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Sleep Disruption and Shift Work Associate with Increased Risk of Reproductive Endocrine Disorders: Evidence from UK Biobank and Mendelian Randomization

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Video Abstract

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Background: Disrupted sleep and shift work are linked to multiple adverse health outcomes, but their association with reproductive endocrine disorders (REDs) and underlying mechanisms remain unclear. Understanding this relationship is crucial for public health, given the growing prevalence of sleep disturbances and shift work in modern societies.

Purpose: To investigate the impact of sleep traits and shift work on RED risk in women, explore inflammatory mediation, and assess potential causality using Mendelian randomisation (MR).

Methods: We analysed 244,561 women in the UK Biobank. Sleep duration, quality, and shift work were self-reported. Cox models estimated hazard ratios (HRs) adjusting for demographic, lifestyle, and comorbidities. Interaction models tested joint effects of sleep and shift work. Mediation analyses examined inflammatory biomarkers. Two-sample MR analyses were conducted using large-scale genome-wide association study (GWAS) summary statistics to evaluate causal effects of sleep length or sleep quality traits on REDs.

Results: A U-shaped association was observed between sleep duration and RED risk, lowest at 7 h/day. Short (≤5 h/day; HR = 1.15, 95% CI: 1.02–1.31) and long (≥9 h/day; HR = 1.16, 95% CI: 1.04–1.29) sleep duration, poor sleep quality, and night shift work (HR = 1.40, 95% CI: 1.11–1.75) independently increased RED risk. The combination of night shift work and ≤5 h/day sleep duration showed the highest risk (HR = 1.72, p = 0.0219). Neutrophils, CRP, and leukocytes mediated 5–13% of these associations. MR analyses supported significant causal effects of short sleep duration, insomnia, and daytime napping on REDs.

Conclusion: Abnormal sleep duration, insomnia, and night shift work are independent risk factors for REDs in women, with inflammation partially mediating these associations. The highest risk was observed in women with short sleep combined with night shift work. MR analyses provide genetic evidence for the causal role of short sleep, insomnia, and daytime napping in REDs. These findings highlight the importance of screening for sleep disturbances and shift work in RED risk assessment, suggesting that interventions targeting sleep duration and shift work schedules may help reduce RED incidence and improve reproductive health. This study is the first to integrate both prospective and genetic evidence to identify causal pathways.

Keywords: sleep duration, shift work, reproductive endocrine disorders, inflammation, Mendelian randomisation, UK Biobank

Introduction

The female reproductive endocrine system plays a central role in regulating overall health. Its functional integrity is essential for fertility, menstrual cycle regulation, pregnancy progression, and the maintenance of systemic endocrine and metabolic homeostasis. Alarmingly, the prevalence of reproductive endocrine disorders (REDs)-encompassing a spectrum of common gynecological endocrine pathologies, including abnormal uterine bleeding (eg, menorrhagia or

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hypomenorrhea), endometriosis, infertility, polycystic ovary syndrome (PCOS), and early pregnancy loss-among women of reproductive age has risen markedly in recent decades.[1,2] This growing trend may be partially attributed to contemporary sociodemographic and lifestyle shifts, such as increasing obesity rates, delayed childbearing, chronic psychosocial stress, decreased physical activity, sleep disturbances, circadian rhythm disruptions, and heightened exposure to endocrine-disrupting chemicals. These factors can induce metabolic and hormonal imbalances and may heighten women's susceptibility to REDs.

Clinically, these conditions often manifest as ovulatory dysfunction, menstrual irregularities, pregnancy failure, and endocrine imbalances, collectively imposing a substantial public health burden.[3–5] Importantly, the impact of REDs extends far beyond reproduction itself. Robust evidence links REDs to metabolic disturbances (eg, insulin resistance and metabolic syndrome in PCOS), significant psychological burdens (including anxiety and depression), and a marked decline in quality of life, creating a multifaceted and interwoven health challenge. In parallel with this rising burden, contemporary diagnostic tools—such as high-resolution imaging, biomarker-based evaluations, and standardized diagnostic criteria—have substantially improved the identification and clinical characterization of REDs. Modern therapeutic strategies, including individualized hormonal regimens, metabolic interventions, and minimally invasive surgical techniques, have also contributed to better symptom control, improved fertility outcomes, and reductions in long-term metabolic and psychological complications.[2,6] However, the majority of them continue to emphasize symptom management rather than preventive interventions. Despite notable clinical heterogeneity, emerging research increasingly points to shared underlying pathophysiological mechanisms, including hypothalamic–pituitary–ovarian (HPO) axis dysregulation, chronic low-grade inflammation, and metabolic pathway abnormalities.[7] For example, in PCOS, hyperinsulinemia stimulates ovarian androgen production, leading to impaired hypothalamic negative feedback and enhanced pulsatile secretion of GnRH. This results in an altered ratio of luteinizing hormone (LH) to follicle-stimulating hormone (FSH), ultimately causing ovulation dysfunction and menstrual irregularities.[8] Furthermore, elevated androgen levels promote the differentiation of preadipocytes into visceral adipocytes via the androgen receptor (AR) signaling pathway while simultaneously inhibiting subcutaneous fat lipolysis. The excessive accumulation of adipose tissue may trigger a systemic inflammatory response and disrupt gut microbiota composition, thereby exacerbating metabolic dysregulation.[9] These mechanisms are highly susceptible to modulation by lifestyle factors, among which sleep, psychological stress, and nutritional status are recognized as key determinants.[10]

Sleep is a critical behavioral factor in maintaining the dynamic balance of the neuroendocrine–immune axis. Sleep disorders and circadian rhythm disturbances (including night shift work) are strongly linked to chronic diseases such as obesity, diabetes, cardiovascular disease, and depression.[11,12] Disruptions in sleep quality or architecture are widely recognized as potential triggers of impaired female reproductive health.[13,14] Multiple dimensions of sleep—including duration, efficiency (integrity and fragmentation), timing, regularity, and subjective quality—can profoundly influence reproductive function. Basic and clinical studies have identified several plausible pathogenic pathways: sleep disturbances may disrupt precise regulation of the hypothalamic–pituitary–gonadal (HPG) axis.[15] Reduced sleep continuity and increased nocturnal arousal have been shown to disrupt suprachiasmatic nucleus (SCN)–mediated circadian signaling to hypothalamic kisspeptin neurons—key drivers of GnRH pulsatility—thereby destabilizing the temporal coordination of the HPG axis.[16] Sleep disturbances diminish nocturnal melatonin secretion, leading to altered hypothalamic sensitivity to metabolic signals including leptin and ghrelin, increased insulin resistance, and impaired glucose homeostasis, thereby exacerbating neuroendocrine dysregulation in women with reproductive endocrine disorders.[17] Additionally, sleep disturbances may promote the release of C-reactive protein (CRP), interleukin-6 (IL-6), nuclear factor-κB (NF-κB) and other pro-inflammatory cytokines, leading to chronic low-grade inflammation that damages ovarian function and endometrial receptivity.[18]

Sleep is also intrinsically linked to circadian rhythms. The circadian clock system—a hierarchical network of central and peripheral oscillators—not only regulates sleep–wake and feeding–fasting cycles but also coordinates reproductive processes. Female reproductive physiology, including HPG axis hormone secretion,[19] ovulation,[20,21] implantation, and parturition, is tightly governed by circadian timing.[22,23] Optimal reproductive function thus relies on precise circadian regulation.[23] Sleep disturbances, such as irregular sleep patterns or shift work, and the resulting circadian misalignment can disrupt this temporal coordination, thereby impairing reproductive endocrine function.[24]

Emerging evidence, primarily from cross-sectional studies, indicates that sleep disorders such as insomnia, obstructive sleep apnea, hypersomnia (eg, narcolepsy), restless legs syndrome, and circadian rhythm sleep-wake disorders (eg, shift work disorder) impair not only sleep quality but also female reproductive function. Increasingly, these disorders are being linked to REDs such as PCOS, miscarriage,[25,26] endometriosis,[27] and menstrual irregularities.[28,29] Circadian misalignment is considered a key mechanistic link, disrupting HPG axis activity, altering hormonal secretion, and contributing to reproductive dysfunction.[30] Clinical observations corroborate these associations, showing that sleep apnea, chronic sleep restriction, shift work-induced circadian disruption, and excessive daytime sleepiness are significantly related to pathologies including anovulation, luteal phase deficiency, and endometrial hyperplasia. These findings underscore the profound impact of sleep disorders on reproductive health and highlight the need for deeper investigation into their complex interrelationships and mechanisms.

The global burden of sleep disorders is rising at an alarming rate.[31] Epidemiological studies reveal that a substantial proportion of women report persistent insufficient sleep duration and poor subjective sleep quality.[32] Concurrently, non-standard work schedules, such as shift work and night shifts, are becoming increasingly prevalent among professional women due to modern occupational demands.[33,34] Preliminary observational evidence suggests that specific sleep disturbances—such as sleep insufficiency, chronic night shift work, and poor sleep quality—are significantly associated with various REDs, including anovulatory cycles, luteal phase deficiency, early pregnancy loss, and hormonal imbalances.[10,35,36] These observations point toward a complex, potentially bidirectional interaction between sleep and female reproductive health.

Despite these emerging associations, critical knowledge gaps persist. High-quality studies systematically evaluating the relationship between sleep behaviors—particularly multidimensional indicators such as objective/subjective duration, sleep quality/efficiency, and circadian rhythm disruptions like shift work—and specific reproductive endocrine outcomes (eg, ovulatory disorders, menstrual cycle characteristics, infertility etiologies, and pregnancy complications) remain scarce. Methodological limitations are widespread: many studies have small sample sizes and insufficient statistical power; cross-sectional designs dominate, limiting causal inference (ie, whether sleep disturbances lead to REDs, or REDs and their comorbidities lead to sleep problems);[28,32,36–38] and confounding factors—such as body mass index, mood disorders, metabolic conditions, and other lifestyle variables—are often inadequately controlled, increasing the risk of bias. Moreover, inconsistencies across studies further impede definitive conclusions.

One emerging mechanistic pathway that may help bridge these gaps is chronic low-grade inflammation. This process is increasingly recognized as a central driver of various health outcomes associated with sleep disorders. Systemic inflammatory markers, such as C-reactive protein (CRP) and white blood cell count, have been closely linked to PCOS[39–42] and endometriosis,[42] with these inflammatory responses strongly modulated by circadian rhythms and steroid hormone levels.[43,44] Notably, shift work, sleep deprivation, and evening chronotype have all been associated with elevated inflammatory markers.[43,45] However, systematic evaluations investigating whether such inflammation mediates the relationship between sleep disturbances and REDs remain lacking.

Building on these considerations, the present study seeks to address this critical knowledge gap by focusing on a potential unifying mechanism—the sleep–reproductive axis. Leveraging the UK Biobank, a large-scale, rigorously designed prospective cohort, we will systematically investigate the longitudinal associations between multidimensional sleep behaviors—including sleep duration, sleep quality/impairment, and history of shift work—and key female reproductive endocrine outcomes (PCOS, infertility, miscarriage, endometriosis, and menorrhagia). The primary aims are to: (1) identify modifiable sleep-related behavioral factors significantly associated with the risk of reproductive endocrine dysfunction; (2) evaluate the independence and robustness of these associations through rigorous adjustment for a wide spectrum of potential confounders, including demographic, socioeconomic, lifestyle, metabolic, and mental health variables; (3) provide high-quality evidence to inform targeted risk stratification and preventive strategies for women's reproductive health; and (4) establish a robust population-based foundation for elucidating the biological mechanisms underlying sleep–reproductive interactions.

Furthermore, to strengthen causal inference, we will integrate Mendelian Randomization (MR) analyses. Using genome-wide association study (GWAS) data from the UK Biobank and the FinnGen biobank database, we will apply a two-sample MR approach to assess the causal effects of sleep-related phenotypes on REDs. This integrative framework

will not only deepen mechanistic insights into the bidirectional relationship between sleep and reproductive health but also provide a strong evidentiary basis for future prevention and intervention strategies aimed at improving women's health across the life course.

Materials and Methods

Study Population

The UK Biobank is a large-scale, population-based prospective cohort study that recruited over 500,000 adults aged 40 to 69 years from 22 assessment centers across England, Wales, and Scotland between 2006 and 2010 (for a geographic distribution of the centers, please refer to: https://www.ukbiobank.ac.uk/about-our-data/our-participants/), during which all participants completed the initial baseline data collection procedure.[46,47] This study uses data from the UK Biobank, under application number 632861, incorporating follow-up data from the baseline assessment through February 2022. The UK Biobank has comprehensively collected extensive phenotypic and genotypic data. Baseline data were gathered through touchscreen questionnaires completed by participants, interviews, and standardized physical examinations. Additionally, the study includes data from biological samples (eg, blood samples) and genome-wide genotyping. Participants provided detailed information on sleep patterns and other health-related factors through questionnaires and interviews. Given that the target outcomes—PCOS, infertility, abnormal uterine bleeding, endometriosis, and abortion-related disorders—are specific to women, and that sex-related differences in endocrine and psychosocial characteristics may modify the relationship between sleep traits, shift work, and reproductive endocrine disorders, the present analysis was restricted to female UK Biobank participants. The UK Biobank study has received ethical approval from the North West Multi-Center Research Ethics Committee, and all participants have signed written informed consent. Additionally, the study has received approval from the Medical Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (approval number 2025–0542, approval date: November 10, 2025).

Data Collection and Definition of REDs

At baseline, participants enrolled in the UK Biobank completed a comprehensive touchscreen questionnaire and underwent physical examinations conducted by trained staff. Data collected included demographic characteristics (eg, age, sex, ethnicity, education level), lifestyle behaviors (eg, smoking status, alcohol consumption, physical activity), and self-reported medical history. Additional health-related information was obtained through linkage with hospital inpatient records, primary care data, and national death registries.

REDs were identified using hospital inpatient records and death registry data based on the International Classification of Diseases, 10th Revision (ICD-10) codes. Specifically, the following conditions were included: polycystic ovarian syndrome (E28.2), infertility (N97), endometriosis (N80), menorrhagia (N92), and abortion-related disorders (O03, O04, O06). Participants with any of the above diagnoses recorded during the follow-up period were classified as having a reproductive endocrine disease outcome. During follow-up, we identified 26,120 incident RED cases among women aged 40–69 years. Consistent with established epidemiological evidence, women who developed REDs were more likely to present with higher adiposity, smoking, socioeconomic disadvantage, and psychological distress at baseline. Supplementary Table S1 provides the ICD codes for REDs and the corresponding data fields from the UK database used in this study.

Sleep Duration

Participants were asked, "On average, how many hours do you sleep within a 24-hour period (including naps)?" They responded with an integer value representing the number of hours per day. Based on their responses, participants were categorized into the following groups: ≤5 hours, 6 hours, 7 hours, 8 hours, or ≥9 hours.

Sleep Quality Score

A Sleep Quality Score was developed based on five sleep-related behavioral factors: chronotype, sleep duration, insomnia symptoms, snoring, and excessive daytime sleepiness. Each factor was classified as either "low risk" or

"high risk" based on its associated health risks, with a score of 1 assigned for "low risk" and 0 for "high risk". The total score, ranging from 0 to 5, was calculated by summing the individual scores, with a higher score indicating a healthier sleep pattern. The criteria for "low risk" classification were as follows: Chronotype: "morning type" or "moderate morning type"; Sleep Duration: 7–8 hours per 24-hour period (including naps); Insomnia Symptoms: "never" or "rarely" experiencing insomnia; Snoring: no self-reported snoring; Excessive Daytime Sleepiness: "never/rarely" or "sometimes" experiencing daytime sleepiness. Based on the total score, participants were categorized into three groups: Healthy Sleep Pattern (score ≥4), Intermediate Sleep Pattern (score of 3), and Poor Sleep Pattern (score ≤2). This classification method, adapted from several prospective cohort studies based on the UK Biobank,[48–51] is widely used to explore the relationship between sleep behaviors and chronic disease risk, supporting its predictive validity as a composite sleep indicator in large-scale epidemiological research. The scoring system details are provided in supplementary Table S2. Conceptually, it follows a multidimensional framework similar to the Pittsburgh Sleep Quality Index (PSQI), capturing key aspects of sleep duration, continuity, timing, and symptoms, while offering a more streamlined and user-friendly format suitable for population-level risk assessment in very large cohorts. Furthermore, the algorithm's effectiveness has been externally validated in the China Kadoorie Biobank study,[48] providing additional support for its reliability and generalisability across populations. In all regression analyses concerning sleep quality, the "Healthy Sleep Pattern" group served as the reference category. Participants who responded "Don't know" or "Prefer not to answer" to any sleep-related question were excluded from the analysis.

Shift Work

Only participants who were still employed at the time of recruitment were included in the shift work analysis. Shift work classification was based on responses to two questions: "Does your work involve shift work?" and "Does your work involve night shifts?" In the UK Biobank, shift work is defined as "work arrangements that occur outside of normal daytime working hours (9 a.m. to 5 p.m)".; while night shifts are specifically defined as "work arrangements occurring during typical sleep hours, such as from midnight to 6 a.m". Participants were required to select one of the following options for each question: "Never/Rarely", "Sometimes", "Often", or "Always". Based on the responses to these two questions, participants were classified into five shift work categories: No Shift Work (reference group), Day Shift, Mixed Shift, Night Shift, and Permanent Night Shift. The specific classification criteria for shift work are provided in Supplementary Table S3.

Statistical Analysis

For baseline characteristics, categorical variables are presented as n (%), normally distributed continuous variables as mean (standard deviation), and non-normally distributed continuous variables as median [interquartile range]. The distribution of baseline characteristics across different lifestyle categories was compared using the χ^2-test, analysis of variance (ANOVA), and Kruskal–Wallis test. It should be noted that, due to the large sample size, these tests may detect statistical significance even for minor differences.

Cox proportional hazards regression models were used to assess the associations between sleep duration, sleep quality score, and shift work type with the risk of REDs. Results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). The exposure variables were categorized with the following reference groups: sleep duration of 7 hours, sleep quality score of ≥4, and no shift work, to examine linear trends. Based on the risk factors of REDs and the associated diseases of sleep disorders described above, we constructed two multivariate models to control for potential confounding factors: Model 1 adjusted for age (continuous), Townsend deprivation index (continuous), ethnicity (White, South Asian, Black, Other), education level (high or low), smoking status (never, past, current), alcohol consumption (never, past, current), and body mass index (BMI, continuous); Model 2 additionally adjusted for three comorbidities: diabetes (yes/no), hypertension (yes/no), and family history of depression (yes/no). The proportional hazards assumption was tested using Schoenfeld residuals, and the results indicated that the assumption was met for all covariates in the models. In both regression models, we assessed potential collinearity among sleep traits (eg, sleep duration and sleep quality) using correlation analysis and the Variance Inflation Factor (VIF). No significant collinearity was detected, with all VIF values remaining below the threshold of 10. To account for multiple comparisons, we applied Bonferroni

correction. Additionally, we used False Discovery Rate (FDR) correction to control for Type I errors while balancing sensitivity and specificity in our analyses.

To test the robustness of the results, the following sensitivity analyses were conducted: (1) Multiple imputations using predictive mean matching (PMM, m = 10) were conducted via the MICE (Multivariate Imputation by Chained Equations) algorithm.[52] Both continuous and categorical variables were imputed, using PMM for continuous variables and predicted probability matching for categorical variables. Model estimates were then pooled across imputed datasets to address missing data bias. (2) When assessing the relationship between sleep duration, sleep traits and REDs, individuals who had pre-existing relevant conditions at baseline were excluded to reduce the potential for reverse causality. A detailed description of the data preprocessing steps (including missing data handling and exclusion criteria) can be found in Supplementary Methods. All statistical analyses were performed using R software version 4.5.1, with a two-sided P-value <0.05 considered statistically significant. Bonferroni correction was applied for multiple comparisons in specific cause analysis.

Mediation Statistical Method

To examine whether the relationship between sleep duration and REDs is mediated by inflammatory markers, a mediation analysis was conducted. The analysis was performed using the mediation package in R 4.5.1, with survival analysis conducted using the survival package. The exposure variable was sleep duration (with 7 hours as the reference group, categorized as ≤5 hours, 6 hours, 8 hours, and ≥9 hours). The mediator variables included inflammatory markers: neutrophils, monocytes, basophils, eosinophils, white blood cells, neutrophil-to-lymphocyte ratio (NLR), and C-reactive protein (CRP). The outcome variable was the occurrence of REDs. Covariates included age, Townsend deprivation index, ethnicity, education level, smoking status, alcohol consumption, BMI, diabetes, hypertension, and family history of depression.

First, linear regression models (lm function) were used to evaluate the association between sleep duration and each inflammatory marker, and to examine whether sleep duration influences the occurrence of REDs through these markers. Next, Cox proportional hazards models (survreg function) were used to model the associations between sleep duration and each mediator variable with REDs. Finally, the mediate function was used to perform the mediation analysis, estimating the direct effect (ADE), indirect effect (ACME), and total effect (Total Effect), and calculating the proportion mediated (Prop Mediated) for each mediator variable. All results were computed using 100 simulations, and robust standard errors (robustSE) were used. To ensure the accuracy of the results, hypothesis testing was performed for each mediator variable, with P-values <0.05 considered statistically significant. The 95% confidence intervals for all mediation effects were calculated.

Causal Inference Using Mendelian Randomization (MR)

To assess the causal effects of sleep-related behavioral factors on REDs outcomes such as PCOS, female infertility, abortion and endometriosis, we performed two-sample Mendelian Randomization (MR) analyses using the "TwoSampleMR" package in R. Summary statistics for the exposures were obtained from two large-scale GWAS, including data from UK Biobank and FinnGen biobank database.[53] For each sleep-related exposure, including daytime sleepiness, sleep duration, long sleep duration, short sleep duration, insomnia, chronotype, and nap during the day, we extracted summary statistics from relevant datasets. Summary statistics for the outcomes of interest—PCOS, female infertility, abortion, and endometriosis—were obtained from the respective datasets, as presented in supplementary Table S4.

For each exposure, we extracted significant SNPs based on the genome-wide significance threshold of $P < 5.0 \times 10^{-8}$. If the number of SNPs for a given trait was fewer than three, we relaxed the threshold to $P < 5.0 \times 10^{-7}$. The extracted SNPs were used as instrumental variables, and linkage disequilibrium (LD) clumping was performed with an $r^2 > 0.001$ within a 10,000 kb window to ensure SNP independence. A detailed description of the genetic instrument selection sensitivity process can be found in the supplementary materials: Supplementary Methods. We harmonized the exposure and outcome datasets and applied the inverse variance weighted (IVW) method under both fixed and random effects models as the primary approach to combine the effects of each SNP. Additionally, we employed weighted median, simple

median, and MR-Egger methods for sensitivity analysis to assess the robustness of the findings.[54] To check for heterogeneity and horizontal pleiotropy, we utilized Cochran's Q test and the MR-Egger regression intercept. Moreover, we applied the MR-PRESSO method to detect and correct for any outliers. We also performed a "leave-one-SNP-out" analysis to ensure that the overall causal estimate was not driven by any single SNP.[55]. To ensure the validity of MR analysis, three core assumptions must be met: (1) the genetic variants (instrumental variables, IVs) must be strongly associated with the exposure (relevance assumption); (2) the genetic variants must not be associated with any confounders (independence assumption); and (3) the genetic variants must affect the outcome only through the exposure and not via alternative pathways (exclusion restriction assumption). In this study, we implemented a rigorous IV selection process and subsequent MR analyses to meet these assumptions and ensure the robustness of our findings. The conduct and reporting of the MR analyses adhered to the STROBE-MR guidelines (see supplementary Table S5).

Results

Baseline Characteristics of the Study Population

This study included 244,561 female participants from the UK Biobank, with a median age of 58 years (interquartile range [IQR]: 51–63; range: 39–71). The median BMI was 26.0 kg/m^2 (IQR: 23.4–29.5). The majority of participants were of White ethnicity (94.9%), with the remaining 5.1% identifying as other ethnicities. In terms of educational attainment, 62.5% had completed secondary education, while 37.5% had attained higher education. Regarding sleep characteristics, 37.7% of participants reported a sleep length of 7 hours per night, 30.1% reported 8 hours, 24.6% reported ≤6 hours, and 7.6% reported ≥9 hours. Sleep quality scores were distributed as follows: 21.8% scored 0–2 points, 38.8% scored 3 points, and 39.4% scored 4–5 points. With respect to shift work status, 85.5% reported having no shift work, 8.4% worked day shifts, 3.5% had mixed shifts, 1.1% worked night shifts, and 1.6% were engaged in permanent night shifts. Figure 1 presents an overview of the sample selection process for all analyses conducted in this study.

Cardiometabolic profiles showed that 24.5% of participants had hypertension, 2.0% had diabetes, and 14.7% reported a family history of depression. Regarding behavioral factors, 59.8% were never smokers, 31.5% were former smokers, and 8.7% were current smokers. Alcohol consumption patterns were as follows: 5.7% never drank, 3.5% were occasional drinkers, and 90.8% reported regular drinking. The detailed baseline characteristics are presented in supplementary Table S6. Stratified characteristics based on sleep duration, sleep quality score, and shift work status are presented in supplementary Table S7–9 for imputed data and in supplementary Tables S10–12 for complete data.

Association Between Sleep Duration, Sleep Quality, and Risk of REDs

To examine the relationship between sleep duration, specific sleep traits, and the potential risk of developing REDs, we conducted Cox regression analyses under two models: a basic model (Model 1) adjusting for demographic and lifestyle factors, and a comorbidity-adjusted model (Model 2) additionally controlling for diabetes, hypertension, and family history of depression.

As shown in Figure 2A, both short (≤5 h/day) and long (≥9 h/day) sleep durations were significantly associated with increased risk compared to the reference group of 7 h/day. In Model 1, the hazard ratio (HR) was 1.17 (95% CI: 1.03–1.32; p = 0.014) for ≤5 h/day and 1.17 (95% CI: 1.05–1.31; p = 0.004) for ≥9 h/day (see supplementary Table S13.1). These associations remained statistically significant after adjustment for comorbidities in Model 2, with slightly attenuated HRs of 1.15 (95% CI: 1.02–1.31; p = 0.024) and 1.16 (95% CI: 1.04–1.29; p = 0.007), respectively (see supplementary Table S13.2). Sleep durations of 6 h and 8 h/day were associated with modestly elevated HRs in both models (range: 1.07–1.08), although the statistical significance was marginal. A U-shaped association was observed across both models, with the lowest risk observed at 7 h/day.

As shown in Figure 2B, poor sleep quality, as indicated by lower sleep scores, was significantly associated with increased risk. In Model 1, the hazard ratios (HRs) were 1.09 (95% CI: 1.01–1.17; p = 0.023) for a score of 3 and 1.17 (95% CI: 1.07–1.27; p = 0.001) for scores ≤2, compared to the reference group (score ≥4) (see supplementary Table S14.1). These associations remained consistent after adjustment for comorbidities in Model 2, with HRs of 1.08 (95% CI: 1.01–1.17; p = 0.033) for a score of 3 and 1.15 (95% CI: 1.05–1.26; p = 0.002) for scores ≤2 (see supplementary Table S14.2).

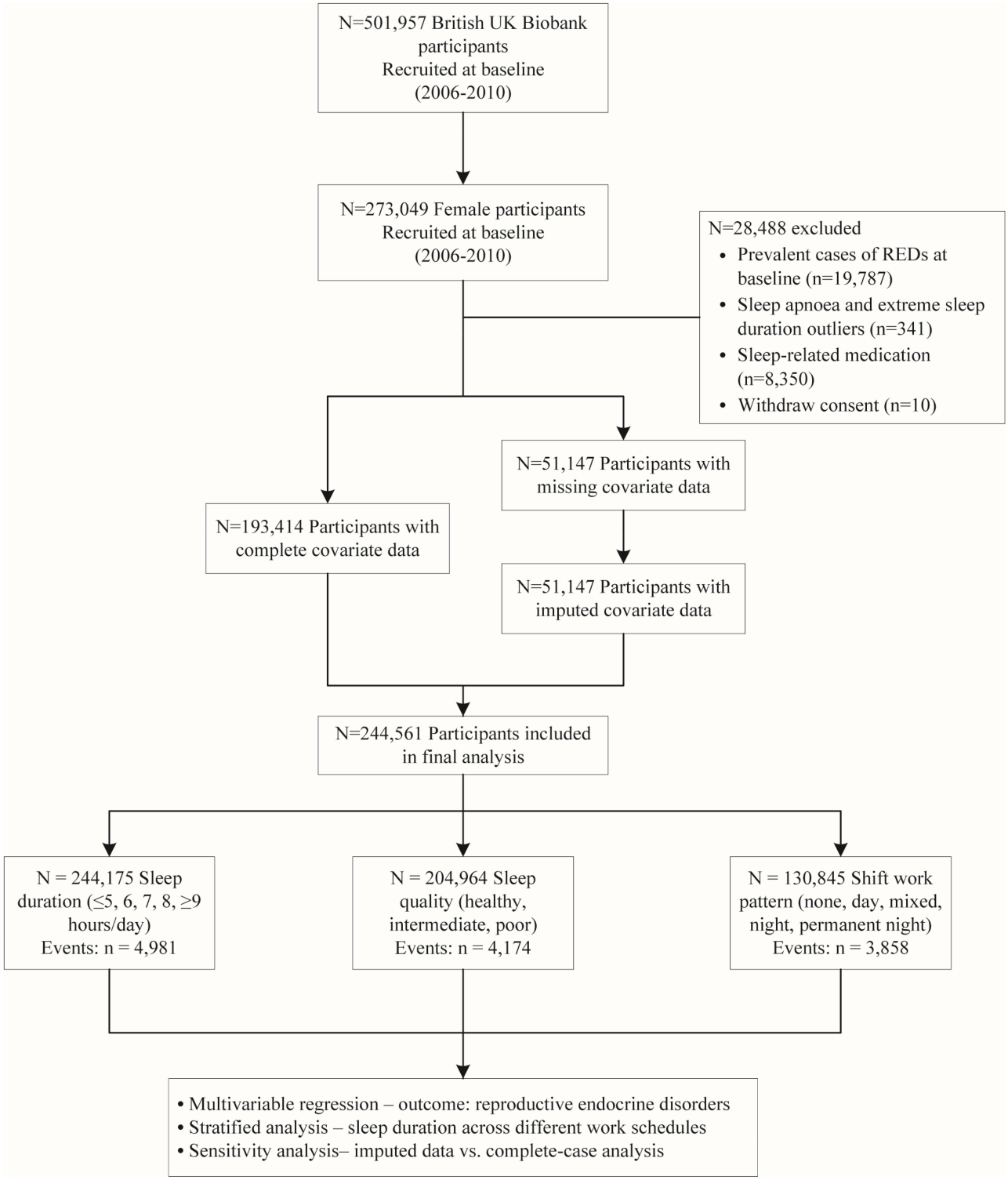

Figure 1 Study flow chart. Participants were classified based on self-reported sleep duration, assigned sleep quality score, and self-reported shift work schedules. The flow chart illustrates participant inclusion and exclusion criteria, as well as the final sample sizes for each group based on these classifications. REDs refer to reproductive endocrine diseases.

In both models, several covariates were consistently associated with the outcome. Older age and higher education were protective factors ($p < 0.001$), whereas higher BMI, ethnic minority status, hypertension, and family history of depression were associated with increased risk ($p < 0.05$).

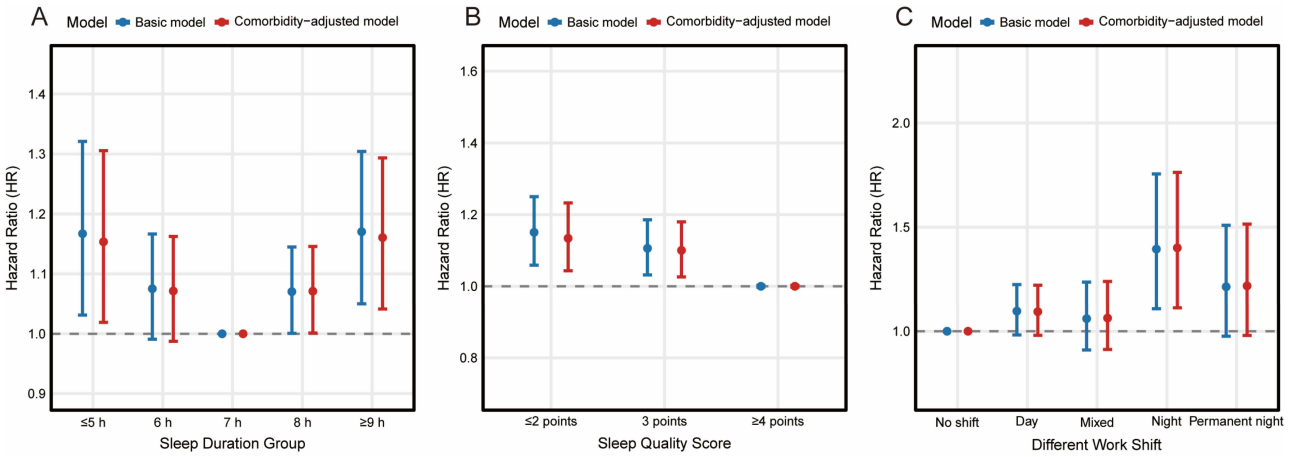

Figure 2 Associations of sleep duration, sleep quality, and shift work type with risk of reproductive endocrine diseases (REDs). Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models under two adjustment strategies: a basic model and a comorbidity-adjusted model. (**A**) Association between sleep duration and REDs risk. Both short (≤5 h) and long (≥9 h) sleep durations were associated with increased risk compared to 7 h, showing a U-shaped relationship. (**B**) Association between sleep quality and REDs risk. Lower sleep quality scores (≤2 and 3 points) were significantly associated with higher REDs risk relative to high sleep quality (≥4 points), indicating a dose-response trend. (**C**) Association between types of shift work and REDs risk. Night shift work was significantly associated with elevated REDs risk (HR = 1.39, 95% CI: 1.11–1.75; p = 0.005), while permanent night shift showed a non-significant trend (HR = 1.21, 95% CI: 0.98–1.51). No significant associations were found for day or mixed shifts. Data are shown as β-estimates ± 95% CIs, with center circles and error bars. See supplementary Tables S13, 14 and S17 for details.

To further assess the robustness of the findings, a sensitivity analysis was performed using a complete-case dataset, excluding participants with any missing covariate data. The results were highly consistent with those derived from the imputed dataset. As illustrated in supplementary Figure S1A, B and Tables S15–S16, the U-shaped association between sleep duration and disease risk, along with the dose–response relationship for sleep quality, remained evident. These findings further support the stability and validity of the observed associations across different analytical strategies.

Collectively, these results indicate that after comprehensive adjusting for demographic, lifestyle, and comorbidities, both abnormal sleep duration (particularly ≤5 or ≥9 hours per day) and poorer sleep quality are independently associated with an increased risk of reproductive endocrine disorders in women.

Association Between Types of Work Shift and Risk of REDs

As shown in Figure 2C and supplementary Table S17, night shift work was significantly associated with an increased risk of REDs compared with no shift work, with a 39% higher hazard in the basic model (HR = 1.39, 95% CI: 1.11–1.75; p = 0.005). Permanent night shift work showed a non-significant trend toward elevated risk (HR = 1.21, 95% CI: 0.98–1.51; p = 0.082). These associations remained directionally consistent in Model 2 after adjustment for comorbidities, with the HR for night shift slightly increased to 1.40 (p = 0.004), and for permanent night shift to 1.22 (p = 0.076), though the latter remained statistically non-significant. Day and mixed shift work were not significantly associated with risk in either model (p > 0.05). Night shift work was linked to a higher risk of REDs, but no linear trend across shift types was evident.

In both models, several covariates were independently associated with REDs risk. Older age was linked to a lower risk (p < 0.001), whereas higher BMI emerged as a strong risk factor (p < 0.001). Ethnic minority status and lower educational attainment were also significantly associated with increased risk (both p < 0.001). In Model 2, comorbidities including hypertension (HR = 1.14, 95% CI: 1.04–1.25; p = 0.005) and a family history of depression (HR = 1.13, 95% CI: 1.04–1.23; p = 0.004) were independently associated with higher risk. Former smoking was linked to reduced risk (p < 0.05), while drinking status showed no significant association.

To evaluate the robustness of the findings, a complete-data analysis was performed by restricting the sample to participants with no missing covariate data. As shown in supplementary Figure S1C and Table S18, the results were consistent with those from the multiply imputed datasets, supporting the validity of the observed associations.

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Joint Effect of Sleep Duration and Shift Work on REDs

The combined effect of sleep duration and shift work on REDs risk was evaluated using interaction models, with non-shift workers sleeping 7 hours/day as the reference group. In the main effects model, consistent with previous analyses, both very short sleep duration (<5 hours) and night shift work were independently associated with elevated risk, with HRs of 1.25 (p = 0.0105) and 1.56 (p = 0.0219), respectively (Figure 3 and Supplementary Table S19.1).

In the interaction model, the highest risk was observed among night shift workers sleeping ≤5 hours/day (HR = 1.72; p = 0.0219), followed by those sleeping 6 hours/day (HR = 1.36; p = 0.0041). Further adjustment for comorbidities, including hypertension, diabetes, and a family history of depression, slightly attenuated these associations. However, the combinations of night shift work with ≤5 or 6 hours of sleep remained significantly associated with REDs (HR = 1.71, p = 0.0044; and HR = 1.36, p = 0.0262, respectively). In contrast, no significant associations were found among night shift workers sleeping ≥7 hours/day (p > 0.05; Figure 3 and supplementary Table S19.2).

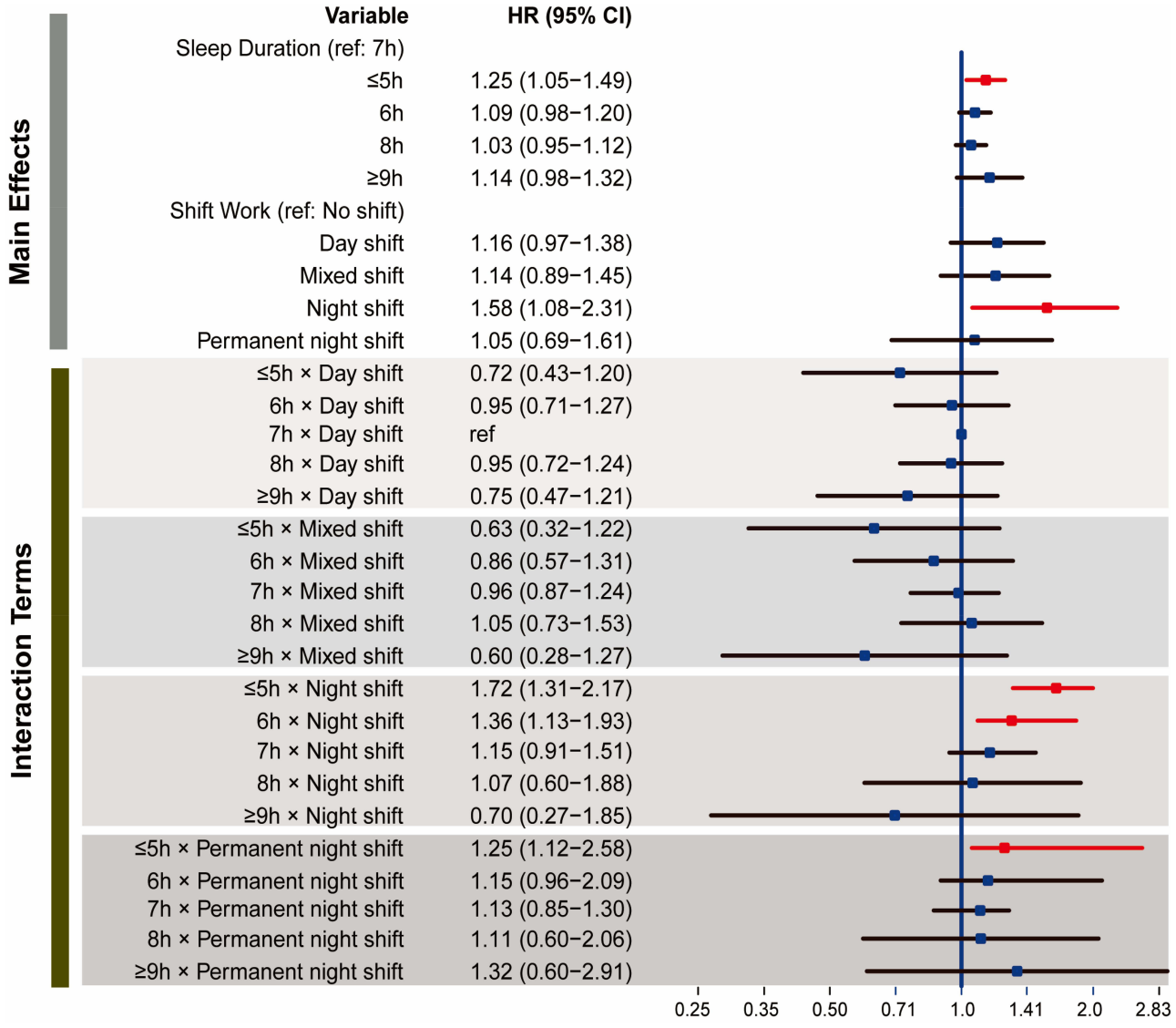

Figure 3 Joint association of sleep duration and night shift work with risk of reproductive endocrine diseases (REDs). Cox proportional hazards models estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for REDs risk across combinations of sleep duration and shift work. Non-shift workers sleeping 7 h/day served as the reference group. The highest risk was observed among night shift workers sleeping ≤5 h/day (HR = 1.72; *p* = 0.0219), followed by those sleeping 6 h/day (HR = 1.36; *p* = 0.0041). These associations remained significant after adjustment for comorbidities. No significant associations were found among night shift workers sleeping ≥7 h/day. Data are shown as HRs ± 95% CIs, with center circles and error bars. See supplementary Table S19 for details.

These findings suggest that sleep duration and shift work interact to influence the risk of REDs, with the highest risk observed among individuals who both worked night shifts and slept ≤5 hours per day.

Mediation by Inflammatory Markers

We conducted mediation analyses to investigate the role of inflammatory biomarkers—including neutrophils, monocytes, basophils, eosinophils, leukocytes, NLR, and CRP—in the associations between sleep duration, night shift work, and REDs.

In the comparison of ≤5 hours versus 7 hours of sleep (reference), neutrophils significantly mediated the relationship, with an average causal mediation effect (ACME) of 1,788.99 (95% CI: 1,138.42–2,646.06; p = 0.04), accounting for 11.82% (95% CI: 4.6%–37.0%; p < 0.001) of the total effect. Leukocytes and CRP also demonstrated significant mediation, with ACMEs of 15,320.24 (p = 0.04) and 15,821.76 (p = 0.02), and mediation proportions of 5.28% and 9.92%, respectively. Monocytes and basophils showed smaller but significant mediation effects (ACME = 79.58 and 138.19; p = 0.02 for both), though monocytes had a marginal mediation proportion (0.5%; p = 0.06). Eosinophils did not exhibit significant mediation despite a significant total effect (Figure 4A-C and Supplementary Table S20.1).

Similar patterns were observed when comparing ≥9 hours versus 7 hours of sleep. Neutrophils again significantly mediated the association (ACME = 2,202.81; p = 0.02), with a mediation proportion of 12.97% (95% CI: 8.1–37.2%). CRP remained a significant mediator (ACME = 1,557.11; 95% CI: 942.45–2,107.07; p = 0.04), with a mediation proportion of 6.89% (Figure 4D, 4E and Supplementary Table S20.2).

In the context of night shift work, neutrophils were also identified as significant mediators, with an ACME of 1,391.47 (95% CI: 512.78–1,935.64; p = 0.04), accounting for 6.55% (95% CI: 3.6–12.7%) of the total effect. NLR showed a borderline mediation effect (ACME = 357.07; p = 0.06), while other biomarkers—including monocytes, basophils, eosinophils, leukocytes, and CRP—did not demonstrate significant mediation effects despite notable total effects (Figure 4F and Supplementary Table S20.3).

Collectively, these findings underscore neutrophils and CRP as key mediators linking sleep duration to REDs, and neutrophils as a critical mediator between night shift work and REDs, suggesting that systemic inflammation may partially account for the pathological mechanisms underlying these associations.

Short Sleep Duration, Insomnia and Daytime Napping are Causally Linked to REDs

To further explore the potential causal effects of sleep length or sleep quality traits on REDs, we conducted two-sample MR analyses using published GWAS summary statistics. The selected exposures included short sleep duration, long sleep duration, insomnia, daytime sleepiness, morning/evening preference, and daytime napping, while the outcomes comprised PCOS, spontaneous abortion, endometriosis, and female infertility (due to the lack of available GWAS data on menorrhagia, this condition was not included in the present MR analyses). Multiple MR methods were applied, including IVW, weighted median, MR-Egger, simple mode, and weighted model, to ensure the robustness of the findings.

As illustrated in Figure 5A–D, short sleep duration showed significant positive associations with PCOS, abortion, and female infertility across multiple methods, suggesting that insufficient sleep may increase the risk of these conditions. Similarly, as shown in Figure 5E–H, insomnia demonstrated consistent causal associations with PCOS, abortion, endometriosis, and infertility, highlighting insomnia as a potential causal risk factor. In addition, daytime napping was positively associated with PCOS, spontaneous abortion, endometriosis, and infertility (Figure 5I–L), further supporting a causal role of daytime sleep habits in female reproductive health.

In contrast, Mendelian randomisation analyses revealed no robust or consistent causal associations for daytime sleepiness, long sleep duration, or chronotype (morning/evening preference) across the different analytical methods employed, suggesting weaker or inconclusive evidence for these sleep traits. Comprehensive MR estimates are presented in supplementary Table S21, and corresponding leave-one-out sensitivity analyses are shown in supplementary Figures S2–S4 of the supplementary materials, further confirming the lack of strong causal signals and supporting the robustness of the null findings.

Taken together, these MR analyses provide genetic evidence supporting significant and consistent causal relationships of short sleep duration, insomnia, and daytime napping with multiple REDs, including PCOS, spontaneous abortion,

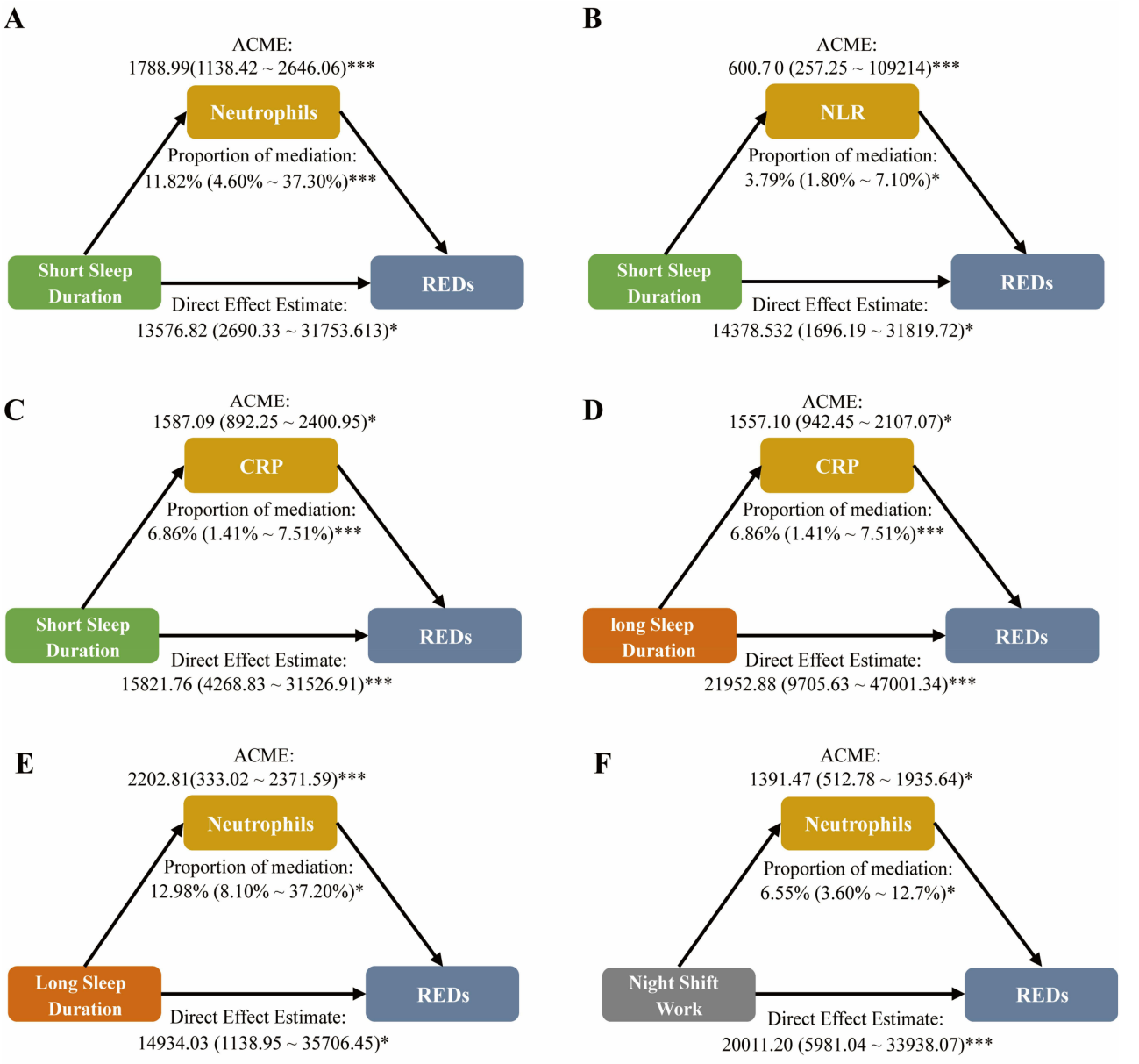

Figure 4 Mediation effects of inflammatory biomarkers on the associations between sleep duration, night shift work, and risk of reproductive endocrine diseases (REDs). Mediation analyses were conducted to estimate the indirect effects of inflammatory biomarkers—including neutrophils, monocytes, basophils, eosinophils, leukocytes, neutrophil-to-lymphocyte ratio (NLR), and C-reactive protein (CRP)—on associations with REDs. (**A–C**) Association between short sleep duration (≤5 h vs 7 h) and REDs. Significant mediation effects were observed for neutrophils, leukocytes, and CRP. Monocytes and basophils showed smaller but significant mediation effects. (**D–E**) Association between long sleep duration (≥9 h vs 7 h) and REDs. Neutrophils and CRP significantly mediated the association, with notable proportions of the total effect explained. (**F**) Association between night shift work and REDs. Neutrophils emerged as a significant mediator, while NLR showed a borderline effect. Other biomarkers did not demonstrate significant mediation. Data are shown as average causal mediation effect (ACME), average direct effect (ADE), total effect, and proportion mediated, with 95% confidence intervals (CIs). *Statistical significance: *p < 0.05; ***p < 0.001*. See supplementary Table S20 for detailed results.

endometriosis, and infertility. Furthermore, these findings corroborate the associations observed in our analyses of the UK Biobank prospective data.

Discussion

To the best of our knowledge, this is the first study to comprehensively investigate the relationship between sleep characteristics, shift work, and the risk of reproductive endocrine disorders (REDs) by integrating large-scale prospective cohort data with MR analyses. This study, based on 244,561 women from the UK Biobank, provides robust and

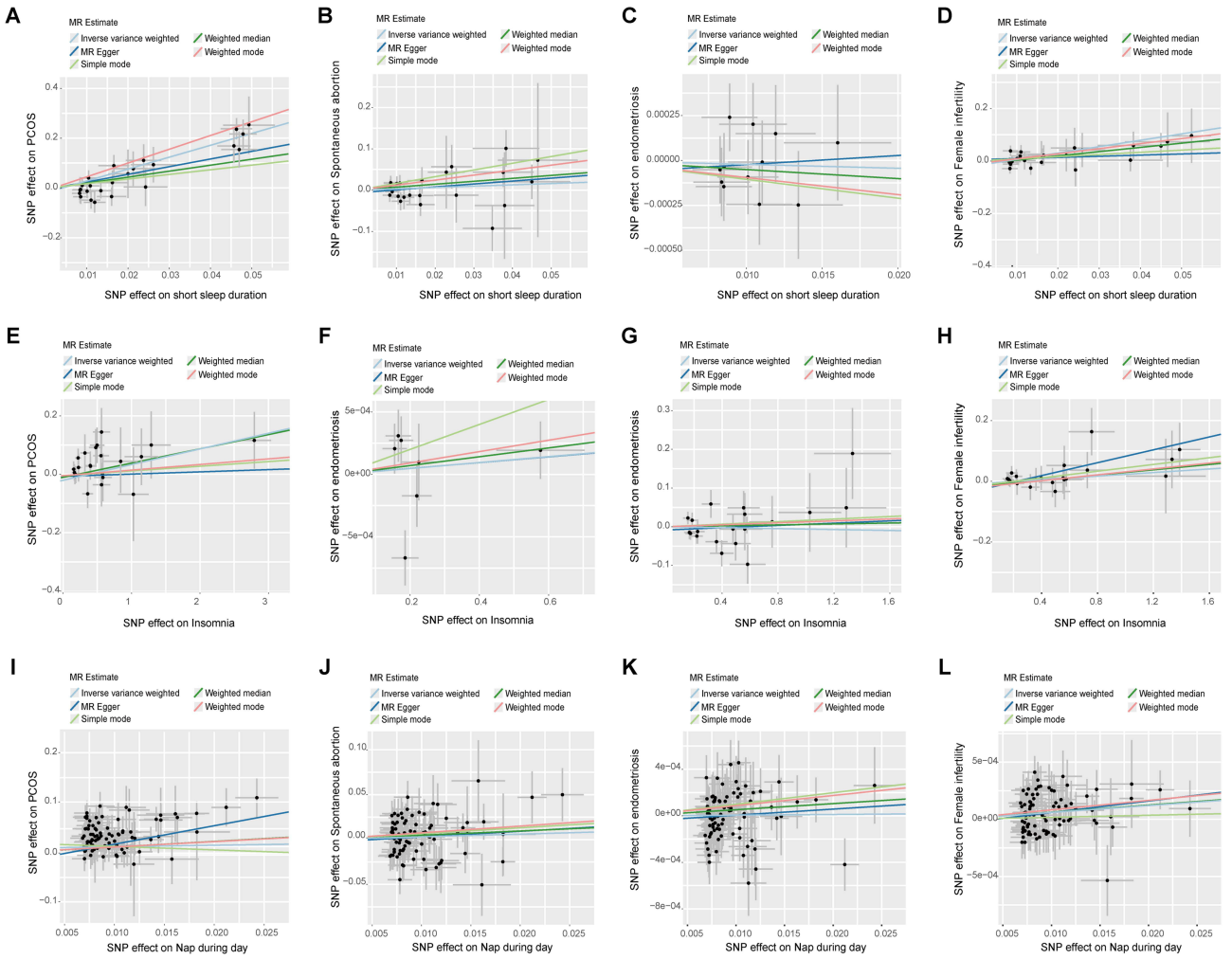

Figure 5 Mendelian randomization analyses of sleep traits and risk of REDs. Two-sample MR analyses were conducted using GWAS summary statistics to evaluate potential causal effects of sleep traits on REDs. Multiple MR methods were applied, including IVW, weighted median, MR-Egger, and mode-based approaches, to ensure robustness. (**A–D**) Causal associations between short sleep duration and REDs. Significant positive associations were observed with PCOS, spontaneous abortion, and female infertility across multiple MR methods. (**E–H**) Causal associations between insomnia and REDs. Insomnia showed consistent causal effects on PCOS, abortion, endometriosis, and infertility. (**I–L**) Causal associations between daytime napping and REDs. Daytime napping was positively associated with all four REDs outcomes, suggesting a potential adverse role of daytime sleep habits. No consistent causal associations were observed between long sleep duration, daytime sleepiness, or chronotype (morning/evening preference) and REDs across the applied MR methods. Estimates are shown as odds ratios (ORs) with 95% confidence intervals (CIs). See supplementary Table S21 for detailed MR results.

multifaceted evidence on this association. Our principal findings are threefold. First, short sleep duration (≤5 hours/day), long sleep duration (≥9 hours/day), poor sleep quality, and night shift work were each independently associated with an increased incidence of REDs. Moreover, the combination of night shift work and short sleep duration (≤5 hours/day) showed a synergistic effect, resulting in the highest observed risk (HR = 1.72, p = 0.0219), reinforcing the critical need to address sleep duration and circadian misalignment in the prevention and management of REDs. These findings suggest that screening for sleep disturbances and shift work should be incorporated into RED risk assessments, enabling clinicians to identify high-risk individuals more effectively. Second, mediation analyses revealed that systemic inflammation—particularly involving neutrophils and CRP—partially explained these associations, suggesting an inflammatory pathway linking sleep disruption to REDs. Third, and most importantly, our MR analyses provided genetic evidence supporting a causal role for short sleep duration, insomnia, and daytime napping in the development of REDs.

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Sleep and Circadian Disruption as Risk Factors for REDs

Studies have shown that lack of sleep is significantly associated with shorter menstrual cycles, PCOS, infertility and adverse pregnancy outcomes.[13,56–58] Long sleep duration is correlated with reduced leukocyte telomere length (LTL),[59] a factor closely associated with reproductive aging, primary ovarian insufficiency, and PCOS.[60,61] A prospective study showed that women undergoing IVF/ICSI who slept ≥10 hours per night had significantly lower numbers of retrieved oocytes, matured oocytes, and good-quality embryos.[62] Poor sleep quality was significantly correlated with menstrual period ≥7 days, menorrhagia, dysmenorrhea and premenstrual syndrome.[63] The results of several studies have shown that night shift work is more likely to cause women to have irregular menstruation and PCOS.[28,33,64,65] Sleep disruption and circadian disruption affect reproductive health through multiple mechanisms. The precise timing of hormone release from the hypothalamus, pituitary gland, and ovary is essential for fertility. The timing, rhythmicity, and tissue sensitivity of hormone release in the HPG axis are regulated by circadian clocks located in the hypothalamus (suprachiasmatic nucleus, rostral peptide, and GnRH neurons), pituitary gland (gonadotropin-secreting cells), ovary (theca cells and granulosa cells), and uterus (endometrium and myometrium). Disruption of clock rhythms impairs the pulsatile secretion of GnRH and LH, increases oxidative stress and inflammation, damages germ cells, and affects egg quality.[66] In addition, studies have shown that sleep disorders such as lack of sleep and circadian rhythm disruption can lead to weight gain,[67] while obesity can damage the reproductive system by directly affecting the HPG axis, ovaries and oocytes, and endometrium, and lead to severe adverse pregnancy outcomes.[68] Interestingly, we found that night shift workers exhibit a higher susceptibility to REDs in comparison to those on permanent night shifts. This phenomenon may be attributed to the fact that a consistent atypical work schedule, such as a fixed night shift, enables the circadian clock to acclimate, while a rotating work schedule necessitates continual adjustment to circadian rhythms, leading to longer post-night shift sleep duration among permanent night shift workers, reduced insomnia symptoms, and decreased perceived sleep deprivation compared to those on rotating shifts.[69–71] Moreover, in our study, it was observed that the risk of REDs was significantly elevated in individuals facing the double burden of night shifts and short sleep, highlighting the combined detrimental effects of circadian dysregulation and sleep deprivation.

Understanding the role of circadian rhythm disruption and sleep disorders in the development of REDs is of significant clinical importance. For individuals at high risk for REDs, lifestyle interventions aimed at restoring circadian rhythms—such as improving sleep hygiene, optimizing diet, managing stress, and engaging in moderate physical activity—may help reduce the incidence of REDs. Studies have shown that for women undergoing assisted reproductive technology, adjusting daily breakfast intake according to the circadian rhythm may improve success rates and reduce the risk of miscarriage.[72] Currently, prospective randomized controlled trials have investigated the effects of the chronobiotic agent melatonin on improving hirsutism and inflammatory markers in women with PCOS. These studies found that 8 weeks of combined supplementation with melatonin and magnesium significantly improved hirsutism, reduced serum TNF-α levels, and enhanced total antioxidant capacity in women with PCOS, with melatonin independently contributing to the reduction in serum TNF-α levels.[73] However, longitudinal studies are still needed to further explore the impact of improving circadian rhythms and sleep quality on the incidence of REDs. Additionally, chronotherapy—where interventions are timed to an individual's circadian rhythm—may offer novel approaches for the prevention and treatment of REDs.

Inflammation as a Mediating Pathway Linking Sleep and REDs

A key mechanistic insight from our study is the role of inflammation as a partial mediator. We found that neutrophils and CRP explained 6.89–12.97% of the excess REDs risk associated with both short and long sleep duration, while neutrophils mediated 6.55% of the association between night shift work and REDs. This is biologically plausible, as both sleep loss and circadian misalignment are potent provocateurs of systemic inflammation.[74–76] A cross-sectional study showed that night shift workers had elevated CRP compared to non-shift workers.[77] Circadian rhythms regulate neutrophil migration, senescence, topology and molecular expression, thus separating the antimicrobial and proinflammatory functions of neutrophils in time and space.[78] Elevated inflammatory markers, particularly CRP and leukocyte count, are well-documented features of REDs like PCOS and endometriosis.[79,80] Inflammation can impair ovarian

steroidogenesis, promote insulin resistance, and disrupt endometrial receptivity. In endometriosis, there is a significant increase in the number of neutrophils in blood, peritoneal fluid and ectopic endometrium. Upon reaching the peritoneal fluid and ectopic endometriosis sites, neutrophils drive disease progression by secreting proinflammatory cytokines such as interleukin-8, vascular endothelial growth factor and C-X-C motif chemokine ligand 10.[80] Furthermore, neutrophils release various cytokines and activate pain-related pathways, playing a crucial role in endometriosis-related pain.[81] Our mediation analysis formally quantifies this pathway, suggesting that sleep and circadian disturbances may contribute to a pro-inflammatory state that fosters an endocrine environment conducive to the development of REDs.

Genetic Evidence from MR Supports a Causal Role of Sleep Disorders in REDs

The most compelling evidence for causality comes from our Mendelian randomisation (MR) analysis. By leveraging genetic instruments as proxies for sleep traits, MR minimizes confounding and reverse causation—two major limitations inherent in observational studies. The consistent causal effects of short sleep duration and insomnia on multiple reproductive endocrine disorders, including PCOS, spontaneous abortion, endometriosis, and infertility, provide strong genetic support for our observational findings. In recent years, the association between daytime napping and increased risks of reproductive and metabolic diseases has garnered growing attention. Consistent with our results, a meta-analysis has demonstrated that habitual daytime napping is associated with elevated risks of all-cause mortality, cardiovascular disease, and metabolic disorders.[82] Another study further indicated that daytime naps exceeding 25 minutes were linked to higher risks of cardiovascular disease and mortality.[83] A longitudinal cohort study from the China Health and Retirement Longitudinal Study reported that longer daytime napping (more than 30 minutes per day) was significantly associated with an increased risk of metabolic syndrome in Chinese adults, with the effect being particularly evident in older women (odds ratio: 1.946, 95% confidence interval: 1.226–3.090).[84] Furthermore, a recent prospective cohort study among women undergoing IVF found that poor sleep quality and prolonged daytime napping (>1 hour) were significantly associated with reduced oocyte retrieval, maturation, and embryo quality. A non-linear inverse relationship between napping duration and oocyte maturation rate was also observed, particularly among women with good baseline sleep quality and normal body mass index.[62] Although the underlying mechanisms remain to be fully elucidated, several plausible biological pathways may link excessive daytime napping to adverse reproductive outcomes. Prolonged daytime napping may also impair melatonin secretion by interfering with nocturnal sleep, thereby disrupting circadian rhythms and potentially increasing the risk of reproductive endocrine disorders. Additionally, extended napping has been associated with elevated systemic inflammation—characterized by increased levels of C-reactive protein and proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α)[85]—which may adversely affect oocyte quality, endometrial receptivity, and embryo implantation. Furthermore, the interaction between altered hormonal regulation and excessive napping may exacerbate insulin resistance,[86] providing an additional pathway linking sleep behavior to reproductive dysfunction. In line with these findings, our MR results provide compelling genetic evidence supporting a potentially causal role of daytime napping in the development of reproductive endocrine disorders. The convergence of observational and genetic evidence strengthens the plausibility of a true biological link and suggests that excessive daytime napping is not merely a marker of poor health status, but may actively contribute to reproductive dysfunction. In contrast, the lack of consistent causal effects observed for long nocturnal sleep duration and chronotype implies that these associations in observational settings may be more susceptible to residual confounding or reverse causality. Therefore, our MR analysis not only confirms the findings of observational studies but also highlights that improving sleep—particularly in middle-aged and older women—may represent a novel and modifiable behavioral target for the prevention of reproductive endocrine disorders. Future interventional studies are warranted to validate these findings and to further elucidate the underlying neuroendocrine and inflammatory mechanisms linking sleep behaviors to female reproductive outcomes.

Limitations

Our study has several limitations that should be acknowledged. First, the majority of participants were of White European ancestry, which may limit the generalizability of our findings to other ethnic populations. Nevertheless, this

research represents the first large-scale investigation of its kind in a European cohort, offering important baseline data and theoretical insights that can inform future cross-ethnic comparative studies. Second, the age distribution of the participants was primarily between 40 and 69 years, and the proportion of individuals engaged in night shift work was relatively small. Although this may introduce sampling bias, the large overall sample size (>240,000) provides sufficient statistical power across different occupational groups, and the inclusion of diverse case data strengthens the robustness and epidemiological relevance of our findings. Third, while the study assessed sleep duration and sleep quality traits, the list of reproductive endocrine diseases (REDs) analyzed was not exhaustive. In addition, the mediating role of inflammatory markers in the relationship between sleep characteristics and REDs remains uncertain, and this mediation may vary across different RED subtypes. Future studies with larger sample sizes for each subtype are required to clarify these distinct pathogenic pathways. It is also important to note that the mediation effects identified in this study are associative, and the causal mechanisms require further validation through experimental or longitudinal studies. Whether targeting specific inflammatory markers may reduce the risk of REDs associated with sleep disturbances remains an important area for future research. Fourth, although we adjusted for a comprehensive set of covariates, residual confounding from unmeasured factors (eg, chrononutrition, psychosocial stress) cannot be entirely excluded. While Mendelian Randomization (MR) is a powerful tool for causal inference, its validity depends on key assumptions: relevance, independence, and exclusion restriction. Violations—particularly horizontal pleiotropy—may introduce bias. To address this, we applied multiple MR methods (eg, IVW, MR-Egger, weighted median) and conducted sensitivity analyses. Nonetheless, potential bias from weak instruments or pleiotropy remains possible, and its direction may vary depending on the nature of the violations. Future studies incorporating even more specific genetic instruments or utilizing alternative methods such as multivariable MR to account for shared genetic influences could further strengthen causal conclusions. Finally, some estimates, particularly in subgroup analyses (eg, permanent night shift workers or specific RED subtypes), may be imprecise due to limited case numbers. Wide confidence intervals in these instances suggest uncertainty and call for cautious interpretation. These limitations highlight the need for future research involving more diverse populations, refined phenotyping, and experimental validation to confirm the observed associations and further elucidate the underlying biological mechanisms.

Conclusion

In conclusion, our study provides compelling evidence that disrupted sleep duration, poor sleep quality, and night shift work are independent risk factors for reproductive endocrine disorders (REDs) in women. The combined exposure to circadian disruption from night shifts and insufficient sleep represents the greatest risk for REDs. Our findings highlight systemic inflammation as a partial mediating pathway and, importantly, genetic evidence supporting a causal role for short sleep and insomnia in the development of REDs. These results have important clinical and public health implications, emphasizing that sleep and circadian health are modifiable lifestyle factors that should be considered in the prevention and management of REDs. Routine gynecologic and endocrine evaluations should include screening for sleep disturbances and shift work history. For women engaged in night shift work, strategies to mitigate circadian misalignment and ensure sufficient sleep duration are crucial. Future intervention studies are needed to explore whether improving sleep hygiene and circadian health can effectively reduce the incidence or severity of REDs.

Abbreviations

ACME, average causal mediation effect; ART, assisted reproductive technology; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; GWAS, genome-wide association study; HPG axis, hypothalamic–pituitary–gonadal axis; HPO axis, hypothalamic–pituitary–ovarian axis; HR, hazard ratio; IL-6, interleukin-6; IV, instrumental variable; IVW, inverse variance weighted; LTL, leukocyte telomere length; MICE, multivariate imputation by chained equations; MR, Mendelian randomization; NLR, neutrophil-to-lymphocyte ratio; PCOS, polycystic ovary syndrome; REDs, reproductive endocrine disorders; RCT, randomized controlled trial; SNP, single nucleotide polymorphism; STROBE-MR, Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization; TNF-α, tumor necrosis factor-alpha; UK Biobank, United Kingdom Biobank.

Data Sharing Statement

All data used in this study are publicly accessible from UK Biobank via their standard data access procedure at http://www.ukbiobank.ac.uk/. Researchers can apply for access to the UK Biobank data via the Access Management System (AMS) (https://www.ukbiobank.ac.uk/use-our-data/apply-for-access/). Summary statistics for sleep duration, sleep quality traits, and reproductive endocrine disorders are publicly available in the Instrumental Variables in Epidemiology (IEU) repository and can be accessed at https://opengwas.io/. Details regarding the repository names and accession numbers can be found in the article and/or Additional Material. Data sharing is not applicable to this article as no datasets were generated during the current study.

Ethics Approval and Consent to Participate

This study involved human participants and utilized de-identified data from the UK Biobank, which has received ethical approval from the North West Multi-Centre Research Ethics Committee (REC reference: 11/NW/0382). All participants provided written informed consent at the time of recruitment. As the analysis was based solely on de-identified, previously collected data, no additional ethics approval or participant consent was required.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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