Sex Hormones and Sleep in Men and Women From the General Population: A Cross-Sectional Observational Study

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Context and Objectives: Associations between sex hormones and sleep habits originate mainly from small and selected patient-based samples. We examined data from a population-based sample with various sleep characteristics and the major part of sex hormones measured by mass spectrometry.

Design, Setting, and Participants: We used data from 204 men and 213 women of the cross-sectional Study of Health in Pomerania-TREND.

Main Outcome and Measures: Associations of total T (TT) and free T, androstenedione (ASD), estrone, estradiol (E2), dehydroepiandrosterone-sulphate, SHBG, and E2 to TT ratio with sleep measures (including total sleep time, sleep efficiency, wake after sleep onset, apnea-hypopnea index [AHI], Insomnia Severity Index, Epworth Sleepiness Scale, and Pittsburgh Sleep Quality Index) were assessed by sex-specific multivariable regression models.

Results: In men, age-adjusted associations of TT (odds ratio 0.62; 95% confidence interval (CI) 0.46–0.83), free T, and SHBG with AHI were rendered nonsignificant after multivariable adjustment. In multivariable analyses, ASD was associated with Epworth Sleepiness Scale (β-coefficient per SD increase in ASD: −0.71; 95% CI: −1.18 to −0.25). In women, multivariable analyses showed positive associations of dehydroepiandrosterone-sulphate with wake after sleep onset (β-coefficient: .16; 95% CI 0.03–0.28) and of E2 and E2 to TT ratio with Epworth Sleepiness Scale. Additionally, free T and SHBG were associated with AHI in multivariable models among premenopausal women.

Conclusions: The present cross-sectional, population-based study observed sex-specific associations of androgens, E2, and SHBG with sleep apnea and daytime sleepiness. However, multivariable-adjusted analyses confirmed the impact of body composition and health-related lifestyle on the association between sex hormones and sleep. **(*J Clin Endocrinol Metab* 101: 3968–3977, 2016)**

Sleep is a complex vital state and a highly dynamic process occupying one-third of a human's lifetime. The global prevalence of insomnia is estimated to be around 10%–30%, with 50% in midlife women (1). If insomnia is manifested as a disorder, meaning a condition with negative consequences based on pathological response (2), it is associated with a higher cardiovascular risk factor burden including hypertension, obesity, metabolic syndrome, and depression (3).

Sleep is neurophysiologically regulated by the central nervous system including the medial preoptic nuclei or the hippocampus, in which steroid receptors for estrogens and androgens were identified. In previous studies there is evidence that sleep pattern are sexually dimorphic (4, 5).

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Abbreviations: AHI, apnea-hypopnea index; ASD, androstenedione; BP, blood pressure; CI, confidence interval; DHEAS, dehydroepiandrosterone-sulphate; E1, estrone; E2, estradiol; ESS, Epworth Sleepiness Scale; fT, free T; HT, hormone therapy; ISI, Insomnia Severity Index; OC, oral contraceptive; OR, odds ratio; OSA, obstructive sleep apnea; OSAHS, OSA-hypopnea syndrome; PSG, polysomnography; PSQI, Pittsburgh Sleep Quality Index; SHIP, Study of Health in Pomerania; TST, total sleep time; TT, total T; WASO, wake after sleep onset.

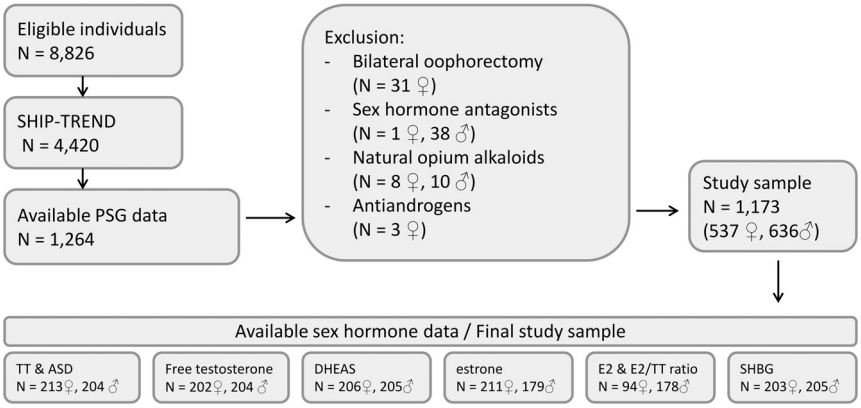

Figure 1. Flow chart of the study population.

This leads to the question whether sex hormones may play a role in the development and manifestation of sex-specific sleep patterns. It is well known that hormonal changes during the menstrual cycle and menopausal transition affect sleep quality in women increasing the risk of insomnia and frequent wake after sleep onset (WASO) (6). However, associations between sex hormones and sleep in women are mainly investigated in connection with hormone therapy (HT) (1, 7), menopausal status (8, 9), and the menstrual cycle (10, 11) and obstructive sleep apnea (OSA) in men (12, 13). On the contrary, associations between endogenous sex hormones and sleep in healthy, nonselected samples have not yet been investigated in a wide range. At this, associations of estradiol (E2) and T levels with subjective sleep measures (sleep quality) and objective sleep measures (WASO) have been reported in women between the ages of 48 and 59 years (14).

T production in men is dependent on sleep pattern, in which the timing of sleep is more important than sleep length. Accordingly, T levels were positively associated with objective and subjective sleep parameters as sleeping efficiency and sleep quality (12) as well as inversely associated with sleep disorders (15). For example, increasing OSA severity is associated with lower levels of SHBG and total T (TT) due to age, obesity, and sleep fragmentation (16). Additionally, SHBG showed an inverse association with sleep restriction (17) and dehydroepiandrosterone sulfate (DHEAS) was positively associated with subjective sleep quality (18).

Taken together, previously reported associations between sex hormones and sleep have not yet been investigated in nonselected, general population samples. Thus, the present study aims to evaluate associations of SHBG and sex hormones (TT, free T [fT], estrone [E1], E2, DHEAS, E2 to TT ratio) with various objective and subjective sleep characteristics in men and women from a population-based sample.

Materials and Methods

Study population

The Study of Health in Pomerania (SHIP)-TREND is a population-based cohort study in northeastern Germany. Details of the study design, recruitment, and procedures were previously published (19). In brief, the SHIP-TREND population is characterized by German citizenship with main residency in the study area. The SHIP-TREND cohort comprised a representative sample of 8826 adults, randomly selected from population registries into 24 age- and sex-specific clusters (19). In total, 4420 (response 50.1%) individuals participated in the baseline examinations conducted between 2008 and 2012. The subsample with available sex hormone data was limited to the first 1000 SHIP-TREND participants who fasted for at least 10 hours prior to blood donation. Cardiorespiratory polysomnography (PSG) was performed in all individuals who agreed to participate. Written informed consent was obtained from each participant and the Ethics Committee of the University of Greifswald authorized the study protocol, which is consistent with the principles of the Declaration of Helsinki. We excluded individuals who: received prescribed drugs in the last seven days, categorized based on the Anatomical Therapeutic Chemical classification index (sex hormone antagonists [n = one woman, 38 men], natural opium alkaloids [n = eight women, 10 men], and antiandrogens [n = three women]); and self-reported bilateral oophorectomy (n = 31 women) and individuals with missing hormone data (n = 324 women, 432 men). Finally, we investigated a study population of 213 women and 204 men with complete sex hormone and PSG data (Figure 1).

Measures

We assessed sociodemographic and behavioral characteristics and medical history conducting a computer-assisted personal interview. Mean daily alcohol consumption was calculated using beverage-specific pure ethanol volume proportions. Participants were considered being physically inactive when they participated in physical training less than 1 hour a week during winter or summer. Participants were divided into three categories of smoking habits: current, former, and never-smokers. The sample was stratified into pre- and postmenopausal women: all women younger than 40 years of age and between 40 and 60 years who reported menstrual cycle were classified as premenopausal and all women 60 years of age or older, together with all women between 40 and 60 years who reported no menstrual cycle were classified as postmenopausal (20).

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Participants were weighed using standard digital scales and height was measured with a digital ultrasound instrument. Body mass index was calculated from the body weight in kilograms and height in meters [body mass index = kilograms per square meter]. Waist circumference was measured using a tape midway between the lower rib margin and the iliac crest. Systolic and diastolic blood pressure (BP) was measured after a resting period of at least 5 minutes and three times on the right arm of seated subjects using an oscillometric digital BP monitor (HEM-705CP; Omron Corp). Hypertension was defined as BP of 140/90 mm Hg or greater or the use of antihypertensive medication (Anatomical Therapeutic Chemical codes C02, C03, C04, C07, C08, C09) (21). Depression was defined based on three questions in a questionnaire: have you experienced more than one period in your life in which 1) you felt most of the time sad, subdued, or depressed? 2) you felt most of the time tired, weary, and exhausted, even if you were not ill or you did not work hard? And 3) you lost interest in almost all fields of activity? If question 1 and additionally question 2 or 3 or both of them were positively answered, the proband was classified as depressive. Hot flashes were assessed based on the question: do you have hot flashes not at all, hardly, moderate, or severe?

Polysomnography

Cardiorespiratory PSG was performed in a sleep laboratory with camera monitoring using a PSG system (Alice 5; Philips Respironics) and assessment of nasal flow, thoracic and abdominal efforts, body position, oxygen saturation, heart rate, and snoring sounds. Sleep stages were analyzed visually (19). Central, mixed, and obstructive apneas, hypopneas, periodic breathing, hypoventilation periods, respiratory-related arousals, and heart rate variability were documented. The apnea-hypopnea index (AHI) was calculated (mean number of apneas and hypopneas per hour, total sleep time [TST]) and categorized in no OSA-hypopnea syndrome (OSAHS) (AHI $\leq$ 5 per hour), mild OSAHS (AHI $>$ 5 per hour, $\leq$ 15 per hour), moderate OSAHS (AHI $>$ 15 per hour, $\leq$ 30 per hour), and severe OSAHS (AHI $>$ 30 per hour) (22). Sleep efficiency was categorized into excellent (90%–100%), adequate (80%–89%), poor (70%–79%), and insufficient (<70%) (22). The Insomnia Severity Index (ISI scale), Epworth sleepiness Scale (ESS), and Pittsburgh Sleep Quality Index (PSQI) were assessed by standardized questionnaires. The ISI is a seven-item self-report questionnaire assessing the nature, severity, and impact of insomnia. The ISI score can range from 0 to 28 (23). ESS scores can range from 0 to 24, with higher scores indicating greater sleepiness (24). PSQI global scores, as an index of habitual sleep quality, can range from 0 to 21, with higher score indicating poor sleep quality (25).

Hormone measurements

We previously published a detailed description of the performed sex hormone measurements (26). Briefly, serum aliquots were established from blood samples, which was taken from the cubital vein in the supine position between 8:00 AM and 7:00 PM

Table 1. Sex-Specific Characteristics of the Study Population

Variable	Women (n = 213)	Men (n = 204)	*P* Value[a]
Age, y			
Mean (SD)	52.1 (12.1)	48.7 (13.8)	.01
Range	22—81	22—79	
TT, nmol/L	0.78 (0.55; 0.96)	17.6 (14.6; 20.7)	<.01
ASD, nmol/L	2.18 (1.47; 3.15)	2.74 (2.23; 3.66)	<.01
fT, nmol/L	0.009 (0.006; 0.012)	0.35 (0.29; 0.41)	<.01
DHEAS, mg/L	0.95 (0.64; 1.44)	1.56 (1.05; 2.57)	<.01
E1, nmol/L	102.8 (65.4; 198.3)	115.5 (94.2; 144.6)	.03
E2, nmol/L	198.98 (64.0; 374.2)	74.7 (59.6; 91.2)	<.01
E2 to TT ratio, nmol/L	234.1 (102.2; 433.5)	4.18 (3.26; 5.41)	<.01
SHBG, nmol/L	54.8 (41.5; 75.7)	35.1 (27.8; 45.4)	<.01
Body mass index, kg/m^2	27.3 (4.8)	27.7 (3.6)	.01
Waist circumference, cm	84.7 (11.6)	93.7 (11.3)	<.01
Current smoking, %	14.6	22.1	<.01
Physical inactivity, %	22.1	26.9	.25
Alcohol consumption, g/d	2.4 (0.72, 5.39)	9.8 (3.22; 19.18)	<.01
Oral contraceptive use, %	14.1		
Hormone replacement therapy, %	5.1		
Metabolic syndrome, %	16.4	23.5	.07
Sleep measures			
TST, min	382.3 (65.4)	380.5 (59.9)	.4
WASO, min	54.9 (44.4)	54.4 (39.7)	.7
ISI	7 (3; 11.5)	4 (2; 8)	<.01
ESS	6 (4; 9)	7 (5; 9)	<.01
PSQI	6 (4; 9)	4 (3; 6)	<.01
Sleep efficiency, %	82.6 (11.7)	83.3 (10.5)	.07
AHI, per hour	5.5 (8.3)	11.3 (14.5)	<.01
Sleep onset latency, min	15.7 (15.4)	13.8 (17.6)	.04

Data are percentages, mean (SD), or median (quartile 1, quartile 3). Oral contraceptive use was defined according to Anatomical Therapeutic Chemical classification code G03AA/B/C/D.

[a] Statistical comparisons were performed with a χ^2 test (nominal data) or a Mann-Whitney *U* test (continuous data).

and stored at −80°C thereafter. Measurements of serum TT, androstenedione (ASD), E1, and E2 concentrations were carried out in the Department of Clinical Chemistry at the University Hospital of South Manchester (Manchester, United Kingdom). Liquid chromatography and tandem mass spectrometry was performed with a validated routine method. The standard curve was linear up to 50.0 nmol/L, the lower limit of quantitation was 0.25 nmol/L, and intra- and interassay coefficients of variation were less than 10% for TT and ASD over the range of 0.3–35 nmol/L. For E1, the interassay imprecision were 5.3%, 3.8%, and 5.1% and for E2 5.4%, 3.7%, and 4.9% at concentrations of 125, 400, and 1500 pmol/L, respectively. The intraassay imprecisions for these concentrations were 4.0%, 3.4%, and 5.0% for E1 and 3.1%, 3.5%, and 4.0% for E2, respectively. The measurement range for E1 and E2 was 25–2000 pmol/L. The lower limit of detection was 3.9 and 8.0 pmol/L for E1 and E2, respectively. Concentrations of SHBG and DHEAS were measured using competitive chemiluminescent immunoassays on an Immulite 2000 XPi (Siemens Healthcare Diagnostics GmbH) with an interassay coefficient of variation of 3.5% and 8.3% in the low pool and 4.8% and 5.4% in the high pool, respectively. fT was calculated as follows: [fT (nmol/L) = $((-a+\sqrt{b})/c)/10^{-9}$ with a = SHBG (nmol/L) − TT (nmol/L) +23.43, b = a^2 + (4*23.43*TT (nmol/L))] and c = $2*23.43*10^9$ for a standard average albumin concentration of 4.3 g/dL (27).

Statistical analysis

Categorical data are given as percentage and continuous data as mean (SE) or median (p25th, p75th). Normality of outcome variables was inspected visually, with WASO naturally log transformed to normalize the distribution. Given a number of significant interactions terms ($P < .05$) between hormones and sex, we performed sex-specific analyses. First, we implemented age- and multivariable-adjusted linear regression models to examine cross-sectional associations of TT, fT, ASD, DHEAS, E1, E2, and DHEAS with sleep measures. Normality of residuals was tested using QQ plots. Effects were reported as β-coefficients and their 95% confidence interval (CI) for continuous (per SD) analyses. Associations of sex hormones and SHBG concentrations with AHI and sleep efficiency were analyzed using ordered logistic regression models. The categories, excellent sleep efficiency and

Table 2. Cross-Sectional Associations of Sex Hormones and SHBG With Sleep Measures in Linear Regression Models, Separately in Men and Women

	β-Coefficient (95% CI)			
	TT	**ASD**	**fT**	**DHEAS**
Men				
TST				
Age adjusted	−3.39 (−10.6; 3.86)	**−7.76 (−14.3; −1.13)***	0.70 (−8.13; 9.54)	−3.01 (−13.4; 7.38)
Mv adjusted	−5.79 (−13.4; 1.82)	−5.25 (−12.0; 1.51)	−2.81 (−11.5; 5.90)	−3.86 (−13.0; 5.29)
WASO				
Age adjusted	0.08 (−0.007; 0.17)	0.10 (−0.001; 0.20)	0.02 (−0.10; 0.14)	0.03 (−0.11; 0.17)
Mv adjusted	0.07 (−0.02; 0.17)	0.07 (−0.02; 0.18)	0.02 (−0.10; 0.15)	0.02 (−0.10; 0.16)
ISI				
Age adjusted	−0.12 (−0.78; 0.53)	−0.36 (−1.01; 0.28)	−0.17 (−0.81; 0.45)	−0.58 (−1.35; 0.19)
Mv adjusted	0.09 (−0.63; 0.81)	−0.39 (−1.08; 0.29)	−0.06 (−0.71; 0.58)	−0.58 (−1.35; 0.18)
ESS				
Age adjusted	−0.33 (−0.74; 0.07)	**−0.68 (−1.13; −0.23)[a]**	−0.26 (−0.77; 0.24)	0.05 (−0.50; 0.60)
Mv adjusted	−0.36 (−0.85; 0.11)	**−0.71 (−1.18; −0.25)[a]**	−0.30 (−0.86; 0.26)	0.01 (−0.52; 0.56)
PSQI				
Age adjusted	−0.27 (−0.74; 0.19)	−0.25 (−0.75; 0.24)	−0.39 (−0.87; 0.09)	−0.19 (−0.90; 0.51)
Mv adjusted	−0.20 (−0.74; 0.32)	−0.31 (−0.84; 0.21)	−0.37 (−0.88; 0.13)	−0.20 (−0.90; 0.49)
Women				
TST				
Age adjusted	−0.72 (−9.51; 8.05)	0.28 (−10.9; 11.4)	0.18 (−8.34; 8.71)	−2.14 (−11.7; 7.42)
Mv adjusted	−0.15 (−8.71; 8.40)	1.30 (−9.94; 12.5)	0.58 (−8.04; 9.21)	−2.02 (−11.7; 7.69)
WASO				
Age adjusted	0.08 (−0.01; 0.18)	0.03 (−0.11; 0.17)	0.04 (−0.05; 0.14)	**0.13 (0.01; 0.25)[a]**
Mv adjusted	0.07 (−0.01; 0.17)	0.04 (−0.01; 0.18)	0.03 (−0.06; 0.13)	**0.16 (0.03; 0.28)[a]**
ISI				
Age adjusted	−0.30 (−1.02; 0.41)	−0.38 (−1.18; 0.42)	−0.43 (−1.14; 0.28)	0.001 (−0.77; 0.77)
Mv adjusted	−0.41 (−1.12; 0.29)	−0.47 (−1.28; 0.33)	−0.63 (−1.36; 0.09)	0.02 (−0.72; 0.78)
ESS				
Age adjusted	0.003 (−0.40; 0.40)	−0.20 (−0.67; 0.27)	−0.15 (−0.57; 0.25)	0.05 (−0.45; 0.56)
Mv adjusted	0.03 (−0.35; 0.43)	−0.17 (−0.64; 0.29)	−0.15 (−0.57; 0.27)	0.04 (−0.45; 0.53)
PSQI				
Age adjusted	−0.07 (−0.60; 0.45)	−0.03 (−0.70; 0.62)	−0.17 (−0.69; 0.35)	0.48 (−0.10; 1.07)
Mv adjusted	−0.12 (−0.67; 0.41)	−0.04 (−0.73; 0.64)	−0.23 (−0.81; 0.33)	0.52 (−0.08; 1.12)

Abbreviation: Mv, multivariable. Data are β-coefficients per SD and their 95% CI. The multivariable model was adjusted for age, waist circumference, smoking status (three categories), physical inactivity, alcohol consumption, and hypertension. The number for all particular hormones can be seen in Figure 1.

[a] Bold values, $P < .05$.

no OSAHS, were used as a reference group for sleep efficiency and AHI, respectively, with effects presented as odds ratios (OR) and their 95% CIs. Stepwise multivariable models were first adjusted for age and waist circumference, subsequently adding smoking habits, physical inactivity, alcohol consumption, and hypertension.

We performed several sensitivity analyses including additional adjustment for HT (women using HT, n = 11), oral contraceptive (OC) use (women using OC, n = 30), hot flushes (women with hot flushes, n = 170), depression (individuals with depression, n = 126), and time and date of blood sampling. To address potential attrition bias, we included inverse probability weights into the multivariable analyses. Finally, multiplicative interaction terms for each hormone and covariate were investigated in multivariable models. Given the number of significant interactions terms ($P < .05$) between hormones and menopausal status, we additionally performed stratified analyses in pre- (n = 82) and postmenopausal (n = 131) women. This manuscript was written in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement, giving guidelines for reporting observational research. All statistical analyses were performed with Stata 13.0 (Stata Corp).

Results

Sex-specific sample characteristics are presented in Table 1. At this, women showed higher SHBG and E2 concentrations compared to men. With respect to sleep measures, women showed higher WASO, ISI, and PSQI but lower ESS compared with men (Table 1).

Table 2 presents associations of sex hormones with sleep measures from linear regression analyses. In men, ASD was inversely associated with ESS (β-coefficient −.71; 95% CI −1.18 to −0.25) after multivariable adjustment (Figure 2A). Age-adjusted associations of E2 to TT ratio and SHBG (β-coefficient per SD .11; 95% CI

Table 2. Continued

β-Coefficient (95% CI)			
E1	**E2**	**E2 TO TT Rati**	**SHBG**
−1.36 (−9.35; 6.63)	3.96 (−4.68; 12.6)	4.86 (−2.52; 12.2)	−6.74 (−14.7; 1.27)
0.28 (−7.90; 8.46)	3.73 (−4.91; 12.3)	7.13 (−0.86; 15.1)	−7.09 (−15.0; 0.82)
−0.06 (−0.17; 0.05)	−0.08 (−0.21; 0.03)	**−0.15 (−0.27; −0.02)[a]**	**0.11 (0.01; 0.21)[a]**
−0.05 (−0.16; 0.05)	−0.06 (−0.19; 0.06)	−0.12 (−0.25; 0.001)	0.08 (−0.01; 0.19)
−0.16 (−0.78; 0.46)	−0.06 (−0.66; 0.53)	0.24 (−0.40: 0.89)	−0.11 (−0.95; 0.73)
−0.19 (−0.79; 0.40)	−0.02 (−0.64; 0.58)	−0.01 (−0.70; 0.67)	0.13 (−0.81; 1.08)
−0.34 (−0.84; 0.16)	−0.39 (−0.88; 0.09)	−0.03 (−0.52; 0.45)	−0.33 (−0.79; 0.13)
−0.34 (−0.85; 0.16)	−0.39 (−0.89; 0.09)	−0.12 (−0.69; 0.44)	−0.33 (−0.82; 0.16)
−0.17 (−0.63; 0.28)	−0.36 (−0.80; 0.07)	0.01 (−0.48; 0.51)	−0.05 (−0.65; 0.55)
−0.24 (−0.69; 0.19)	−0.39 (−0.82; 0.03)	−0.21 (−0.76; 0.34)	0.09 (−0.59; 0.78)
3.21 (−5.09; 11.5)	−7.65 (−21.0; 5.72)	−6.28 (−18.5; 6.02)	−1.12 (−9.21; 6.96)
3.69 (−4.74; 12.1)	−9.39 (−22.9; 4.20)	−9.87 (−22.3; 2.59)	−1.06 (−10.9; 8.77)
0.04 (−0.06; 0.16)	0.11 (−0.08; 0.31)	0.05 (−0.13; 0.24)	0.05 (−0.05; 0.15)
0.05 (−0.06; 0.16)	0.13 (−0.06; 0.33)	0.08 (−0.11; 0.28)	0.08 (−0.03; 0.20)
−0.50 (−1.22; 0.22)	−0.46 (−1.70; 0.78)	−0.48 (−1.72; 0.74)	0.15 (−0.67; 0.98)
−0.48 (−1.20; 0.22)	−0.32 (−1.60; 0.96)	−0.37 (−1.70; 0.95)	0.39 (−0.46; 1.26)
0.38 (−0.05; 0.83)	**0.99 (0.33; 1.64)[a]**	**0.95 (0.23; 1.68)[a]**	0.17 (−0.24; 0.60)
0.39 (−0.03; 0.82)	**1.04 (0.37; 1.72)[a]**	**0.98 (0.24; 1.73)[a]**	0.28 (−0.22; 0.79)
−0.44 (−1.04; 0.14)	**−0.83 (−1.59; −0.07)[a]**	**−0.82 (−1.62; −0.02)[a]**	0.06 (−0.50; 0.63)
−0.43 (−1.03; 0.16)	−0.66 (−1.42; 0.09)	−0.63 (−1.44; 0.16)	0.06 (−0.54; 0.67)

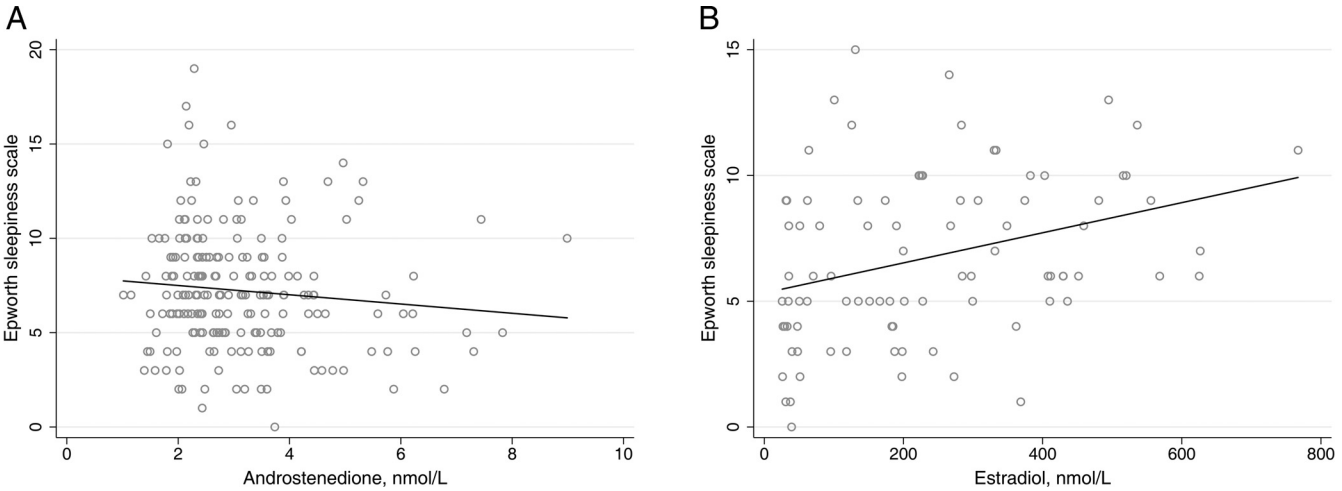

Figure 2. Scatterplot of ESS by ASD in men and by E2 in women. Distribution of ESS by ASD (A) in men and E2 (B) in women.

0.01–0.21) with WASO were not retained after multivariable adjustment. In women, we observed a positive association of DHEAS with WASO (β-coefficient per SD .16; 95% CI 0.03–0.28). Additionally, there was an independent positive association of E2 (β-coefficient per SD 1.04; 95% CI 0.37–1.72) (Figure 2B) and E2 to TT ratio (β-coefficient per SD .98; 95% CI 0.24–1.73) with ESS.

Table 3 presents associations between sex hormones and categorized sleep measures from logistic regression analyses. Despite a number of significant associations in age-adjusted analyses, including associations of TT, fT, E2 to TT ratio, and SHBG with AHI (Figure 3), these effects were rendered nonsignificant after multivariable adjustment (Table 3). Similarly, the association of SHBG with AHI in women was present only in age-adjusted models (OR 0.55; 95% CI 0.38–0.78). Sensitivity analyses with stratification by menopausal status did not substantially alter the revealed estimates (data not shown), except an additional positive association in multivariable models of fT (OR 2.43; 95% CI 1.07–5.55) and SHBG (OR 0.43; 95% CI 0.19–0.96) with AHI among premenopausal women. Stratification by depression, OC use, hormone replacement therapy or hot flushes did not reveal any statistical evidence of relevant subgroup differences. Finally, an additional adjustment for the time and date of the blood sampling did not substantially alter the revealed estimates (data not shown).

Discussion

The present cross-sectional study revealed sex-specific associations between sex hormones and sleep in men and women from the general population. In line with previous clinical research, we observed similar sex-spe-

Table 3. Cross-Sectional Associations of Sex Hormones and SHBG With Sleep Measures in Logistic Regression Models, Separately in Men and Women

	OR (95% CI)							
	TT	ASD	fT	DHEAS	E1	E2	E2 to TT Ratio	SHBG
Men								
Sleep efficiency								
Age adjusted	1.22 (0.94; 1.58)	**1.37 (1.03; 1.82)**[a]	0.97 (0.72; 1.32)	0.96 (0.69; 1.35)	0.90 (0.67; 1.19)	0.78 (0.59; 1.04)	0.72 (0.54; 0.95)	**1.43 (1.08; 1.89)**[a]
Mv adjusted	1.14 (0.85; 1.55)	1.26 (0.94; 1.69)	0.94 (0.68; 1.30)	0.98 (0.69; 1.37)	0.89 (0.66; 1.20)	0.83 (0.62; 1.11)	0.76 (0.55; 1.05)	1.31 (0.96; 1.79)
AHI								
Age adjusted	**0.62 (0.46; 0.83)**[a]	0.80 (0.59; 1.08)	**0.71 (0.51; 0.99)**[a]	0.94 (0.66; 1.33)	1.02 (0.76; 1.37)	1.21 (0.89; 1.64)	**1.69 (1.24; 2.28)**[a]	**0.65 (0.49; 0.88)**[a]
Mv adjusted	0.78 (0.56; 1.08)	0.90 (0.65; 1.22)	0.85 (0.59; 1.21)	0.99 (0.69; 1.41)	0.95 (0.69; 1.29)	1.06 (0.77; 1.46)	1.29 (0.91; 1.83)	0.82 (0.59; 1.14)
Women								
Sleep efficiency								
Age adjusted	1.23 (0.96; 1.59)	1.06 (0.79; 1.42)	1.17 (0.90; 1.52)	1.18 (0.89; 1.57)	1.01 (0.78; 1.30)	1.09 (0.72; 1.65)	0.94 (0.62; 1.41)	1.08 (0.84; 1.39)
Mv adjusted	1.20 (0.93; 1.55)	1.09 (0.81; 1.48)	1.16 (0.88; 1.51)	1.23 (0.92; 1.65)	1.02 (0.78; 1.32)	1.19 (0.76; 1.89)	1.06 (0.67; 1.67)	1.11 (0.83; 1.48)
Apnea-hypopnea index								
Age adjusted	1.05 (0.77; 1.41)	0.95 (0.67; 1.35)	1.31 (0.96; 1.78)	1.03 (0.74; 1.42)	1.08 (0.79; 1.48)	0.80 (0.45; 1.43)	0.76 (0.42; 1.39)	**0.55 (0.38; 0.78)**[a]
Mv adjusted	1.15 (0.84; 1.58)	1.04 (0.71; 1.53)	1.21 (0.87; 1.69)	1.14 (0.79; 1.65)	0.95 (0.68; 1.34)	1.40 (0.64; 3.06)	1.24 (0.51; 3.00)	0.78 (0.53; 1.15)

Abbreviation: mv, multivariable. Data are ORs and their 95% CI. The multivariable model was adjusted for age, waist circumference, smoking status (three categories), physical inactivity, alcohol consumption, and hypertension. Best category in sleep efficiency (excellent) and AHI (no OSAHS) served as the reference. Thus, the OR can be interpreted as the risk to descend in a next lower category per unit sex hormone/SHBG. The number for all particular hormones can be seen in Figure 1. [a] Bold values, $P < .05$.

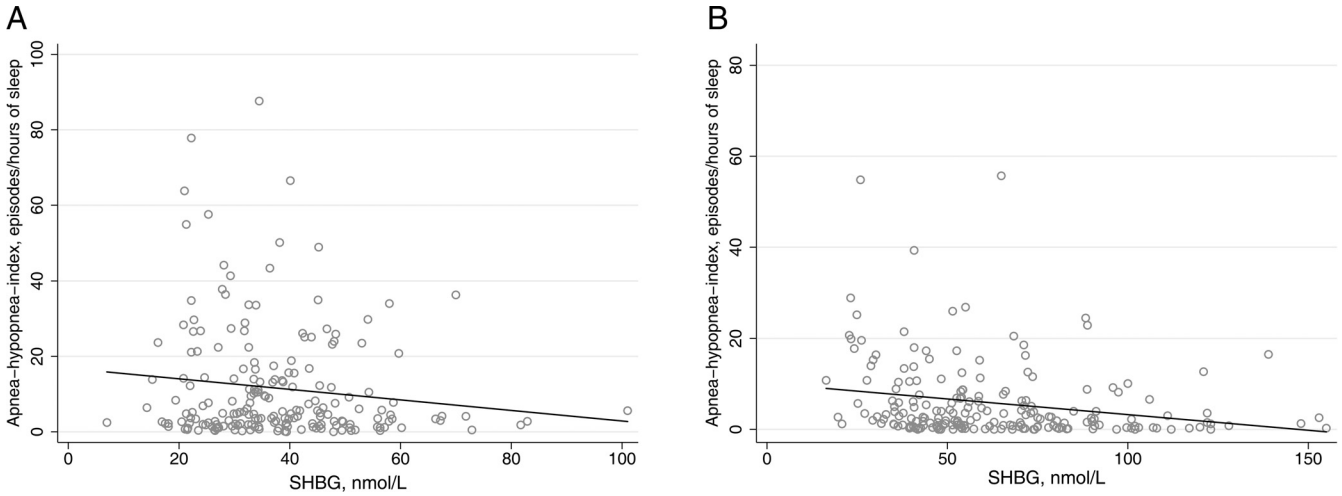

Figure 3. Scatterplot of AHI by SHBG, separately in men and women. Distribution of AHI by SHBG in men (A) and women (B) is shown.

cific differences in sleep measurements among individuals from the general population, including higher daytime sleepiness and sleep disturbances among woman compared with men. Previous studies showed a similar sex-specific sleep pattern with higher sleep onset latency and higher sleepiness in women than in men (5). These differences appear to be even more pronounced with increased comorbidity, polymedication, and sleep deprivation (5). However, given a well-known sex-specific reporting bias, with women reporting sleep-related symptoms differently from men, differences in self-reported sleep patterns must take this potential source of bias into account (5).

In men, ASD was associated with ESS, and in women, DHEAS and E2 were associated with ESS and WASO, respectively. However, most of the associations between sex hormones and sleep were rendered nonsignificant after multivariable adjustment, indicating a relevant impact of sex, body composition, and health-related lifestyle. Thus, understanding the exact interplay between sex hormones and measures of sleep is crucial to further advance theories of sleep.

Evidence for an association between androgens and sleep in men bases on several previous studies (12, 15, 28), whereas little is known about the association among ASD and ESS, observed in the present study. Adrenocorticotropin might play a mechanistic role in the interaction between ASD and sleep. The circadian-regulated adrenocorticotropin is in fact not a sufficient but a required factor for the production of ASD in the adrenal cortex (29), and its production can be stimulated as a consequence of wake-up reactions. However, alternative explanations for underlying mechanisms of this link remain to be elucidated because physiological ASD production is mainly extraadrenal (30). Although studies among ASD and sleep are relatively sparse, androgen status is known to be linked with sleep duration and sleep quality in men (28). TT, for example, appears to be associated with rapid-eye movement sleep, sleep efficiency (15), and sleep duration. In contrast, we found no significant associations of TT with any sleep characteristic in men. The present results are most likely diverging from previous studies due to a population-based, rather than patient-based sample, measurement variability of the analyzed hormones, and heterogeneous measures of sleep. Additionally, the present sample comprised of middle-aged (mean age 50.4 y), whereas associations of low TT with sleep were mainly observed among older men (31).

In women, we observed independent associations of E2 and E2 to TT ratio with ESS. A link between exogenous estrogen (31) and menopausal transition (32) with subjective vigilance during the day or ESS was reported in previous studies (31). In rodents, E2 inhibits the activation of ventrolateral preoptic nucleus neurons and down-regulates the mRNA of the sleep promoting prostaglandin D2 (33), which might suppress sleep and coincidentally increase arousal. However, these mechanisms could not be directly translated to humans in general (34) or specifically to sleep research (35). However, assuming that E2 might also suppress sleep in humans, the expected relationship between E2 and ESS is not clear-cut. Supposing that high E2 levels suppress day sleep, there might be an inverse association between E2 and ESS. But if high E2 levels additionally suppress night sleep, this might lead to increased daytime sleepiness and a positive association between E2 and ESS. Thus, the present results suggesting a positive association between E2 and ESS rather contribute to the latter hypothesis. Nevertheless, epidemiological research, like observational research in general, does not allow any conclusions about causality (36). Thus, high-quality clinical trials are strongly needed to gain more

insights into the association between E2 and sleep in men and women.

The significant interaction between sex hormones and menopausal status (premenopausal, n = 82, and postmenopausal, n = 131) in our study corroborate the suggested impact of menopausal hormone changes on sleep. Thus, several previous studies observed that the perimenopausal state, with decreased E2 levels due to less ovarian production (31), is associated with lower sleep quality and increased insomnia prevalence (33). Additionally, women with decreasing E2 to TT ratio are moving toward completion of the menopausal transition process and have more sleep consolidation (4, 14). In the present study, we observed all significant results of E2 to TT ratio sleep in women consistent with significant results of E2, interpreting the results of E2 to TT ratio as effects of E2 and not consequently as a link between the more androgenic nature in hormone profiles during menopausal transition. It is not clear whether the unstable hormone milieu alone or other symptoms of the menopausal transition may cause changes in sleep patterns (4). For example, hot flashes are suggested as a risk factor for daytime sleepiness, measured by ESS (32). However, in line with previous studies (14), we detected no change in the overall estimates after adjustment for hot flushes. With regard to AHI, the prevalence of disordered breathing during sleep is higher in postmenopausal women compared with premenopausal women. Thus, we observed an independent association between fT and SHBG with AHI in pre- but not in postmenopausal women. Accordingly, postmenopausal women using HT show half the prevalence of disordered breathing compared with nonusers (7).

The interplay between sex hormones and AHI has been widely investigated in previous studies. There is evidence that OSA (as insomnia) might be a causal factor for cardiovascular diseases including hypertension, myocardial infarction, and stroke (37). Increasing OSA severity is associated with lower levels of SHBG and TT in men due to age and sleep fragmentation (16), and most of the previous studies observed a large impact of body composition (16, 38). In line with these findings, we observed only in age-adjusted models significant associations of TT, fT, E2 to TT ratio in men and SHBG in both sexes with AHI but not after adjustment for waist circumference. Possible mechanisms that may explain the association of androgen with AHI include the impact of T on the soft tissue deposition in the pharynx, leading to change in compliance or size of the pharyngeal airway and thus more collapse (39). However, the link between androgens and AHI seems to have a bidirectional nature because studies among men suffering from OSA also revealed decreased TT levels (15). Thus, obesity might mediate the association of TT and AHI, as the nonsignificant results in multivariable models in our study may indicate.

In summary, the present associations between sex hormones and PSG data in women are in line with results from the population-based Study of Women's Health Across the Nation. Despite slightly varying sample characteristics (Study of Women's Health Across the Nation focused on midlife women), different hormone measurement methods, and blood sampling procedures, androgenization in women was generally associated with poor sleep quality (14). In terms of AHI, previous studies consistently suggest a link between AHI and T in men but identified obesity as a relevant mediator (12, 16, 38). Additionally, identified associations between sex hormones and sleep measures were mostly rendered nonsignificant after adjustment for cofactors in both genders. Thus, we conclude that cofactors including body composition, health-related lifestyle, and comorbidities exert a stronger influence on sleep than to sex hormones alone.

Strengths and limitations

The strengths of the present study include the population-based sample and the accurate assessment of a broad range of sleep parameters. Additionally, TT, ASD, and estrogens were measured by liquid chromatography and tandem mass spectrometry instead of immunoassay, providing a reliable assessment of androgen status, especially in the low concentrations range of women. Potential limitations might have arisen from the lack of data about polycystic ovary syndrome and the menstrual cycle. However, previous studies suggest that objective changes in sleep architecture during menstrual cycle were not found in all women of child-bearing age (4). Furthermore, we addressed the potential impact of polycystic ovary syndrome, with its known effects on obesity and insulin sensitivity, by adjusting all multivariable analyses for waist-circumference.

Because PSG data stem from merely one night in a sleep laboratory, sleep might be artificially disturbed and therefore could impact the associations between sex hormones and sleep measures (40). Finally, the external validity in the interpretation of the ESS might be limited because this scale is an adequate instrument for OSA patients but not necessarily for individuals from the general population.

Conclusions

This cross-sectional study revealed sex-specific associations of androgens, E2, and SHBG with sleep quality, showing new insights as DHEAS was associated with WASO in women and ASD with ESS in men. Multivari-

able-adjusted analyses support the relevant impact and mediating role of body composition on the observed associations. To further elucidate the interplay between sex hormones and sleep, additional research from longitudinal observational studies as well as randomized clinical trials is needed.

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