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RESEARCH

Associations between estradiol levels and subjective sleep parameters in a large cohort of men and women

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This paper forms part of a themed collection, exploring the latest discoveries and advancements in the fluctuations and cyclical patterns of hormones. The Collection Editors were Sander Kooijman, Liesbeth Winter, and Henrik Oster.

Abstract

Introduction: Estradiol may influence sleep–wake rhythms via modulation of the circadian timing system, but evidence is limited and often based on small samples. This study examined associations between serum estradiol levels and sleep parameters in men and in pre- and postmenopausal women from the general population.

Methods: This cross-sectional analysis used baseline data from the Netherlands Epidemiology of Obesity (NEO) study. Estradiol was measured in fasting serum using LC-MS/MS. Sleep quality and timing were assessed with the Pittsburgh Sleep Quality Index (PSQI). Associations were evaluated using multivariable weighted linear regression.

Results: In the 4,754 participants (51% men; mean age 56 years), serum estradiol levels were not associated with sleep quality or timing. Participants in the highest 10th percentile of estradiol showed marginally better sleep quality compared with those in the middle range (difference in PSQI = -0.74 ; 95% CI: -1.11 to -0.36).

Discussion: These findings suggest that, under physiological conditions, estradiol levels are not clearly linked to sleep quality or timing.

Keywords: sleep; estradiol levels; hormones; disturbed sleep; fluctuating

Introduction

Estradiol is produced in premenopausal women by the ovaries in a monthly cycle and in men through the aromatization of testosterone in the testes and adipose tissue. As a steroid hormone, estradiol binds to estrogen receptor alpha (ER α) or estrogen beta (ER β), facilitating transcription initiation of target genes. ER α has been shown to bind to the promoter regions of core clock genes, such as *CLOCK* (1) and *PER2* (2), which regulate the endogenous ~24 h circadian rhythm. This rhythm (process C) is governed by the suprachiasmatic nucleus (SCN) in the hypothalamus and interacts with sleep–wake homeostasis (process S), reflecting the buildup and dissipation of sleep pressure (3, 4, 5). The circadian system is driven by a transcriptional feedback loop involving activator genes (*CLOCK* and *ARNTL*) and repressor genes (*PER* and *CRY*) (6). Through these mechanisms, estradiol may influence sleep timing and rhythm.

Human chronotype, commonly expressed as the midpoint of sleep, is determined by the circadian timing system and depends on the light sensitivity of the SCN and the intrinsic speed of the molecular clock (7, 8). Women tend to have earlier chronotypes than men, but this difference disappears after menopause when estradiol production declines (9, 10). In transwomen starting feminizing hormone treatment including estradiol, chronotype advances by 21 min (11). However, findings across studies are inconsistent. For example, in another study of 177 women, postmenopausal women showed a phase advance of approximately one hour in rest–activity rhythms compared to premenopausal women (12).

In addition to potential circadian effects, estradiol may influence sleep quality. Sleep disturbances, particularly insomnia, are more prevalent in women than in men (13). The sex difference, with a 2.75-fold increased risk of insomnia in young women, emerges after menarche (14), and postmenopausal women experience more insomnia than premenopausal women (15), suggesting a hormonal contribution. Perimenopausal women often report more difficulty falling and staying asleep and reduced sleep quality (16, 17, 18, 19), suggesting a hormonal contribution. Estrogen replacement therapy has been shown to improve sleep quality in postmenopausal women (20). Together, these findings suggest that estradiol may affect sleep quality, potentially independent of age.

Although evidence suggests a relationship between estrogens and sleep timing and quality, existing studies have generally been small and often restricted to either women or men. Therefore, this study aimed to investigate the cross-sectional association between serum estradiol concentrations and sleep parameters in men and pre- and postmenopausal women from the general population.

Methodology

Study design

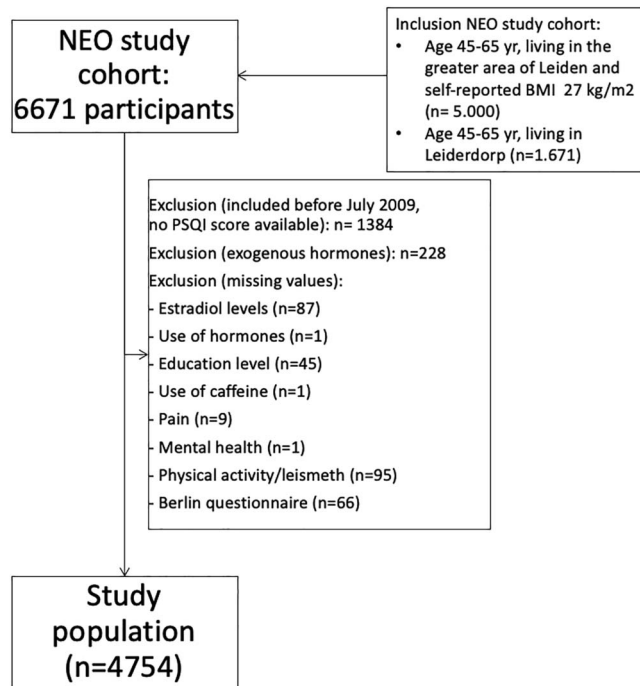
This study uses a cross-sectional approach based on the baseline measurements of the Netherlands Epidemiology of Obesity (NEO) study, a large population-based, prospective cohort study designed to investigate pathways that lead to obesity-related diseases. The NEO study commenced recruitment in 2008 and ultimately enrolled 6,671 adults between 45 and 65 years old, deliberately incorporating a higher proportion of participants with overweight or obesity. The study design and population are described in detail elsewhere (21). Residents aged 45–65 years from the broader Leiden region (Western Netherlands) were eligible if they reported a BMI of at least 27 kg/m². Independently of BMI, all individuals in this age range living in the municipality of Leiderdorp received an invitation to participate. Participants attended a baseline assessment at the NEO study facility following an overnight fast. Prior to this visit, they filled out questionnaires at home covering lifestyle, demographic characteristics, and medical history. During the study baseline visit, all participants underwent an extensive physical examination, including anthropometry and blood sampling. Research nurses recorded names and dosages of current medication used in the month preceding the study visit.

All participants provided written informed consent. For the present analysis, we excluded individuals with missing values for estradiol levels, sleep outcomes, or one of the confounders (Fig. 1). We further excluded participants enrolled in the NEO study before July 2009, as the sleep quality questionnaire was added to the NEO study baseline measurements hereafter and women who used exogenous hormones, because in their case, the measured estradiol level does not reflect endogenous estrogen activity.

The study population was stratified based on menopausal status and by age in men, resulting in four subgroups: i) premenopausal or perimenopausal women, ii) postmenopausal women, iii) men aged 45–54 years, and iv) men aged 55–65 years. Men were stratified by age to account for the gradual decline in sex hormone levels and age-related changes in sleep quality across midlife. As pre- and postmenopausal status have clearly defined criteria, while perimenopause represents a transitional stage with partly preserved ovarian function, perimenopausal women were grouped with premenopausal women.

Data collection

On the questionnaire, participants reported their highest level of education in ten categories according to the Dutch education system and were grouped into high

**Figure 1**

Flow diagram of the selection, inclusion, and exclusion of participants in the NEO cohort study.

(including higher vocational school, university, and postgraduate education) versus low education (reference). Tobacco smoking was classified as current, former, or never (reference). In addition, all medication use in the month prior to the study visit was recorded. In women, we grouped use of contraceptives and hormone replacement therapy into current, past, and never (reference) use of estrogens. Menopausal state was categorized in pre- and postmenopausal state (reference) based on questionnaire data regarding oophorectomy, hysterectomy, and self-reported state of menopause in the questionnaire. Pain and mental health were assessed using the Short Form Health Survey (SF-36) (22), based on the respective subscale scores. Physical activity during leisure time was measured with the Short Questionnaire to Assess Health-Enhancing Physical Activity (SQUASH) (23) and expressed as MET-hours per week. Risk of sleep apnea was evaluated using the Berlin Questionnaire, from which participants were categorized as high or low risk (24).

Body weight and body fat percentage were measured using a Tanita bioimpedance device (TBF-310; Tanita International Division, UK). Measurements were taken without shoes, and a standard correction of 1 kg was applied to account for clothing. BMI was derived by dividing body weight (kg) by height squared (m²).

Blood sampling and hormone concentrations

After an overnight fast of at least 10 h, fasting blood samples were drawn from the antecubital vein, between 07:30 and 09:30 h, after five minutes of rest. Aliquots were stored at -80°C . Frozen serum samples were transported to the Endocrine Laboratory of the Amsterdam UMC in 2021, where estradiol concentrations were measured using a well-validated liquid chromatography–mass spectrometry (LC-MS/MS) method (25).

Measurements of sleep

Subjective sleep quality was evaluated using the Pittsburg Sleep Quality Index (PSQI) (26). This instrument is a self-reported questionnaire that captures various aspects of sleep quality and disturbances during the previous month. The PSQI contains nineteen questions that are combined into seven components: perceived sleep quality, time needed to fall asleep, total sleep duration, sleep efficiency, sleep interruptions, use of sleep medication, and daytime impairment. These components are aggregated into a global score ranging from 0 to 21, with higher values reflecting poorer overall sleep quality (26). A global PSQI score above 5 has been shown to distinguish poor sleepers from good sleepers with a sensitivity of 89.6% and a specificity of 86.5% ($\kappa = 0.75$, $P < 0.001$) (26). Midpoint of sleep and sleep duration were calculated from this PSQI. For analyses, the primary outcome was overall sleep quality. Secondary outcomes were midpoint of sleep and sleep duration.

Statistical analysis

Given the purposeful oversampling of participants with higher BMI in the NEO study, analyses were weighted to match the BMI profile of the Leiderdorp population, which closely reflects the general Dutch population. All analyses were weighted accordingly, making the findings representative of a population-based study without oversampling individuals with a BMI ≥ 27 kg/m² (21). Characteristics of the population were summarized for the total population and stratified by the four subgroups. Normality was checked by visually inspecting Q–Q plots and histograms. Normally distributed continuous variables were expressed as mean and standard deviation (SD). Continuous variables that were not normally distributed were expressed by their median and interquartile range (IQR). The association between estradiol levels and sleep quality, midpoint of sleep, and sleep duration were evaluated with linear regression analyses. This was done for the total population, as well as per subgroup. The mean differences with 95% confidence interval (CI) were reported.

Table 1 Baseline characteristics of study population of participants of the NEO study, stratified by menopausal status and sex hormone use in women and by age in men. Data are presented as mean \pm SD or as median (IQR).

	All participants (n = 4,754)	Pre- or peri-menopausal women not using sex hormones (n = 834)	Postmenopausal women not using sex hormones (n = 1,496)	Men 45–55 years (n = 1,104)	Men 56–65 years (n = 1,320)
Demographic/anthropometric					
Age, years	56.0 \pm 6.0	50 \pm 3.1	59 \pm 4.0	50 \pm 3.1	61 \pm 2.9
BMI, (kg/m ²)	26.0 \pm 4.3	25.5 \pm 4.9	25.5 \pm 4.6	26.7 \pm 3.6	26.5 \pm 3.7
Education level high (%)	47	51	42	50	48
Smoking status never (%)	38	42	40	43	30
Leisure-time physical activity (MET-h/week*)	30.5 (16–50.2)	25.0 (13.8–42.8)	32.6 (18.7–52.3)	27.0 (14.0–45.5)	33.8 (18.0–56.0)
Coffee use (%)					
0–4 cups a day	65	70	77	48	58
\geq 5 cups a day	35	30	23	52	42
Medication use					
Use of sedatives (%) [†]	4	5	6	3	3
Use of oral corticosteroids (%)	0.4	0.2	0.5	0.3	0.6
Use of antihypertensives (%)	23	15	26	13	31
Use of anticonvulsants (%)	1	1	2	1	1
Use of antipsychotics (%)	0.6	1.0	0.3	0.5	0.8
Short Form Health Survey (SF-36)					
Bodily pain score	84 (62–100)	84 (62–100)	84 (62–100)	84 (72–100)	84 (72–100)
Mental health/well-being score	84 (72–88)	80 (68–88)	80 (68–88)	84 (72–88)	88 (76–92)
Sleep					
Sleep apnea: high risk (%)	21	18	17	22	26
Total PSQI score	4.8 \pm 3.1	5.2 \pm 3.2	5.6 \pm 3.4	4.3 \pm 2.7	4.1 \pm 2.7
Sleep duration (hours)	7.0 \pm 1.0	7.0 \pm 1.0	7.0 \pm 1.0	6.8 \pm 0.9	7.1 \pm 1.0
Sleep efficiency (%)	88 \pm 12	88 \pm 12	85 \pm 12	91 \pm 11	90 \pm 11
Midpoint of sleep (hours:min)	03:16 \pm 1:00	03:11 \pm 0:58	03:21 \pm 0:46	03:06 \pm 1:06	03:22 \pm 1:09
Biomarkers					
Estradiol (pmol/L)	63.9 (17.2–94.1)	160 (24.4–455.7)	14.5 (10.8–21.1)	81.2 (66.9–99.0)	79.7 (66.4–96.0)

*MET-h, metabolic equivalent of task-hours. [†]Sedatives: anxiolytics, benzodiazepine derivatives, benzodiazepines related drugs, and other hypnotics and sedatives.

In a secondary analysis, we examined whether the association between estradiol levels and total PSQI scores differed across the distribution of estradiol. For this, estradiol levels were categorized into three groups: the lowest 10th percentile, the middle 80th percentile (reference group), and the highest 10th percentile.

The analyses were adjusted for several potential confounding factors. First, crude models were performed (model 1). Second, models that adjusted for the confounding factors age, sex (only in total population), and education were made (model 2). Models were additionally adjusted for BMI, smoking, physical activity, and caffeine use (model 3). Finally, models were additionally adjusted for pain, mental health, sleep apnea risk, and use of sedatives, oral corticosteroids, antihypertensives, antipsychotics, and anticonvulsants (model 4).

Results

For the analyses, data of 4,754 participants were included (Fig. 1), of whom 2,424 (51%) were men.

The study population was stratified based on menopausal status in women and by age in men. Baseline characteristics are shown in Table 1. There were differences in estradiol levels between the groups, as a result of stratification by sex and menopausal status. The PSQI score was slightly higher in women than in men.

Total PSQI score

Across all models in the total study population, there was no association between estradiol levels and total PSQI score (Table S1 (see section on Supplementary materials given at the end of the article)). In the fully adjusted model (model 4), the coefficient was -0.0006 (95% CI: -0.0012 to 0.0001). Similarly, no associations were observed in the stratified subgroups of men and women not using sex hormones.

In a secondary analysis, we examined the association between estradiol levels and total PSQI scores by comparing participants in the lowest and highest 10th percentiles of estradiol with those between those cutoffs ($>P_{10}$ and $<P_{90}$), adjusting for multiple covariates (Table 2). Among participants in the lowest 10th

Table 2 Mean differences in total PSQI score (with 95% CI) of participants of the NEO study, comparing the lowest 10th percentile and highest 10th percentile of serum estradiol levels with the middle 80% (reference).

	All participants (n = 4,754)	Pre- or peri-menopausal women not using sex hormones (n = 834)	Postmenopausal women not using sex hormones (n = 1,496)	Men 44-55 years old (n = 1,104)	Men 56-66 years old (n = 1,320)
Lowest 10th percentile					
Range in estradiol levels (pmol/L)	0.5-14.2	0.5-16.6	1.8-9.5	23.1-58.7	6-57.6
Model 1	1.03 (0.63- to1.43)	0.44 (-0.56 to 1.43)	0.32 (-0.41 to 1.04)	-0.15 (-0.75 to 0.46)	-0.07 (-0.65 to 0.51)
Model 2	0.19 (-0.26 to 0.64)	0.10 (-0.87 to 1.08)	0.32 (-0.41 to 1.05)	-0.15 (-0.76 to 0.46)	-0.12 (-0.69 to 0.45)
Model 3	0.38 (-0.09 to 0.85)	0.13 (-0.88 to 1.14)	0.51 (-0.23 to 1.25)	-0.08 (-0.70 to 0.53)	-0.12 (-0.69 to 0.45)
Model 4	0.40 (-0.01 to 0.81)	0.19 (-0.70 to 1.08)	0.56 (-0.10 to 1.23)	-0.20 (-0.74 to 0.34)	-0.01 (-0.56 to 0.54)
Highest 10th percentile					
Range in estradiol level (pmol/L)	142-4,142.1	691.5-4,142.1	41.5-1,079.8	122.2-274.4	118.6-232
Model 1	-0.11 (-0.49 to 0.27)	0.20 (-0.61 to 1.01)	-0.11 (-0.74 to 0.53)	-0.43 (-1.02 to 0.18)	0.30 (-0.46 to 1.06)
Model 2	-0.92 (-1.36 to -0.48)	0.31 (-0.47 to 1.10)	-0.07 (-0.71 to 0.57)	-0.44 (-1.04 to 0.17)	0.29 (-0.47 to 1.05)
Model 3	-0.81 (-1.25 to -0.37)	0.33 (-0.43 to 1.09)	-0.52 (-1.23 to 0.18)	-0.53 (-1.11 to 0.06)	0.15 (-0.63 to 0.92)
Model 4	-0.74 (-1.11 to -0.36)	0.29 (-0.46 to 1.05)	-0.40 (-1.07 to 0.27)	-0.40 (-0.86 to 0.07)	-0.06 (-0.80 to 0.66)

Model 1: crude model (unadjusted).

Model 2: adjusted for age, sex (only in total population), and education.

Model 3: additionally adjusted for BMI, smoking, leisure-time physical activity (LTPA), and caffeine use.

Model 4: additionally adjusted for pain, mental health, Berlin high-risk category, and use of sedatives, oral corticosteroids, antihypertensives, antipsychotics, and anticonvulsants.

percentile, the fully adjusted model (model 4) showed no difference in PSQI scores in the overall population and the different subgroups. In the highest 10th percentile of estradiol levels, model 4 indicated lower PSQI scores in the total study population (difference in PSQI score = -0.74 (95% CI: -1.11 to -0.36)). This indicates that individuals with the highest estradiol concentrations reported slightly better overall sleep quality than those in the middle range.

Secondary outcomes

Midpoint of sleep

In the total study population ($n = 4,754$), there was no association observed between estradiol levels and midpoint of sleep after adjusting for confounders. No associations were observed in the different subgroups (Table S1).

Sleep duration

In the total study population, no associations were observed between estradiol levels and sleep duration (in minutes), with a mean difference in model 4 of 0.0105 (9% CI: -0.0036 to 0.0246) (Table S1).

Discussion

This study investigated the associations between serum estradiol levels and various sleep parameters, including sleep quality (assessed using the PSQI questionnaire), midpoint of sleep, and sleep duration, in a large population. In the total population, no association was found between estradiol levels and sleep quality, sleep timing, or sleep duration after adjustment for confounders.

However, in the highest 10th percentile of serum estradiol levels, the fully adjusted model (model 4) showed a modest association with lower PSQI scores, suggesting that individuals with the highest estradiol concentrations have slightly better overall sleep quality than those in the middle range. The magnitude of this difference was relatively small, and its clinical relevance may be limited. In the two large subgroups of women, no associations were observed between estradiol and any sleep parameters.

It was hypothesized that an exposure-response relationship between serum estradiol levels and sleep parameters would be present in postmenopausal women, given their relatively stable estradiol concentrations (25). However, no such association was identified, suggesting that the effects of estradiol on sleep may be threshold dependent or possibly influenced by dynamic changes in estradiol levels, such as rising or falling concentrations. These interpretations are supported by findings in men, who also have stable low to intermediate estradiol levels and show no

association between estradiol and sleep outcomes (27, 28, 29). Dose–response curves between estradiol levels and brain activity are complex and can vary between sigmoidal, linear, and inverted U shape, depending on the species and brain region studied (30). Potentially, the relation between estradiol and sleep is sigmoidal with clear effects only at supraphysiological levels.

Women using exogenous sex hormones were excluded from the analyses, as measured serum estradiol in these individuals does not reliably reflect overall estrogenic activity. In women using hormonal contraceptives or hormone therapy, estradiol levels measured by LC-MS/MS may be suppressed, while estrogenic effects continue via receptor activation. This exclusion was necessary for biological interpretability but limits generalizability to the substantial proportion of women who use exogenous hormones. While this approach ensured biologically interpretable estradiol levels, it also prevented us from examining potential associations between exogenous hormone use and sleep, an area of increasing clinical relevance, particularly for women undergoing menopause or using hormonal contraception.

Strengths and limitations

A major strength of this study is its large population, which includes both men and women. Among women, the study further differentiates between premenopausal and postmenopausal individuals. This comprehensive study population enhances the generalizability of the findings and allows for detailed subgroup analyses. Another important strength is the use of an accurate LC-MS/MS method for estradiol measurement, which enables accurate detection of even very low concentrations, particularly relevant for studying postmenopausal women and men, who typically have lower estradiol levels.

A limitation of the study is that among premenopausal or perimenopausal women, results must be interpreted with caution due to the lack of information about the phase of the menstrual cycle at the time of blood sampling. Estradiol levels fluctuate considerably throughout the menstrual cycle, and sleep patterns are also known to vary by cycle phase (31), which complicates the interpretation of potential associations between estradiol and sleep in this group. Another consideration is the use of the PSQI, a subjective sleep questionnaire. Although the PSQI is a well-validated and widely used instrument (26), it remains a self-reported measure and may not fully capture the complexity of sleep patterns. However, given the scale of the current dataset, the inclusion of objective measures, such as polysomnography, was not feasible.

Future research

The absence of associations in our study may indicate that estradiol levels within the physiological range do not have strong effects on sleep outcomes, or that such effects are dependent on threshold levels or dynamic hormonal changes rather than static concentrations. These possibilities highlight the need for future research to include repeated hormonal measurements across the menstrual cycle in a large cohort and to assess sleep in populations undergoing hormonal transitions or receiving exogenous hormone therapy.

Clarifying these relationships will be essential to better understand the role of sex hormones in sleep regulation and to guide clinical decision-making for hormone use in relation to sleep complaints.

Conclusion

In this large population-based study, there were no associations between estradiol levels and sleep parameters – including sleep quality, midpoint of sleep, and sleep duration – in the overall population, including both women and men. These findings suggest that, under physiological conditions with stable estradiol levels, there is no clear relationship between estradiol and sleep.

Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/EC-26-0014>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the work reported.

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Author contribution statement

For the author contributions of the NEO study, please refer to the original publication (21). For the current article, conceptualization was carried out by CG, JvdV, RdM, and DJS. Formal analysis was performed by CG and JvdV, while supervision was provided by JvdV, RdM, and DJS. The original draft was written by CG. All other authors contributed to the interpretation of the data, as well as to the writing, editing, and reviewing of the manuscript.

Data availability

Due to the privacy of the participants of the NEO study and legal reasons, we cannot publicly deposit the data. In addition, NEO study participants did not sign informed consent to make their data publicly available. Data will be made available upon reasonable request to qualified researchers according to the NEO study research procedure. Data requests should be sent to the NEO Executive Board, who can be contacted via <https://www.lumc.nl/org/neo-studie/contact/>.

Ethics

The Medical Ethical Committee of the Leiden University Medical Center (LUMC) approved the design of the study.

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