including those that may exhibit treatment-confounder feedback, and censored participants at their first missed clinic visit. This approach avoids exposure misclassification and misspecification of inverse probability weights, which improves study validity. Given the established effect of UL on poor sleep health, our prospective design prevented reverse causation bias.

We utilized self-reported measures of sleep health, which may introduce exposure misclassification. Because we used a prospective study design and examined sleep health prior to outcome assessment, any misclassification would be non-differential and would likely result in an underestimation of effect estimates. In this case, the true findings may be stronger than those reported.<sup>89</sup> Our measures of sleep health are not validated, which may limit the accuracy of sleep assessment. We observed imprecise estimates for sleep duration  $\geq 9$  hours/day due to small sample size. Finally, though participants could miss clinic visits, we accounted for skipped visits by censoring participants at their first missed visit and incorporating inverse probability of continuation weights.

In conclusion, short and long sleep duration and decreased frequency of feeling well-rested were associated with decreased incidence rates of UL, while increased frequency of sleep trouble was positively associated with UL incidence rates. We did not observe strong associations between poor sleep health and UL growth. These results may provide an improved understanding for UL pathogenesis and the impact of lifestyle factors on UL incidence and growth.

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## 2.6 TABLES AND FIGURES

**Table 2.1** Baseline characteristics by sleep health among 1,137 participants, Study of Environment, Lifestyle, and Fibroids, 2010–2012

Characteristic <sup>a</sup>	Sleep duration (hours/day)					Frequency of sleep trouble (days/month)			Frequency of feeling well-rested (days/week)	
	<6	6	7	8	≥9	0	1–14	≥15	<4	≥4
Number of participants	292	362	270	156	57	320	710	107	695	442
Age (years), mean	29.3	29.0	28.7	28.6	28.4	29.0	28.8	29.4	29.1	28.7
Educational attainment, %										
≤High school or GED	25.7	19.1	16.3	33.4	27.3	22.7	23.1	18.4	22.7	22.0
Some college/Associate degree	57.4	53.7	45.7	44.6	54.7	48.8	52.5	55.5	52.1	51.5
≥Bachelor degree	16.9	27.2	38.0	22.0	18.0	28.5	24.4	26.1	25.2	26.5
Household income (USD), %										
<20,000	54.3	42.9	35.6	54.9	46.5	40.5	47.3	51.1	47.0	43.7
20,000–50,000	32.2	39.2	45.7	33.7	44.7	44.7	36.9	32.3	37.1	41.4
>50,000	13.4	17.9	18.8	11.5	8.9	14.8	15.8	16.6	15.9	14.9
Employment status, %										
Employed, ≥30 hours/week	48.1	51.2	39.5	34.3	31.8	54.8	45.3	43.1	50.1	44.0
Employed, <30 hours/week	12.4	14.7	34.2	13.3	11.2	12.9	13.0	15.5	11.9	15.2
Unemployed	39.5	34.2	33.5	52.4	57.0	32.3	41.7	41.3	38.0	40.8
Job hours/week, mean <sup>b</sup>	22.7	24.4	24.6	16.0	16.3	25.4	21.3	21.3	23.4	21.0
Night work in the past month, %	20.8	14.0	9.0	12.2	13.2	16.6	13.9	10.4	14.4	13.9
Current rotating shift work, %	18.5	21.4	13.9	11.4	15.3	15.8	18.5	12.3	16.2	18.7

Body mass index (kg/m <sup>2</sup> ), %										
<25	18.8	16.5	27.1	24.0	16.4	19.7	20.4	21.0	21.0	19.3
25–29	19.7	22.9	20.7	19.8	19.5	20.1	20.9	24.9	20.9	21.1
30–34	19.7	20.5	18.2	13.0	16.3	16.4	20.1	16.9	19.2	17.9
35–39	15.9	16.2	16.4	21.1	16.5	18.8	16.6	12.3	15.6	18.4
≥40	25.9	23.9	17.7	22.2	31.3	24.9	22.1	25.0	23.4	23.2
Current cigarette smoker, %	23.1	17.6	14.5	22.5	17.4	14.4	20.8	20.5	19.7	18.0
Alcohol intake (heavy <sup>c</sup> ), %	21.9	19.7	14.9	22.8	14.8	14.8	21.3	19.5	20.2	17.8
Exercise intensity (low <sup>d</sup> ), %	13.2	16.5	19.1	19.4	17.8	16.9	17.1	11.9	16.4	17.1
History of diagnosed hypertension, %	11.0	7.9	9.1	8.9	12.1	10.5	8.3	11.9	10.1	8.2
History of diagnosed diabetes, %	3.3	2.0	2.7	3.0	10.5	3.1	3.3	0.8	2.4	3.9
History of diagnosed anxiety, %	10.6	10.4	9.6	9.5	7.8	6.3	10.4	18.3	10.3	9.5
History of diagnosed depression, %	17.3	14.8	11.9	13.9	15.3	9.6	14.5	28.3	16.3	11.9
PSS-4 score, mean	6.9	6.6	6.0	5.9	5.9	5.5	6.6	7.3	6.8	5.8
Current use of DMPA, %	8.7	4.6	7.0	5.9	14.9	5.1	7.3	12.0	6.7	7.7
Current use of hormonal contraceptives, %	30.2	28.0	34.9	23.9	28.9	24.7	30.7	38.3	30.7	28.3
Parous, %	70.1	61.6	60.0	64.4	55.4	61.7	64.5	64.3	65.8	60.5
Years since last birth, mean <sup>e</sup>	4.6	5.2	5.2	4.9	4.9	4.9	5.0	5.0	5.2	4.8
Total breastfeeding duration (months), mean <sup>e</sup>	5.5	5.9	5.6	4.2	4.0	5.3	5.2	6.8	5.0	5.6
Season-adjusted 25(OH)D serum level <20 ng/mL, %	74.2	71.2	73.8	76.7	75.6	74.1	74.1	68.9	74.3	72.6
Sleep duration (hours/day), %										
<6						20.1	24.3	49.3	34.9	11.2
6						28.4	34.6	25.2	36.5	24.4

7						26.3	23.5	19.1	17.2	33.8
8						16.6	13.9	3.6	8.9	21.7
≥9						8.5	3.8	2.8	2.6	8.9
Frequency of sleep trouble (days/month), %										
0	22.2	25.3	31.2	33.9	49.0				21.4	38.8
1–<15	59.2	67.5	61.8	63.7	46.0				65.3	58.0
≥15	18.6	7.3	7.0	2.4	5.0				13.4	3.2
Frequency of feeling well-rested (days/week), %										
<4	83.3	70.0	44.6	37.9	28.8	46.4	63.9	86.7		
≥4	16.7	30.0	55.4	62.1	71.2	53.6	36.1	13.3		

25(OH)D: 25-hydroxyvitamin D; DMPA: depot medroxyprogesterone acetate; GED: General Educational Development; kg: kilogram; m: meter; PSS-4: Perceived Stress Scale-4; USD: United States dollars.

<sup>a</sup> All characteristics, except age, are standardized to the age distribution of the cohort at baseline.

<sup>b</sup> Job hours/week includes participants who are unemployed, who have a value of 0 hours/week.

<sup>c</sup> Heavy alcohol consumption is defined as ≥6 drinks/day on days the participant drinks or ≥4 drinks at a single sitting at least twice per month.

<sup>d</sup> Low exercise intensity is defined as <1 hour/week of vigorous physical activity, 2 hours/week of moderate physical activity, and 14 hours/week of walking.

<sup>e</sup> Among parous participants.

**Table 2.2** Count of participants by outcome or censor group in UL incidence analyses, Study of Environment, Lifestyle, and Fibroids, 2010–2022

Outcome or censor group	N (%)
1: UL outcome detected via SELF ultrasound	349 (26.7)
2: UL outcome detected via hysterectomy procedural report	2 (0.2)
3: Hysterectomy procedure	10 (0.8)
4: Censored at fourth follow-up visit	565 (43.2)
5: Censored at third follow-up visit	89 (6.8)
6: Censored at second follow-up visit	20 (1.5)
7: Censored at first follow-up visit	102 (7.8)
8: Did not complete the first follow-up visit	171 (13.1)

SELF: Study of Environment, Lifestyle, and Fibroids; UL: uterine leiomyomata.

**Table 2.3** Association between sleep health and UL incidence among 1,137 participants, Study of Environment, Lifestyle, and Fibroids, 2010–2022

Sleep exposure	Cases/PM	Unweighted HR (95% CI)	Weighted HR (95% CI) <sup>a</sup>
Sleep duration (hours/day)			
<6	77/21,696	0.39 (0.25, 0.63)	0.30 (0.17, 0.55)
6	118/25,896	0.64 (0.42, 0.97)	0.56 (0.34, 0.94)
7	85/16,532	0.72 (0.46, 1.13)	0.71 (0.39, 1.30)
8	57/10,062	<i>Reference</i>	<i>Reference</i>
≥9	14/2,895	0.75 (0.29, 1.91)	0.59 (0.09, 3.67)
Frequency of sleep trouble (days/month)			
0	111/23,673	<i>Reference</i>	<i>Reference</i>
1–14	205/45,792	0.99 (0.71, 1.37)	1.32 (0.82, 2.13)
≥15	35/7,616	1.08 (0.67, 1.76)	1.96 (0.76, 5.09)
Frequency of feeling well-rested (days/week)			
<4	201/46,645	0.80 (0.61, 1.05)	0.78 (0.56, 1.08)
≥4	150/30,435	<i>Reference</i>	<i>Reference</i>

CI: confidence interval; HR: hazard ratio; PM: person-month.

<sup>a</sup> Weighted for loss to follow-up and the following confounders: age, educational attainment, household income, employment status, job hours per week, night work in the past month, rotating shift work, body mass index, cigarette smoking, alcohol intake, exercise intensity, history of diagnosed hypertension, history of diagnosed diabetes, history of diagnosed anxiety, history of diagnosed depression, Perceived Stress Scale-4 score, hormonal contraceptive use, parity, years since last birth, total breastfeeding duration, and season-adjusted 25(OH)D serum level.

**Table 2.4** Count of matched intervals by group in UL growth analyses, Study of Environment, Lifestyle, and Fibroids, 2010–2022

Interval group	N (%)
1: Baseline to first follow-up visit	343 (25.2)
2: Baseline to second follow-up visit	21 (1.6)
3: Baseline to third follow-up visit	5 (0.4)
4: First follow-up to second follow-up	417 (30.7)
5: First follow-up to third follow-up	13 (1.0)
6: Second follow-up to third follow-up	560 (41.2)

UL: uterine leiomyomata.

**Table 2.5** Association between sleep health and UL growth among 434 participants, Study of Environment, Lifestyle, and Fibroids, 2010–2018

Sleep exposure	Number of UL growth intervals <sup>a</sup>	Model 1 Unadjusted %D (95% CI)	Model 2 Adjusted %D (95% CI) <sup>b</sup>	Model 3 Adjusted %D (95% CI) <sup>c</sup>
<b>Sleep duration (hours/day)</b>				
<6	356	-6 (-18, 8)	-2 (-14, 13)	-1 (-14, 13)
6	444	-4 (-16, 10)	1 (-11, 15)	1 (-11, 15)
7	316	-6 (-18, 8)	-4 (-15, 9)	-3 (-16, 11)
8	201	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
≥9	42	-18 (-37, 6)	-12 (-32, 14)	-12 (-32, 14)
<b>Frequency of sleep trouble (days/month)</b>				
0	405	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
1–14	787	-7 (-15, 3)	-9 (-17, 0)	-9 (-17, 0)
≥15	167	-3 (-16, 12)	-6 (-19, 9)	-7 (-20, 8)
<b>Frequency of feeling well-rested (days/week)</b>				
<4	842	-1 (-9, 8)	1 (-8, 9)	1 (-8, 10)
≥4	517	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>

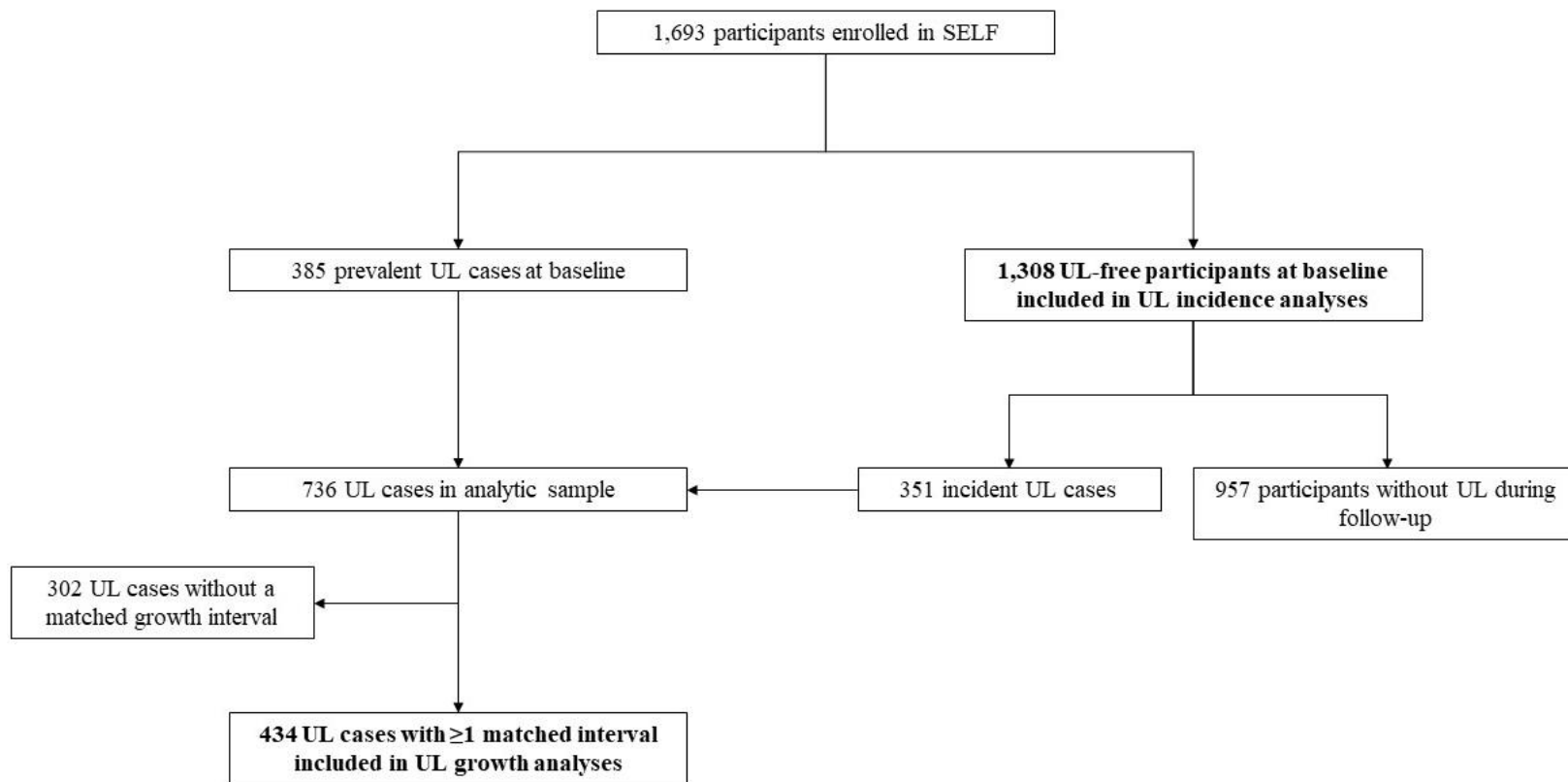
%D: percent difference; CI: confidence interval; UL: uterine leiomyomata.

<sup>a</sup> Participants contributed 754 unique UL within 1,359 growth intervals.

<sup>b</sup> Adjusted for the following confounders: age, educational attainment, household income, employment status, job hours per week, night work in the past month, rotating shift work, body mass index, cigarette smoking, alcohol intake, exercise intensity, history of diagnosed hypertension, history of diagnosed diabetes, contraceptive use, parity, years since last birth, total breastfeeding duration, season-adjusted 25(OH)D serum level, number of UL at the beginning of each interval, and UL volume at the beginning of each interval.

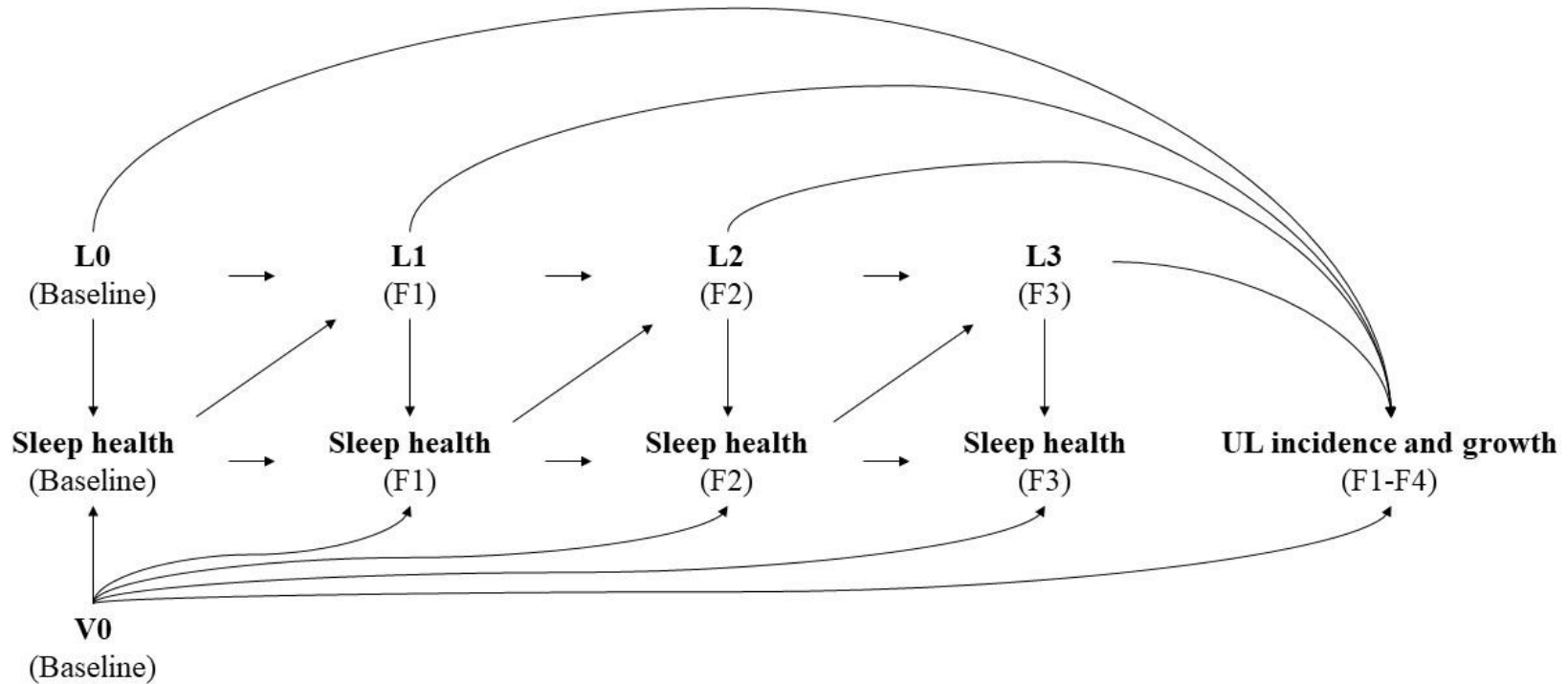
<sup>c</sup> Adjusted for all covariates in Model 2 and further adjusted for history of diagnosed depression, history of diagnosed anxiety, and Perceived Stress Scale-4 score.

**Figure 2.1** Study population and exclusions, Study of Environment, Lifestyle, and Fibroids, 2010–2022



SELF: Study of Environment, Lifestyle, and Fibroids; UL: uterine leiomyomata.  
 Bold text indicates the analytic samples for UL incidence and growth analyses.

**Figure 2.2** Directed acyclic graph for confounding in the association of sleep health and UL incidence and growth

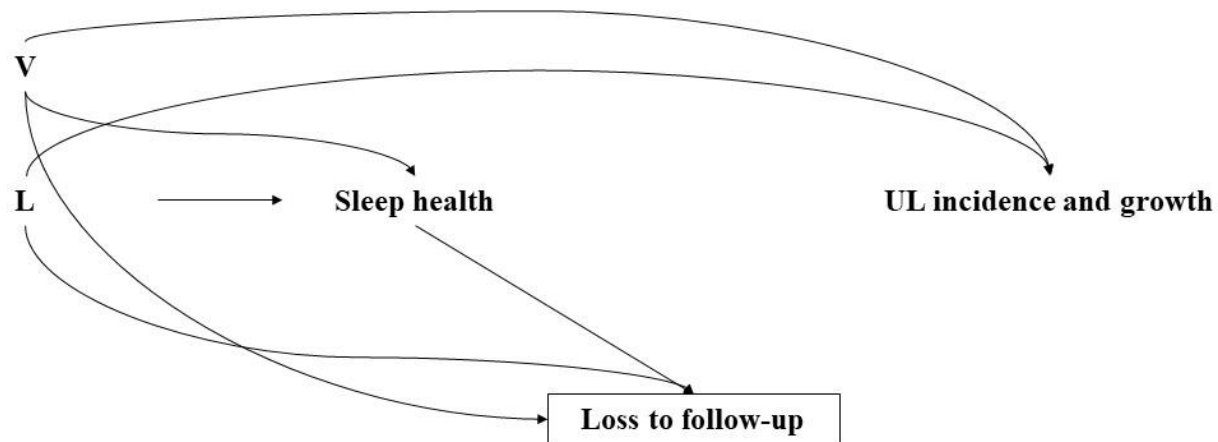


F: follow-up; UL: uterine leiomyomata.

V represents a series of time-invariant confounders, including history of diagnosed diabetes, history of diagnosed hypertension, history of diagnosed anxiety, and history of diagnosed depression.

L represents a series of time-varying confounders, including age, education, household income, employment status, job hours/week, any night work in the previous month, current rotating shift work, body mass index, cigarette smoking, alcohol intake, exercise intensity, perceived stress, hormonal contraceptive use, parity, time since last birth, total breastfeeding duration, and 25(OH)D serum level.

**Figure 2.3** Directed acyclic graph for loss to follow-up in the association of sleep health and UL incidence and growth



UL: uterine leiomyomata.

V represents a series of time-invariant confounders, including history of diagnosed diabetes, history of diagnosed hypertension, history of diagnosed anxiety, and history of diagnosed depression.

L represents a series of time-varying confounders, including age, education, household income, employment status, job hours/week, any night work in the previous month, current rotating shift work, body mass index, cigarette smoking, alcohol intake, exercise intensity, perceived stress, hormonal contraceptive use, parity, time since last birth, total breastfeeding duration, and 25(OH)D serum level.

This directed acyclic graph is limited to the first follow-up interval for exemplary purposes.

### **3. A NORTH AMERICAN PROSPECTIVE COHORT STUDY OF SELF-REPORTED SLEEP HEALTH AND MENSTRUAL CYCLE DISTURBANCES**

#### **3.1 INTRODUCTION**

Menstruation, the cyclic physiologic process through which blood and tissue are discharged from the uterine corpus,<sup>1,2</sup> is experienced by half of the population during their lifetime.<sup>3</sup> Global estimates indicate that 1.8 billion people menstruate each month.<sup>4</sup> Menstrual cycle disturbances include abnormal uterine bleeding (AUB) and dysmenorrhea (*i.e.*, menstrual pain).<sup>5,6</sup> Estimated to affect up to 30% of reproductive-aged individuals with a uterus,<sup>5</sup> symptoms of AUB include amenorrhea (*i.e.*, missing one or more periods), intermenstrual and unscheduled bleeding, and abnormal cycle frequency, duration, regularity, and flow volume.<sup>5</sup> Severe dysmenorrhea (*e.g.*, abdominal pain and cramping associated with menstrual bleeding requiring bed rest and missing work or activities) is estimated to affect up to 29% of individuals with a uterus.<sup>3,6</sup> Menstrual cycle disturbances can result from a variety of factors, including gynecologic disorders, coagulopathies, ovulatory dysfunction, hormonal imbalances, medication use, and infections.<sup>5,7,8</sup> Sequelae of menstrual cycle disturbances include increased risk of certain cancers,<sup>9,10</sup> diabetes,<sup>11–13</sup> cardiovascular disease,<sup>14</sup> and premature mortality.<sup>15</sup> For these reasons, the American College of Obstetricians and Gynecologists has labeled menstrual health as a vital sign for overall health.<sup>16</sup> Identification of modifiable risk factors may provide important interventions to improve menstrual health.

There are several mechanisms through which poor sleep health may influence menstrual cycle disturbances. Poor sleep health can activate the hypothalamic-pituitary-

adrenal axis and inhibit the hypothalamic-pituitary-gonadal axis, which can induce glucocorticoid secretion and interrupt reproductive hormone production, impeding menstruation and ovarian function.<sup>17-22</sup> Luteinizing hormone (LH), a reproductive hormone that controls recruitment of ovarian follicles,<sup>23</sup> undergoes pulsatile secretion and is inhibited during sleep.<sup>24,25</sup> Frequent awakenings prompt LH pulse secretion,<sup>24,25</sup> which may result in menstrual cycle irregularity and abnormal cycle length. Additionally, poor sleep may induce circadian dysrhythmia, a condition wherein the body's sleep-wake cycle conflicts with ambient environmental cues, which can affect ovulation and steroidogenesis.<sup>22</sup> *CLOCK* gene expression, which generates and controls circadian rhythms, is associated with menstrual cycle regularity.<sup>26</sup> Also, secretion of melatonin, a critical sleep hormone, is known to influence endocrine function.<sup>22,27</sup> Finally, poor sleep can induce inflammation, which can influence menstrual function and affect timing of ovulation,<sup>3,22,28,29</sup> as well as dysmenorrhea and heavy flow volume through elevated uterine prostaglandin concentrations from inflammatory and immune systemic responses.<sup>30,31</sup>

While menstrual cycle disturbances are an established risk factor for poor sleep,<sup>23,32-35</sup> few studies have examined the effect of sleep on menstrual cycle disturbances.<sup>36</sup> Alterations in work schedule (*i.e.*, rotating shift and night work) that affect opportunity for optimal sleep timing and duration have been shown to influence menstrual cycle disturbances.<sup>37-42</sup> Several cross-sectional studies have found associations between short sleep duration and increased prevalence of menstrual cycle irregularity,<sup>43-47</sup> short or long cycle length,<sup>48</sup> and greater flow volume.<sup>45</sup> Additionally, worse sleep

quality has been associated with increased prevalence of cycle irregularity,<sup>45,46</sup> menstrual pain,<sup>49</sup> short cycle length,<sup>46</sup> and longer bleed length.<sup>46,49</sup> One prospective analysis found associations between continuous sleep duration and serum concentrations of reproductive hormones, including estradiol and luteal phase progesterone, as well as an association between sleep duration of <7 hours/day and earlier peak production of LH, follicle-stimulating hormone, and progesterone.<sup>50</sup> However, there are no prospective studies of sleep duration or quality on menstrual cycle disturbances.

In the present study, we estimate prospectively the effect of self-reported sleep health, specifically duration and quality, on two-month risk of menstrual cycle disturbances among North American pregnancy planners. We hypothesize that short sleep duration and poor sleep quality will be associated with increased risk of menstrual cycle irregularity, short and long cycle length, prolonged bleed length, heavy flow volume, dysmenorrhea, and AUB (a comprehensive measure of several menstrual cycle disturbances).

## **3.2 METHODS**

### *3.2.1 Study population*

We analyzed data from Pregnancy Study Online (PRESTO), an Internet-based prospective preconception cohort study of North American pregnancy planners.<sup>51</sup> Recruitment began in June 2013 and is ongoing. Eligible participants are aged 21–45 years, assigned female at birth, and are not using contraception or fertility treatments. On a baseline questionnaire, participants provide data on socio-demographics, lifestyle

factors, medical history, typical menstrual cycle characteristics, and reproductive and contraceptive histories. Participants complete follow-up questionnaires every two months until pregnancy or for up to 12 months (for a total of six possible follow-up questionnaires), providing updated data on exposure information, reproductive health (including recent menstrual cycle characteristics), and pregnancy status. The Boston University Medical Campus Institutional Review Board approved the study protocols and all participants provided informed consent.

For the current analysis, we leveraged data on sleep health and menstrual cycle characteristics reported on the follow-up questionnaires. Specifically, we assessed the short-term effect of sleep health reported on a follow-up questionnaire (*i.e.*, start-of-interval questionnaire) with menstrual cycle characteristics reported two months later on the next follow-up questionnaire (*i.e.*, end-of-interval questionnaire). This study design allowed us to restrict the analysis to participants who did not have the outcome of interest at the start of each analytic interval, thus minimizing concerns about reverse causation bias. Participants could contribute multiple intervals (*i.e.*, data from two consecutive follow-up questionnaires) to the analysis.

### *3.2.2 Exposure assessment: Sleep health*

On the baseline questionnaire and, beginning in October 2020, the follow-up questionnaires, we ascertained data on two domains of sleep health: quality and duration. Participants completed the Pittsburgh Sleep Quality Index (PSQI), a validated instrument that collects data on sleep quality during the previous month (sensitivity: 89.6%,

specificity: 86.5% vs. the gold standard of polysomnography and clinical interviews).<sup>52</sup>

The PSQI includes 19 questions that measure seven domains of sleep: subjective sleep quality, latency, duration, habitual sleep efficiency, disturbances, use of sleep medications or aids, and daytime dysfunction. We scored responses for each domain (range: 0–3) and summed the seven domain-specific scores to create a global score (range: 0–21) using pre-specified scoring guidelines, with higher scores indicating worse sleep quality.

We ascertained data on sleep duration as part of the PSQI with the question “During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed).” Participants reported their sleep duration in a free-text field, which allowed for non-integer responses (*e.g.*, 7.5 hours/day).

### *3.2.3 Outcome assessment: Menstrual cycle disturbances*

At baseline, participants reported information on their typical menstrual cycle characteristics. Specifically, participants were asked if their menstrual period had been regular within the past couple of years, the number of menstrual periods they experienced in a year, their typical cycle length, and information about their usual cycle (*i.e.*, usual flow length, volume, and pain). On follow-up questionnaires, participants reported information pertaining to the menstrual cycle most proximal to questionnaire completion. Participants reported the date of their last menstrual period(s) (LMP), if their period was “regular (in a way that you can usually predict about when the next period will start),”

and the length of their most recent cycle (*i.e.*, “the number of days from the first day of the previous menstrual period to the first day of the latest menstrual period”). Beginning in May 2021, participants also reported information on other characteristics from their most recent cycle, including bleed length, flow volume, intermenstrual bleeding, and menstrual pain. To assess bleed length, we asked participants “How many days did your menstrual period flow (bleeding, not spotting)?” with response options of  $<3$ , 3, 4, 5, 6, and  $\geq 7$  days. To assess flow volume, we asked participants “How would you classify the total amount of your menstrual flow?” with response options of light ( $\leq 10$  pads or tampons per period), moderate (11–20), moderate/heavy (21–30), or heavy ( $>30$ ). Participants reported the presence of any intermenstrual bleeding, including spotting, in the middle of their cycle. Finally, for menstrual pain, we asked participants if they experienced any pain during their menstrual period, and, if yes, the severity of pain (response options: mild cramps with no medication needed, moderate cramps with medication needed, and severe cramps with medications and bed rest required).

#### *3.2.4 Covariate assessment*

We ascertained covariate data on baseline and follow-up questionnaires. Participants reported information on socio-demographics, lifestyle factors, anthropometrics, reproductive and sexual health, medical history, mental health, and stress. We calculated body mass index (BMI) as self-reported weight (kilograms) divided by height (meters) squared. We assessed physical activity using metabolic equivalent of task (MET) hours/week, which was calculated by multiplying the average number of

hours per week engaged in various activities by METs from the Compendium of Physical Activities.<sup>53</sup>

### 3.2.5 Exclusions

We restricted our analyses to participants who enrolled on or after October 2020, as this was when we included questions related to sleep and menstrual cycle characteristics on follow-up questionnaires. For each interval, we included participants who were not pregnant and had not initiated fertility treatment before their eligibility to complete the start-of-interval questionnaire (Figure 3.1). As such, 4,938 participants were eligible for the first analytic interval (*i.e.*, 2-to-4-month questionnaire interval), 3,719 were eligible for the second analytic interval (*i.e.*, 4-to-6-month questionnaire interval), and 3,019 were eligible for the third analytic interval (*i.e.*, 6-to-8-month questionnaire interval). We did not analyze data from the 8-to-10-month and 10-to-12-month questionnaire intervals due to limited sample size. Within each analytic interval, we excluded participants who did not complete the start-of-interval questionnaire, reported implausible menstrual cycle data (*e.g.*, implausible LMP reported at each questionnaire), were pregnant or initiated fertility treatment prior to completion of the start-of-interval questionnaire, or were lost to follow-up during the interval. We analyzed data from 1,799 participants from the first interval, 971 from the second interval, and 596 from the third interval. Thus, our final analytic sample comprised 1,984 participants who contributed 3,366 intervals. In each menstrual cycle disturbance-specific analysis, we further excluded intervals where participants reported the outcome at the start to improve study

validity (*i.e.*, to avoid reverse causation bias).

### 3.2.6 Statistical analysis

We categorized sleep duration as <7, 7–7.9, 8–8.9, and  $\geq 9$  hours/day, which aligns with categories used by the American Academy of Sleep Medicine and Sleep Research Society.<sup>54</sup> Because the physiologic benefit of long sleep duration (*i.e.*,  $\geq 9$  hours/day) is debated<sup>54</sup> and long sleep duration may be associated with adverse health outcomes,<sup>55</sup> we defined this category separately from recommended sleep duration. We used the PSQI global score to dichotomize sleep quality as good ( $\leq 5$ ) and poor ( $> 5$ ), in accordance with instrument scoring guidelines.<sup>52</sup>

We defined menstrual cycle disturbances based on the International Federation of Gynecology and Obstetrics (FIGO) guidelines<sup>5,56,57</sup> as follows: irregular cycles (yes, no), short cycles (<24 days), long cycles (>38 days), prolonged bleed length ( $\geq 7$  days), heavy flow volume (>20 pads or tampons per period), intermenstrual bleeding (any unscheduled spotting or bleeding), and dysmenorrhea (severe menstrual pain requiring medication usage and bed rest). We created a composite AUB outcome per FIGO guidelines, defined as any report of irregular cycles, short or long cycle length, prolonged bleed length, and/or heavy flow volume.<sup>5</sup>

We fitted log-binomial regression models to estimate risk ratios (RRs) and 95% confidence intervals (CIs) for each sleep health exposure and menstrual cycle disturbance.<sup>58</sup> To examine incidence, we excluded participants who reported the menstrual disturbance at the start-of-interval questionnaire for each outcome-specific

analysis. We fitted restricted cubic splines for the associations of PSQI global score and menstrual cycle disturbance risk to assess non-linearity of the association.<sup>59</sup>

Guided by directed acyclic graphs, we constructed three sets of stabilized inverse probability weights at each analytic interval.<sup>60,61</sup> First, we generated treatment (exposure) weights among those included in our sample to control for confounding (Figure 3.2). We fitted logistic and multinomial<sup>62</sup> logistic regression models for sleep quality and duration, respectively, to estimate the probability of having the exposure category reported by the participant, conditional upon a series of hypothesized confounders. We constructed treatment weights ( $sw$ ) for participant  $i$  at interval  $j$  using the following equation:

$$sw_{ij} = \Pr[A_k | A_{k-1}] / \Pr[A_k | A_{k-1}, L_k]$$

where  $A$  represents treatment,  $k$  represents time, and  $L$  represents the hypothesized confounders. We included the following time-invariant confounders: age (<30, 30–34,  $\geq 35$  years), annual household income (<50,000, 50,000–99,999, 100,000–149,999,  $\geq 150,000$  U.S. dollars), education (<16, 16,  $\geq 17$  years), employment status (yes, no), job hours/week, any night work in the previous month (yes, no), any shift work in the previous month (yes, no), BMI (<25, 25–29,  $\geq 30$  kg/m<sup>2</sup>), parity (parous, nulliparous), years since last birth, and last method of contraception (hormonal, non-hormonal). We also included the following time-varying confounders: physical activity (MET hours/week), cannabis use in the previous two months (yes, no), alcohol intake (drinks/week), perceived stress (Perceived Stress Scale [PSS]-10 score), depressive symptoms (Major Depression Inventory [MDI] score), current psychotropic medication use (yes, no), caffeine intake (milligrams/day), and sugar-sweetened beverage intake

(drinks/week). In these models, we upweighted participants whose covariate levels were less consistent with probability of reporting the exposure status they reported.

Second, we generated loss to follow-up weights among those included in our sample to account for non-completion *within* the analytic interval (*i.e.*, completed the start-of-interval questionnaire but not the end-of-interval questionnaire; Figure 3.3).<sup>60,61,63</sup> We fitted logistic regression models for probability of completion of the end-of-interval questionnaire conditional upon treatment and a series of hypothesized predictors of loss to follow-up. We developed loss to follow-up weights ( $sw^c$ ) for participant  $i$  at interval  $j$  using the following equation:

$$sw_{ij}^c = \Pr[C_{ik}=0|C_{i(k-1)}=0, A_{i(k-1)}] / \Pr[C_{ik}=0|C_{i(k-1)}=0, A_{i(k-1)}, L_{i(k-1)}]$$

where  $C$  represents censoring status,  $k$  represents time,  $A$  represents treatment, and  $L$  represents predictors of loss to follow-up. We included the following predictors, some of which were time-varying: age (<30, 30–34, ≥35 years), race/ethnicity (White, non-White), marital status (married, not married), geographic region of residence (Northeast U.S., South U.S., Midwest U.S., West U.S., Canada), relationship length with current partner (years), annual household income (<50,000, 50,000–99,999, 100,000–149,999, ≥150,000 U.S. dollars), education (<16, 16, ≥17 years), employment status (yes, no), job hours/week, health insurance status (private, government program or pay out-of-pocket), last method of contraception (hormonal, non-hormonal), gravidity (gravid, nulligravid), parity (parous, nulliparous), years since last birth, history of infertility (yes, no), history of spontaneous abortion (yes, no), diagnosis of polycystic ovary syndrome (yes, no), diagnosis of uterine leiomyomata (yes, no), diagnosis of endometriosis (yes, no), history

of sexually transmitted infections (yes, no), frequency of primary care physician appointments in the past year (none, once, 2–3 times,  $\geq 4$  times), any Pap exam in the past three years (yes, no), history of abnormal Pap exam (yes, no), BMI ( $< 25$ , 25–29,  $\geq 30$  kg/m<sup>2</sup>), invited male partner to enroll in PRESTO (yes, no), completion of the Food Frequency Questionnaire (yes, no), pregnancy attempt time at study entry (cycles), intercourse frequency ( $\leq 3$  times/month, 1 time/week, 2–3 times/week,  $\geq 4$  times/week), doing something to improve chances of becoming pregnant (yes, no), fertility tracking software use (yes, no), daily multivitamin and folic acid intake (yes, no), alcohol intake (drinks/week), cigarette smoking (yes, no), cannabis use in the previous two months (yes, no), physical activity (MET hours/week), perceived stress (PSS-10 score), depressive symptoms (MDI score), diagnosis of anxiety (yes, no), diagnosis of depression (yes, no), caffeine intake (milligrams/day), sugar-sweetened beverage intake (drinks/week), and environmental tobacco smoke exposure in the home (yes, no). We constructed these weights using baseline and start-of-interval questionnaire data and upweighted participants whose covariate and exposure levels were predictive of lower probability of continuation.

Third, we built sampling weights among all participants eligible for analysis to account for non-completion *before* the analytic interval (*i.e.*, eligible but did not complete the start-of-interval questionnaire; Figure 3.4).<sup>60,61,63</sup> We fitted logistic regression models for probability of completion of the start-of-interval questionnaire conditional upon treatment and hypothesized predictors of sampling, and developed weights using the same equation and predictors as loss to follow-up weights; however, we constructed these

weights using baseline questionnaire data only. We upweighted participants whose covariate and exposure levels were less consistent with probability of inclusion in the analytic sample.

We multiplied the three sets of weights (*i.e.*, treatment, loss to follow-up, and sampling) to create one final weight at each interval. We trimmed the final weight at the 99<sup>th</sup> percentile to avoid influence of extreme weights.<sup>64</sup> We applied each interval-specific weight to the log-binomial regression models to estimate weighted RRs and 95% CIs.

We performed several sensitivity analyses. First, we excluded participants who reported each specific menstrual cycle disturbance at baseline (*i.e.*, typically have the menstrual cycle disturbance) to better estimate new onset of each outcome. Second, we excluded participants with diagnosis of a benign gynecologic condition (*i.e.*, uterine leiomyomata, endometriosis, and/or polycystic ovary syndrome) at baseline to determine the extent to which observed associations reflect underlying gynecologic disorders. We chose not to include history of benign gynecologic conditions in inverse probability of treatment weights, as these conditions may represent underlying pathologies for the menstrual cycle disturbances<sup>5,7</sup> and sleep health may exacerbate these conditions.<sup>65–67</sup> Third, we restricted analyses to participants with <3 cycles of pregnancy attempt at study entry to mitigate potential reverse causation bias, wherein increased pregnancy attempt time may cause sleep disturbances.<sup>68</sup> Fourth, we adjusted for recency of COVID-19 vaccination relative to reporting of menstrual cycle characteristics ( $\leq 60$  days from reported LMP). Previous research,<sup>69</sup> including PRESTO,<sup>70</sup> found that COVID-19 vaccination may slightly affect menstrual function and that these disruptions resolve

within one to two cycles after vaccination.<sup>71</sup> In all sensitivity analyses, we present sleep duration in three categories (<7, 7–8.9, and  $\geq$ 9 hours/day) to reduce potential for sparse data bias.<sup>72</sup>

We used fully conditional specification methods to multiply impute missing exposure, outcome, and covariate data.<sup>73–75</sup> We generated 20 imputed datasets and statistically combined regression estimates using Rubin’s rules.<sup>75</sup> Sleep duration was missing for 1.0%, 1.4%, and 1.9% in the first, second, and third intervals, respectively. PSQI component score missingness ranged from 0.8% to 9.7%. Outcome missingness ranged from 1.5–4.7%, 1.9–3.1%, and 0.2–1.7% in the first, second, and third intervals, respectively. Covariate missingness ranged from 0% (*e.g.*, age) to 8.1% (any night work in the past month). We performed all analyses using SAS version 9.4 (SAS Institute, Cary, NC).

### 3.3 RESULTS

Of the 1,984 participants who contributed 3,366 analytic intervals, 20.5% reported <7 hours/day and 6.0% reported  $\geq$ 9 hours/day of sleep during the previous month in their first completed interval (Table 3.1). Forty-six percent of participants met criteria for poor sleep quality.

Prevalence of menstrual cycle disturbances was consistent across intervals (Table 3.2). In descending order, prevalence of menstrual cycle disturbances in the cohort was 22.9% for irregular cycles, 17.5% for intermenstrual bleeding, 15.7% for heavy flow volume, 10.0% for long cycle length, 5.4% for prolonged bleed length, 4.1% for

dysmenorrhea, and 4.0% for short cycle length. Forty percent of participants met the criteria for AUB.

Participants who slept <7 hours/day or had poor sleep quality had lower education and annual household income and were more likely to be non-Hispanic Black, report night and/or rotating shift work, smoke cigarettes, and use cannabis compared to those who slept 7–8.9 hours/day or had good sleep quality (Table 3.1). These participants were also more likely to have a BMI  $\geq 30$  kg/m<sup>2</sup>, be parous, be diagnosed with depression and/or anxiety, and currently use psychotropic medications. Participants with worse sleep health reported lower physical activity and higher MDI and PSS-10 scores and caffeine intake. Participants who reported short sleep duration consistently had poor sleep quality.

Short sleep duration (<7 hours/day) was generally associated with increased risk of menstrual cycle disturbances (Table 3.3). Compared with 8–8.9 hours/day, we observed the strongest effect estimates for short cycle length (RR=1.98, 95% CI: 0.93, 4.20), dysmenorrhea (RR=1.80, 95% CI: 0.52, 6.16), and prolonged bleed length (RR=1.64, 95% CI: 0.70, 3.84), though there was some imprecision in results. We also observed positive associations of short sleep duration (<7 vs. 8–8.9 hours/day) with heavy flow volume (RR=1.35, 95% CI: 0.75, 2.45) and long cycle length (RR=1.19, 95% CI: 0.71, 2.01). Short sleep duration was not appreciably associated with increased risk of irregular cycles (RR=0.86, 95% CI: 0.55, 1.35), intermenstrual bleeding (RR=0.78, 95% CI: 0.46, 1.31), or AUB (RR=0.96, 95% CI: 0.63, 1.48).

Poor sleep quality (PSQI global score >5 vs.  $\leq 5$ ) was positively associated with most menstrual cycle disturbances (Table 3.4), including dysmenorrhea (RR=2.15, 95%

CI: 0.91, 5.08) and prolonged bleed length (RR=1.63, 95% CI: 0.71, 3.74), and was also positively associated with heavy flow volume (RR=1.29, 95% CI: 0.80, 2.08) and short (RR=1.31, 95% CI: 0.69, 2.48) and long (RR=1.40, 95% CI: 0.90, 2.18) cycle lengths. Similar to short sleep duration, poor sleep quality was not markedly associated with risk of irregular cycles (RR=1.01, 95% CI: 0.72, 1.41), intermenstrual bleeding (RR=0.86, 95% CI: 0.58, 1.26), and AUB (RR=1.07, 95% CI: 0.80, 1.43). Restricted cubic splines of the continuous PSQI global score were generally consistent with these findings (Figures 3.5), with the exception of AUB, which was positively associated with greater PSQI global score. Additionally, PSQI global score was inversely associated with risk of irregular cycles until a score of 8, after which it was positively associated with risk (Figure 3.5).

After further excluding participants who reported the menstrual cycle disturbance outcomes at PRESTO baseline, results were generally consistent with primary analyses (Tables 3.5, 3.6). However, short sleep duration was no longer appreciably associated with heavy flow volume (RR=1.04, 95% CI: 0.59, 1.84). Conversely, poor sleep quality was associated with increased risk of AUB (RR=1.31, 95% CI: 0.91, 1.88), as opposed to the null finding in primary analyses.

Exclusion of participants with a history of benign gynecologic conditions did not materially affect most findings (Tables 3.7, 3.8). Among those without a history of benign gynecologic conditions, poor sleep quality was associated with increased risk of irregular cycles (RR=1.25, 95% CI: 0.87, 1.78), but not associated with short cycle length (RR=1.05, 95% CI: 0.53, 2.09).

Among participants with <3 cycles of attempt at study entry, some RRs for short sleep duration were attenuated (Table 3.9, 3.10). Notably, we found null associations of short sleep duration with long cycle length (RR=0.96, 95% CI: 0.48, 1.89) and dysmenorrhea (RR=0.91, 95% CI: 0.29, 2.91).

Adjustment for recency of COVID-19 vaccination did not affect study estimates (Tables 3.11, 3.12), indicating little confounding effect of COVID-19 vaccination in our data.

### **3.4 DISCUSSION**

In this North American prospective cohort study of non-contracepting pregnancy planners, short sleep duration and poor sleep quality were associated with increased risks of most menstrual cycle disturbances, most notably short and long cycle length, prolonged bleed length, heavy flow volume, and dysmenorrhea. Poor sleep quality was also associated with increased risk of irregular cycles and AUB in restricted cubic spline analyses. We observed the strongest associations for both sleep duration and quality with dysmenorrhea and prolonged bleed length, though estimates were imprecise.

Our findings were mostly consistent with previous cross-sectional studies, although we are able to better establish temporality between sleep and menstrual cycle disturbances. In agreement with the literature,<sup>45,48</sup> we identified associations between short sleep duration, short and long cycle length, and heavy flow volume. Additionally, we found that poor sleep quality was associated with increased risk of dysmenorrhea, short cycle length, prolonged bleed length, and cycle irregularity, which aligns with prior

literature.<sup>45,46,49</sup> However, we found an inverse association between short sleep duration and risk of irregular cycles, which differs from positive relationships previously reported.<sup>43–47</sup> Notably, we also found associations of short sleep duration with prolonged bleed length and dysmenorrhea, and poor sleep quality with long cycle length and abnormal flow volume—findings that have not been previously reported.

There are several explanations for inconsistencies in findings related to short sleep duration and cycle irregularity. Our study was the only prospective analysis, which improves validity of our results relative to cross-sectional studies. Also, there were differences across studies in exposure definition: while we defined short sleep duration as <7 hours/day, other positive studies defined short sleep duration as  $\leq 5$  hours/day.<sup>43,44,47</sup> It may be possible that shorter sleep durations in PRESTO were associated with cycle irregularity, but data were too limited to explore this possibility in categorical analyses. We observed this similar phenomenon in restricted cubic splines for PSQI global score and risk of irregular cycles (*i.e.*, poor sleep quality was associated with increased risk of irregular cycles at higher PSQI global score values). Similarly, discrepancies across studies may be attributable to outcome definitions; we defined our outcomes using FIGO guidelines, while most other studies did not.<sup>43–45,47</sup> Finally, we weighted our effect estimates for a variety of novel confounders (*e.g.*, night and/or rotating shift work, perceived stress, depressive symptoms) that were updated across intervals. Prior studies may have been affected by residual confounding to a greater degree.

We found null-to-inverse associations between poor sleep health and intermenstrual bleeding, which is counter to our hypothesis. As we conducted this study

in a cohort of pregnancy planners, report of intermenstrual bleeding may be indicative of implantation. Spotting or bleeding may occur due to successful attachment of the fertilized oocyte to the uterine lining, though the prevalence of implantation bleeding is unclear.<sup>76,77</sup> We have previously identified an association between sleep duration and fecundability (*i.e.*, time-to-pregnancy) in PRESTO.<sup>78</sup> Thus, reports of intermenstrual bleeding attributable to implantation may occur more frequently among those who conceive. Also, those who had better sleep health may have been more likely to conceive (*i.e.*, a competing risk). We mitigated outcome misclassification by including participants whose questionnaire completion date associated with their reported menstrual cycle characteristics preceded their pregnancy LMP; however, some participants who reported intermenstrual bleeding may have unknowingly experienced implantation bleeding, which could help explain our findings.

In sensitivity analyses, further exclusion of participants with the specific outcome of interest (*i.e.*, menstrual cycle disturbance) and restriction to participants with <3 cycles of pregnancy attempt at study entry attenuated some effects of short sleep duration, while we observed little effect of sensitivity analyses on associations of sleep quality with menstrual cycle characteristics. It may be possible that sleep quality has a greater impact on menstrual cycle disturbances than sleep duration. It has been postulated that, while both sleep quality and quantity are vital for health, poor sleep quality has a more deleterious impact on health.<sup>79</sup> Also, instead of average duration, deviation from optimal duration may be a better marker of sleep quantity's impact on health.<sup>79</sup> Prolonged pregnancy attempt time may be indicative of worse overall health.<sup>80,81</sup> As such, the extent

to which poor sleep health affects menstrual cycle disturbances may be stronger among participants who are already experiencing physiologic dysregulation.

Previous research identified an association between short sleep duration and reduced serum concentrations of reproductive hormones.<sup>50</sup> Our findings expand upon this work and provide support for exploring the underlying biologic mechanism linking poor sleep health to menstrual cycle disturbances through endocrine dysfunction. Sleep duration is associated with reproductive hormone synthesis and function.<sup>50</sup> Reproductive hormones are regulated via endogenous circadian rhythms and routine sleep-wake cycles.<sup>17</sup> Sleep disruption alters routine hormonal fluctuations,<sup>17</sup> which, as a result, can influence the menstrual cycle through altered frequency and timing of ovulation.<sup>22,27</sup>

Sleep is restorative for pain<sup>82-84</sup> and inflammation,<sup>85,86</sup> which are hallmark physiological responses throughout the menstrual cycle.<sup>87,88</sup> Prostaglandins, hormone-like lipids found in the uterus, are inflammatory mediators.<sup>89</sup> Secretion of prostaglandins cause uterine contraction during menstruation.<sup>30</sup> Elevated prostaglandin levels in the endometrium may result in greater uterine contractility, which can influence the frequency and amount of menstrual blood and tissue excreted,<sup>90</sup> as well as greater menstrual pain.<sup>91</sup> Estradiol and progesterone exert anti-inflammatory effects through regulation of prostaglandins in the uterus.<sup>30,92</sup> As such, poor sleep may induce menstrual cycle disturbances through inhibition of estradiol and progesterone production and, subsequently, dysregulated uterine prostaglandins.

Our use of a prospective design allowed us to better establish temporality between exposure and outcome and avoid reverse causation bias, which is a major limitation of

most of the prior literature. We used a multidimensional approach to examine sleep health, and utilized a validated instrument to measure multiple sleep exposures.<sup>52</sup> Similarly, we defined menstrual cycle disturbance outcomes using FIGO definitions,<sup>5</sup> which improves comparability of study findings to clinical standards. There is strong accuracy of self-reported menstrual data in PRESTO,<sup>51,93</sup> and sexually active individuals are more likely to accurately report their cycle data.<sup>94</sup> We have previously shown in PRESTO that report of LMP dates, cycle length, and bleed length on the baseline questionnaire are generally similar to prospectively reported data from a menstrual charting app.<sup>51,93</sup> We performed our analyses in multiple follow-up intervals, which allowed for assessment of the effect throughout pregnancy attempt time. Finally, our study design was guided by directed acyclic graphs and we utilized inverse probability weights to account for confounding and inclusion in the analytic sample. We performed our analyses in a cohort of people who may become pregnant and subsequently do not complete follow-up questionnaires, and continuation in later intervals may be associated with worse menstrual function. We avoided biases due to differential continuation through inverse probability weights.

Our reliance on self-reported sleep data introduces potential for exposure misclassification. We expect this misclassification to be non-differential, as we measured sleep health prior to outcome assessment. In previous research in PRESTO comparing self-reported sleep duration to Fitbit-measured actigraphy, we found that participants often overestimate their sleep (Pearson correlation coefficient=0.42).<sup>95</sup> This discordance would result in an expected bias towards the null, indicating that true findings may be

stronger than those reported. Second, our study results were imprecise due to use of inverse probability weights<sup>64</sup> and low prevalence of some outcomes. Third, PRESTO is comprised of mostly non-Hispanic White participants with high education and income, which may limit generalizability. Finally, we cannot entirely rule out the potential for reverse causation bias. Because we did not collect daily sleep and menstrual cycle data, and were not able to identify the first occurrence of each menstrual cycle disturbance, we were not entirely able to ensure that sleep was not influenced by menstrual cycle disturbances. We attempted to minimize this bias by excluding those without each menstrual cycle disturbance at the start of each analytic interval.

In summary, we found that poor sleep health, specifically short sleep duration and poor sleep quality, was associated with increased risk of menstrual cycle disturbances, including short and long cycle length, prolonged bleed length, heavy flow volume, and dysmenorrhea. Poor sleep quality was also associated with increased risk of irregular cycles and AUB. As improved interventions are needed to address menstrual cycle disturbances,<sup>96</sup> especially in the primary care setting, these results provide insight into innovative intervention opportunities and have important clinical implications for reproductive and gynecologic health.

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### 3.6 TABLES AND FIGURES

**Table 3.1** Characteristics of study participants by sleep health among 1,984 participants, Pregnancy Study Online, 2020–2024

Characteristic <sup>b</sup>	Sleep duration (hours/day) <sup>a</sup>				PSQI global score <sup>a</sup>	
	<7	7–7.9	8–8.9	≥9	≤5	>5
Number of participants	407	560	897	120	1063	921
<b>Baseline questionnaire</b>						
Age (years), mean	32.3	31.4	31.4	30.5	31.5	31.6
Race/ethnicity, %						
Asian, non-Hispanic	3.4	2.3	2.3	2.1	2.8	2.1
Black, non-Hispanic	6.0	3.6	1.0	2.8	1.8	4.1
White, non-Hispanic	81.0	83.2	85.6	84.0	84.6	82.8
Other race, non-Hispanic <sup>c</sup>	3.5	4.3	4.8	5.9	4.7	4.3
Hispanic/Latina/Latinx	6.2	6.7	6.4	5.3	6.1	6.7
Education, %						
<College degree	25.1	13.1	11.5	16.8	11.4	19.2
College degree	31.4	32.0	31.1	28.0	30.9	32.0
Graduate school	43.5	54.9	57.4	55.2	57.7	48.8
Annual household income (USD), %						
<50,000	14.5	9.3	7.9	15.5	8.6	11.7
50,000–99,999	30.2	27.3	26.6	29.0	25.5	30.7
100,000–149,999	32.3	30.1	31.2	23.3	30.2	31.4
≥150,000	23.0	33.2	34.2	32.2	35.8	26.2
Geographic region, %						
Northeastern U.S.	18.9	20.4	20.9	21.0	21.4	19.0
Southern U.S.	26.5	23.8	22.5	23.0	23.0	24.8

Midwestern U.S.	27.7	20.1	20.9	23.9	21.0	23.4
Western U.S.	13.8	21.7	22.0	22.3	20.9	19.4
Canada	13.1	14.1	13.7	9.8	13.7	13.4
Currently employed, %	87.8	90.5	91.8	78.1	91.2	88.2
Job hours/week, mean <sup>d</sup>	34.8	35.0	35.5	29.9	35.6	34.0
Night work in the past month, %	16.2	12.0	8.1	14.3	8.7	14.3
Rotating shift work in the past month, %	14.6	13.6	10.8	9.9	11.0	14.1
Body mass index (kg/m <sup>2</sup> ), %						
<18.5	1.6	1.5	2.2	0.9	2.4	1.1
18.5–24.9	30.7	41.4	46.4	44.1	48.1	34.0
25.0–29.9	25.9	28.0	25.5	21.2	26.2	25.6
≥30.0	41.7	29.1	25.9	33.8	23.3	39.4
Parous, %	38.1	29.8	21.8	24.7	24.7	30.8
Time since last birth (years), mean <sup>e</sup>	4.1	3.5	3.9	5.6	4.0	4.0
Last method of contraception, hormonal, %	33.3	36.2	31.2	30.4	32.3	34.0
History of diagnosed uterine leiomyomata, %	4.5	3.4	3.3	3.4	3.3	3.9
History of diagnosed polycystic ovary syndrome, %	12.8	8.4	8.9	10.8	7.6	12.1
History of diagnosed endometriosis, %	4.6	2.2	2.7	4.6	2.4	3.9
<b>Follow-up questionnaire<sup>a</sup></b>						
Physical activity (MET hours/week), mean	27.7	32.3	29.7	25.8	31.4	28.0
Current cigarette smoking, %	6.6	3.6	2.6	4.4	2.6	5.1
Cannabis use in the previous 2 months, %	17.5	10.9	12.6	12.9	11.2	15.1
Alcohol intake (drinks/week), mean	2.4	2.6	2.5	2.2	2.4	2.5
Current caffeine intake (mg/day), mean	123.2	114.7	110.6	100.5	108.2	120.7
Current sugar-sweetened beverage intake (drinks/week), mean	2.6	2.0	1.5	2.7	1.5	2.5
History of diagnosed anxiety, %	34.3	31.1	29.9	39.0	26.2	38.2

History of diagnosed depression, %	33.3	27.3	26.3	40.4	23.0	35.3
Current psychotropic medication use, %	22.0	16.8	18.5	29.4	14.3	25.2
MDI score, mean	15.3	11.3	9.8	10.7	8.3	15.1
PSS-10 score, mean	18.1	16.6	15.5	15.8	14.6	18.4
Sleep duration (hours/day), % <sup>a</sup>						
<7					3.6	39.8
7–7.9					23.3	34.1
8–8.9					65.1	22.4
≥9					8.0	3.8
PSQI global score, % <sup>a</sup>						
≤5	9.6	44.3	77.3	72.2		
>5	90.4	55.7	22.7	27.8		

kg: kilograms; m: meters; MDI: Major Depression Inventory; MET: metabolic equivalent of task; mg: milligrams; PSQI: Pittsburgh Sleep Quality Index; PSS: Perceived Stress Scale; U.S.: United States; USD: United States dollars.

<sup>a</sup> Reported at the start of the first completed interval in the first imputed dataset.

<sup>b</sup> All characteristics, except age, are standardized to the age distribution of the cohort at baseline.

<sup>c</sup> Other race, non-Hispanic includes mixed race, American Indian/Alaskan Native, and self-identified other.

<sup>d</sup> Job hours/week includes participants who are unemployed, who have a value of 0 hours/week.

<sup>e</sup> Among parous participants.

**Table 3.2** Prevalence of menstrual cycle disturbances at each questionnaire, Pregnancy Study Online, 2020–2024

Menstrual cycle disturbance	2-month questionnaire N (%)	4-month questionnaire N (%)	6-month questionnaire N (%)
Irregular cycles	414 (23.0%)	221 (22.8%)	137 (23.0%)
Short cycle length (<24 days)	71 (4.0%)	37 (3.8%)	26 (4.4%)
Long cycle length (>38 days)	153 (8.5%)	108 (11.1%)	77 (12.9%)
Prolonged bleed length ( $\geq 7$ days) <sup>a</sup>	70 (5.9%)	43 (5.8%)	17 (3.5%)
Abnormal flow volume (moderate/heavy, heavy) <sup>a</sup>	183 (15.5%)	121 (16.3%)	72 (15.0%)
Intermenstrual bleeding <sup>a</sup>	215 (18.2%)	126 (17.0%)	80 (16.7%)
Dysmenorrhea <sup>a</sup>	43 (3.6%)	37 (5.0%)	19 (4.0%)
Abnormal uterine bleeding <sup>a</sup>	475 (40.3%)	304 (40.9%)	193 (40.2%)

<sup>a</sup> Calculated among participants who completed follow-up questionnaires on or after May 27, 2021 (due to addition of item to PRESTO questionnaires).

**Table 3.3** Association between sleep duration and menstrual cycle disturbances, Pregnancy Study Online, 2020–2024

	<b>Sleep duration (hours/day)</b>			
	<b>&lt;7</b>	<b>7–7.9</b>	<b>8–8.9</b>	<b>≥9</b>
<b>Irregular cycles</b>				
Number of events (%) <sup>a</sup>	66 (12.5%)	72 (10.0%)	125 (10.6%)	16 (9.6%)
Crude RR (95% CI)	1.18 (0.89, 1.58)	0.98 (0.75, 1.29)	<i>Reference</i>	0.88 (0.53, 1.43)
Weighted model 1 RR (95% CI) <sup>b</sup>	0.99 (0.70, 1.39)	0.89 (0.66, 1.19)	<i>Reference</i>	0.68 (0.38, 1.22)
Weighted model 2 RR (95% CI) <sup>c</sup>	0.86 (0.55, 1.35)	0.75 (0.51, 1.12)	<i>Reference</i>	0.54 (0.27, 1.08)
<b>Short cycle length (&lt;24 days)<sup>d</sup></b>				
Number of events (%) <sup>a</sup>	26 (4.4%)	30 (3.6%)	41 (3.1%)	8 (4.4%)
Crude RR (95% CI)	1.47 (0.89, 2.42)	1.08 (0.66, 1.75)	<i>Reference</i>	1.45 (0.69, 3.05)
Weighted model 1 RR (95% CI) <sup>b</sup>	1.24 (0.69, 2.22)	0.85 (0.50, 1.45)	<i>Reference</i>	0.71 (0.31, 1.65)
Weighted model 2 RR (95% CI) <sup>c</sup>	1.98 (0.93, 4.20)	0.93 (0.47, 1.87)	<i>Reference</i>	0.58 (0.24, 1.38)
<b>Long cycle length (&gt;38 days)<sup>e</sup></b>				
Number of events (%) <sup>a</sup>	49 (8.2%)	62 (7.5%)	76 (5.8%)	9 (5.1%)
Crude RR (95% CI)	1.38 (0.97, 1.95)	1.21 (0.88, 1.67)	<i>Reference</i>	0.70 (0.33, 1.49)
Weighted model 1 RR (95% CI) <sup>b</sup>	1.25 (0.84, 1.86)	1.06 (0.75, 1.49)	<i>Reference</i>	0.90 (0.36, 2.30)
Weighted model 2 RR (95% CI) <sup>c</sup>	1.19 (0.71, 2.01)	1.06 (0.66, 1.70)	<i>Reference</i>	1.45 (0.44, 4.80)
<b>Prolonged bleed length (≥7 days)</b>				
Number of events (%) <sup>a</sup>	20 (4.2%)	14 (2.2%)	29 (2.9%)	4 (2.8%)
Crude RR (95% CI)	1.67 (0.94, 2.95)	0.76 (0.39, 1.46)	<i>Reference</i>	0.78 (0.24, 2.55)
Weighted model 1 RR (95% CI) <sup>b</sup>	1.79 (0.91, 3.54)	0.61 (0.30, 1.25)	<i>Reference</i>	1.15 (0.31, 4.29)
Weighted model 2 RR (95% CI) <sup>c</sup>	1.64 (0.70, 3.84)	0.69 (0.25, 1.88)	<i>Reference</i>	0.94 (0.22, 4.05)
<b>Abnormal flow volume (moderate/heavy, heavy)<sup>f</sup></b>				
Number of events (%) <sup>a</sup>	48 (16.5%)	45 (11.3%)	60 (9.9%)	9 (12.2%)
Crude RR (95% CI)	1.66 (1.16, 2.37)	1.14 (0.79, 1.64)	<i>Reference</i>	1.14 (0.57, 2.26)
Weighted model 1 RR (95% CI) <sup>b</sup>	1.22 (0.79, 1.86)	0.87 (0.58, 1.30)	<i>Reference</i>	0.88 (0.40, 1.94)
Weighted model 2 RR (95% CI) <sup>c</sup>	1.35 (0.75, 2.45)	0.69 (0.41, 1.17)	<i>Reference</i>	0.68 (0.27, 1.70)
<b>Intermenstrual bleeding</b>				

Number of events (%) <sup>a</sup>	34 (8.5%)	67 (11.9%)	99 (11.0%)	16 (13.0%)
Crude RR (95% CI)	0.83 (0.57, 1.19)	1.08 (0.80, 1.45)	<i>Reference</i>	1.02 (0.59, 1.75)
Weighted model 1 RR (95% CI) <sup>b</sup>	0.90 (0.59, 1.36)	1.01 (0.74, 1.40)	<i>Reference</i>	0.74 (0.36, 1.53)
Weighted model 2 RR (95% CI) <sup>c</sup>	0.78 (0.46, 1.31)	0.78 (0.51, 1.19)	<i>Reference</i>	0.57 (0.23, 1.46)
<b>Dysmenorrhea</b>				
Number of events (%) <sup>a</sup>	14 (2.9%)	12 (1.8%)	28 (2.9%)	10 (6.7%)
Crude RR (95% CI)	1.00 (0.53, 1.90)	0.66 (0.34, 1.28)	<i>Reference</i>	2.42 (1.19, 4.92)
Weighted model 1 RR (95% CI) <sup>b</sup>	0.67 (0.31, 1.42)	0.76 (0.37, 1.57)	<i>Reference</i>	2.89 (1.35, 6.21)
Weighted model 2 RR (95% CI) <sup>c</sup>	1.80 (0.52, 6.16)	0.77 (0.28, 2.08)	<i>Reference</i>	2.42 (0.98, 6.01)
<b>Abnormal uterine bleeding<sup>g</sup></b>				
Number of events (%) <sup>a</sup>	67 (24.8%)	84 (20.5%)	115 (17.4%)	17 (18.5%)
Crude RR (95% CI)	1.46 (1.11, 1.91)	1.19 (0.92, 1.53)	<i>Reference</i>	1.03 (0.65, 1.63)
Weighted model 1 RR (95% CI) <sup>b</sup>	1.18 (0.86, 1.63)	0.98 (0.74, 1.29)	<i>Reference</i>	1.00 (0.55, 1.79)
Weighted model 2 RR (95% CI) <sup>c</sup>	0.96 (0.63, 1.48)	0.83 (0.56, 1.22)	<i>Reference</i>	0.97 (0.40, 2.36)

CI: confidence interval; RR: risk ratio.

<sup>a</sup> Calculated in the first imputed dataset.

<sup>b</sup> Applies inverse probability weighting for exposure and loss to follow-up. The following confounders were included in inverse probability weighing for exposure: from baseline questionnaire – age, household income, education, employment status, job hours per week, any night work in the previous month, any shift work in the previous month, body mass index, parity, time since last birth, and last method of contraception; from follow-up questionnaire – physical activity, cannabis use, alcohol intake, perceived stress, depressive symptoms, psychotropic medication usage, caffeine intake, and sugar-sweetened beverage intake.

<sup>c</sup> Applies inverse probability weighting for exposure, loss to follow-up, and sampling.

<sup>d</sup> Excludes participants with long cycle length. Reference group is participants with regular cycle length (24–38 days).

<sup>e</sup> Excludes participants with short cycle length. Reference group is participants with regular cycle length (24–38 days).

<sup>f</sup> Excludes participants with light flow volume. Reference group is participants with moderate flow volume.

<sup>g</sup> Abnormal uterine bleeding is a composite variable for any report of irregular menstrual cycles, short or long cycle length, prolonged bleed length, and/or moderate/heavy or heavy flow volume.

**Table 3.4** Association between sleep quality and menstrual cycle disturbances, Pregnancy Study Online, 2020–2024

	Sleep quality (PSQI global score)	
	≤5	>5
<b>Irregular cycles</b>		
Number of events (%) <sup>a</sup>	147 (9.9%)	132 (11.9%)
Crude RR (95% CI)	<i>Reference</i>	1.25 (0.99, 1.56)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	1.11 (0.86, 1.44)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	1.01 (0.72, 1.41)
<b>Short cycle length (&lt;24 days)<sup>d</sup></b>		
Number of events (%) <sup>a</sup>	61 (3.7%)	44 (3.5%)
Crude RR (95% CI)	<i>Reference</i>	0.98 (0.66, 1.45)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	0.85 (0.54, 1.34)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	1.31 (0.69, 2.48)
<b>Long cycle length (&gt;38 days)<sup>e</sup></b>		
Number of events (%) <sup>a</sup>	89 (5.5%)	107 (8.3%)
Crude RR (95% CI)	<i>Reference</i>	1.60 (1.20, 2.14)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	1.41 (1.00, 1.99)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	1.40 (0.90, 2.18)
<b>Prolonged bleed length (≥7 days)</b>		
Number of events (%) <sup>a</sup>	29 (2.3%)	38 (3.8%)
Crude RR (95% CI)	<i>Reference</i>	1.87 (1.13, 3.10)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	1.40 (0.76, 2.59)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	1.63 (0.71, 3.74)
<b>Abnormal flow volume (moderate/heavy, heavy)<sup>f</sup></b>		
Number of events (%) <sup>a</sup>	69 (9.2%)	93 (15.1%)
Crude RR (95% CI)	<i>Reference</i>	1.69 (1.25, 2.29)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	1.32 (0.92, 1.90)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	1.29 (0.80, 2.08)

<b>Intermenstrual bleeding</b>		
Number of events (%) <sup>a</sup>	122 (10.7%)	94 (11.2%)
Crude RR (95% CI)	<i>Reference</i>	1.06 (0.82, 1.37)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	1.01 (0.75, 1.37)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	0.86 (0.58, 1.26)
<b>Dysmenorrhea</b>		
Number of events (%) <sup>a</sup>	28 (2.2%)	36 (3.6%)
Crude RR (95% CI)	<i>Reference</i>	2.42 (1.19, 4.92)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	2.89 (1.35, 6.21)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	2.42 (0.98, 6.01)
<b>Abnormal uterine bleeding<sup>g</sup></b>		
Number of events (%) <sup>a</sup>	145 (17.3%)	138 (23.3%)
Crude RR (95% CI)	<i>Reference</i>	1.38 (1.12, 1.71)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	1.15 (0.90, 1.47)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	1.07 (0.80, 1.43)

CI: confidence interval; PSQI: Pittsburgh Sleep Quality Index; RR: risk ratio.

<sup>a</sup> Calculated in the first imputed dataset.

<sup>b</sup> Applies inverse probability weighting for exposure and loss to follow-up. The following confounders were included in inverse probability weighting for exposure: from baseline questionnaire – age, household income, education, employment status, job hours per week, any night work in the previous month, any shift work in the previous month, body mass index, parity, time since last birth, and last method of contraception; from follow-up questionnaire – physical activity, cannabis use, alcohol intake, perceived stress, depressive symptoms, psychotropic medication usage, caffeine intake, and sugar-sweetened beverage intake.

<sup>c</sup> Applies inverse probability weighting for exposure, loss to follow-up, and sampling.

<sup>d</sup> Excludes participants with long cycle length. Reference group is participants with regular cycle length (24–38 days).

<sup>e</sup> Excludes participants with short cycle length. Reference group is participants with regular cycle length (24–38 days).

<sup>f</sup> Excludes participants with light flow volume. Reference group is participants with moderate flow volume.

<sup>g</sup> Abnormal uterine bleeding is a composite variable for any report of irregular menstrual cycles, short or long cycle length, prolonged bleed length, and/or moderate/heavy or heavy flow volume.

**Table 3.5** Association between sleep duration and menstrual cycle disturbances, excluding participants with given menstrual disturbance at baseline questionnaire, Pregnancy Study Online, 2020–2024

	Sleep duration (hours/day)		
	<7	7–8.9	≥9
<b>Irregular cycles</b>			
Number of events (%) <sup>a</sup>	56 (11.6%)	162 (9.1%)	15 (9.7%)
Crude RR (95% CI)	1.23 (0.91, 1.65)	<i>Reference</i>	1.00 (0.60, 1.68)
Weighted model 1 RR (95% CI) <sup>b</sup>	1.02 (0.72, 1.45)	<i>Reference</i>	0.81 (0.44, 1.50)
Weighted model 2 RR (95% CI) <sup>c</sup>	0.85 (0.54, 1.32)	<i>Reference</i>	0.76 (0.37, 1.53)
<b>Short cycle length (&lt;24 days)<sup>d</sup></b>			
Number of events (%) <sup>a</sup>	24 (4.1%)	69 (3.3%)	8 (4.5%)
Crude RR (95% CI)	1.36 (0.85, 2.19)	<i>Reference</i>	1.44 (0.71, 2.95)
Weighted model 1 RR (95% CI) <sup>b</sup>	1.30 (0.76, 2.24)	<i>Reference</i>	0.79 (0.35, 1.77)
Weighted model 2 RR (95% CI) <sup>c</sup>	2.10 (1.04, 4.25)	<i>Reference</i>	0.62 (0.27, 1.41)
<b>Long cycle length (&gt;38 days)<sup>e</sup></b>			
Number of events (%) <sup>a</sup>	48 (8.1%)	136 (6.4%)	9 (5.1%)
Crude RR (95% CI)	1.26 (0.91, 1.74)	<i>Reference</i>	0.65 (0.31, 1.37)
Weighted model 1 RR (95% CI) <sup>b</sup>	1.17 (0.81, 1.70)	<i>Reference</i>	0.87 (0.34, 2.18)
Weighted model 2 RR (95% CI) <sup>c</sup>	1.15 (0.70, 1.89)	<i>Reference</i>	1.43 (0.43, 4.73)
<b>Prolonged bleed length (≥7 days)</b>			
Number of events (%) <sup>a</sup>	17 (3.7%)	36 (2.2%)	3 (2.1%)
Crude RR (95% CI)	1.84 (1.04, 3.28)	<i>Reference</i>	0.68 (0.17, 2.82)
Weighted model 1 RR (95% CI) <sup>b</sup>	2.01 (1.01, 4.03)	<i>Reference</i>	1.34 (0.30, 6.06)
Weighted model 2 RR (95% CI) <sup>c</sup>	1.65 (0.67, 4.04)	<i>Reference</i>	0.94 (0.18, 5.02)
<b>Abnormal flow volume (moderate/heavy, heavy)<sup>f</sup></b>			
Number of events (%) <sup>a</sup>	30 (12.6%)	64 (7.7%)	3 (5.0%)
Crude RR (95% CI)	1.58 (1.05, 2.39)	<i>Reference</i>	0.68 (0.23, 2.04)
Weighted model 1 RR (95% CI) <sup>b</sup>	1.29 (0.78, 2.13)	<i>Reference</i>	0.32 (0.10, 1.05)
Weighted model 2 RR (95% CI) <sup>c</sup>	1.04 (0.59, 1.84)	<i>Reference</i>	0.23 (0.06, 0.85)

<b>Dysmenorrhea</b>			
Number of events (%) <sup>a</sup>	9 (2.0%)	29 (1.8%)	8 (5.7%)
Crude RR (95% CI)	1.03 (0.48, 2.23)	<i>Reference</i>	3.18 (1.47, 6.89)
Weighted model 1 RR (95% CI) <sup>b</sup>	0.69 (0.27, 1.74)	<i>Reference</i>	3.58 (1.57, 8.16)
Weighted model 2 RR (95% CI) <sup>c</sup>	1.65 (0.31, 8.79)	<i>Reference</i>	2.86 (1.10, 7.46)
<b>Abnormal uterine bleeding<sup>g</sup></b>			
Number of events (%) <sup>a</sup>	47 (21.6%)	132 (15.3%)	9 (12.2%)
Crude RR (95% CI)	1.41 (1.04, 1.91)	<i>Reference</i>	0.75 (0.39, 1.45)
Weighted model 1 RR (95% CI) <sup>b</sup>	1.23 (0.86, 1.75)	<i>Reference</i>	0.75 (0.34, 1.66)
Weighted model 2 RR (95% CI) <sup>c</sup>	0.99 (0.63, 1.56)	<i>Reference</i>	0.76 (0.33, 1.78)

CI: confidence interval; RR: risk ratio.

<sup>a</sup> Calculated in the first imputed dataset.

<sup>b</sup> Applies inverse probability weighting for exposure and loss to follow-up. The following confounders were included in inverse probability weighting for exposure: from baseline questionnaire – age, household income, education, employment status, job hours per week, any night work in the previous month, any shift work in the previous month, body mass index, parity, time since last birth, and last method of contraception; from follow-up questionnaire – physical activity, cannabis use, alcohol intake, perceived stress, depressive symptoms, psychotropic medication usage, caffeine intake, and sugar-sweetened beverage intake.

<sup>c</sup> Applies inverse probability weighting for exposure, loss to follow-up, and sampling.

<sup>d</sup> Excludes participants with long cycle length. Reference group is participants with regular cycle length (24–38 days).

<sup>e</sup> Excludes participants with short cycle length. Reference group is participants with regular cycle length (24–38 days).

<sup>f</sup> Excludes participants with light flow volume. Reference group is participants with moderate flow volume.

<sup>g</sup> Abnormal uterine bleeding is a composite variable for any report of irregular menstrual cycles, short or long cycle length, prolonged bleed length, and/or moderate/heavy or heavy flow volume.

**Table 3.6** Association between sleep quality and menstrual cycle disturbances, excluding participants with given menstrual disturbance at baseline questionnaire, Pregnancy Study Online, 2020–2024

	Sleep quality (PSQI global score)	
	≤5	>5
<b>Irregular cycles</b>		
Number of events (%) <sup>a</sup>	127 (9.1%)	106 (10.5%)
Crude RR (95% CI)	<i>Reference</i>	1.22 (0.94, 1.57)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	1.11 (0.83, 1.49)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	0.97 (0.67, 1.41)
<b>Short cycle length (&lt;24 days)<sup>d</sup></b>		
Number of events (%) <sup>a</sup>	61 (3.8%)	40 (3.2%)
Crude RR (95% CI)	<i>Reference</i>	0.89 (0.59, 1.33)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	0.81 (0.51, 1.29)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	1.26 (0.66, 2.39)
<b>Long cycle length (&gt;38 days)<sup>e</sup></b>		
Number of events (%) <sup>a</sup>	87 (5.4%)	106 (8.3%)
Crude RR (95% CI)	<i>Reference</i>	1.63 (1.23, 2.17)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	1.40 (0.99, 1.97)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	1.37 (0.87, 2.14)
<b>Prolonged bleed length (≥7 days)</b>		
Number of events (%) <sup>a</sup>	23 (1.8%)	33 (3.5%)
Crude RR (95% CI)	<i>Reference</i>	2.02 (1.16, 3.54)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	1.39 (0.70, 2.75)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	1.57 (0.58, 4.25)
<b>Abnormal flow volume (moderate/heavy, heavy)<sup>f</sup></b>		
Number of events (%) <sup>a</sup>	38 (6.0%)	59 (11.9%)
Crude RR (95% CI)	<i>Reference</i>	2.01 (1.34, 3.02)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	1.70 (1.03, 2.79)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	1.36 (0.70, 2.65)

<b>Dysmenorrhea</b>		
Number of events (%) <sup>a</sup>	23 (1.8%)	23 (2.4%)
Crude RR (95% CI)	<i>Reference</i>	1.30 (0.73, 2.31)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	1.01 (0.52, 1.98)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	1.70 (0.63, 4.57)
<b>Abnormal uterine bleeding<sup>g</sup></b>		
Number of events (%) <sup>a</sup>	93 (13.5%)	95 (20.6%)
Crude RR (95% CI)	<i>Reference</i>	1.60 (1.23, 2.09)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	1.46 (1.08, 1.97)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	1.31 (0.91, 1.88)

CI: confidence interval; PSQI: Pittsburgh Sleep Quality Index; RR: risk ratio.

<sup>a</sup> Calculated in the first imputed dataset.

<sup>b</sup> Applies inverse probability weighting for exposure and loss to follow-up. The following confounders were included in inverse probability weighting for exposure: from baseline questionnaire – age, household income, education, employment status, job hours per week, any night work in the previous month, any shift work in the previous month, body mass index, parity, time since last birth, and last method of contraception; from follow-up questionnaire – physical activity, cannabis use, alcohol intake, perceived stress, depressive symptoms, psychotropic medication usage, caffeine intake, and sugar-sweetened beverage intake.

<sup>c</sup> Applies inverse probability weighting for exposure, loss to follow-up, and sampling.

<sup>d</sup> Excludes participants with long cycle length. Reference group is participants with regular cycle length (24–38 days).

<sup>e</sup> Excludes participants with short cycle length. Reference group is participants with regular cycle length (24–38 days).

<sup>f</sup> Excludes participants with light flow volume. Reference group is participants with moderate flow volume.

<sup>g</sup> Abnormal uterine bleeding is a composite variable for any report of irregular menstrual cycles, short or long cycle length, prolonged bleed length, and/or moderate/heavy or heavy flow volume.

**Table 3.7** Association between sleep duration and menstrual cycle disturbances, excluding participants with diagnosis of benign gynecologic conditions (*i.e.*, uterine leiomyomata, endometriosis, and/or polycystic ovary syndrome) at baseline questionnaire, Pregnancy Study Online, 2020–2024

	Sleep duration (hours/day)		
	<7	7–8.9	≥9
<b>Irregular cycles</b>			
Number of events (%) <sup>a</sup>	53 (12.2%)	165 (9.8%)	13 (9.0%)
Crude RR (95% CI)	1.23 (0.91, 1.66)	<i>Reference</i>	0.93 (0.55, 1.55)
Weighted model 1 RR (95% CI) <sup>b</sup>	1.01 (0.70, 1.46)	<i>Reference</i>	0.70 (0.38, 1.29)
Weighted model 2 RR (95% CI) <sup>c</sup>	1.07 (0.66, 1.75)	<i>Reference</i>	0.64 (0.31, 1.31)
<b>Short cycle length (&lt;24 days)<sup>d</sup></b>			
Number of events (%) <sup>a</sup>	21 (4.3%)	60 (3.2%)	7 (4.5%)
Crude RR (95% CI)	1.47 (0.89, 2.43)	<i>Reference</i>	1.48 (0.69, 3.18)
Weighted model 1 RR (95% CI) <sup>b</sup>	1.44 (0.82, 2.54)	<i>Reference</i>	0.87 (0.36, 2.07)
Weighted model 2 RR (95% CI) <sup>c</sup>	1.99 (0.90, 4.41)	<i>Reference</i>	0.68 (0.28, 1.66)
<b>Long cycle length (&gt;38 days)<sup>e</sup></b>			
Number of events (%) <sup>a</sup>	35 (7.2%)	108 (5.7%)	7 (4.6%)
Crude RR (95% CI)	1.24 (0.85, 1.82)	<i>Reference</i>	0.65 (0.28, 1.52)
Weighted model 1 RR (95% CI) <sup>b</sup>	1.20 (0.78, 1.86)	<i>Reference</i>	1.00 (0.35, 2.87)
Weighted model 2 RR (95% CI) <sup>c</sup>	1.17 (0.64, 2.14)	<i>Reference</i>	1.70 (0.46, 6.35)
<b>Prolonged bleed length (≥7 days)</b>			
Number of events (%) <sup>a</sup>	16 (4.1%)	35 (2.4%)	3 (2.5%)
Crude RR (95% CI)	1.82 (1.02, 3.26)	<i>Reference</i>	0.73 (0.18, 3.00)
Weighted model 1 RR (95% CI) <sup>b</sup>	2.03 (1.01, 4.10)	<i>Reference</i>	0.81 (0.18, 3.63)
Weighted model 2 RR (95% CI) <sup>c</sup>	1.75 (0.71, 4.33)	<i>Reference</i>	0.63 (0.12, 3.39)
<b>Abnormal flow volume (moderate/heavy, heavy)<sup>f</sup></b>			
Number of events (%) <sup>a</sup>	32 (13.3%)	86 (9.6%)	7 (10.8%)
Crude RR (95% CI)	1.40 (0.95, 2.04)	<i>Reference</i>	1.01 (0.46, 2.20)
Weighted model 1 RR (95% CI) <sup>b</sup>	1.23 (0.79, 1.94)	<i>Reference</i>	0.90 (0.37, 2.17)

Weighted model 2 RR (95% CI) <sup>c</sup>	1.55 (0.80, 2.99)	<i>Reference</i>	0.74 (0.26, 2.11)
<b>Intermenstrual bleeding</b>			
Number of events (%) <sup>a</sup>	29 (8.9%)	138 (10.8%)	13 (13.0%)
Crude RR (95% CI)	0.86 (0.59, 1.25)	<i>Reference</i>	1.18 (0.69, 2.02)
Weighted model 1 RR (95% CI) <sup>b</sup>	0.99 (0.65, 1.51)	<i>Reference</i>	0.90 (0.44, 1.85)
Weighted model 2 RR (95% CI) <sup>c</sup>	1.02 (0.60, 1.72)	<i>Reference</i>	0.86 (0.36, 2.03)
<b>Dysmenorrhea</b>			
Number of events (%) <sup>a</sup>	11 (2.8%)	30 (2.1%)	8 (6.4%)
Crude RR (95% CI)	1.28 (0.64, 2.59)	<i>Reference</i>	3.11 (1.44, 6.70)
Weighted model 1 RR (95% CI) <sup>b</sup>	0.84 (0.37, 1.91)	<i>Reference</i>	3.20 (1.41, 7.25)
Weighted model 2 RR (95% CI) <sup>c</sup>	1.88 (0.39, 9.02)	<i>Reference</i>	2.81 (1.07, 7.33)
<b>Abnormal uterine bleeding<sup>g</sup></b>			
Number of events (%) <sup>a</sup>	53 (22.2%)	176 (17.8%)	13 (15.9%)
Crude RR (95% CI)	1.27 (0.96, 1.67)	<i>Reference</i>	0.90 (0.54, 1.48)
Weighted model 1 RR (95% CI) <sup>b</sup>	1.12 (0.81, 1.56)	<i>Reference</i>	0.89 (0.46, 1.71)
Weighted model 2 RR (95% CI) <sup>c</sup>	0.99 (0.63, 1.53)	<i>Reference</i>	1.07 (0.39, 2.93)

CI: confidence interval; RR: risk ratio.

<sup>a</sup> Calculated in the first imputed dataset.

<sup>b</sup> Applies inverse probability weighting for exposure and loss to follow-up. The following confounders were included in inverse probability weighting for exposure: from baseline questionnaire – age, household income, education, employment status, job hours per week, any night work in the previous month, any shift work in the previous month, body mass index, parity, time since last birth, and last method of contraception; from follow-up questionnaire – physical activity, cannabis use, alcohol intake, perceived stress, depressive symptoms, psychotropic medication usage, caffeine intake, and sugar-sweetened beverage intake.

<sup>c</sup> Applies inverse probability weighting for exposure, loss to follow-up, and sampling.

<sup>d</sup> Excludes participants with long cycle length. Reference group is participants with regular cycle length (24–38 days).

<sup>e</sup> Excludes participants with short cycle length. Reference group is participants with regular cycle length (24–38 days).

<sup>f</sup> Excludes participants with light flow volume. Reference group is participants with moderate flow volume.

<sup>g</sup> Abnormal uterine bleeding is a composite variable for any report of irregular menstrual cycles, short or long cycle length, prolonged bleed length, and/or moderate/heavy or heavy flow volume.

**Table 3.8** Association between sleep quality and menstrual cycle disturbances, excluding participants with diagnosis of benign gynecologic conditions (*i.e.*, uterine leiomyomata, endometriosis, and/or polycystic ovary syndrome) at baseline questionnaire, Pregnancy Study Online, 2020–2024

	Sleep quality (PSQI global score)	
	≤5	>5
<b>Irregular cycles</b>		
Number of events (%) <sup>a</sup>	123 (9.3%)	108 (11.4%)
Crude RR (95% CI)	<i>Reference</i>	1.28 (1.00, 1.65)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	1.21 (0.91, 1.62)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	1.25 (0.87, 1.78)
<b>Short cycle length (&lt;24 days)<sup>d</sup></b>		
Number of events (%) <sup>a</sup>	52 (3.6%)	36 (3.4%)
Crude RR (95% CI)	<i>Reference</i>	0.98 (0.64, 1.51)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	0.82 (0.50, 1.35)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	1.05 (0.53, 2.09)
<b>Long cycle length (&gt;38 days)<sup>e</sup></b>		
Number of events (%) <sup>a</sup>	72 (5.0%)	78 (7.2%)
Crude RR (95% CI)	<i>Reference</i>	1.54 (1.11, 2.13)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	1.44 (0.96, 2.14)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	1.33 (0.78, 2.27)
<b>Prolonged bleed length (≥7 days)</b>		
Number of events (%) <sup>a</sup>	26 (2.3%)	28 (3.4%)
Crude RR (95% CI)	<i>Reference</i>	1.60 (0.92, 2.78)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	1.20 (0.60, 2.37)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	1.27 (0.48, 3.36)
<b>Abnormal flow volume (moderate/heavy, heavy)<sup>f</sup></b>		
Number of events (%) <sup>a</sup>	56 (8.1%)	69 (13.4%)
Crude RR (95% CI)	<i>Reference</i>	1.70 (1.20, 2.41)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	1.34 (0.90, 2.01)

Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	1.32 (0.77, 2.26)
<b>Intermenstrual bleeding</b>		
Number of events (%) <sup>a</sup>	104 (10.4%)	76 (10.7%)
Crude RR (95% CI)	<i>Reference</i>	1.02 (0.77, 1.36)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	1.01 (0.73, 1.40)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	0.86 (0.56, 1.33)
<b>Dysmenorrhea</b>		
Number of events (%) <sup>a</sup>	20 (1.7%)	29 (3.5%)
Crude RR (95% CI)	<i>Reference</i>	1.94 (1.10, 3.42)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	1.73 (0.91, 3.28)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	2.74 (1.04, 7.19)
<b>Abnormal uterine bleeding<sup>g</sup></b>		
Number of events (%) <sup>a</sup>	128 (16.5%)	114 (21.5%)
Crude RR (95% CI)	<i>Reference</i>	1.35 (1.07, 1.70)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	1.13 (0.87, 1.48)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	1.08 (0.78, 1.49)

CI: confidence interval; PSQI: Pittsburgh Sleep Quality Index; RR: risk ratio.

<sup>a</sup> Calculated in the first imputed dataset.

<sup>b</sup> Applies inverse probability weighting for exposure and loss to follow-up. The following confounders were included in inverse probability weighting for exposure: from baseline questionnaire – age, household income, education, employment status, job hours per week, any night work in the previous month, any shift work in the previous month, body mass index, parity, time since last birth, and last method of contraception; from follow-up questionnaire – physical activity, cannabis use, alcohol intake, perceived stress, depressive symptoms, psychotropic medication usage, caffeine intake, and sugar-sweetened beverage intake.

<sup>c</sup> Applies inverse probability weighting for exposure, loss to follow-up, and sampling.

<sup>d</sup> Excludes participants with long cycle length. Reference group is participants with regular cycle length (24–38 days).

<sup>e</sup> Excludes participants with short cycle length. Reference group is participants with regular cycle length (24–38 days).

<sup>f</sup> Excludes participants with light flow volume. Reference group is participants with moderate flow volume.

<sup>g</sup> Abnormal uterine bleeding is a composite variable for any report of irregular menstrual cycles, short or long cycle length, prolonged bleed length, and/or moderate/heavy or heavy flow volume.

**Table 3.9** Association between sleep duration and menstrual cycle disturbances, restricted to participants with <3 cycles of attempt at study entry, Pregnancy Study Online, 2020–2024

	Sleep duration (hours/day)		
	<7	7–8.9	≥9
<b>Irregular cycles</b>			
Number of events (%) <sup>a</sup>	33 (11.5%)	135 (13.4%)	12 (15.8%)
Crude RR (95% CI)	0.84 (0.58, 1.21)	<i>Reference</i>	1.09 (0.63, 1.90)
Weighted model 1 RR (95% CI) <sup>b</sup>	0.61 (0.40, 0.94)	<i>Reference</i>	1.12 (0.59, 2.13)
Weighted model 2 RR (95% CI) <sup>c</sup>	0.43 (0.24, 0.75)	<i>Reference</i>	0.89 (0.41, 1.95)
<b>Short cycle length (&lt;24 days)<sup>d</sup></b>			
Number of events (%) <sup>a</sup>	14 (4.2%)	38 (3.2%)	5 (5.9%)
Crude RR (95% CI)	1.40 (0.76, 2.57)	<i>Reference</i>	1.94 (0.80, 4.71)
Weighted model 1 RR (95% CI) <sup>b</sup>	1.37 (0.70, 2.68)	<i>Reference</i>	1.14 (0.40, 3.23)
Weighted model 2 RR (95% CI) <sup>c</sup>	1.63 (0.72, 3.70)	<i>Reference</i>	1.06 (0.38, 2.97)
<b>Long cycle length (&gt;38 days)<sup>e</sup></b>			
Number of events (%) <sup>a</sup>	30 (9.1%)	85 (7.1%)	5 (6.3%)
Crude RR (95% CI)	1.24 (0.83, 1.86)	<i>Reference</i>	0.67 (0.24, 1.89)
Weighted model 1 RR (95% CI) <sup>b</sup>	1.09 (0.69, 1.74)	<i>Reference</i>	0.73 (0.24, 2.21)
Weighted model 2 RR (95% CI) <sup>c</sup>	0.96 (0.48, 1.89)	<i>Reference</i>	0.85 (0.24, 2.95)
<b>Prolonged bleed length (≥7 days)</b>			
Number of events (%) <sup>a</sup>	11 (4.2%)	24 (2.5%)	3 (4.3%)
Crude RR (95% CI)	1.68 (0.83, 3.39)	<i>Reference</i>	1.17 (0.28, 4.85)
Weighted model 1 RR (95% CI) <sup>b</sup>	2.19 (0.98, 4.90)	<i>Reference</i>	2.62 (0.59, 11.57)
Weighted model 2 RR (95% CI) <sup>c</sup>	2.11 (0.70, 6.32)	<i>Reference</i>	2.38 (0.44, 12.77)
<b>Abnormal flow volume (moderate/heavy, heavy)<sup>f</sup></b>			
Number of events (%) <sup>a</sup>	29 (19.0%)	60 (10.5%)	4 (11.8%)
Crude RR (95% CI)	1.81 (1.21, 2.70)	<i>Reference</i>	0.85 (0.28, 2.57)
Weighted model 1 RR (95% CI) <sup>b</sup>	1.37 (0.83, 2.26)	<i>Reference</i>	0.91 (0.27, 3.14)
Weighted model 2 RR (95% CI) <sup>c</sup>	1.89 (0.92, 3.85)	<i>Reference</i>	0.89 (0.23, 3.50)

<b>Intermenstrual bleeding</b>			
Number of events (%) <sup>a</sup>	16 (6.8%)	88 (10.4%)	8 (13.3%)
Crude RR (95% CI)	0.68 (0.41, 1.13)	<i>Reference</i>	0.98 (0.44, 2.18)
Weighted model 1 RR (95% CI) <sup>b</sup>	0.92 (0.54, 1.57)	<i>Reference</i>	0.70 (0.26, 1.93)
Weighted model 2 RR (95% CI) <sup>c</sup>	0.88 (0.43, 1.79)	<i>Reference</i>	0.65 (0.18, 2.33)
<b>Dysmenorrhea</b>			
Number of events (%) <sup>a</sup>	6 (2.2%)	19 (1.9%)	3 (4.2%)
Crude RR (95% CI)	1.10 (0.45, 2.72)	<i>Reference</i>	2.18 (0.66, 7.22)
Weighted model 1 RR (95% CI) <sup>b</sup>	0.65 (0.22, 1.94)	<i>Reference</i>	3.25 (0.94, 11.31)
Weighted model 2 RR (95% CI) <sup>c</sup>	0.91 (0.29, 2.91)	<i>Reference</i>	3.50 (0.92, 13.30)
<b>Abnormal uterine bleeding<sup>g</sup></b>			
Number of events (%) <sup>a</sup>	34 (23.6%)	114 (19.4%)	10 (24.4%)
Crude RR (95% CI)	1.20 (0.86, 1.68)	<i>Reference</i>	1.14 (0.63, 2.07)
Weighted model 1 RR (95% CI) <sup>b</sup>	0.96 (0.63, 1.47)	<i>Reference</i>	1.34 (0.69, 2.59)
Weighted model 2 RR (95% CI) <sup>c</sup>	0.71 (0.42, 1.20)	<i>Reference</i>	1.07 (0.45, 2.55)

CI: confidence interval; RR: risk ratio.

<sup>a</sup> Calculated in the first imputed dataset.

<sup>b</sup> Applies inverse probability weighting for exposure and loss to follow-up. The following confounders were included in inverse probability weighting for exposure: from baseline questionnaire – age, household income, education, employment status, job hours per week, any night work in the previous month, any shift work in the previous month, body mass index, parity, time since last birth, and last method of contraception; from follow-up questionnaire – physical activity, cannabis use, alcohol intake, perceived stress, depressive symptoms, psychotropic medication usage, caffeine intake, and sugar-sweetened beverage intake.

<sup>c</sup> Applies inverse probability weighting for exposure, loss to follow-up, and sampling.

<sup>d</sup> Excludes participants with long cycle length. Reference group is participants with regular cycle length (24–38 days).

<sup>e</sup> Excludes participants with short cycle length. Reference group is participants with regular cycle length (24–38 days).

<sup>f</sup> Excludes participants with light flow volume. Reference group is participants with moderate flow volume.

<sup>g</sup> Abnormal uterine bleeding is a composite variable for any report of irregular menstrual cycles, short or long cycle length, prolonged bleed length, and/or moderate/heavy or heavy flow volume.

**Table 3.10** Association between sleep quality and menstrual cycle disturbances, restricted to participants with <3 cycles of attempt at study entry, Pregnancy Study Online, 2020–2024

	Sleep quality (PSQI global score)	
	≤5	>5
<b>Irregular cycles</b>		
Number of events (%) <sup>a</sup>	105 (12.9%)	75 (13.4%)
Crude RR (95% CI)	<i>Reference</i>	1.08 (0.81, 1.44)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	0.94 (0.68, 1.31)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	0.74 (0.47, 1.16)
<b>Short cycle length (&lt;24 days)<sup>d</sup></b>		
Number of events (%) <sup>a</sup>	33 (3.5%)	24 (3.7%)
Crude RR (95% CI)	<i>Reference</i>	1.04 (0.62, 1.77)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	0.97 (0.53, 1.77)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	1.23 (0.59, 2.56)
<b>Long cycle length (&gt;38 days)<sup>e</sup></b>		
Number of events (%) <sup>a</sup>	57 (6.1%)	63 (9.4%)
Crude RR (95% CI)	<i>Reference</i>	1.63 (1.16, 2.31)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	1.56 (1.04, 2.35)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	1.37 (0.79, 2.35)
<b>Prolonged bleed length (≥7 days)</b>		
Number of events (%) <sup>a</sup>	17 (2.2%)	21 (4.1%)
Crude RR (95% CI)	<i>Reference</i>	1.90 (0.99, 3.64)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	2.04 (0.97, 4.29)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	2.11 (0.57, 7.76)
<b>Abnormal flow volume (moderate/heavy, heavy)<sup>f</sup></b>		
Number of events (%) <sup>a</sup>	44 (9.8%)	49 (15.8%)
Crude RR (95% CI)	<i>Reference</i>	1.66 (1.12, 2.46)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	1.25 (0.77, 2.02)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	1.24 (0.64, 2.42)

<b>Intermenstrual bleeding</b>		
Number of events (%) <sup>a</sup>	71 (10.3%)	41 (9.1%)
Crude RR (95% CI)	<i>Reference</i>	0.86 (0.59, 1.25)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	0.94 (0.61, 1.46)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	0.69 (0.38, 1.25)
<b>Dysmenorrhea</b>		
Number of events (%) <sup>a</sup>	14 (1.8%)	14 (2.6%)
Crude RR (95% CI)	<i>Reference</i>	1.41 (0.68, 2.93)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	1.17 (0.49, 2.78)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	1.49 (0.53, 4.24)
<b>Abnormal uterine bleeding<sup>g</sup></b>		
Number of events (%) <sup>a</sup>	88 (18.3%)	70 (24.0%)
Crude RR (95% CI)	<i>Reference</i>	1.35 (1.02, 1.79)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	1.08 (0.77, 1.50)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	0.90 (0.61, 1.34)

CI: confidence interval; PSQI: Pittsburgh Sleep Quality Index; RR: risk ratio.

<sup>a</sup> Calculated in the first imputed dataset.

<sup>b</sup> Applies inverse probability weighting for exposure and loss to follow-up. The following confounders were included in inverse probability weighting for exposure: from baseline questionnaire – age, household income, education, employment status, job hours per week, any night work in the previous month, any shift work in the previous month, body mass index, parity, time since last birth, and last method of contraception; from follow-up questionnaire – physical activity, cannabis use, alcohol intake, perceived stress, depressive symptoms, psychotropic medication usage, caffeine intake, and sugar-sweetened beverage intake.

<sup>c</sup> Applies inverse probability weighting for exposure, loss to follow-up, and sampling.

<sup>d</sup> Excludes participants with long cycle length. Reference group is participants with regular cycle length (24–38 days).

<sup>e</sup> Excludes participants with short cycle length. Reference group is participants with regular cycle length (24–38 days).

<sup>f</sup> Excludes participants with light flow volume. Reference group is participants with moderate flow volume.

<sup>g</sup> Abnormal uterine bleeding is a composite variable for any report of irregular menstrual cycles, short or long cycle length, prolonged bleed length, and/or moderate/heavy or heavy flow volume.

**Table 3.11** Association between sleep duration and menstrual cycle disturbances, further adjusted for recency of COVID-19 vaccination, Pregnancy Study Online, 2020–2024

	Sleep duration (hours/day)		
	<7	7–8.9	≥9
<b>Irregular cycles</b>			
Number of events (%) <sup>a</sup>	66 (12.5%)	197 (10.4%)	16 (9.6%)
Crude RR (95% CI)	1.19 (0.91, 1.56)	<i>Reference</i>	0.89 (0.55, 1.44)
Weighted model 1 RR (95% CI) <sup>b</sup>	1.02 (0.74, 1.40)	<i>Reference</i>	0.71 (0.40, 1.26)
Weighted model 2 RR (95% CI) <sup>c</sup>	0.94 (0.62, 1.45)	<i>Reference</i>	0.59 (0.30, 1.16)
<b>Short cycle length (&lt;24 days)<sup>d</sup></b>			
Number of events (%) <sup>a</sup>	26 (4.4%)	71 (3.3%)	8 (4.4%)
Crude RR (95% CI)	1.43 (0.92, 2.23)	<i>Reference</i>	1.42 (0.70, 2.89)
Weighted model 1 RR (95% CI) <sup>b</sup>	1.33 (0.79, 2.24)	<i>Reference</i>	0.78 (0.35, 1.74)
Weighted model 2 RR (95% CI) <sup>c</sup>	2.10 (1.06, 4.17)	<i>Reference</i>	0.61 (0.27, 1.39)
<b>Long cycle length (&gt;38 days)<sup>e</sup></b>			
Number of events (%) <sup>a</sup>	49 (8.2%)	138 (6.5%)	9 (5.1%)
Crude RR (95% CI)	1.24 (0.89, 1.71)	<i>Reference</i>	0.60 (0.27, 1.32)
Weighted model 1 RR (95% CI) <sup>b</sup>	1.20 (0.83, 1.72)	<i>Reference</i>	0.87 (0.35, 2.19)
Weighted model 2 RR (95% CI) <sup>c</sup>	1.14 (0.70, 1.86)	<i>Reference</i>	1.40 (0.43, 4.58)
<b>Prolonged bleed length (≥7 days)</b>			
Number of events (%) <sup>a</sup>	20 (4.2%)	43 (2.6%)	4 (2.8%)
Crude RR (95% CI)	1.85 (1.09, 3.14)	<i>Reference</i>	0.89 (0.28, 2.85)
Weighted model 1 RR (95% CI) <sup>b</sup>	2.14 (1.15, 3.98)	<i>Reference</i>	1.42 (0.40, 5.08)
Weighted model 2 RR (95% CI) <sup>c</sup>	1.87 (0.85, 4.13)	<i>Reference</i>	1.10 (0.27, 4.52)
<b>Abnormal flow volume (moderate/heavy, heavy)<sup>f</sup></b>			
Number of events (%) <sup>a</sup>	48 (16.5%)	105 (10.5%)	9 (12.2%)
Crude RR (95% CI)	1.56 (1.14, 2.15)	<i>Reference</i>	1.07 (0.55, 2.07)
Weighted model 1 RR (95% CI) <sup>b</sup>	1.34 (0.91, 1.97)	<i>Reference</i>	0.98 (0.46, 2.09)
Weighted model 2 RR (95% CI) <sup>c</sup>	1.60 (0.92, 2.79)	<i>Reference</i>	0.83 (0.34, 2.02)

<b>Intermenstrual bleeding</b>			
Number of events (%) <sup>a</sup>	34 (8.5%)	166 (11.4%)	16 (13.0%)
Crude RR (95% CI)	0.79 (0.56, 1.12)	<i>Reference</i>	0.98 (0.58, 1.65)
Weighted model 1 RR (95% CI) <sup>b</sup>	0.89 (0.60, 1.32)	<i>Reference</i>	0.73 (0.36, 1.50)
Weighted model 2 RR (95% CI) <sup>c</sup>	0.85 (0.52, 1.37)	<i>Reference</i>	0.62 (0.25, 1.54)
<b>Dysmenorrhea</b>			
Number of events (%) <sup>a</sup>	14 (2.9%)	40 (2.4%)	10 (6.7%)
Crude RR (95% CI)	1.14 (0.62, 2.11)	<i>Reference</i>	2.80 (1.42, 5.53)
Weighted model 1 RR (95% CI) <sup>b</sup>	0.73 (0.35, 1.49)	<i>Reference</i>	3.13 (1.52, 6.44)
Weighted model 2 RR (95% CI) <sup>c</sup>	1.98 (0.60, 6.56)	<i>Reference</i>	2.67 (1.16, 6.15)
<b>Abnormal uterine bleeding<sup>g</sup></b>			
Number of events (%) <sup>a</sup>	67 (24.8%)	199 (18.6%)	17 (18.5%)
Crude RR (95% CI)	1.36 (1.06, 1.74)	<i>Reference</i>	0.98 (0.63, 1.54)
Weighted model 1 RR (95% CI) <sup>b</sup>	1.20 (0.89, 1.61)	<i>Reference</i>	1.03 (0.59, 1.80)
Weighted model 2 RR (95% CI) <sup>c</sup>	1.05 (0.71, 1.56)	<i>Reference</i>	1.07 (0.45, 2.55)

CI: confidence interval; RR: risk ratio.

<sup>a</sup> Calculated in the first imputed dataset.

<sup>b</sup> Applies inverse probability weighting for exposure and loss to follow-up. The following confounders were included in inverse probability weighting for exposure: from baseline questionnaire – age, household income, education, employment status, job hours per week, any night work in the previous month, any shift work in the previous month, body mass index, parity, time since last birth, and last method of contraception; from follow-up questionnaire – physical activity, cannabis use, alcohol intake, perceived stress, depressive symptoms, psychotropic medication usage, caffeine intake, and sugar-sweetened beverage intake. Model further adjusted for recency of COVID-19 vaccination.

<sup>c</sup> Applies inverse probability weighting for exposure, loss to follow-up, and sampling. Model further adjusted for recency of COVID-19 vaccination.

<sup>d</sup> Excludes participants with long cycle length. Reference group is participants with regular cycle length (24–38 days).

<sup>e</sup> Excludes participants with short cycle length. Reference group is participants with regular cycle length (24–38 days).

<sup>f</sup> Excludes participants with light flow volume. Reference group is participants with moderate flow volume.

<sup>g</sup> Abnormal uterine bleeding is a composite variable for any report of irregular menstrual cycles, short or long cycle length, prolonged bleed length, and/or moderate/heavy or heavy flow volume.

**Table 3.12** Association between sleep quality and menstrual cycle disturbances, further adjusted for recency of COVID-19 vaccination, Pregnancy Study Online, 2020–2024

	Sleep quality (PSQI global score)	
	≤5	>5
<b>Irregular cycles</b>		
Number of events (%) <sup>a</sup>	147 (9.9%)	132 (11.9%)
Crude RR (95% CI)	<i>Reference</i>	1.25 (0.99, 1.56)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	1.13 (0.86, 1.47)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	1.01 (0.72, 1.43)
<b>Short cycle length (&lt;24 days)<sup>d</sup></b>		
Number of events (%) <sup>a</sup>	61 (3.7%)	44 (3.5%)
Crude RR (95% CI)	<i>Reference</i>	0.98 (0.66, 1.45)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	0.86 (0.55, 1.36)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	1.29 (0.69, 2.41)
<b>Long cycle length (&gt;38 days)<sup>e</sup></b>		
Number of events (%) <sup>a</sup>	89 (5.5%)	107 (8.3%)
Crude RR (95% CI)	<i>Reference</i>	1.60 (1.20, 2.14)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	1.40 (1.00, 1.97)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	1.35 (0.87, 2.09)
<b>Prolonged bleed length (≥7 days)</b>		
Number of events (%) <sup>a</sup>	29 (2.3%)	38 (3.8%)
Crude RR (95% CI)	<i>Reference</i>	1.87 (1.13, 3.10)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	1.37 (0.74, 2.54)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	1.51 (0.64, 3.59)
<b>Abnormal flow volume (moderate/heavy, heavy)<sup>f</sup></b>		
Number of events (%) <sup>a</sup>	69 (9.2%)	93 (15.1%)
Crude RR (95% CI)	<i>Reference</i>	1.69 (1.25, 2.29)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	1.32 (0.92, 1.90)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	1.27 (0.78, 2.07)

<b>Intermenstrual bleeding</b>		
Number of events (%) <sup>a</sup>	122 (10.7%)	94 (11.2%)
Crude RR (95% CI)	<i>Reference</i>	1.06 (0.82, 1.37)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	1.00 (0.74, 1.35)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	0.82 (0.56, 1.22)
<b>Dysmenorrhea</b>		
Number of events (%) <sup>a</sup>	28 (2.2%)	36 (3.6%)
Crude RR (95% CI)	<i>Reference</i>	1.60 (0.98, 2.62)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	1.27 (0.72, 2.23)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	2.14 (0.94, 4.84)
<b>Abnormal uterine bleeding<sup>g</sup></b>		
Number of events (%) <sup>a</sup>	145 (17.3%)	138 (23.3%)
Crude RR (95% CI)	<i>Reference</i>	1.38 (1.12, 1.71)
Weighted model 1 RR (95% CI) <sup>b</sup>	<i>Reference</i>	1.16 (0.91, 1.48)
Weighted model 2 RR (95% CI) <sup>c</sup>	<i>Reference</i>	1.07 (0.80, 1.43)

CI: confidence interval; PSQI: Pittsburgh Sleep Quality Index; RR: risk ratio.

<sup>a</sup> Calculated in the first imputed dataset.

<sup>b</sup> Applies inverse probability weighting for exposure and loss to follow-up. The following confounders were included in inverse probability weighing for exposure: from baseline questionnaire – age, household income, education, employment status, job hours per week, any night work in the previous month, any shift work in the previous month, body mass index, parity, time since last birth, and last method of contraception; from follow-up questionnaire – physical activity, cannabis use, alcohol intake, perceived stress, depressive symptoms, psychotropic medication usage, caffeine intake, and sugar-sweetened beverage intake. Model further adjusted for recency of COVID-19 vaccination.

<sup>c</sup> Applies inverse probability weighting for exposure, loss to follow-up, and sampling. Model further adjusted for recency of COVID-19 vaccination.

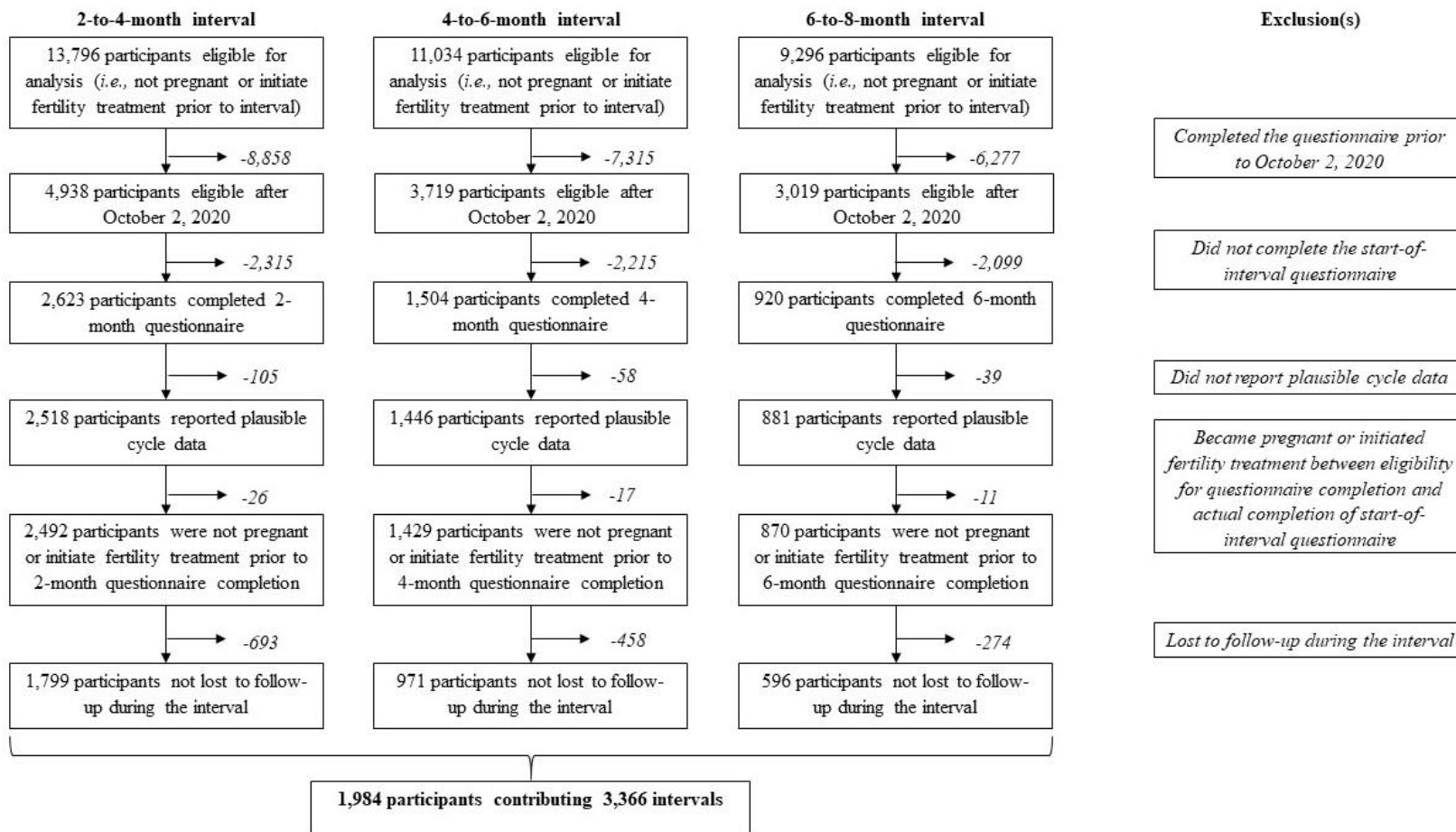
<sup>d</sup> Excludes participants with long cycle length. Reference group is participants with regular cycle length (24–38 days).

<sup>e</sup> Excludes participants with short cycle length. Reference group is participants with regular cycle length (24–38 days).

<sup>f</sup> Excludes participants with light flow volume. Reference group is participants with moderate flow volume.

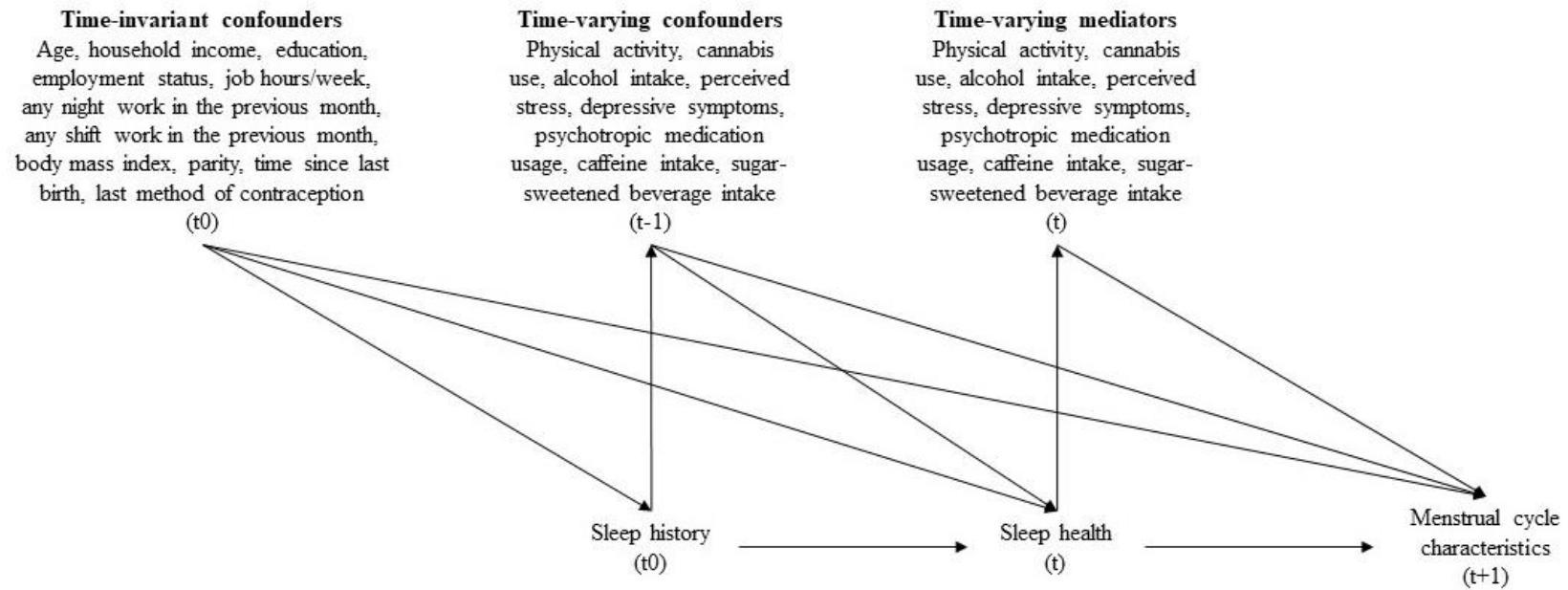
<sup>g</sup> Abnormal uterine bleeding is a composite variable for any report of irregular menstrual cycles, short or long cycle length, prolonged bleed length, and/or moderate/heavy or heavy flow volume.

**Figure 3.1** Study population and exclusions by analytic interval, Pregnancy Study Online, 2020–2024



**Figure 3.2** Simplified directed acyclic graph for confounding in the association of sleep health and menstrual cycle characteristics

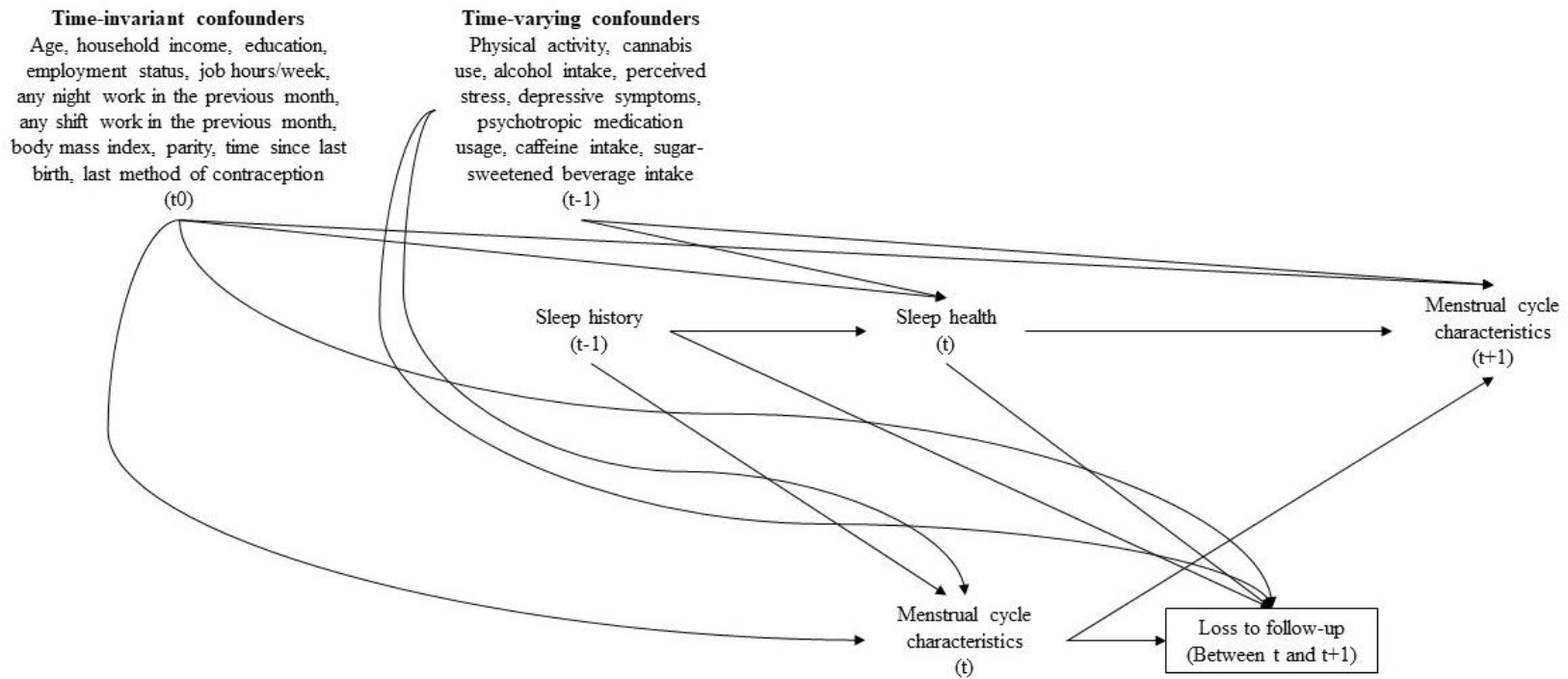
### Confounding DAG



DAG: directed acyclic graph.

**Figure 3.3** Simplified directed acyclic graph for loss to follow-up in the association of sleep health and menstrual cycle characteristics

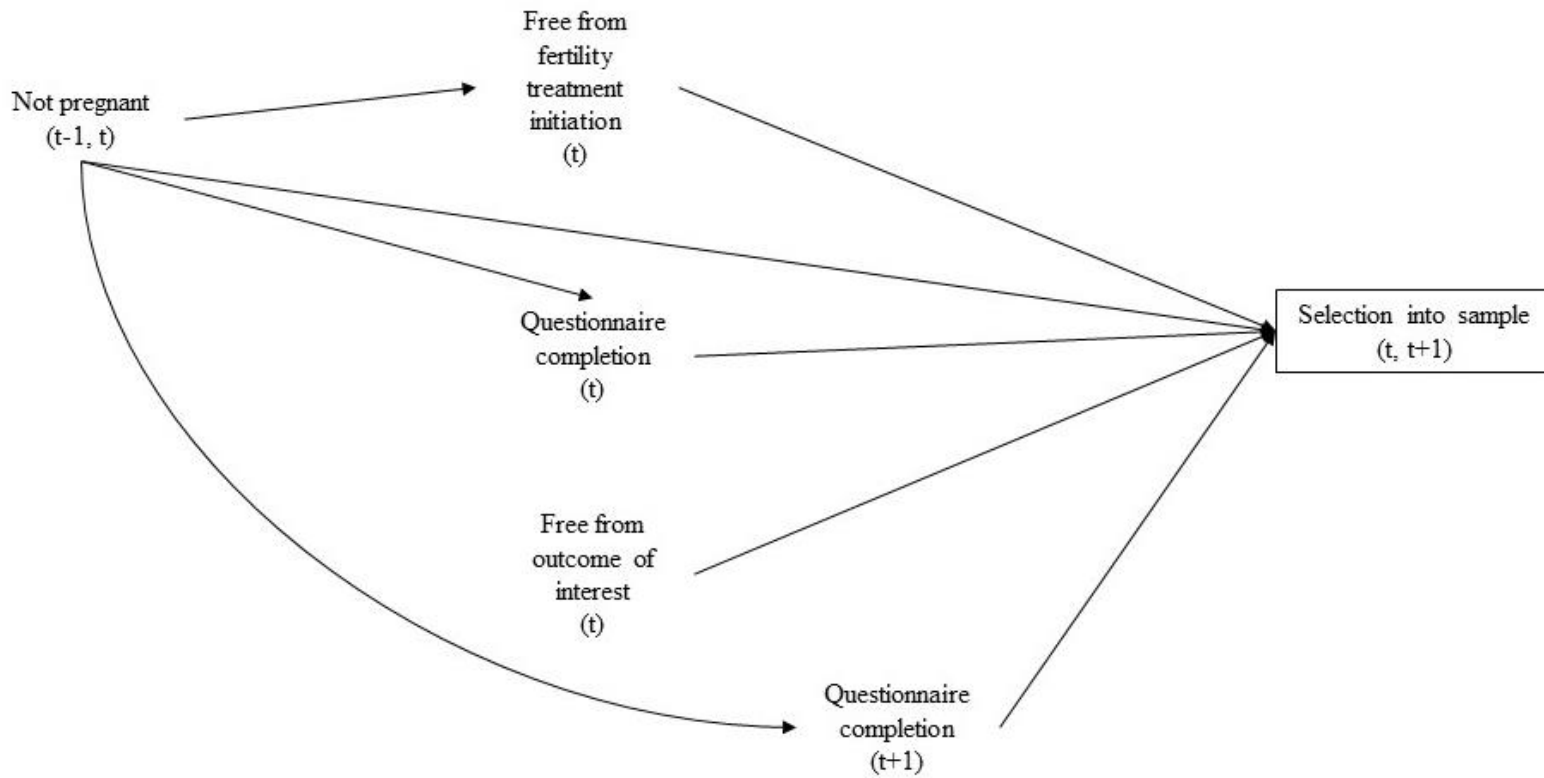
**Loss to follow-up DAG**



DAG: directed acyclic graph.

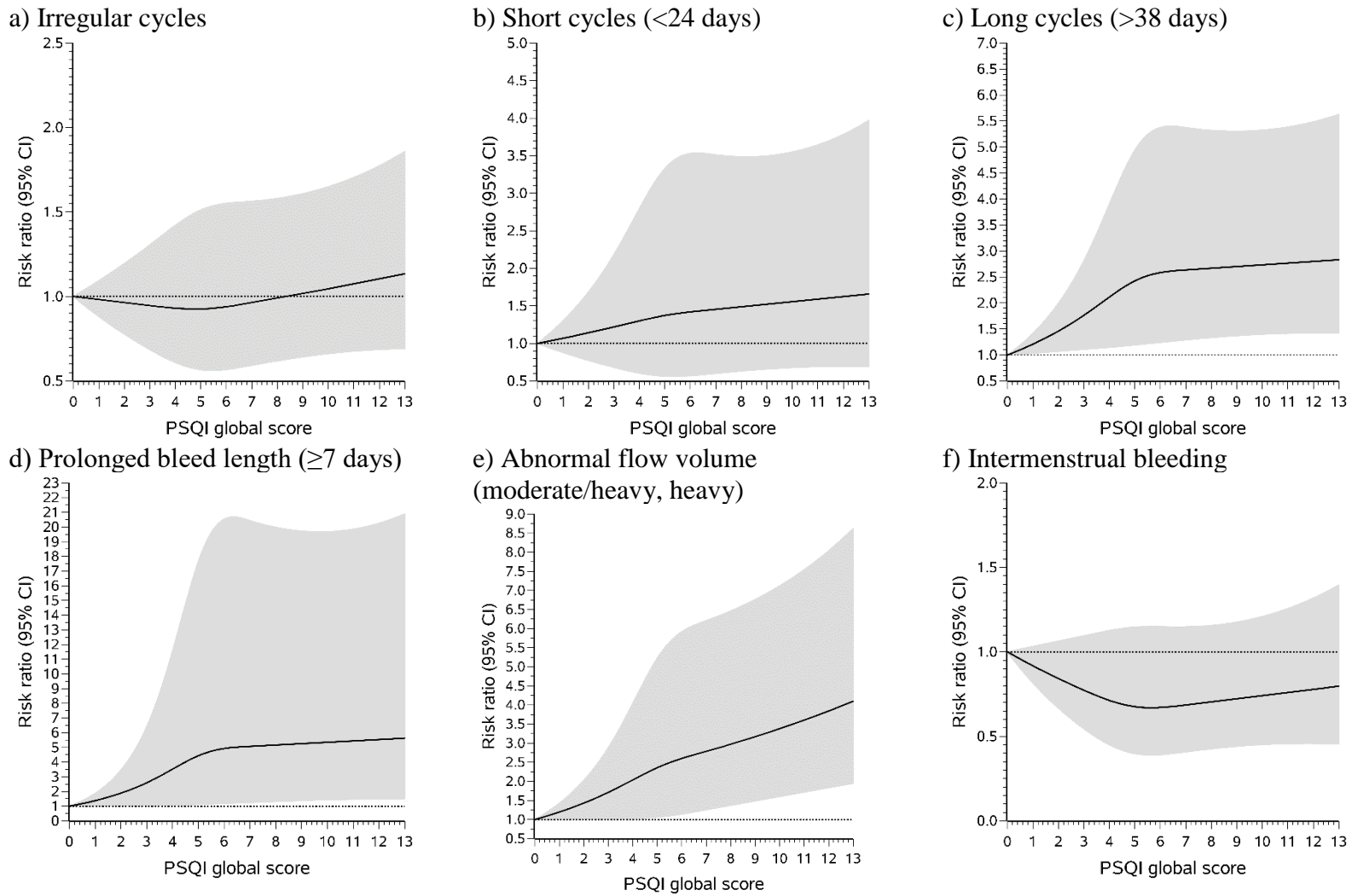
**Figure 3.4** Directed acyclic graph for sample selection in the association of sleep health and menstrual cycle characteristics

### Sample selection DAG

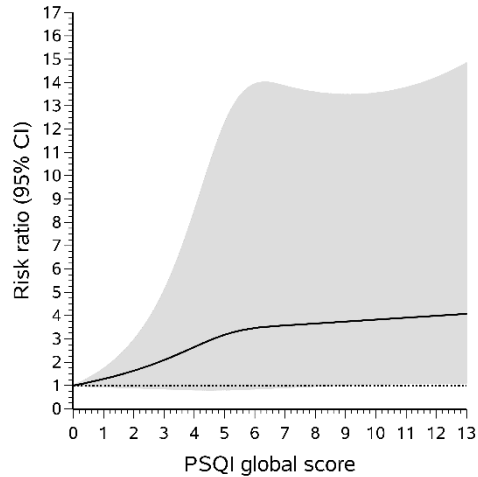


DAG: directed acyclic graph.

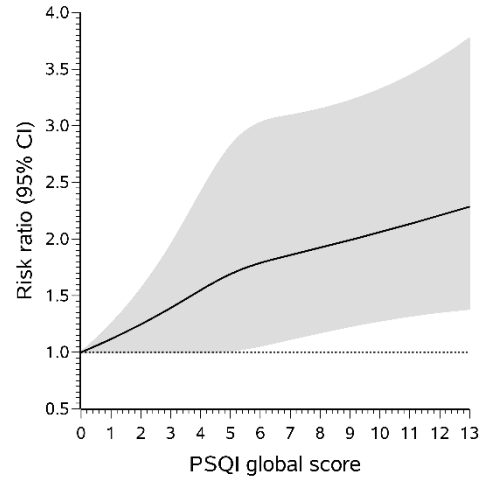
**Figure 3.5** Restricted cubic splines for the association of Pittsburgh Sleep Quality Index global score and menstrual cycle disturbances, Pregnancy Study Online, 2020–2024



g) Dysmenorrhea



h) Abnormal uterine bleeding



CI: confidence interval; PSQI: Pittsburgh Sleep Quality Index.

Restricted cubic splines weighted for probability of exposure (baseline questionnaire – age, household income, education, employment status, job hours per week, any night work in the previous month, any shift work in the previous month, body mass index, parity, time since last birth, and last method of contraception; from follow-up questionnaire – physical activity, cannabis use, alcohol intake, perceived stress, depressive symptoms, psychotropic medication usage, caffeine intake, and sugar-sweetened beverage intake), loss to follow-up, and sampling. For each spline, we set knots at the 25<sup>th</sup>, 50<sup>th</sup>, and 75<sup>th</sup> percentiles (PSQI global score: 3, 5, and 7). To avoid influence of extreme exposure values, we trimmed each spline at PSQI global score of 13.

## 4. A PRECONCEPTION COHORT STUDY OF WEARABLE-MEASURED SLEEP HEALTH AND FECUNDABILITY

### 4.1 INTRODUCTION

Infertility, defined as the inability to conceive after  $\geq 12$  months of unprotected intercourse,<sup>1</sup> affects up to 15% of couples.<sup>2-4</sup> Known or suspected risk factors for infertility include older age, obesity, poor diet, alcohol and tobacco consumption, exposure to environmental chemicals, and stress.<sup>5</sup> Infertility rates in the U.S. are higher among lower income and non-Hispanic Black individuals.<sup>6</sup> Infertility can impose significant emotional and financial burden on affected individuals. Assisted reproductive technology is expensive<sup>7-9</sup> and less accessible to low-income individuals and racial minorities.<sup>10,11</sup> Further, assisted reproductive technology is associated with adverse birth outcomes,<sup>12,13</sup> and infertility itself has been linked to greater long-term morbidity and mortality.<sup>14-19</sup> Thus, further research is necessary to identify modifiable risk factors for infertility.

Poor sleep health may influence fertility through several biologic pathways. Circadian rhythms, the endogenous 24-hour fluctuations of several human physiologic systems including the sleep-wake cycle, are vital for the maintenance and regulation of reproductive hormones,<sup>20,21</sup> and are involved in the luteinizing hormone surge, which affects the timing of ovulation.<sup>20</sup> Circadian disruption alters *CLOCK* gene expression and affects ovarian cyclicity, steroidogenesis, normal fluctuations of reproductive hormone levels and, ultimately, pregnancy initiation and maintenance.<sup>20,22-25</sup> For example, animal studies have shown that circadian disruption through altered light-dark cycles results in

irregular or absent estrus cycles in mice.<sup>26</sup> Stress due to poor sleep health can also activate the hypothalamic-pituitary-adrenal (HPA) axis and inhibit the hypothalamic-pituitary-gonadal (HPG) axis,<sup>23-25,27</sup> thereby increasing glucocorticoid concentrations and suppressing reproductive hormone production necessary for pregnancy.<sup>23,24</sup> In addition, sleep disturbances have been linked directly to altered concentrations of several reproductive hormones, including follicle-stimulating hormone, luteinizing hormone, and prolactin.<sup>28</sup> Prior epidemiologic research has identified associations between poor sleep health and impaired ovarian function, including menstrual cycle disturbances and premature ovarian failure.<sup>29</sup> Finally, inflammatory responses to poor sleep, including elevated interleukin-6 and C-reactive protein, may result in infertility.<sup>23,24,30</sup>

Several epidemiologic studies have found that poor sleep health is associated with reduced fertility among female adults,<sup>22,29,31-37</sup> however, these studies relied on self-reported sleep assessments, which may be prone to misclassification.<sup>38,39</sup> There has been limited investigation of the association between objective measures of sleep health and fertility,<sup>22</sup> with prior research focusing exclusively on in vitro fertilization populations.<sup>40-42</sup> In one prospective cohort study, a one-hour increase in actigraph-measured sleep duration prior to initiation of ovarian stimulation was associated with an increase of 1.5 retrieved oocytes.<sup>40</sup> Additionally, short sleep duration, later sleep midpoint, and later bedtime were associated with increased odds of uncompleted in vitro fertilization cycles.<sup>41</sup> In another prospective cohort study of individuals attending a tertiary fertility clinic, shorter sleep time was associated with implantation failure.<sup>42</sup> No study has examined the association between objective sleep health and spontaneous conception.

In an earlier publication from the present cohort, Pregnancy Study Online (PRESTO), female participants who reported trouble sleeping at night had reduced fecundability—the per-menstrual cycle probability of conception.<sup>37,43,44</sup> Self-reported short sleep duration was also associated with reduced fecundability, though the relationship was weaker.<sup>37</sup> Given that use of actigraphy increases the validity with which sleep health is measured,<sup>39</sup> we sought to build on our previous work in PRESTO by estimating prospectively the association of actigraph-measured preconception sleep health and fecundability among U.S. pregnancy planners. We hypothesized that shorter sleep duration, greater wake after sleep onset (WASO), reduced sleep maintenance efficiency, and greater midpoint variability during the preconception period would be associated with reduced fecundability.

## **4.2 METHODS**

### *4.2.1 Study population*

PRESTO is an Internet-based prospective preconception cohort study of couples attempting to conceive spontaneously.<sup>45</sup> Eligible participants were assigned female at birth, reside in the U.S. or Canada, are aged 21–45 years, are non-contracepting, and are not using fertility treatments. Recruitment began in 2013 and is ongoing. Participants completed a baseline questionnaire and follow-up questionnaires every eight weeks until pregnancy or for up to 12 months. At baseline, participants provided information on socio-demographics, lifestyle factors, medical history, and reproductive health. Follow-up questionnaires updated data on selected time-varying exposures, covariates, and

pregnancy status.

Beginning in February 2021, residents of the contiguous U.S. who reported  $\leq 6$  months of pregnancy attempt at study entry were invited to participate in a Fitbit (Google Fitbit, Inc., San Francisco, CA) substudy. The Boston University Medical Campus Institutional Review Board approved the study protocols and all participants provided informed consent.

#### *4.2.2 Exposure assessment: Objective sleep health*

Enrolled substudy participants were instructed to wear a study-issued Fitbit Inspire 2 (February 2021–February 2023) or Inspire 3 (February 2023–present) device on the wrist for 24 hours/day, except when showering, swimming, or charging the device, for a two-month period. After the two-month protocol, participants had the option to continue to wear the Fitbit device and elected whether to continue sharing sleep data with PRESTO. The validity of Fitbit for sleep actigraphy relative to polysomnography or electroencephalography (gold standard) has been documented in several studies,<sup>46–50</sup> indicating high sensitivity (range: 87–99%) and moderate specificity (range: 45–69%) in epoch-by-epoch sleep-wake analyses, although one study reported a specificity of 13%.<sup>50</sup>

Daily sleep data were shared with PRESTO by Fitbit. Each sleep assessment consisted of summary-level and stage-specific data. Summary-level output data included sleep period start (onset) and end (offset) clock times, sleep period duration, sleep onset latency, total time in bed, and time awake throughout the sleep period. Stage-specific data included clock time of each sleep stage (*i.e.*, light, deep, rapid eye movement), duration

of each stage, and periods of wake and restlessness. We extracted data from the Fitbit output files using Python version 3.9.6 (Python Software Foundation, Wilmington, DE).

For each day of sleep, we assessed four sleep health exposures: duration (hours/day), WASO (minutes), sleep maintenance efficiency (percentage), and midpoint variability (minutes). We selected these exposures because they allowed us to assess three domains of sleep, including duration, continuity (WASO, sleep maintenance efficiency), and regularity (midpoint variability).<sup>38</sup> Using output from the Fitbit, we calculated WASO as the sum of all wake periods between sleep onset and sleep offset, and sleep maintenance efficiency as the total sleep time divided by the total time between sleep onset and sleep offset, in line with other actigraphy studies.<sup>51–53</sup> We identified the midpoint of each sleep period using clock time, and assessed variability using a standard deviation approach from the mean midpoint.<sup>54</sup>

#### *4.2.3 Outcome assessment: Fecundability*

We estimated fecundability, the per-cycle probability of conception,<sup>43,44</sup> using data from baseline and follow-up questionnaires. We operationalized fecundability as time-to-pregnancy (TTP), measured as the total number of discrete menstrual cycles at risk of conception. At baseline, participants reported the number of menstrual cycles they had since they began attempting to conceive and their last menstrual period (LMP) date. At each follow-up, participants reported their LMP dates since their last completed questionnaire. We used these responses to derive dates of each menstrual cycle under observation,<sup>55</sup> and further estimated the follicular phase of each cycle. Among individuals

with average menstrual cycle lengths (approximately 28 days), the fertile window typically falls in the six days prior to, and including, the day of ovulation (*i.e.*, day 14).<sup>56,57</sup> In the present analysis, we considered the follicular phase of each cycle as the etiologically relevant exposure window for conception. We followed participants from their baseline LMP through their LMP associated with pregnancy (including fetal loss) or a censoring event, including fertility treatment initiation or no longer attempting to conceive. Participants who reported a pregnancy were asked to report the date and method of pregnancy confirmation (*e.g.*, positive at-home pregnancy test, blood or urine test by a physician, ultrasound).

#### 4.2.4 Covariate assessment

We collected covariate data on baseline and follow-up questionnaires. Participants reported information on socio-demographics, lifestyle factors, reproductive and medical histories, mental health, and stress. We calculated body mass index (BMI) as self-reported weight (kilograms) divided by height (meters) squared. We assessed physical activity using metabolic equivalent of task (MET) hours/week by multiplying the average number of hours per week engaged in various physical activities by METs from the Compendium of Physical Activity.<sup>58</sup> We summed the number of sugar-sweetened sodas, energy drinks, sports drinks, and fruit juices consumed in a week to estimate weekly sugar-sweetened beverage intake,<sup>59</sup> and the number of caffeinated sodas, energy drinks, coffee, and tea consumed in a week to estimate daily caffeine intake.<sup>60</sup> We updated time-varying covariates at each follow-up questionnaire, and assigned covariate values at the

start of each menstrual cycle relative to completion date of each questionnaire.

#### 4.2.5 Exclusions

Between 2021–2024, we invited 1,549 participants to enroll in the Fitbit substudy (Figure 4.1). Of those invited, 989 (64%) participants consented and 734 (74%) of those participants synced their data at least once. Among those who synced their data, we excluded 101 participants who did not have the opportunity to complete any follow-up questionnaires at the time of data analysis, 14 participants with invalid Fitbit data (*e.g.*, error files), and 136 participants with Fitbit sleep assessments that were outside of the relevant exposure window. Finally, we excluded 31 participants with <5 sleep assessments overall in order to more accurately estimate typical sleep health. Our final analytic sample included 452 participants with  $\geq 5$  sleep assessments. To ensure sufficient accuracy in analyses of midpoint variability, we further excluded 133 menstrual cycles (contributed by 118 participants) in which there were <5 days/cycle of wear time.<sup>61–63</sup>

#### 4.2.6 Statistical analysis

We estimated the follicular phase for each menstrual cycle at risk as the period between the start of the cycle and the day of ovulation. The luteal phase (*i.e.*, the phase of the menstrual cycle that occurs between ovulation and menstruation) is relatively invariable across individuals and lasts approximately 14 days.<sup>64–66</sup> Thus, for each menstrual cycle at risk, we subtracted off 14 days from the end of the cycle to estimate the end of the follicular phase (*i.e.*, day of ovulation).

Participants contributed menstrual cycles at risk from the first cycle with Fitbit sleep data collected during the follicular phase until the cycle of pregnancy or censoring event (*i.e.*, fertility treatment initiation, cessation of pregnancy attempts, loss to follow-up, end of substudy participation, or 12 total cycles of pregnancy attempt), whichever came first. We used an Andersen-Gill data structure with one observation per menstrual cycle to account for variation in pregnancy attempt time at study entry and left truncation due to delayed entry into the risk set.<sup>67–69</sup> We also used this method to update time-varying exposures and covariates over follow-up.

We averaged all sleep assessments collected within each follicular phase to estimate time-varying cycle-specific sleep health exposures. We categorized sleep duration as <6, 6–6.9, 7–7.9, and 8–9.9 hours/day, which has been used previously in PRESTO analyses<sup>37</sup> and aligns with categories used by the American Academy of Sleep Medicine and the Sleep Research Society.<sup>70</sup> In primary analyses, to avoid the influence of outliers, we winsorized day-specific sleep duration values <1<sup>st</sup> percentile (*i.e.*, <2.6 hours/day) and >99<sup>th</sup> percentile (*i.e.*, >10.3 hours/day) of the analytic cohort to the 1<sup>st</sup> and 99<sup>th</sup> percentiles, respectively. The winsorized values were used in cycle-specific averages for sleep duration. We performed sensitivity analyses in which we: 1) incorporated all day-specific sleep duration assessments in cycle-specific averages without trimming at the 1<sup>st</sup> and 99<sup>th</sup> percentiles, and 2) removed all day-specific sleep duration assessments <1<sup>st</sup> percentile and >99<sup>th</sup> percentile from cycle-specific averages. We categorized WASO as <30, 30–44, 45–59, and ≥60 minutes, sleep maintenance efficiency as <88%, 88–89%, 90–91%, and ≥92%, and midpoint variability as <30, 30–59, 60–89, and ≥90 minutes, as

these categories were evenly-spaced across the exposure distributions in the analytic cohort.

We fitted proportional probabilities regression models<sup>71</sup> to estimate fecundability ratios (FRs) and 95% confidence intervals (CIs) for the association between each sleep measure and fecundability. The proportional probabilities regression model is an applied form of the log-binomial regression model that includes an indicator variable for menstrual cycle at risk and accounts for decline in fecundability with increased pregnancy attempt time. The FR is the per-cycle probability of conception comparing each exposure category to the reference category and  $FR < 1.0$  indicates delayed TTP and reduced fecundability. Additionally, we fitted restricted cubic splines for the association of continuous sleep health exposures and fecundability to assess non-linearity of the association.<sup>72</sup>

We performed three secondary analyses. First, we cross-classified exposures and examined the combined effect of sleep duration and sleep maintenance efficiency. We hypothesized that participants with both short sleep duration and reduced sleep maintenance efficiency would experience greater reductions in fecundability relative to those with short sleep duration or reduced sleep maintenance efficiency alone. We calculated the relative excess risk due to interdependence to quantify the joint effect of short sleep duration and reduced sleep maintenance efficiency on fecundability, relative to the baseline risk.<sup>73</sup> Second, we further adjusted analyses of WASO, sleep maintenance efficiency, and midpoint variability for sleep duration. Third, we restricted analyses of WASO, sleep maintenance efficiency, and midpoint variability to those cycles with

recommended sleep duration (7–8.9 hours/day). In these restricted analyses, we hypothesized that greater WASO, reduced sleep maintenance efficiency, and greater midpoint variability among those with recommended sleep duration would still result in reduced fecundability.

We used a directed acyclic graph to guide the selection of confounders (Figure 4.2). In adjusted regression models, we controlled for the following time-invariant confounders: age (<30, 30–34, ≥35 years), education (<16, 16, ≥17 years), annual household income (<50,000, 50,000–99,999, 100,000–149,999, ≥150,000 U.S. dollars), employment status (yes, no), job hours/week, any night work in the past month (yes, no), any shift work in the past month (yes, no), BMI (<25, 25–29, ≥30 kg/m<sup>2</sup>), parity (parous, nulliparous), years since last birth, years since breastfeeding cessation, and last method of contraception (hormonal, non-hormonal). We also controlled for the following time-varying confounders: physical activity (MET hours/week), cannabis use in the previous two months (yes, no), alcohol intake (drinks/week), perceived stress (Perceived Stress Scale [PSS]-10 score), depressive symptoms (Major Depression Inventory [MDI] score), current psychotropic medication use (yes, no), caffeine intake (milligrams/day), and sugar-sweetened beverage intake (drinks/week).

In a sensitivity analysis, we restricted to participants without a birth in the previous year as those with a recent birth (*i.e.*, demonstrated fertility) may be more likely to have worse sleep health given their childcare responsibilities.

We used fully conditional specification methods to multiply impute missing covariate and outcome data.<sup>74–76</sup> We generated 20 imputed datasets and statistically

combined regression estimates using Rubin's rules.<sup>74</sup> Covariate missingness ranged from 0% (*e.g.*, age) to 4.4% (any night work in the past month). For participants who did not complete any follow-up questionnaires (n=4; 0.9%), we assigned one cycle of observation and multiply imputed their pregnancy status. We performed all analyses using SAS version 9.4 (SAS Institute, Cary, NC).

### **4.3 RESULTS**

We analyzed data from 452 participants who contributed 1,258 menstrual cycles of pregnancy attempt and 194 pregnancies (Table 4.1). Of these participants, 146 (32.3%) reported a viable pregnancy, 48 (10.6%) reported a pregnancy loss, 165 (36.5%) were censored at the end of their substudy participation, 11 (2.4%) were censored at 12 cycles of pregnancy attempt, 8 (1.8%) stopped trying to conceive, 20 (4.4%) initiated fertility treatment, 22 (4.9%) were still participating, and 32 (7.1%) were lost to follow-up. The median follow-up time among participants was 2 cycles (range: 1–11 cycles). There were minimal differences in baseline characteristics between those participants who did not provide consent, those who provided consent but did not complete the protocol, and those who completed the protocol (Table 4.2). However, participants who provided consent but did not complete the protocol had lower education and annual household income compared to those who did not consent or consented and completed the protocol.

In the follicular phase of their first analytic cycle, 44 (9.8%) participants had a sleep duration of <6 hours/day, 166 (36.8%) participants had 6–6.9 hours/day, 199 (44.1%) had 7–7.9 hours/day, and 42 (9.3%) had 8–9.9 hours/day (Table 4.1). More than

85% of participants had WASO  $\geq 30$  minutes and 34 (7.5%) had WASO  $\geq 60$  minutes. Additionally, 154 (34.1%) participants had sleep maintenance efficiency  $< 90\%$  and 148 (39.4%) had midpoint variability  $\geq 60$  minutes (Table 4.3). Across all cycles included in analyses, median (range) for sleep duration was 7.1 hours/day (2.6–9.9 hours/day), WASO was 43.8 minutes (0–96.0 minutes), sleep maintenance efficiency was 90.7% (82.9–100.0%), and midpoint variability was 49.6 minutes (9.9–663.9 minutes; Table 4.4).

Participants who slept  $< 6$  hours/day and had WASO  $\geq 60$  minutes tended to have lower education and annual household income, and were less likely to have private health insurance, have a BMI  $< 25$  kg/m<sup>2</sup>, consume caffeine, and be nulliparous than those who slept 7–7.9 hours/day and had WASO  $< 60$  minutes (Table 4.1). These participants were less likely to be currently employed and worked fewer hours/week. Participants who slept  $< 6$  hours/day were more likely to report shift work, have greater consumption of sugar-sweetened beverages, and have greater MDI and PSS-10 scores. Participants who slept 8–9.9 hours/day were more likely to have a history of diagnosed depression, currently use psychotropic medications, have used hormonal contraceptives as their last method of birth control, and have greater time since last birth. We observed U-shaped relationships for sleep duration and diagnoses of benign gynecologic conditions and anxiety. Participants with WASO  $\geq 60$  minutes were less likely to have used hormonal contraceptives as their last method of birth control and have lower physical activity, and were more likely to be diagnosed with depression or anxiety but less likely to use psychotropic medications. In general, there was concordance between most sleep health

measures, such that those with worse sleep health for one exposure (*e.g.*, sleep duration) often had worse sleep health for the other exposures (*i.e.*, WASO, sleep maintenance efficiency, midpoint variability) (Table 4.3). However, an exception was that greater sleep duration was associated with greater WASO. Also, short and long sleep durations were associated with greater sleep maintenance efficiency. Finally, WASO was inversely associated with midpoint variability.

We observed an inverted U-shaped relationship between sleep duration and fecundability (Table 4.5). Relative to 7–7.9 hours/day of sleep duration, FRs for sleep durations of <6 hours/day and 8–9.9 hours/day were 0.73 (95% CI: 0.44, 1.23) and 0.72 (95% CI: 0.41, 1.29) respectively. These results were consistent with restricted cubic spline analyses (Figure 4.3).

Compared with <30 minutes, the FR for WASO  $\geq$ 60 minutes was 0.73 (95% CI: 0.37, 1.43; Table 4.5). The FRs for the intermediate categories of 30–44 minutes and 45–59 minutes were 1.10 (95% CI: 0.69, 1.76) and 1.12 (95% CI: 0.70, 1.79), respectively. The restricted cubic spline for continuous WASO was consistent with these findings (Figure 4.4): relative to 0–20 minutes, WASO  $\geq$ 65 minutes was inversely associated with fecundability.

Similarly, the FR for sleep maintenance efficiency <88% (*vs.*  $\geq$ 92%) was 0.69 (95% CI: 0.39, 1.24), while FRs for 88–89% and 90–91% were 1.02 (95% CI: 0.70, 1.49) and 1.24 (95% CI: 0.89, 1.73), respectively (Table 4.5). Again, this association was consistent with the restricted cubic spline for the continuous exposure (Figure 4.5).

In categorical analyses, midpoint variability was not appreciably associated with

fecundability (Table 4.5). However, the restricted cubic spline showed a linear association between continuous midpoint variability and fecundability, such that greater midpoint variability was associated with decreased fecundability (Figure 4.6).

Relative to sleep duration  $\geq 7$  hours/day and sleep maintenance efficiency  $\geq 88\%$ , the joint effect of short sleep duration ( $< 7$  hours/day) and reduced sleep maintenance efficiency ( $< 88\%$ ) was more strongly associated with reduced fecundability (FR=0.49, 95% CI: 0.21, 1.15) than the individual exposures alone ( $\geq 7$  hours/day and  $< 88\%$ : FR=0.81, 95% CI: 0.42, 1.55;  $< 7$  hours/day and  $\geq 88\%$ : FR=1.06, 95% CI: 0.80, 1.41; Table 4.5). The relative excess risk due to interdependence for the joint effect of short sleep duration and reduced sleep maintenance efficiency was -0.35 (95% CI: -1.08, 0.39), indicating that the risk of conception due to the interdependence between short sleep duration and reduced sleep maintenance efficiency is 0.35 times the risk among those with sleep duration  $\geq 7$  hours/day and sleep maintenance efficiency  $\geq 88\%$ .

Further adjustment for sleep duration strengthened the relationship of WASO  $\geq 60$  minutes (FR=0.68, 95% CI: 0.34, 1.36) and sleep maintenance efficiency  $< 88\%$  (FR=0.67, 95% CI: 0.38, 1.20) with fecundability; however, there was little difference in the FR for midpoint variability  $\geq 90$  minutes (0.99, 95% CI: 0.60, 1.64; Table 4.5).

In menstrual cycles where participants slept the recommended duration (7–8.9 hours/day), we observed stronger relationships between WASO  $\geq 60$  minutes (FR=0.58, 95% CI: 0.24, 1.41), midpoint variability  $\geq 90$  minutes (FR=0.74, 95% CI: 0.33, 1.68), and decreased fecundability (Table 4.6). The association with sleep maintenance efficiency  $< 88\%$  was attenuated (FR=0.90, 95% CI: 0.41, 1.95).

Exclusion of participants with a birth in the previous year (Table 4.7) attenuated the effect of WASO  $\geq 60$  minutes (FR=0.90, 95% CI: 0.44, 1.82) and sleep maintenance efficiency  $< 88\%$  (FR=0.90, 95% CI: 0.49, 1.64), but strengthened the relationship with sleep duration  $< 6$  hours/day (FR=0.60, 95% CI: 0.33, 1.11) and midpoint variability  $\geq 90$  minutes (FR=0.89, 95% CI: 0.54, 1.48), though results were imprecise. There was little effect of this exclusion for sleep duration 8–9.9 hours/day (FR=0.72, 95% CI: 0.40, 1.29).

Inclusion of all day-specific sleep assessments in cycle-specific averages for sleep duration, regardless of whether they were  $< 1^{\text{st}}$  percentile or  $> 99^{\text{th}}$  percentile, did not appreciably change effect estimates for sleep duration and fecundability (Table 4.8). Exclusion of sleep assessments  $< 1^{\text{st}}$  percentile and  $> 99^{\text{th}}$  percentile slightly attenuated effect estimates for sleep duration  $< 6$  hours/day (FR=0.84, 95% CI: 0.49, 1.44) and 8–9.9 hours/day (FR=0.87, 95% CI: 0.50, 1.52; Table 4.9).

#### **4.4 DISCUSSION**

In this prospective cohort study of U.S. pregnancy planners, short and long sleep duration, greater WASO, reduced sleep maintenance efficiency, and greater midpoint variability during preconception were associated with reduced fecundability. Results were generally consistent for categorical and continuous sleep health exposures. We observed stronger effects for greater WASO, reduced sleep maintenance efficiency, and greater midpoint variability with reduced fecundability after adjustment for sleep duration and restriction to menstrual cycles with recommended sleep duration (7–8.9 hours/day). The joint effect of short sleep duration and reduced sleep maintenance efficiency was

more strongly associated with reduced fecundability when compared with the individual effects alone.

Findings from this current study are generally consistent with previous analyses in this cohort, though we observed stronger relationships between short sleep duration and reduced fecundability using objective measures.<sup>37</sup> Specifically, the previous study identified an association of self-reported short sleep duration with reduced fecundability (FR for <6 hours/day vs. 8 hours/day: 0.89, 95% CI: 0.75, 1.06). However, the major limitation associated with our earlier findings was non-differential exposure misclassification due to self-reported sleep duration, which may have attenuated associations.<sup>77</sup> Indeed, we previously reported that PRESTO participants tend to overestimate their sleep duration compared with Fitbit-measured actigraphy (Pearson correlation coefficient=0.42),<sup>78</sup> consistent with findings from other cohorts.<sup>79,80</sup> Thus, the stronger observed associations between sleep duration and fecundability based on Fitbit actigraphy may relate to reduced exposure misclassification.<sup>38,81,82</sup>

In the same PRESTO study, there was a monotonic association between frequency of trouble sleeping at night in the past month, measured via the MDI, and reduced fecundability (FRs for <50% and >50% of the time vs. none: 0.93, 95% CI: 0.88–1.00, and 0.87, 95% CI: 0.79–0.95, respectively).<sup>37</sup> In this present study, we identified novel relationships between objectively-measured WASO, sleep maintenance efficiency, and midpoint variability with reduced fecundability. These findings are likely aligned, as they all estimate aspects of sleep quality, and indicate that both self-reported and objective measures of sleep are related to fertility. As individuals may sleep “well”

according to objective assessments and still report poor sleep quality (or vice versa),<sup>83</sup> these studies underscore the importance of using both self-reported and objective sleep measures in research and clinical settings for infertility.

Most research on sleep health and fertility has been cross-sectional in design<sup>31–35</sup> or focused on infertility clinic populations.<sup>40–42</sup> In the only other prospective analysis of sleep and fertility among the general population, diagnosis of non-apnea sleep disorders (*e.g.*, insomnia) was associated with increased risk of infertility.<sup>36</sup> Our study distinguishes itself from previous research through several key strengths. First, we measured fecundability, rather than infertility, which avoids including those with undiagnosed infertility who have never attempted to become pregnant or attempted for <12 months in a “fertile” comparison group. Second, we measured sleep health during the preconception period—specifically, the follicular phase of each menstrual cycle at risk of conception—and prospectively examined fertility. Finally, we performed our analyses in a cohort of pregnancy planners with no known fertility problems at the start of their study-related pregnancy attempt.

We observed non-monotonic inverse associations between WASO and sleep maintenance efficiency with fecundability. These non-linear patterns of association were unexpected. A consensus panel from the National Sleep Foundation concluded that WASO  $\leq 20$  minutes and sleep efficiency  $\geq 85\%$  is appropriate for adults.<sup>84</sup> When paired with our results, this recommendation may indicate that some level of WASO and reduced sleep maintenance efficiency is acceptable with respect to fecundability and supports the non-monotonic relationship. However, the curvilinear associations could

also reflect residual confounding, as we observed that those with longer sleep durations tended to have longer WASO, and we found stronger associations with fecundability when we controlled for sleep duration and cross-classified sleep duration and sleep maintenance efficiency.

In secondary analyses, greater WASO, reduced sleep maintenance efficiency, and greater midpoint variability were consistently associated with reduced fecundability when accounting for sleep duration. Also, short sleep duration and reduced sleep maintenance efficiency combined were more strongly related to reduced fecundability than the individual effects of each exposure alone. Previous literature shows that optimal sleep quality is just as important as sleep duration for health,<sup>62,83,85-90</sup> even though duration is the most widely-studied and commonly used sleep metric.<sup>70</sup> Our findings indicate that optimal sleep duration in combination with other measures of sleep health are associated with improved fecundability, and a multidimensional approach to sleep health is necessary for better fertility outcomes.<sup>90,91</sup>

Study strengths include the enrollment of participants early in their pregnancy attempts, which allowed us to examine preconception sleep health and fecundability across the fertility spectrum. The prospective study design reduced the potential for reverse causation bias.<sup>92</sup> We measured sleep using Fitbit actigraphy, which mitigated exposure misclassification. Participants were instructed to wear the Fitbit for a two-month period, a longer time period than that recommended for accurate wearable estimation,<sup>38,81,93</sup> which likely reduced measurement error.<sup>39,81</sup> The Fitbit produced multiple metrics of sleep, allowing us to perform a multidimensional analysis of sleep

health. Prospective collection of menstrual data allowed for estimation of the start and end dates of each menstrual cycle, and the identification of the follicular phase (*i.e.*, etiologically relevant window of exposure),<sup>56,57</sup> Sleep may vary across stages of the menstrual cycle, which further supports the use of sleep assessments measured during the etiologically relevant window of exposure.<sup>24,94,95</sup> Finally, we updated time-varying exposures and covariates throughout follow-up, which reduces the potential for exposure and confounder misclassification.

While the use of actigraphy likely mitigated most biases, device failure or incomplete protocol adherence could contribute to some exposure misclassification and selection bias. To increase protocol adherence, we sent reminders to participants about the substudy. Median participation time was 2 months (interquartile range: 1–3 months), which equated to the substudy protocol period. Also, previous research has demonstrated concordance between actigraphy and polysomnography in shorter study periods.<sup>96</sup> Thus, sleep assessments will likely still be valid even if data are not collected for the entirety of the protocol period, assuming sleep health is constant during data collection.

Misclassification of the exposure window may be possible given our estimation method of the follicular phase of the menstrual cycle. Luteal phase deficiency, the result of insufficient progesterone duration, insufficient progesterone levels, and endometrial progesterone resistance, has an estimated prevalence of approximately 8%<sup>97</sup> and results in abnormally short luteal phase length (approximately 10 days).<sup>98,99</sup> While the luteal phase is typically stable, it is possible that we misclassified the timing of the menstrual cycle stages if a participant had luteal phase deficiency. Additionally, our study did not

evaluate the effects of sleep health during the luteal phase. If there are effects of adverse sleep health on luteal phase reproductive events (*e.g.*, implantation failure), our study would not have captured these associations. Outcome misclassification is also possible due to self-report of pregnancy attempt time at study entry, LMP dates, and pregnancy status. A validation study in PRESTO showed that participants report their menstrual data with high accuracy.<sup>45</sup> Relative to day-specific data from a menstrual charting application, >95% of participants accurately reported their LMP dates within one day. Also, most participants tested for pregnancy at home and the median gestational weeks at first pregnancy test was 4 weeks (interquartile range: 3.7–4.4 weeks), which would detect a large percentage of early pregnancies. Finally, PRESTO tends to overrepresent participants with higher income and education than the general population, which may limit study generalizability.

In conclusion, in a preconception cohort of participants who wore Fitbits for up to two months, we found that short and long sleep duration, greater WASO, reduced sleep maintenance efficiency, and greater midpoint variability were associated with reduced fecundability. The combined effect of short sleep duration and reduced sleep maintenance efficiency resulted in the lowest fecundability, highlighting the importance of evaluating multiple domains of sleep health to optimize fertility, as has been recommended for other health outcomes.<sup>100</sup> This present study expands upon prior research, providing insight into a modifiable risk factor for infertility, and may inform public health interventions for reproductive health.

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## 4.6 TABLES AND FIGURES

**Table 4.1** Characteristics of study participants by selected sleep health exposures among 452 participants, Pregnancy Study Online, 2021–2024

Characteristic <sup>c</sup>	Sleep duration (hours/day) <sup>a,b</sup>				Wake after sleep onset (minutes) <sup>a</sup>			
	<6	6–6.9	7–7.9	8–9.9	<30	30–44	45–59	≥60
Number of participants	44	166	199	42	64	180	174	34
<b>Baseline questionnaire</b>								
Age (years), mean	34.0	32.7	31.4	31.7	33.1	32.3	31.8	31.7
Race/ethnicity, %								
Asian, non-Hispanic	12.6	3.6	0.9	0	3.5	3.8	2.3	0
Black, non-Hispanic	3.4	2.5	1.4	5.5	8.3	1.7	0.6	3.2
White, non-Hispanic	79.4	86.4	87.4	73.6	81.7	85.7	86.2	84.5
Other race, non-Hispanic <sup>d</sup>	0	2.2	3.9	15.2	4.8	4.9	2.5	6.1
Hispanic/Latina/Latinx	4.6	5.4	6.4	5.7	1.8	3.9	8.5	6.2
Education, %								
<College degree	20.6	14.1	14.3	8.9	15.4	11.9	12.2	22.7
College degree	25.7	30.0	31.5	25.8	28.1	30.5	35.5	23.0
Graduate school	53.8	56.0	54.3	65.4	56.5	57.6	52.4	54.3
Annual household income (USD), %								
<50,000	18.8	7.0	9.7	8.9	11.5	8.9	6.2	20.3
50,000–99,999	49.2	27.8	22.3	23.5	31.5	23.2	27.1	31.3
100,000–149,999	13.7	26.4	28.9	27.2	30.4	30.0	25.9	18.0
≥150,000	18.3	38.8	39.3	40.4	26.7	37.9	40.8	30.5
Geographic region, %								
Northeastern U.S.	21.2	21.2	25.7	13.8	18.9	23.8	21.6	23.8
Southern U.S.	29.6	33.2	29.9	33.0	43.1	29.5	31.4	23.3
Midwestern U.S.	37.8	27.6	25.7	24.1	21.4	29.0	26.8	25.5

Western U.S.	11.4	17.9	18.7	29.2	16.6	17.7	20.3	27.4
Currently employed, %	73.2	86.4	87.9	88.5	85.1	87.8	90.0	59.8
Job hours/week, mean <sup>e</sup>	29.0	34.3	34.0	33.9	34.6	34.6	34.6	23.0
Night work in the past month, %	24.6	16.0	10.3	6.9	18.9	10.6	12.4	14.0
Rotating shift work in the past month, %	20.6	10.3	10.5	12.6	15.0	10.1	9.9	11.2
Private health insurance, %	85.8	92.5	92.3	90.0	91.6	91.2	93.6	88.5
Body mass index (kg/m <sup>2</sup> ), %								
<25.0	30.2	41.4	54.5	64.8	40.4	48.4	49.9	58.9
25.0–29.9	38.4	25.0	21.7	10.6	26.8	24.0	22.4	9.2
≥30.0	31.4	33.6	23.6	24.6	32.7	27.7	27.7	32.0
Parous, %	58.8	48.5	33.9	25.2	40.5	40.1	38.4	54.4
Time since last birth (years), mean <sup>f</sup>	3.0	3.6	3.5	6.6	3.9	3.6	3.5	4.1
Time since breastfeeding cessation (years), mean <sup>g</sup>	0.9	1.5	1.8	1.0	0.9	1.8	1.8	1.6
Last method of contraception, hormonal, %	29.2	26.0	28.5	37.5	35.0	28.6	25.9	17.4
Cycles of attempt at study enrollment, mean	2.3	2.2	2.2	2.6	2.1	2.2	2.3	2.5
History of diagnosed uterine leiomyomata, %	3.4	2.8	1.9	5.2	3.6	1.6	4.0	3.2
History of diagnosed polycystic ovary syndrome, %	9.1	7.9	5.0	10.6	14.3	4.5	8.0	8.9
History of diagnosed endometriosis, %	6.9	4.3	1.8	7.7	3.0	4.4	2.8	8.8
<b>Follow-up questionnaire<sup>a</sup></b>								
Physical activity (MET hours/week), mean	35.4	32.0	34.3	30.7	34.7	35.7	31.3	26.6
Cannabis use in the past two months, %	13.7	14.9	21.9	13.5	20.2	15.2	16.5	23.4
Alcohol intake (drinks/week), mean	1.8	2.1	2.4	1.9	2.4	2.2	2.1	1.8
Current caffeine intake (mg/day), mean	103.6	135.8	137.8	131.5	140.0	128.9	140.6	130.2
Current sugar-sweetened beverage intake (drinks/week), mean	4.1	2.3	2.3	1.9	3.0	2.2	2.4	2.0
History of diagnosed anxiety, %	42.9	27.4	33.4	46.1	29.3	33.0	35.1	39.6
History of diagnosed depression, %	24.6	27.4	33.1	37.0	28.7	30.6	30.1	40.3
Current psychotropic medication usage, %	21.2	17.1	19.2	43.9	16.2	21.6	23.6	9.2
MDI score, mean	13.9	10.2	9.0	10.8	10.2	10.4	9.5	11.2
PSS-10 score, mean	17.6	15.3	14.9	13.6	15.2	15.4	15.1	15.6

kg: kilograms; m: meters; MDI: Major Depression Inventory; MET: metabolic equivalent of task; mg: milligrams; PSS: Perceived Stress Scale; U.S.: United States; USD: United States dollars.

<sup>a</sup> Reported at the first cycle contributed to analyses.

<sup>b</sup> Excludes 1 participant whose sleep duration was  $\geq 10$  hours/day.

<sup>c</sup> All characteristics, except age, are standardized to the age distribution of the cohort at baseline.

<sup>d</sup> Other race, non-Hispanic includes multiracial, American Indian/Alaskan Native, and self-identified other.

<sup>e</sup> Job hours/week includes participants who are unemployed, who have a value of 0 hours/week.

<sup>f</sup> Among parous participants.

<sup>g</sup> Among parous participants who reported breastfeeding after their most recent birth.

**Table 4.2** Baseline characteristics of participants by consent and participation status for the Fitbit substudy, Pregnancy Study Online, 2021–2024

Characteristic <sup>a</sup>	Did not provide consent <sup>b</sup>	Provided consent <sup>b</sup>	
		Did not complete protocol <sup>c</sup>	Completed protocol <sup>c</sup>
Number of participants	560	255	734
Age at baseline (years), mean	31.0	31.5	31.7
Race/ethnicity, %			
Asian, non-Hispanic	3.9	5.1	4.4
Black, non-Hispanic	3.1	4.3	2.6
White, non-Hispanic	82.6	76.8	80.4
Other race, non-Hispanic <sup>d</sup>	2.8	4.3	5.3
Hispanic/Latina/Latinx	7.6	9.4	7.2
Education, %			
<College degree	12.8	22.8	14.1
College degree	28.6	28.3	33.0
Graduate degree	58.7	48.9	52.8
Annual household income (USD), %			
<50,000	8.2	15.8	9.3
50,000–99,999	19.2	23.8	24.3
100,000–149,999	25.3	19.8	26.9
≥150,000	47.4	40.7	39.6
Geographic region of residence, %			
Northeast U.S.	24.0	21.9	20.3
South U.S.	29.3	29.8	32.1
Midwest U.S.	28.5	25.7	25.8
West U.S.	18.1	22.7	21.8

Currently employed, %	92.3	85.1	86.7
Job hours/week, mean <sup>e</sup>	36.3	32.3	33.6
Night work in the past month, %	10.8	15.5	12.1
Rotating shift work in the past month, %	13.5	13.1	11.2
Private health insurance, %	94.3	85.7	92.4
Body mass index (kg/m <sup>2</sup> ), %			
<25.0	50.5	43.9	47.3
25.0–29.9	24.7	23.7	25.3
≥30.0	24.9	32.4	27.5
Parous, %	27.1	41.9	38.9
Time since last birth (years), mean <sup>f</sup>	3.3	4.0	3.6
Time since breastfeeding cessation (years), mean <sup>g</sup>	1.7	2.1	1.7
History of subfertility or infertility, %	11.1	15.9	15.3
Last method of contraception, hormonal, %	32.3	27.4	27.5
Cycles of attempt at study enrollment, mean	1.7	2.3	1.5
History of diagnosed uterine leiomyomata, %	2.5	2.0	2.2
History of diagnosed polycystic ovary syndrome, %	7.8	6.4	7.8
History of diagnosed endometriosis, %	1.9	2.0	3.0
Physical activity (MET hours/week), mean	33.5	37.4	32.4
Cannabis use in the past two months, %	21.2	16.3	15.3
Alcohol intake (drinks/week), mean	2.8	2.4	2.2
Current caffeine intake (mg/day), mean	130.9	120.4	131.7
Current sugar-sweetened beverage intake (drinks/week), mean	2.0	3.0	2.3
History of diagnosed anxiety, %	33.9	31.7	33.6
History of diagnosed depression, %	24.5	21.2	29.1

Current psychotropic medication usage, %	19.7	19.0	20.4
MDI score, mean	9.8	10.2	10.3
PSS-10 score, mean	15.6	14.8	15.4

kg: kilograms; m: meters; MDI: Major Depression Inventory; MET: metabolic equivalent of task; mg: milligrams; PSS: Perceived Stress Scale; U.S.: United States; USD: United States dollars.

<sup>a</sup> All characteristics, except age, are standardized to the age distribution of the cohort at baseline.

<sup>b</sup> Consented is defined as agreed to participate in the Fitbit substudy.

<sup>c</sup> Participated is defined as agreed to participate and synced Fitbit sleep data with PRESTO at least once.

<sup>d</sup> Other race, non-Hispanic includes multiracial, American Indian/Alaskan Native, and self-identified other.

<sup>e</sup> Job hours/week includes participants who are unemployed, who have a value of 0 hours/week.

<sup>f</sup> Among parous participants.

<sup>g</sup> Among parous participants who reported breastfeeding after their most recent birth.

**Table 4.3** Distribution of Fitbit-measured sleep health exposures, Pregnancy Study Online, 2021–2024

	Sleep duration (hours/day) <sup>a</sup>				Wake after sleep onset (minutes)				Sleep maintenance efficiency (%)				Midpoint variability (minutes) <sup>b</sup>			
	<6	6–6.9	7–7.9	8–9.9	<30	30–44	45–59	≥60	<88	88–89	90–91	≥92	<30	30–59	60–89	≥90
N	44	166	199	42	64	180	174	34	39	115	170	128	51	177	82	66
Sleep duration (hours/day), % <sup>a</sup>																
<6					26.6	11.1	4.0	0	12.8	7.0	7.1	14.8	2.0	1.7	8.5	33.3
6–6.9					42.2	45.6	30.5	12.1	30.8	37.4	37.9	36.7	43.1	36.2	40.2	34.9
7–7.9					18.8	37.8	55.2	69.7	48.7	47.8	47.9	34.4	45.1	53.1	46.3	24.2
8–9.9					12.5	5.6	10.3	18.2	7.7	7.8	7.1	14.1	9.8	9.0	4.9	7.6
Wake after sleep onset (minutes), %																
<30	38.6	16.3	6.0	19.1					0	0	1.8	47.7	15.7	8.5	7.3	24.2
30–44	45.5	49.4	34.2	23.8					0	9.6	60.0	52.3	39.2	40.7	45.1	40.9
45–59	15.9	31.9	48.2	42.9					33.3	84.4	37.7	0	35.3	42.9	40.2	31.8
≥60	0	2.4	11.6	14.3					66.7	6.1	0.6	0	9.8	7.9	7.3	3.0
Sleep maintenance efficiency (%), %																
<88	11.4	7.2	9.6	7.1	0	0	7.5	76.5					5.9	10.7	7.3	7.6
88–89	18.2	25.9	27.6	21.4	0	6.1	55.8	20.6					39.2	23.7	30.5	18.2
90–91	27.3	38.5	40.7	28.6	4.7	56.7	36.8	2.9					23.5	42.9	42.7	39.4
≥92	43.2	28.3	22.1	42.9	95.3	37.2	0	0					31.4	22.6	19.5	34.9
Midpoint variability (minutes), % <sup>b</sup>																
<30	3.0	15.5	13.5	16.7	17.8	12.8	12.2	18.5	9.1	20.2	8.1	16.8				
30–59	9.1	45.1	55.0	53.3	33.3	46.2	51.4	51.9	57.6	42.4	51.0	42.1				
60–89	21.2	23.2	22.2	13.3	13.3	23.7	22.3	22.2	18.2	25.3	23.5	16.8				
≥90	66.7	16.2	9.4	16.7	35.6	17.3	14.2	7.4	15.2	12.1	17.5	24.2				

<sup>a</sup> Excludes participants with average sleep duration ≥10 hours/day in their first cycle (n=1).

<sup>b</sup> Excludes participants with <5 days of wear time in their first cycle (n=76).

**Table 4.4** Descriptive statistics of sleep health exposures, overall and by cycle, Pregnancy Study Online, 2021–2024

Sleep health exposure	Number of cycles	Minimum	25 <sup>th</sup> percentile	Median	Mean	75 <sup>th</sup> percentile	Maximum
<b>Sleep duration (hours/day)<sup>a</sup></b>	1257	2.6	6.6	7.1	7.0	7.5	9.9
Cycle 1	451	2.6	6.6	7.1	7.0	7.5	9.2
Cycle 2	332	4.0	6.6	7.0	7.0	7.5	9.2
Cycle 3	200	4.5	6.5	7.0	6.9	7.4	8.8
Cycle 4	105	4.2	6.7	7.2	7.1	7.6	9.2
Cycle 5	69	2.6	6.8	7.4	7.2	7.7	9.9
Cycle 6	42	5.1	6.6	6.9	7.0	7.4	9.0
Cycle 7	25	5.4	6.1	6.8	6.8	7.5	8.4
Cycle 8	18	5.9	6.5	7.1	7.0	7.5	8.3
Cycle 9	10	6.3	6.7	7.2	7.2	7.8	8.1
Cycle 10	4	5.8	5.8	6.1	6.5	7.1	7.7
Cycle 11	1	--	--	--	--	--	--
<b>Wake after sleep onset (minutes)</b>	1258	0	36.5	43.8	43.7	51.7	96.0
Cycle 1	452	0	35.5	43.8	42.8	50.7	96.0
Cycle 2	332	0	36.9	43.5	43.4	51.2	76.0
Cycle 3	200	0	37.5	44.6	45.1	53.7	77.5
Cycle 4	105	22.8	37.1	45.0	45.3	53.1	74.5
Cycle 5	69	0	35.8	46.5	45.4	57.1	77.0
Cycle 6	42	19.7	37.3	43.0	44.7	51.2	77.3
Cycle 7	25	19.0	38.3	41.7	42.9	49.9	60.9
Cycle 8	18	22.0	37.2	41.8	41.3	47.3	61.9
Cycle 9	10	32.3	38.9	45.4	45.2	51.1	59.2
Cycle 10	4	31.2	32.8	36.5	36.7	40.5	42.5
Cycle 11	1	--	--	--	--	--	--

<b>Sleep maintenance efficiency (%)</b>	1258	82.9	89.4	90.7	90.8	92.1	100.0
Cycle 1	452	82.9	89.5	90.8	91.0	92.2	100.0
Cycle 2	332	85.5	89.4	90.8	90.8	92.1	100.0
Cycle 3	200	84.3	89.0	90.6	90.4	91.8	100.0
Cycle 4	105	85.4	89.4	90.5	90.6	91.8	95.3
Cycle 5	69	86.3	88.7	90.5	90.8	92.1	100.0
Cycle 6	42	86.9	89.7	90.7	90.6	91.6	95.7
Cycle 7	25	87.0	89.8	91.0	90.9	91.9	95.5
Cycle 8	18	87.5	90.1	91.4	91.3	92.2	94.5
Cycle 9	10	88.9	89.5	90.6	90.7	91.8	92.8
Cycle 10	4	90.7	90.8	91.2	91.3	91.7	91.9
Cycle 11	1	--	--	--	--	--	--
<b>Midpoint variability (minutes)<sup>b</sup></b>	1125	9.9	35.3	49.6	70.6	72.2	663.9
Cycle 1	376	10.0	35.2	51.0	71.6	73.6	663.9
Cycle 2	318	16.0	35.0	49.1	69.3	66.7	651.9
Cycle 3	180	14.2	35.5	46.9	65.4	71.4	505.6
Cycle 4	94	9.9	38.6	50.3	66.4	71.7	521.2
Cycle 5	61	16.8	41.0	56.1	72.4	79.3	528.5
Cycle 6	40	16.8	30.9	50.4	91.6	87.0	524.8
Cycle 7	23	18.5	41.8	59.8	89.8	88.1	484.3
Cycle 8	18	20.4	35.2	59.1	84.9	90.9	431.9
Cycle 9	10	23.7	33.1	48.7	51.5	66.6	117.7
Cycle 10	4	22.6	23.5	42.7	49.2	74.9	88.7
Cycle 11	1	--	--	--	--	--	--

-- indicates that descriptive statistics could not be calculated.

<sup>a</sup> Excludes cycles with average sleep duration  $\geq 10$  hours/day (n=1).

<sup>b</sup> Excludes cycles with <5 days of wear time (n=133).

**Table 4.5** Association between Fitbit-measured sleep health and fecundability, Pregnancy Study Online, 2021–2024

	Number of pregnancies	Number of cycles	Crude FR (95% CI)	Adjusted FR (95% CI) <sup>a</sup>	Adjusted FR (95% CI) <sup>b</sup>
<b>Sleep duration (hours/day)<sup>c</sup></b>					
<6	16	127	0.78 (0.48, 1.28)	0.73 (0.44, 1.23)	--
6–6.9	73	457	1.01 (0.76, 1.33)	1.05 (0.79, 1.39)	--
7–7.9	93	569	<i>Reference</i>	<i>Reference</i>	--
8–9.9	12	104	0.72 (0.41, 1.27)	0.72 (0.41, 1.29)	--
<b>Wake after sleep onset (minutes)</b>					
<30	19	139	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
30–44	83	530	1.10 (0.69, 1.75)	1.10 (0.69, 1.76)	1.02 (0.63, 1.64)
45–59	79	479	1.17 (0.73, 1.86)	1.12 (0.70, 1.79)	1.02 (0.63, 1.66)
≥60	13	110	0.86 (0.45, 1.67)	0.73 (0.37, 1.43)	0.68 (0.34, 1.36)
<b>Sleep maintenance efficiency (%)</b>					
<88	14	121	0.82 (0.47, 1.45)	0.69 (0.39, 1.24)	0.67 (0.38, 1.20)
88–89	49	326	1.09 (0.75, 1.58)	1.02 (0.70, 1.49)	1.00 (0.68, 1.46)
90–91	86	487	1.27 (0.91, 1.77)	1.24 (0.89, 1.73)	1.20 (0.86, 1.68)
≥92	45	324	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
<b>Midpoint variability (minutes)<sup>d</sup></b>					
<30	29	160	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
30–59	91	556	0.87 (0.60, 1.27)	0.93 (0.63, 1.37)	0.93 (0.63, 1.37)
60–89	34	225	0.83 (0.53, 1.30)	0.89 (0.56, 1.42)	0.89 (0.56, 1.43)
≥90	31	184	0.97 (0.61, 1.54)	0.95 (0.58, 1.54)	0.99 (0.60, 1.64)
<b>Cross-classified sleep duration (hours/day) and sleep maintenance efficiency (%)<sup>c</sup></b>					
<7 hours/day and <88%	5	61	0.53 (0.22, 1.24)	0.49 (0.21, 1.15)	--
≥7 hours/day and <88%	9	60	0.96 (0.51, 1.79)	0.81 (0.42, 1.55)	--
<7 hours/day and ≥88%	84	523	1.05 (0.80, 1.38)	1.06 (0.80, 1.41)	--
≥7 hours/day and ≥88%	96	613	<i>Reference</i>	<i>Reference</i>	--

CI: confidence interval; FR: fecundability ratio.

<sup>a</sup> Adjusted for the following confounders: time-invariant – age, education, household income, employment status, job hours per week, any night work in the previous month, any shift work in the previous month, body mass index, parity, time since last birth, time since breastfeeding cessation, and last method of contraception; time-varying – physical activity, cannabis use, alcohol intake, perceived stress, depressive symptoms, psychotropic medication usage, caffeine intake, and sugar-sweetened beverage intake.

<sup>b</sup> Further adjusted for sleep duration.

<sup>c</sup> Excludes cycles with average sleep duration  $\geq 10$  hours/day (n=1).

<sup>d</sup> Excludes cycles with <5 days of wear time (n=133).

**Table 4.6** Association between Fitbit-measured sleep health and fecundability restricted to cycles with recommended sleep duration (7–8.9 hours/day), Pregnancy Study Online, 2021–2024

	Number of pregnancies	Number of cycles <sup>a</sup>	Crude FR (95% CI)	Adjusted FR (95% CI) <sup>b</sup>
<b>Wake after sleep onset (minutes)</b>				
<30	8	40	<i>Reference</i>	<i>Reference</i>
30–44	35	225	0.80 (0.40, 1.59)	0.79 (0.38, 1.65)
45–59	50	312	0.80 (0.41, 1.58)	0.83 (0.41, 1.68)
≥60	12	91	0.70 (0.31, 1.59)	0.58 (0.24, 1.41)
<b>Sleep maintenance efficiency (%)</b>				
<88	9	60	1.09 (0.54, 2.24)	0.90 (0.41, 1.95)
88–89	26	187	0.99 (0.58, 1.67)	0.98 (0.56, 1.72)
90–91	48	268	1.29 (0.81, 2.06)	1.30 (0.81, 2.09)
≥92	22	153	<i>Reference</i>	<i>Reference</i>
<b>Midpoint variability (minutes)<sup>c</sup></b>				
<30	22	94	<i>Reference</i>	<i>Reference</i>
30–59	55	341	0.65 (0.42, 1.01)	0.66 (0.42, 1.05)
60–89	17	116	0.59 (0.33, 1.04)	0.57 (0.31, 1.05)
≥90	7	52	0.59 (0.27, 1.29)	0.74 (0.33, 1.68)

CI: confidence interval; FR: fecundability ratio.

<sup>a</sup> Restricted to cycles with recommended sleep duration (n=668).

<sup>b</sup> Adjusted for the following confounders: time-invariant – age, education, household income, employment status, job hours per week, any night work in the previous month, any shift work in the previous month, body mass index, parity, time since last birth, time since breastfeeding cessation, and last method of contraception; time-varying – physical activity, cannabis use, alcohol intake, perceived stress, depressive symptoms, psychotropic medication usage, caffeine intake, and sugar-sweetened beverage intake.

<sup>c</sup> Excludes cycles with <5 days of wear time (n=65).

**Table 4.7** Association between Fitbit-measured sleep health and fecundability restricted to participants without a birth in the previous year, Pregnancy Study Online, 2021–2024

	Number of pregnancies	Number of cycles	Crude FR (95% CI)	Adjusted FR (95% CI) <sup>a</sup>
<b>Sleep duration (hours/day)<sup>b</sup></b>				
<6	11	104	0.67 (0.37, 1.22)	0.60 (0.33, 1.11)
6–6.9	69	423	1.07 (0.80, 1.42)	1.12 (0.84, 1.50)
7–7.9	88	551	<i>Reference</i>	<i>Reference</i>
8–9.9	12	104	0.74 (0.42, 1.30)	0.72 (0.40, 1.29)
<b>Wake after sleep onset (minutes)</b>				
<30	17	132	<i>Reference</i>	<i>Reference</i>
30–44	76	500	1.14 (0.70, 1.86)	1.21 (0.73, 1.98)
45–59	75	452	1.25 (0.77, 2.04)	1.27 (0.77, 2.10)
≥60	12	99	0.95 (0.48, 1.91)	0.90 (0.44, 1.82)
<b>Sleep maintenance efficiency (%)</b>				
<88	13	103	0.97 (0.54, 1.73)	0.90 (0.49, 1.64)
88–89	44	303	1.12 (0.76, 1.67)	1.07 (0.72, 1.60)
90–91	82	464	1.35 (0.96, 1.91)	1.38 (0.97, 1.94)
≥92	41	313	<i>Reference</i>	<i>Reference</i>
<b>Midpoint variability (minutes)<sup>c</sup></b>				
<30	26	149	<i>Reference</i>	<i>Reference</i>
30–59	86	524	0.88 (0.60, 1.32)	0.96 (0.64, 1.42)
60–89	31	212	0.82 (0.51, 1.31)	0.87 (0.54, 1.40)
≥90	28	170	0.96 (0.59, 1.56)	0.89 (0.54, 1.48)

CI: confidence interval; FR: fecundability ratio.

<sup>a</sup> Adjusted for the following confounders: time-invariant – age, education, household income, employment status, job hours per week, any night work in the previous month, any shift work in the previous month, body mass index, parity, time since last birth, time since breastfeeding cessation, and last method of contraception; time-varying – physical activity, cannabis use, alcohol intake, perceived stress, depressive symptoms, psychotropic medication usage, caffeine intake, and sugar-sweetened beverage intake.

<sup>b</sup> Excludes cycles with average sleep duration ≥10 hours/day (n=1).

<sup>c</sup> Excludes cycles with <5 days of wear time (n=128).

**Table 4.8** Association between Fitbit-measured sleep duration and fecundability, including all sleep assessments in cycle-specific averages, Pregnancy Study Online, 2021–2024

	Number of pregnancies	Number of cycles	Crude FR (95% CI)	Adjusted FR (95% CI) <sup>a</sup>
<b>Sleep duration (hours/day)</b>				
<6	16	129	0.76 (0.47, 1.25)	0.72 (0.43, 1.21)
6–6.9	73	454	1.01 (0.76, 1.34)	1.04 (0.78, 1.38)
7–7.9	93	566	<i>Reference</i>	<i>Reference</i>
8–9.9	12	108	0.70 (0.40, 1.22)	0.70 (0.39, 1.24)

CI: confidence interval; FR: fecundability ratio.

<sup>a</sup> Adjusted for the following confounders: time-invariant – age, education, household income, employment status, job hours per week, any night work in the previous month, any shift work in the previous month, body mass index, parity, time since last birth, time since breastfeeding cessation, and last method of contraception; time-varying – physical activity, cannabis use, alcohol intake, perceived stress, depressive symptoms, psychotropic medication usage, caffeine intake, and sugar-sweetened beverage intake.

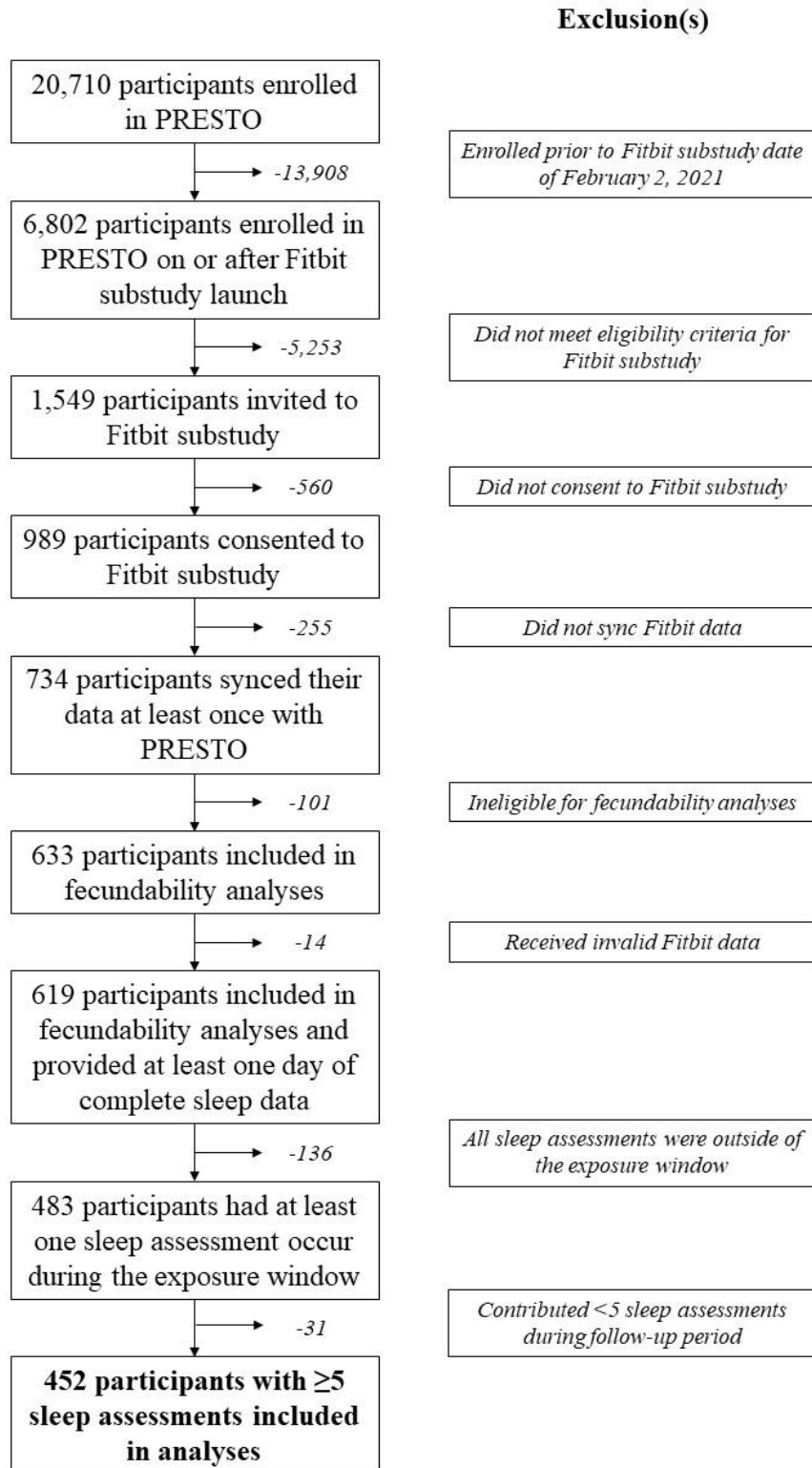
**Table 4.9** Association between Fitbit-measured sleep duration and fecundability, excluding sleep assessments below the 1<sup>st</sup> percentile or above the 99<sup>th</sup> percentile in cycle-specific averages, Pregnancy Study Online, 2021–2024

	Number of pregnancies	Number of cycles	Crude FR (95% CI)	Adjusted FR (95% CI) <sup>a</sup>
<b>Sleep duration (hours/day)<sup>b</sup></b>				
<6	14	105	0.84 (0.50, 1.42)	0.84 (0.49, 1.44)
6–6.9	73	465	1.02 (0.77, 1.35)	1.06 (0.80, 1.41)
7–7.9	94	589	<i>Reference</i>	<i>Reference</i>
8–9.9	13	96	0.87 (0.51, 1.49)	0.87 (0.50, 1.52)

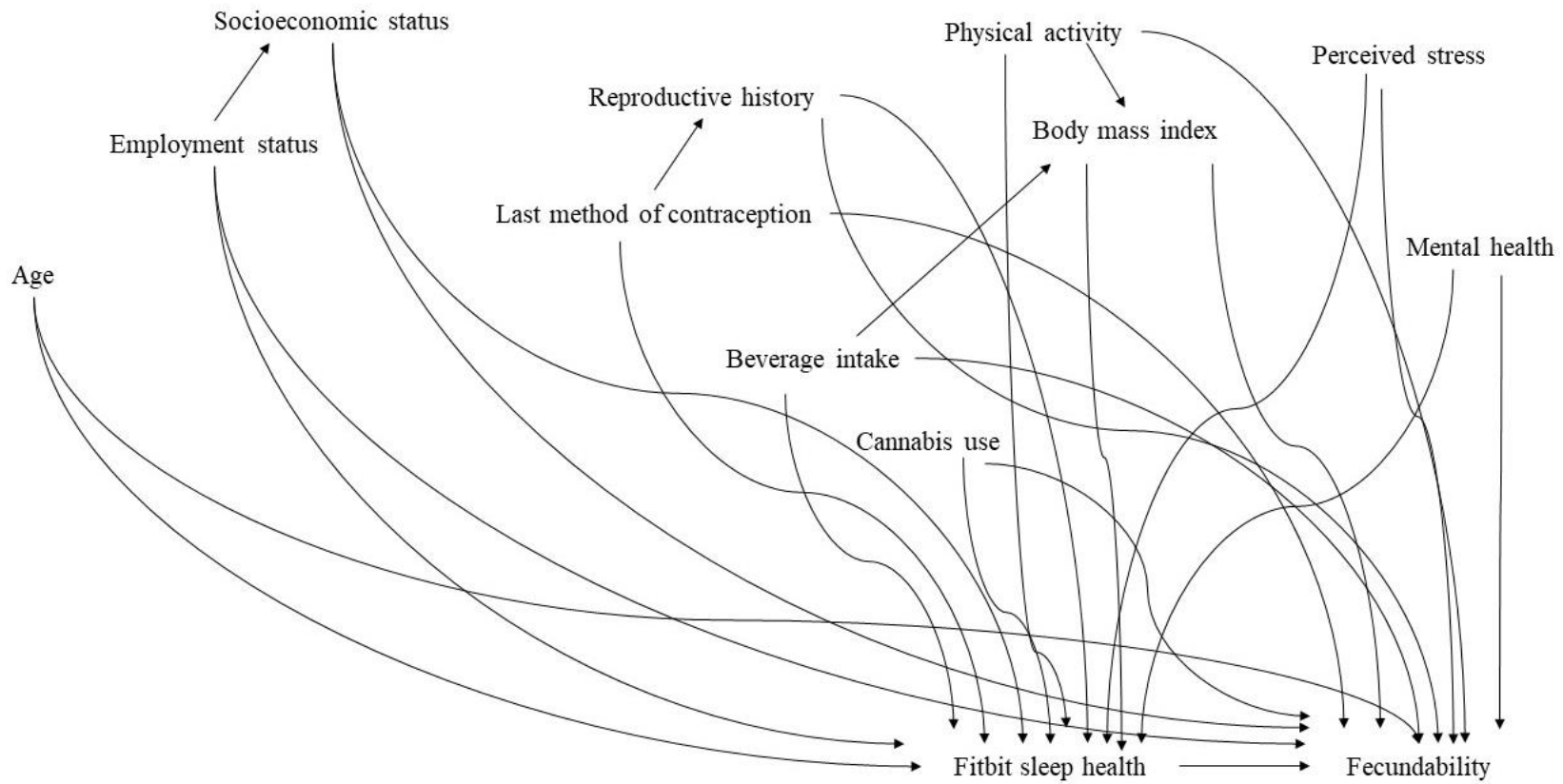
CI: confidence interval; FR: fecundability ratio.

<sup>a</sup> Adjusted for the following confounders: time-invariant – age, education, household income, employment status, job hours per week, any night work in the previous month, any shift work in the previous month, body mass index, parity, time since last birth, time since breastfeeding cessation, and last method of contraception; time-varying – physical activity, cannabis use, alcohol intake, perceived stress, depressive symptoms, psychotropic medication usage, caffeine intake, and sugar-sweetened beverage intake.

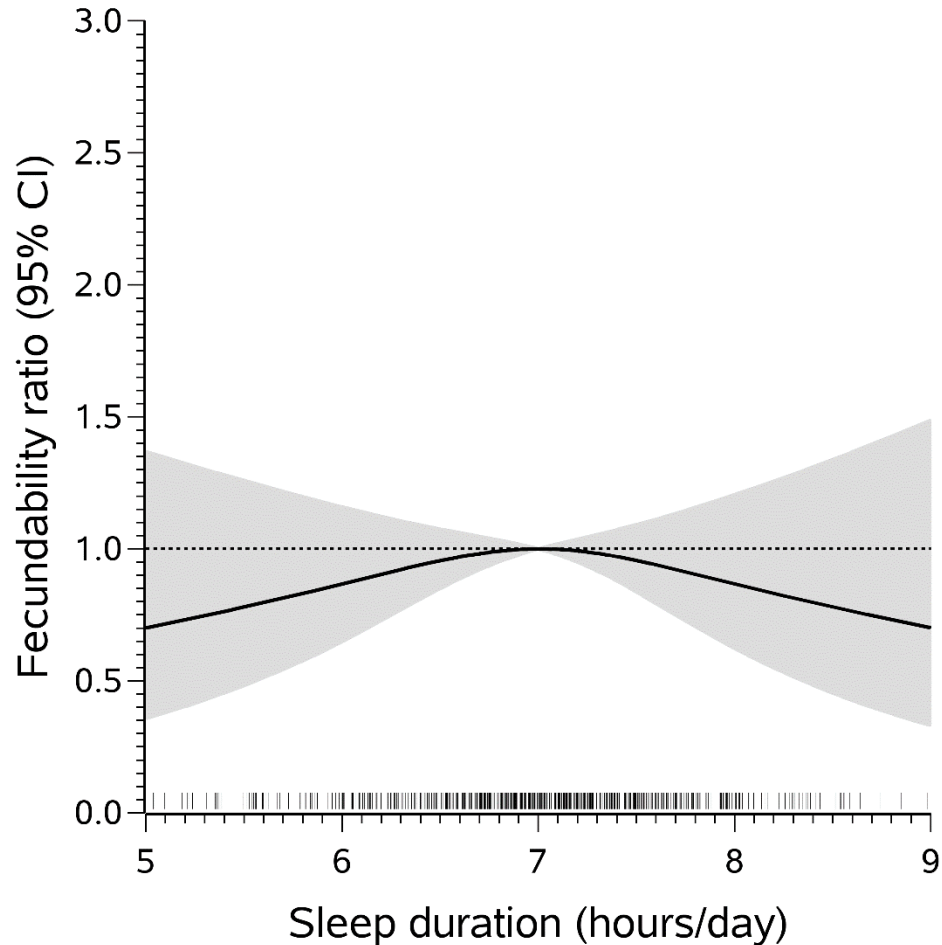
<sup>b</sup> Excludes cycles where all sleep assessment(s) were <1<sup>st</sup> or >99<sup>th</sup> percentile of the analytic cohort (n=2).

**Figure 4.1** Study population and exclusions, Pregnancy Study Online, 2021–2024

**Figure 4.2** Directed acyclic graph for the association of Fitbit-measured sleep health and fecundability



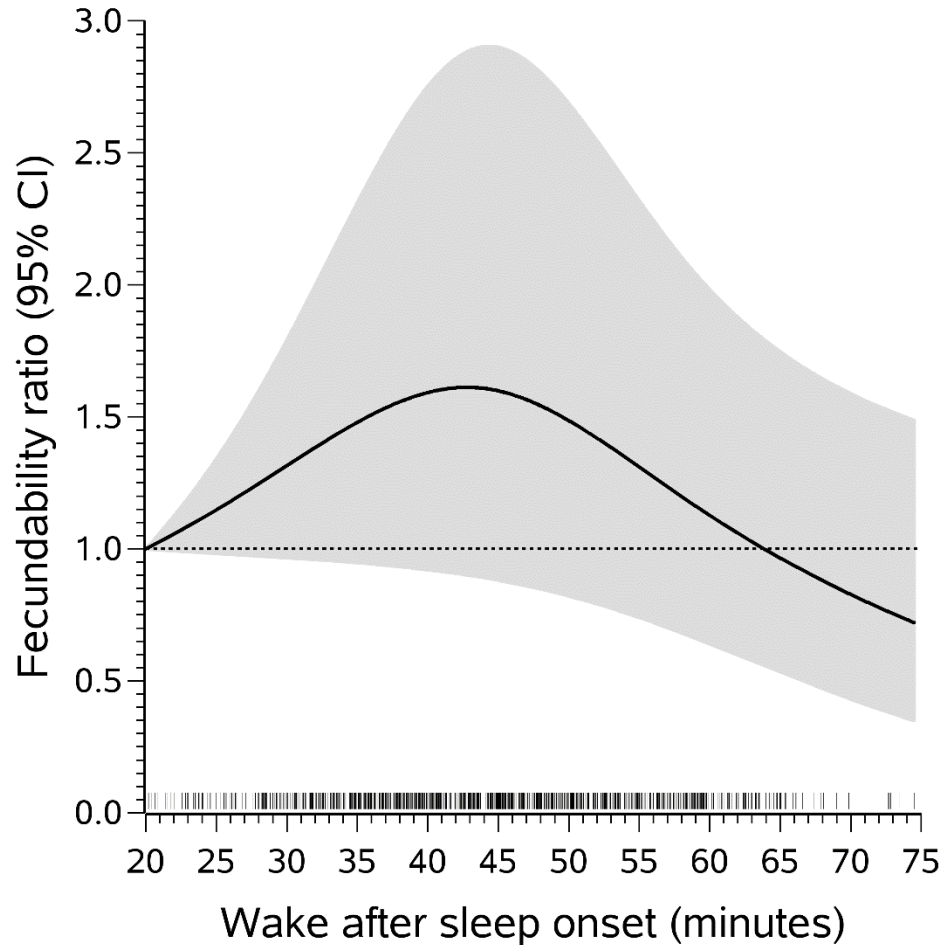
**Figure 4.3** Restricted cubic spline for the association of sleep duration and fecundability, Pregnancy Study Online, 2021–2024



CI: confidence interval.

Restricted cubic spline is adjusted for the following confounders: time-invariant – age, education, household income, employment status, job hours per week, any night work in the previous month, any shift work in the previous month, body mass index, parity, time since last birth, time since breastfeeding cessation, and last method of contraception; time-varying – physical activity, cannabis use, alcohol intake, perceived stress, depressive symptoms, psychotropic medication usage, caffeine intake, and sugar-sweetened beverage intake. The reference value is set at 420 minutes, and there are three knots at the 10<sup>th</sup> (359.1 minutes), 50<sup>th</sup> (423.3 minutes), and 90<sup>th</sup> (476.5 minutes) percentiles. We trimmed splines at the 1<sup>st</sup> percentile (lower end) and 9 hours/day (upper end) to avoid influence of extreme exposure values. Tick marks are a rug plot of the distribution of sleep duration in the cohort.

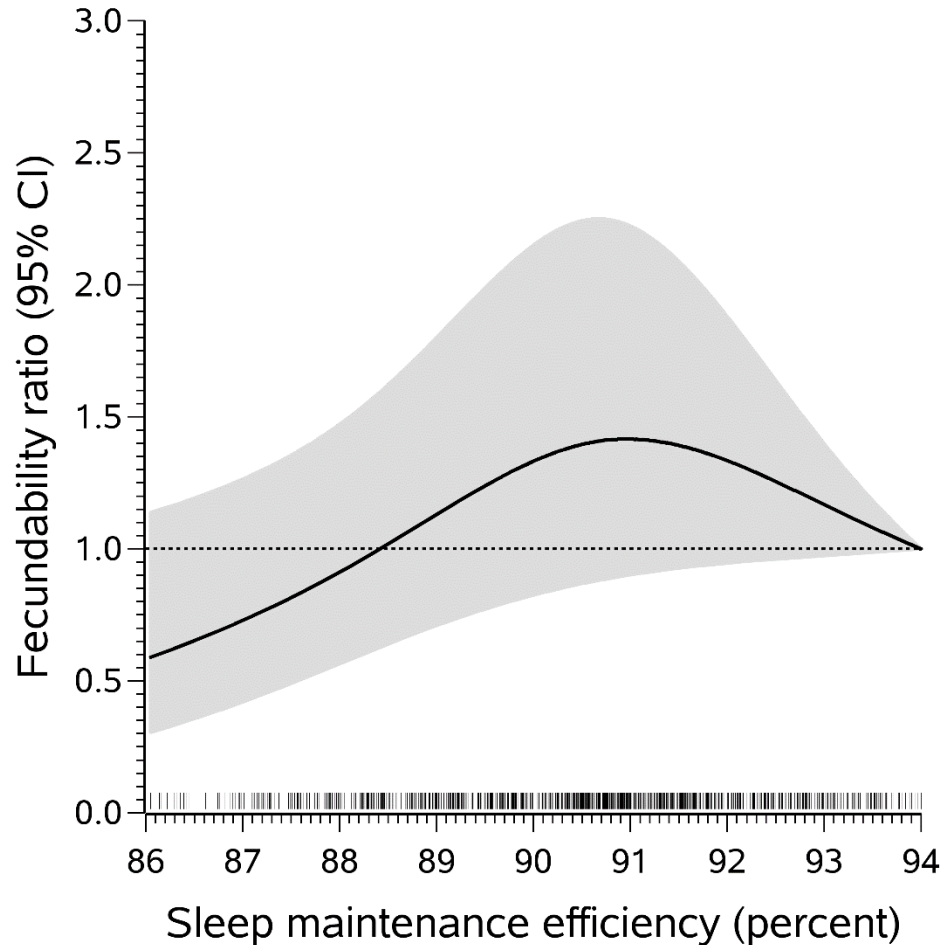
**Figure 4.4** Restricted cubic spline for the association of wake after sleep onset and fecundability, Pregnancy Study Online, 2021–2024



CI: confidence interval.

Restricted cubic spline is adjusted for the following confounders: time-invariant – age, education, household income, employment status, job hours per week, any night work in the previous month, any shift work in the previous month, body mass index, parity, time since last birth, time since breastfeeding cessation, and last method of contraception; time-varying – physical activity, cannabis use, alcohol intake, perceived stress, depressive symptoms, psychotropic medication usage, caffeine intake, and sugar-sweetened beverage intake. We winsorized wake after sleep onset values  $\leq 20$  minutes and set the reference value of 0–20 minutes. There are three knots at the 10<sup>th</sup> (26.3 minutes), 50<sup>th</sup> (43.8 minutes), and 90<sup>th</sup> (59.4 minutes) percentiles. We trimmed splines at the 99<sup>th</sup> percentile to avoid influence of extreme exposure values. Tick marks are a rug plot of the distribution of wake after sleep onset in the cohort.

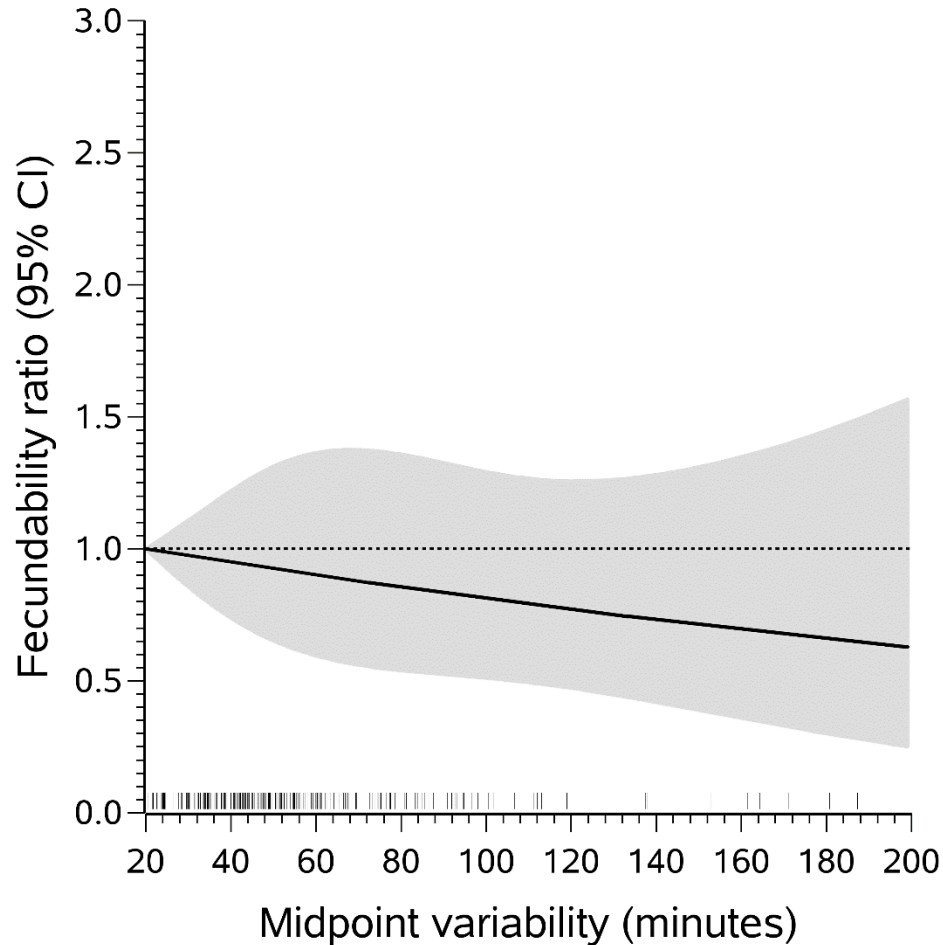
**Figure 4.5** Restricted cubic spline for the association of sleep maintenance efficiency and fecundability, Pregnancy Study Online, 2021–2024



CI: confidence interval.

Restricted cubic spline is adjusted for the following confounders: time-invariant – age, education, household income, employment status, job hours per week, any night work in the previous month, any shift work in the previous month, body mass index, parity, time since last birth, time since breastfeeding cessation, and last method of contraception; time-varying – physical activity, cannabis use, alcohol intake, perceived stress, depressive symptoms, psychotropic medication usage, caffeine intake, and sugar-sweetened beverage intake. We winsorized sleep maintenance efficiency values  $\geq 94\%$  to 94% and set the reference value of 94–100%. There are three knots at the 10th (88.0%), 50th (90.7%), and 90th (93.4%) percentiles. We trimmed splines at the 1<sup>st</sup> percentile to avoid influence of extreme exposure values. Tick marks are a rug plot of the distribution of sleep maintenance efficiency in the cohort.

**Figure 4.6** Restricted cubic spline for the association of sleep midpoint variability and fecundability, Pregnancy Study Online, 2021–2024



CI: confidence interval.

Restricted cubic spline adjusted for the following confounders: time-invariant – age, education, household income, employment status, job hours per week, any night work in the previous month, any shift work in the previous month, body mass index, parity, time since last birth, time since breastfeeding cessation, and last method of contraception; time-varying – physical activity, cannabis use, alcohol intake, perceived stress, depressive symptoms, psychotropic medication usage, caffeine intake, and sugar-sweetened beverage intake. We winsorized midpoint variability values  $\leq 20$  minutes and set the reference value of 0–20 minutes. There are three knots at the 10<sup>th</sup> (26.4 minutes), 50<sup>th</sup> (49.6 minutes), and 90<sup>th</sup> (114.4 minutes) percentiles. We trimmed splines at the 95<sup>th</sup> percentile to avoid influence of extreme exposure values. Tick marks are a rug plot of the distribution of midpoint variability in the cohort. We restricted analyses to cycles with  $\geq 5$  days of wear time.

## 5. CONCLUSION

This dissertation employed novel data collection and analytic methods to prospectively examine the association between sleep health and three reproductive outcomes: uterine leiomyomata (UL), menstrual cycle disturbances, and fecundability. First, we used data from the Study of Environment, Lifestyle, and Fibroids, an ultrasound-based prospective cohort study of reproductive-aged Black individuals from Detroit, Michigan between 2010 and 2022,<sup>1</sup> to study the effect of self-reported sleep health on UL incidence and growth. Second, using data from Pregnancy Study Online (PRESTO), a North American web-based prospective preconception cohort study of non-contracepting pregnancy planners that began in 2013,<sup>2</sup> we estimated the effect of self-reported sleep health on menstrual cycle disturbance risk. Third, using PRESTO data, we studied the association of objective preconception sleep health, measured using wrist actigraphy, and fecundability. We measured multiple domains of sleep<sup>3</sup> through self-reported and objective assessments. As there are few prospective studies of this association,<sup>4,5</sup> we were able to address an important limitation of prior research. Overall, our results suggest that poor sleep health is associated with increased menstrual cycle disturbance risk and reduced fecundability and may be protective against UL incidence.

In the first study, while we found that increased frequency of sleep trouble was associated with greater UL incidence rate, short and long sleep durations and feeling well-rested less than half the week were associated with decreased UL incidence rates. Also, we found that poor sleep health was not appreciably associated with UL growth. These latter findings of decreased UL incidence rates for short and long sleep durations

and feeling well-rested less than half the week, as well as no association between poor sleep and UL growth, were counter to our hypothesis. Major strengths of this study include: 1) the use of serial ultrasonography to detect and measure UL, as most prior research relies on self-reported diagnoses and may only identify cases with worse symptomatology,<sup>6</sup> and 2) use of inverse probability weighting to prevent biases from time-varying exposures and confounders.<sup>7</sup> These contradictory findings may be the result of several study limitations. Exposure misclassification may be possible due to the self-report of sleep health.<sup>3,8,9</sup> Further, it is possible that we misspecified our exposure definition, and more extreme definitions of short and/or long sleep duration (*e.g.*, <5 hours/day) and decreased feeling well-rested (*e.g.*, <3 days/week) may be associated with worse UL outcomes. Our available sample size in the extreme ends of these exposure distributions precluded us from exploring other exposure definitions. Finally, unmeasured confounding was possible because we were unable to longitudinally measure mental health symptoms and treatment, which are strongly related to sleep.<sup>10</sup> However, these findings may also lend support for other biologic mechanisms, including antagonistic effects of reproductive hormones on sleep health and UL outcomes, as well as chronic stress due to poor sleep and allostatic load. This was the first study to examine sleep health as a determinant of UL incidence and growth.

In the second study, short sleep duration and poor sleep quality, as measured using the Pittsburgh Sleep Quality Index,<sup>11</sup> were associated with increased risk of menstrual cycle disturbances among non-contracepting pregnancy planners, including abnormal cycle length, prolonged bleed length, heavy flow volume, and dysmenorrhea.

Poor sleep quality was also associated with increased risk of irregular cycles. These findings were in line with our hypothesis and are consistent with several cross-sectional studies.<sup>12-15</sup> Importantly, our study was prospective, which is a major strength given the established effect of menstrual cycle disturbances on sleep.<sup>16</sup> In addition, we defined menstrual cycle disturbances using International Federation of Gynecology and Obstetrics guidelines,<sup>17</sup> which improved salience of outcome definitions. We utilized inverse probability weights to account for sampling and confounding.<sup>7</sup> However, this approach, along with small sample sizes, caused imprecision in study results.<sup>18</sup> Also, we utilized self-reported measures of sleep health, though they were adapted from a validated questionnaire.<sup>11</sup> This study is the first prospective analysis of sleep health and menstrual cycle disturbances.

In the third study, we observed that short and long sleep duration, greater wake after sleep onset, reduced sleep maintenance efficiency, and greater midpoint variability during the preconception period were associated with decreased fecundability in a cohort of United States (U.S.) pregnancy planners. Additionally, we consistently documented associations between worse sleep health and reduced fecundability even in the presence of recommended sleep duration. While a previous PRESTO study found that self-reported short sleep duration and increased frequency of sleep trouble were associated with reduced fecundability,<sup>19</sup> these results could be biased due to exposure misclassification. To improve validity,<sup>20</sup> we measured sleep health in this present study using Fitbit (Google Fitbit Inc., San Francisco, CA) wrist actigraphy and affirmed these prior findings.<sup>19</sup> We were able to approximate each menstrual cycle at risk of conception

using participant-reported menstrual and reproductive data on baseline and follow-up questionnaires. We used these dates to estimate the relevant exposure window for sleep health relative to conception,<sup>21</sup> as sleep fluctuates throughout the menstrual cycle.<sup>22–24</sup> Although misspecification could be possible if cycle dates were estimated incorrectly, validation studies in PRESTO show high accuracy in the reporting of menstrual data.<sup>2</sup> This study was the first to examine objective preconception sleep health and fecundability.

In conclusion, self-reported and objective sleep health were associated with increased risk of menstrual cycle disturbances and reduced fecundability. Additionally, increased frequency of sleep trouble was associated with increased UL incidence rate. However, short and long sleep duration and feeling well-rested less than half the week were associated with decreased UL incidence rates, and sleep health showed little association with UL growth. Our findings have important public health implications, given the growing prevalence of sleep disturbances and disorders among reproductive-aged U.S. adults.<sup>25</sup> This dissertation reinforces the importance of studying sleep health in menstruating individuals and may inform potential interventions of a modifiable risk factor to improve reproductive outcomes.

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**CURRICULUM VITAE**

