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RESEARCH ARTICLE

Sleep characteristics and parameters of bone turnover and strength in the adult population: results from the Study of Health in Pomerania-TREND

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Summary

Poor sleep quality or sleep deprivation may be related to decreased bone mineral density. We aimed to assess whether associations of sleep characteristics and bone turnover or strength are present in adults from the general population and whether these are independent of common risk factors such as sex, age, and obesity. A total of 1037 participants from the Study of Health in Pomerania-TREND underwent laboratory-based polysomnography and quantitative ultrasound measurements at the heel. Of these participants, 804 completed standardised questionnaires to assess daytime sleepiness, insomnia, and sleep quality. Serum concentrations of two bone turnover markers, intact amino-terminal propeptide of type 1 procollagen (P1NP) and carboxy-terminal telopeptide of type 1 collagen (CTX) were measured. Cross-sectional associations of polysomnography variables (total sleep time, sleep efficiency, time spent wake after sleep onset, oxygen desaturation index, apnea–hypopnea index, and obstructive sleep apnea [OSA]), as well as sleep questionnaire scores with the bone turnover markers and the ultrasound-based stiffness index were assessed in linear regression models. In adjusted models, higher insomnia scores and lower sleep quality scores were related to a higher bone turnover in women but not in men. However, associations between polysomnography variables or questionnaire scores and the stiffness index were absent. Our study provides limited evidence for relationships between sleep characteristics and bone turnover and strength independent of common risk factors for OSA and osteoporosis. Nevertheless, women reporting poor sleep or insomnia in combination with risk factors for osteoporosis might benefit from an evaluation of bone health.

KEYWORDS
bone quality, estimated bone mineral density, self-report, sex-specific, sleep disorders

1 | INTRODUCTION

In an ageing society, degenerative diseases of muscles, bone, and joints, such as osteoarthritis and osteoporosis, are gaining in importance. Osteoporosis is a chronic disease with reduced bone strength and increased fracture risk (Camacho et al., 2020). It is a silent disease without typical symptoms, until osteoporotic fractures occur, which lead to pain, an increased risk of enduring disability, an increased mortality risk, and a reduced quality of life (Camacho et al., 2020).

The majority of patients with osteoporosis in Germany are female and aged ≥ 70 years (Hadji et al., 2020). Next to age and sex, there are various risk factors for osteoporosis, some of which can be modified, like smoking and being underweight, while others are unmodifiable, e.g., age, early menopause, or intake of certain medication, such as glucocorticoids (Camacho et al., 2020). In addition, poor sleep quality and sleep disorders, e.g., obstructive sleep apnea (OSA), may impact bone health and metabolism (Cherian et al., 2022; Eimar et al., 2017).

Poor sleep quality is highly prevalent in the general population (Kocevska et al., 2021) and can be accompanied by decreased physical and mental productivity, as well as increased morbidity and mortality (Saadat, 2021). Previous studies demonstrated associations between worse sleep quality, as assessed by the Pittsburgh Sleep Quality Index (PSQI), and osteopenia, a condition in which bone mineral density is already reduced but still above the threshold for osteoporosis (Lucassen et al., 2017). Worse sleep quality was also associated with lower bone stiffness index values, indicating bone strength, obtained by quantitative ultrasound at the heel (Sasaki et al., 2016). Furthermore, associations between sleep deprivation and decreased bone mineral density were observed (Fu et al., 2011; Specker et al., 2007), although not at all examined sites (Specker et al., 2007). A prospective study among 190 Indian postmenopausal women showed that a shorter sleep duration was related to a higher 2-year decline in bone mineral density and that insomnia was predictive of incident osteoporosis (Cherian et al., 2022). Similarly, Chen et al. (2021) reported an association between self-reported short (< 7 h) but also long sleep duration (> 8 h) and estimated bone mineral density, measured by quantitative ultrasound of the heel. Also, OSA, a sleep-related breathing disorder, was frequently found to be related to lower bone mass in mostly smaller or selected samples, as reviewed by Eimar et al. (2017).

While sleep characteristics, as well as bone strength, change with ageing, several further independent mechanisms connecting both traits may exist (Swanson et al., 2018). In an interventional study, including 10 men, it was reported that sleep restriction and circadian disruption caused a decoupling of bone metabolism (Swanson et al., 2017). These results are in line with studies suggesting adverse effects of shift work on bone mineral density (Kim et al., 2013) and fracture risk (Feskanich et al., 2009).

While accumulating evidence points towards relevant relationships between sleep characteristics and bone turnover and strength, most previous studies were limited by small sample sizes (Cherian et al., 2022; Swanson et al., 2017), the restriction to questionnaires to assess sleep disorders (Chen et al., 2021; Cherian et al., 2022; Specker et al., 2007), the limitation to selected single markers of sleep quality (Specker et al., 2007), or the isolated assessment of bone turnover (Swanson et al., 2017). We therefore aimed to comprehensively investigate the relationship between sleep characteristics with bone turnover markers and quantitative ultrasound-based parameters among adults from the general population, using data from the Study of Health in Pomerania-TREND (SHIP-TREND). For this, we assessed subjective and objective information on sleep characteristics obtained by polysomnography (PSG) and dedicated questionnaires (Epworth Sleepiness Scale [ESS], Insomnia Severity Index [ISI], PSQI). We hypothesised the detection of associations between sleep characteristics and bone health independent of shared traditional risk factors.

2 | METHODS

2.1 | THE SHIP-TREND

The SHIP-TREND is a population-based cohort study in Northeast Germany (Völzke et al., 2011; Völzke et al., 2022). It includes adult Caucasian participants. The study population was selected based on a representative sample of the 20–79-year-old inhabitants of the study region, which included the cities Greifswald, Stralsund, Anklam, and the surrounding communities. From this sample, 4420 adult men and women participated in the baseline SHIP-TREND examinations (response 50.1%). The study was conducted between 2008 and 2012.

Written informed consent was obtained from all individual participants included in the study. All procedures were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Further details on study design, sampling procedures, and rationale are given elsewhere (Völzke et al., 2011; Völzke et al., 2022).

2.2 | Study population

The SHIP-TREND programme offered a broad range of medical examinations to the study participants. These included, e.g., a computer-assisted personal interview, blood pressure measurements, and blood sampling. Moreover, a quantitative ultrasound measurement at the heel, as well as a PSG examination were part of the study programme and offered to the participants. Of the 4420 SHIP-TREND participants, 1264 (28.6%) underwent PSG. The main reason for non-participation was the requirement of staying overnight. Among the 1264 men and women who participated in the PSG, 56 had to be excluded from the present analyses due to missing or incomplete data, technical problems, low-quality recordings, recording time < 300 min, or usage of a continuous positive airway pressure (CPAP) mask. From the remaining 1208 participants all those with missing data for the bone turnover markers and the heel ultrasound measurement, or missing information on self-reported osteoporosis, were excluded.

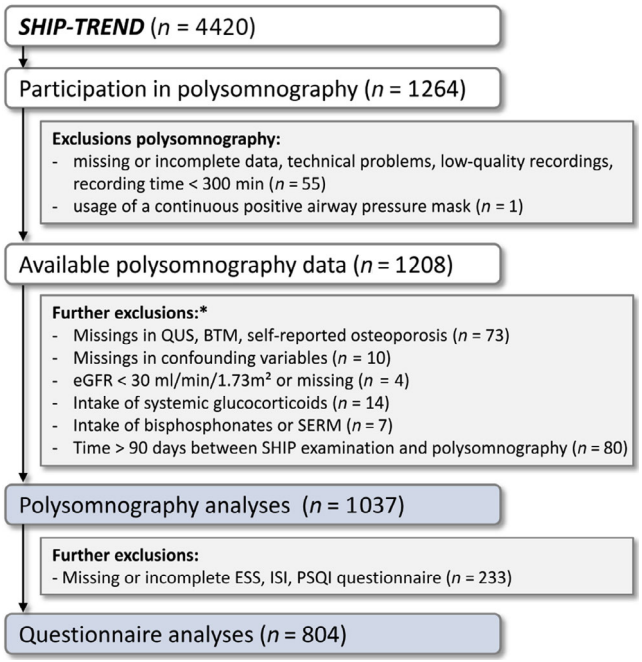

FIGURE 1 Selection of the study population. *Several criteria may apply to one participant. BTM, bone turnover marker; eGFR, estimated glomerular filtration rate; ESS, Epworth Sleepiness Scale; ISI; Insomnia Severity Index; PSQI, Pittsburgh Sleep Quality Index; QUS, quantitative ultrasound; SERM, selective oestrogen receptor modulator; SHIP, Study of Health in Pomerania.

Further, all participants with missing information in any of the confounding variables, with renal insufficiency or missing estimated glomerular filtration rate (eGFR), with the intake of systemic glucocorticoids or anti-osteoporotic drugs or with > 90 days between the core examination and PSG were excluded from the analyses. This resulted in a population of 1037 participants to examine associations between PSG and bone variables. Finally, 233 participants with missing information in the sleep questionnaires were excluded, resulting in a study population of 804 participants to examine the associations between ESS, ISI, PSQI, and the bone variables (Figure 1).

2.3 | Measurements

Information on sociodemographic characteristics, lifestyle, and medical histories, including a physician's diagnosis of osteoporosis, were obtained by personal interviews. Participants were classified into non-smoker, current-smoker, and ex-smoker based on self-reported current smoking and smoking history. The average daily alcohol consumption was calculated in g/day. Physical inactivity was defined when participants reported < 1 h/week of regular physical activity during summer and winter. Intake of medication was recorded and classified using the anatomical therapeutic chemical classification system (ATC). Glucocorticoids for systemic use were defined as ATC-code H02AB and H02BX. Anti-osteoporotic drugs were defined as bisphosphonates (ATC-code M05BA and M05BB) or selective oestrogen receptor modulators (ATC-code G03XC). Further specific anti-osteoporotic drugs, including denosumab (ATC-code M05BX04) or parathyroid hormone and analogues (ATC-code H05AA), were not taken. Standardised measurements of body height and weight were performed with calibrated scales. The body mass index (BMI) was calculated as weight (kg)/height^2 (m^2). Systolic and diastolic blood pressures were measured three times on the right arm of seated participants, using a digital blood pressure monitor (HEM-705CP, Omron Corporation, Tokyo, Japan). The mean of the second and third measurements was used for statistical analyses. Hypertension was defined as systolic blood pressure of ≥ 140 mmHg or diastolic blood pressure of ≥ 90 mmHg or self-reported intake of antihypertensive medication.

2.4 | Polysomnography and sleep questionnaires

The single-night, laboratory-based PSG (Alice 5 System, Philips Respironics, Eindhoven, The Netherlands), was conducted in compliance with the 2007 American Academy of Sleep Medicine rules that were current at the time of study design (Iber et al., 2007) and was previously described in detail (Stubbe et al., 2016). It included an assessment of nasal flow, thoracic and abdominal efforts, body position, oxygen saturation, heart rate, and snoring sounds. Sleep stages were analysed visually. Central, mixed, and obstructive apneas, hypopneas, periodic breathing, hypoventilation periods, respiratory-related arousals, and heart rate variability were documented. For the present study we analysed total sleep time (min), sleep efficiency (%, defined as total sleep time/time in bed), time spent wake after sleep onset (WASO; min), and the apnea–hypopnea index (AHI). The AHI was calculated as the mean number of apneas and hypopneas per hour (events/h). OSA was defined according to the AHI as: no OSA (AHI of < 5.0 events/h), mild OSA (AHI of 5.0–14.9 events/h), moderate OSA (AHI of 15.0–29.9 events/h), and severe OSA (AHI of ≥ 30.0 events/h). However, as severe OSA was rare ($n = 88$) in our study population, we collapsed the two upper categories to moderate-to-severe OSA. The oxygen desaturation index (ODI) was defined as the number of ≥4% oxygen desaturations per hour of total sleep time determined by pulse oximetry.

Polysomnography participants were asked to complete standardised sleep questionnaires. These included the ESS (Johns, 1991), the ISI (Bastien et al., 2001), and the PSQI (Buysse et al., 1989). The ESS measures daytime sleepiness using eight questions. The derived sum score ranges between 0 and 24, with higher scores implying greater daytime sleepiness (Johns, 1991). The ISI measures the nature, severity, and impact of insomnia in the past fortnight. The derived sum score ranges between 0 and 28, with higher scores implying higher severity of insomnia (Bastien et al., 2001). The PSQI measures sleep quality over a 1-month interval using seven components. The derived global sum score ranges between 0 and 21, with higher scores implying poorer sleep quality (Buysse et al., 1989).

2.5 | Quantitative ultrasound measurements

Quantitative ultrasound measurements were performed successively on both feet by trained and certified examiners using the Achilles InSight (GE Medical Systems Ultrasound, GE Healthcare, USA), as previously described (Berg et al., 2015). In short, the Achilles InSight is a water-based bone ultrasonometer, which measures the speed of sound and the frequency-dependent attenuation of the sound waves, which pass through an individual's heel (os calcis). Both characteristics are combined to form the stiffness index, which is indicative of the individual osteoporotic fracture risk. The stiffness index was calculated according to the following formula: stiffness index = (0.67 × broadband ultrasound attenuation) + (0.28 × speed of sound) − 420. The stiffness index is dependent on bone quantity and structure, and higher values indicate better bone properties. It does not have a unit. The data from the foot with the lower stiffness index was used for statistical analyses.

2.6 | Laboratory methods

Venous blood samples were taken from the cubital vein of participants in the supine position. Blood sampling was performed in the mornings with the majority of samples (78.6%) being taken before 10:00 a.m. and the remaining samples until 12:00 a.m. Information on fasting status was also collected. The majority of the participants (782 [75.4%]) were fasting for ≥ 8 h before blood sampling. Among the non-fasting participants, 21 (2.0%) had their last caloric intake 4–8 h before blood sampling and 234 participants (22.6%) < 4 h before blood sampling.

Serum and plasma samples were stored at −80 °C in the Integrated Research Biobank (Liconic, Lichtenstein) of the University Medicine Greifswald and used in accordance with its regulations (Winter et al., 2020). Serum intact amino-terminal propeptide of type 1 procollagen (P1NP) and C-terminal telopeptides of type 1 collagen (CTX) concentrations were determined by automated chemiluminescent immunoassays on the IDS-iSYS Multi-Discipline Automated Analyser (Immunodiagnostic Systems Limited, Frankfurt am Main, Germany). The coefficients of variation of P1NP and CTX were 4.4% and 7.5% at low concentrations, 4.5% and 5.2% at medium concentrations, and 4.3% and 4.5% at high concentrations, respectively, of control material. Serum creatinine concentrations were determined with a modified kinetic Jaffé method. The eGFR was calculated according to the creatinine-based Chronic Kidney Disease Epidemiology Collaboration formula (Levey et al., 2009). Renal insufficiency was defined as an eGFR of < 30 ml/min/1.73 m^2.

2.7 | Statistical analysis

We reported the general characteristics of the study population, stratified by OSA category, as medians with 25th and 75th quartiles (continuous data) or as proportions (nominal data). Group differences between the OSA categories were tested with chi-squared or Kruskal–Wallis tests and a $p < 0.05$ was considered statistically significant.

We then assessed the associations between the PSG variables or sleep questionnaire scores and the bone turnover marker concentrations, the ultrasound-based stiffness index, and self-reported osteoporosis in multivariable regression models. The two bone turnover marker concentrations and the quantitative ultrasound-based stiffness index were our main outcomes, while self-reported osteoporosis was defined as the secondary outcome. This differentiation was deemed necessary, as self-reported osteoporosis is considered a rather weak variable. It probably underestimates the 'true' proportion of patients with osteoporosis among the study population, as osteoporosis itself is known to be underdiagnosed (Rausch et al., 2018).

First, we examined the associations between the PSG variables or the questionnaire scores with the bone turnover marker concentrations (continuous) in separate, sex-specific, linear regression models. As both bone turnover markers were non-normally distributed, they were log-transformed before being entered into the regression models. The models were calculated sex specifically, as effect modification by sex was observed in all models except from total sleep time and ESS. Second, we examined the associations between the PSG variables or the questionnaire scores with the ultrasound-based stiffness index (continuous). In the fully-adjusted linear regression models, neither sex nor age (categorised as < 60 and ≥ 60 years), represented effect modifiers. Third, we examined the associations between the PSG variables or the questionnaire scores with our secondary outcome, self-reported osteoporosis (dichotomous; yes/no), in separate logistic regression models.

In all regression models, the exposure variables, i.e., the PSG variables and the questionnaire scores, were entered as continuous variables. In the analyses a 30-min increase in total sleep time or WASO, a 10% increase in sleep efficiency, an increase of 5 oxygen desaturations/h, a 5-point increase in AHI, and a 2-point increase in the questionnaire scores was modelled. Confounders were selected following the theory of directed acyclic graphs (Greenland et al., 1999) using daggity.net (Textor et al., 2017; Figure S1). Unadjusted models as well as models adjusted for sex, age, BMI, and fully-adjusted models (sex, age, BMI, smoking, alcohol, and physical inactivity) were calculated. We report β-coefficients with 95% confidence intervals (CIs) from the linear regression models and odds ratios (ORs) with 95% CIs from the logistic regression models. To account for multiple testing, we adjusted the p values by controlling the false discovery rate (FDR) at 5% using the Benjamini–Hochberg procedure (Benjamini & Hochberg, 1995).

Finally, we performed two sensitivity analyses. As mentioned above, the study population was selected from the subgroup of the SHIP-TREND participants who underwent PSG ($n = 1264$). The finally included participants ($n = 1037$) differed in several aspects from the excluded participants ($n = 3383$), e.g., the excluded participants were less often male, consumed less alcohol but reported more often snoring than the included participants (Table S1). In a first sensitivity analysis, we accounted for a possible bias due to these differences by applying inverse probability weights. The weights were generated using sex, age, smoking, alcohol consumption, hypertension, self-reported snoring, and hours of sleep per night as explanatory

TABLE 1 Characteristics of the study population.

Characteristic	No OSA ($n = 525$)	Mild OSA ($n = 276$)	Moderate-to-severe OSA ($n = 236$)	p
Male, %	41.9	63.4	73.1	<0.01
Age, years, median (IQR)	47.0 (36.0–57.0)	57.0 (50.0–64.5)	60.0 (53.0–68.0)	<0.01
BMI, kg/m^2, median (IQR)	25.9 (23.4–28.9)	29.5 (26.4–32.2)	30.5 (27.8–34.2)	<0.01
Smoking, %				<0.01
Non-smoking, %	44.4	38.0	34.7	
Current-smoking, %	33.3	44.9	47.9	
Ex-smoking, %	22.3	17.0	17.4	
Alcohol, g/day, median (IQR)	3.60 (1.11–11.14)	3.98 (1.11–14.65)	4.76 (0.99–13.74)	0.29
Physical inactivity, %	26.9	23.6	29.2	0.34
Hypertension, %	33.3	56.5	66.5	<0.01
Days between core examination and polysomnography, median (IQR)	7 (0–24)	7 (0–27)	9 (0–27)	0.54
TST, min, median (IQR)	389 (342–427)	378 (338–412)	368 (323–409)	<0.01
Sleep efficiency, %, median (IQR)	85.6 (77.4–91.7)	84.5 (75.3–90.4)	80.5 (71.4–88.0)	<0.01
WASO, min, median (IQR)	43.0 (22.5–74.0)	50.0 (30.8–85.3)	66.0 (37.8–97.8)	<0.01
AHI, events/h, median (IQR)	1.4 (0.6–2.7)	8.9 (7.1–11.4)	26.0 (19.0–36.4)	<0.01
ODI, desaturations/h, median (IQR)	0.70 (0.20–1.70)	5.10 (3.10–8.10)	18.1 (10.4–27.7)	<0.01
ESS score[a], median (IQR)	7 (5–9)	7 (5–9)	7 (5–9)	0.46
ISI score[a], median (IQR)	6 (3–10)	7 (4–11)	7 (4–11)	<0.01
PSQI score[a], median (IQR)	5 (3–8)	5 (4–9)	5 (4–8)	0.08
Self-reported osteoporosis, %	2.48	3.62	8.47	<0.01
Stiffness index, median (IQR)	95.1 (82.7–110.7)	93.5 (81.8–106.3)	92.6 (78.6–105.7)	0.09
P1NP, ng/ml, median (IQR)	47.2 (35.4–60.9)	42.8 (33.9–57.0)	43.0 (32.9–55.6)	0.02
CTX, ng/ml, median (IQR)	0.27 (0.17–0.40)	0.24 (0.15–0.37)	0.25 (0.15–0.36)	0.14

Note: Data are median (IQR) or proportions. Group differences were tested with chi-squared or Kruskal–Wallis tests.
Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; CTX, C-terminal telopeptides of Type I collagen; ESS, Epworth Sleepiness Scale; IQR, interquartile range (first–third quartile); ISI, Insomnia Severity Index; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; P1NP, intact amino-terminal propeptide of type I procollagen; PSQI, Pittsburgh Sleep Quality Index; TST, total sleep time; WASO, wake after sleep onset.
[a]Questionnaire data restricted to 804 participants.

variables. These variables were assumed to have the largest effect on participation in PSG, the main reason for exclusion. Fully-adjusted models assessing the associations between the sleep characteristics and the bone turnover marker concentrations, or the ultrasound-based stiffness index were re-calculated applying these weights. In a second sensitivity analysis, we assessed whether the associations with CTX were affected by fasting status. Therefore, we re-calculated the fully-adjusted sex-specific regression models for CTX separately in fasting and non-fasting participants.

All statistical analyses were performed with the Statistical Analysis System (SAS®), version 9.4 (SAS Institute Inc., Cary, NC, USA).

3 | RESULTS

Amongst the 1037 study participants with PSG, 568 were male and 469 were female. Half of the participants had no OSA (50.6%), another quarter (26.6%) had mild OSA, and 22.8% had moderate-to-severe OSA (Table 1). Participants with moderate-to-severe OSA were older, had a higher BMI, and more often hypertension than participants without or with mild OSA. Moreover, total sleep time and sleep efficiency were decreased, while WASO and the ODI were increased in participants with moderate-to-severe OSA compared to those without or with mild OSA. Regarding bone health, ~8.5% of participants with moderate-to-severe OSA reported a physician's diagnosis of osteoporosis versus only 2.5% of those without OSA. The quantitative ultrasound-based stiffness index was comparable between the three groups.

3.1 | Sleep characteristics and bone turnover

In sex-specific, unadjusted models all PSG variables except for total sleep time were associated with P1NP and CTX concentrations in men. In age- and BMI- and also in fully-adjusted models, these associations were no longer present. In women associations between the PSG variables and P1NP or CTX concentrations were absent in all models. Conversely, in women, associations between the ISI score

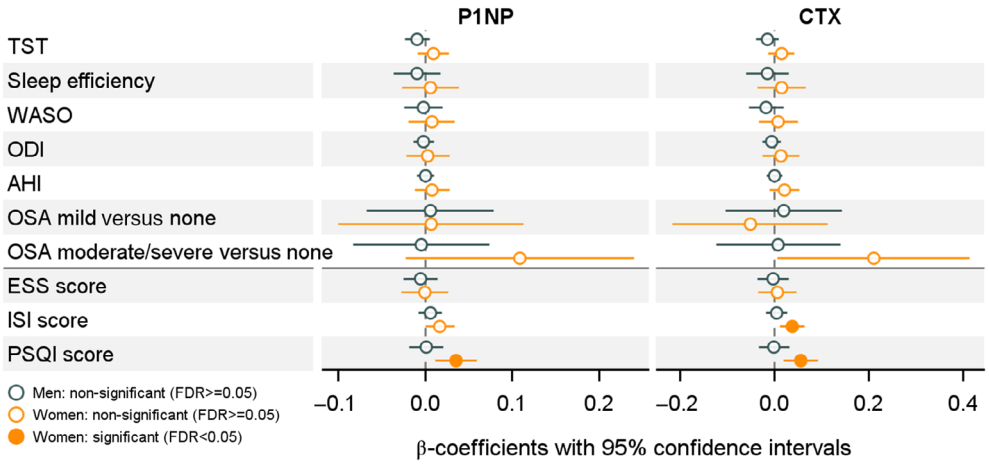

FIGURE 2 Sex-specific associations of polysomnography (PSG) variables and questionnaire scores with bone turnover markers from fully-adjusted models. Presented are β-coefficients with 95% confidence intervals for a 30-min increase in total sleep time (TST) and wake after sleep onset (WASO), a 10% increase in sleep efficiency, an increase of 5 oxygen desaturations/h, a 5-point increase in the apnea–hypopnea index (AHI), and a 2-point increase in questionnaire scores from fully-adjusted linear regression models. Fully-adjusted models included age, sex, body mass index, alcohol consumption, smoking, and physical inactivity. PSG analyses included 1037 participants and questionnaire data 804 participants. CTX, C-terminal telopeptides of type I collagen; ESS, Epworth Sleepiness Scale; FDR, false discovery rate; ISI, Insomnia Severity Index; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; P1NP, intact amino-terminal propeptide of type I procollagen; PSQI, Pittsburgh Sleep Quality Index.

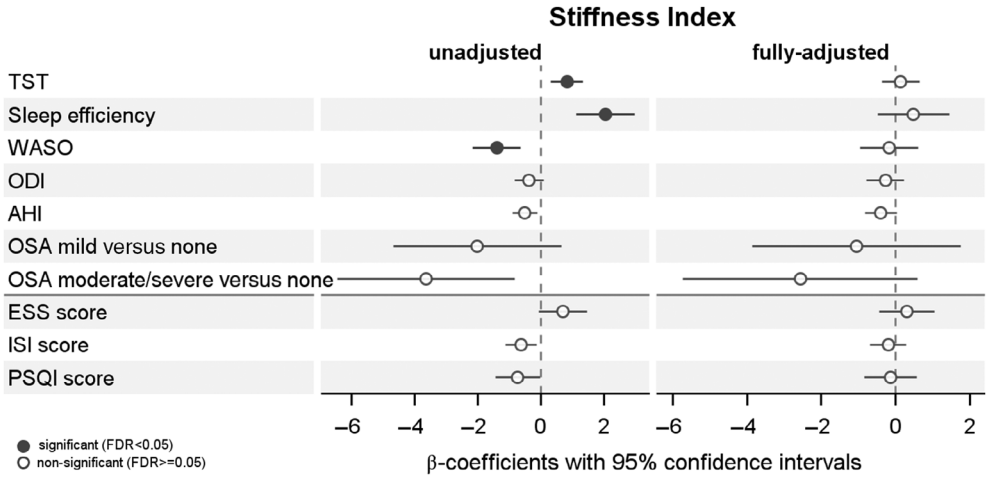

FIGURE 3 Association of polysomnography (PSG) variables and questionnaire scores with the quantitative ultrasound-derived stiffness index. Presented are β-coefficients with 95% confidence intervals for a 30-min increase in total sleep time (TST) and wake after sleep onset (WASO), a 10% increase in sleep efficiency, an increase of 5 oxygen desaturations/h, a 5-point increase in apnea–hypopnea index (AHI), and a 2-point increase in questionnaire scores from linear regression models. Fully-adjusted models included age, sex, body mass index, alcohol consumption, smoking, and physical inactivity. PSG analyses included 1037 participants and questionnaire data 804 participants. ESS, Epworth Sleepiness Scale; FDR, false discovery rate; ISI, Insomnia Severity Index; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; PSQI, Pittsburgh Sleep Quality Index.

and CTX and between the PSQI score and both bone turnover markers were detected in all models independent of the adjustment set. In the fully-adjusted model, each 2-point increase in the ISI or PSQI score was related to increases in P1NP and CTX concentrations. However, these associations were close to the threshold of statistical significance with FDR values between 0.03 and 0.05. There were no comparable associations with questionnaire scores in men (Figure 2 and Tables S2a, S2b).

3.2 | Sleep characteristics and parameters of bone strength

Next, the associations between the sleep variables and the quantitative ultrasound-based stiffness index were examined (Figure 3 and Table S3). In unadjusted models, we found positive associations between total sleep time and sleep efficiency with stiffness index and an inverse association between the WASO and stiffness index. In age-

, sex-, and BMI-adjusted, as well as in fully-adjusted models, these associations were no longer statistically significant.

3.3 | Sleep characteristics and self-reported osteoporosis

Finally, we examined the associations with self-reported osteoporosis, our secondary outcome. In unadjusted logistic regression models associations between sleep efficiency, WASO, the AHI, moderate-to-severe OSA, the ISI, and PSQI score with self-reported osteoporosis were found. However, in adjusted models only the associations with the ISI and the PSQI score and the association with moderate-to-severe OSA remained statistically significant (Table S5). Increasing ISI scores (2-point increase), indicating higher severity of insomnia, as well as increasing PSQI scores (2-point increase), indicating worse sleep quality, were related to increased odds of self-reported osteoporosis (OR, 95% CI from the fully-adjusted model for ISI: 1.28, 1.10–1.49; and for PSQI: 1.37, 1.12–1.67). Moreover, participants with moderate-to-severe OSA had higher odds for self-reported osteoporosis (OR 2.67, 95% CI 1.13–6.51) than those without OSA.

3.4 | Sensitivity analyses

The first sensitivity analysis, i.e., the re-calculation of the regression models using inverse probability weights to account for the large number of excluded participants, largely confirmed the above results. Fully-adjusted weighted and non-weighted models demonstrated no association between PSG variables or questionnaire scores and the quantitative ultrasound-based stiffness index (Table S3). The effects of the ISI and PSQI score on bone turnover in women were also similar in weighted and non-weighted models, but the FDR increased slightly to values between 0.03 and 0.08 in weighted models (Table S2).

In the second sensitivity analysis, the fully-adjusted sex-specific regression models for CTX were re-calculated separated by fasting status. As the majority of study participants were fasting, the size of the groups varied substantially (PSG variables fasting/non-fasting: men $n = 408/n = 160$, women 374/95; questionnaire variables fasting/non-fasting: men $n = 329/n = 127$, women 285/63). These analyses replicated the positive associations with the ISI and PSQI scores in fasting women (Table S4) but with increased FDR values (between 0.05 and 0.08). The β-coefficients derived from the models in non-fasting women for the ISI and PSQI score were quite similar but not statistically significant. Associations in men, independent of their fasting status, were absent.

4 | DISCUSSION

Our study of 1037 adults from the general adult population revealed a lack of association between the examined sleep characteristics and the quantitative ultrasound-based stiffness index after adjustment for relevant confounders. Yet, in women, high insomnia symptoms were related to higher bone resorption. Additionally, worse sleep quality was related to higher bone formation and resorption in women. In men, associations between sleep characteristics and bone formation or resorption were absent in adjusted models.

4.1 | Sleep characteristics and bone turnover

The present results argue against associations between sleep characteristics and bone turnover in adult men. This is in line with the results obtained from a study including 1927 elderly men who participated in the Osteoporotic Fractures in Men (MrOS) Sleep study, which suggests no association between self-reported sleep duration, ESS, or PSQI scores and P1NP or CTX (Swanson et al., 2021).

In women, on the other side, our data suggest a rise in bone turnover with increasing ISI and PSQI scores. Bone formation and resorption are closely linked processes that ensure the maintenance of adult human bone mass. An uncoupling of these processes leads to decreased stability of bone and subsequently to osteoporosis (Rachner et al., 2011). A previous interventional study by Swanson et al. (2017) demonstrated a connection between sleep disturbances and bone turnover. A strict protocol was followed by 10 men, including sleep restriction and circadian disruption. After 3 weeks of the intervention, a decoupling of bone turnover became apparent (Swanson et al., 2017). While P1NP concentrations—indicating bone formation—decreased, concentrations of CTX—indicating bone resorption—remained unchanged compared to baseline values (Swanson et al., 2017). These results were later confirmed by a study including nine women, with the addition that in young women (aged 18–24 years) not only decreases in P1NP but also increases in CTX were observed (Swanson et al., 2020). A prospective study including 190 Indian postmenopausal women further demonstrated meaningful effects of short sleep duration and insomnia on bone turnover (Cherian et al., 2022). Over the 2-year observation period, women with insomnia had greater increases in P1NP and CTX and higher odds of incident osteoporosis than those with normal sleep (Cherian et al., 2022). Nevertheless, the observed sex differences in our study, i.e., the restriction of the associations to women, merit comment. It is well known that sex differences are present in traits and associations related to poor sleep. Insomnia was, for example, more strongly linked to all-cause mortality in men than in women (Sivertsen et al., 2014). Relevant sex-specific relations of the ISI score with the bone turnover markers are therefore plausible. Nevertheless, our results in women must be interpreted cautiously and require validation as they were barely statistically significant.

4.2 | Sleep characteristics and parameters of bone strength

In the SHIP-TREND, associations between three PSG variables (total sleep time, sleep efficiency, and WASO) and the stiffness index were

found in unadjusted but not in adjusted models. Associations between the examined sleep questionnaires and stiffness index were absent in all models.

Previously and in contrast to our results, relationships of sleep characteristics with bone mineral density, ultrasound-based parameters, or fractures have been documented (Bevilacqua et al., 2020; Cauley et al., 2019; Chen et al., 2014; Fu et al., 2011; Lucassen et al., 2017; Ochs-Balcom et al., 2020; Sasaki et al., 2016; Sforza et al., 2013; Specker et al., 2007; Swanson et al., 2021; Tang et al., 2022; Terzi & Yilmaz, 2016). Yet, most previous studies (Bevilacqua et al., 2020; Cauley et al., 2019; Chen et al., 2014; Fu et al., 2011; Lucassen et al., 2017; Ochs-Balcom et al., 2020; Sasaki et al., 2016; Sforza et al., 2013; Specker et al., 2007; Swanson et al., 2021; Tang et al., 2022; Terzi & Yilmaz, 2016) assessed sleep characteristics solely by self-reports using standardised or study-specific questionnaires.

In postmenopausal women from the Women's Health Initiative, short sleep (≤ 5 h) was associated with decreased bone mineral density and an increased risk of osteoporosis (Ochs-Balcom et al., 2020). In addition, short sleep was related to an increased fracture risk (Cauley et al., 2019), and both, short and long sleep (≤ 5 or ≥ 10 h) were accompanied by an increased risk of falls (Cauley et al., 2019). Long sleep duration (> 8 h) was further reported to be related to reduced bone mineral density among nearly 4400 National Health and Nutrition Examination Survey (NHANES) participants (Tang et al., 2022). In another study, Lucassen et al. (2017) found that lower sleep quality and late sleep onset, as assessed by the PSQI, present risk factors for osteopenia and sarcopenia in middle-aged (aged 45–65 years) men and women. Likewise, the PSQI score—and especially sleep disturbances—were shown to be related to the quantitative ultrasound-based stiffness index among 1032 Japanese adults (Sasaki et al., 2016).

While sleep questionnaires are easy to implement in study settings, PSG is the 'gold standard' to diagnose OSA. However, PSG examinations are time-consuming and expensive, and therefore mainly used in smaller studies (Sforza et al., 2013; Terzi & Yilmaz, 2016). For example, Terzi and Yilmaz (2016), who had PSG available, found significantly lower bone mineral density at the femoral neck in 30 male patients with OSA compared to 20 healthy controls but comparable values at the lumbar spine. Significant associations of nocturnal hypoxia, a major symptom of OSA, with incident falls and fractures were also found in older men in the MrOS sleep study (Cauley et al., 2014). Larger, longitudinal studies generally assessed self-reported OSA and mainly found deleterious effects on bone mass (for a review see Eimar et al., 2017). Additionally, self-reported OSA was associated with vertebral but not hip fracture incidence in >55,000 female participants of the US Nurses' Health Study over a follow-up of 12 years (Huang et al., 2020).

As outlined above, previous work differs strongly regarding study design, especially the measurement of sleep characteristics and results. Our study, using the 'gold standard' method to diagnose OSA, highlights the substantial impact of confounding variables on the relation between sleep characteristics and bone strength. In our data, the sleep characteristics appeared to be no longer independently associated with stiffness index after adjustment for common risk factors for OSA and osteoporosis such as sex, age, and BMI. It is thus questionable whether an independent association between sleep characteristics and bone strength exists. In line with this, Chen et al. (2021) showed an increased risk of low ultrasound-based estimated bone mineral density in those with long and short self-reported sleep duration in their cross-sectional analysis of 398,137 individuals from the UK Biobank. Yet, in subsequent Mendelian randomisation analyses, a causal relationship could not be found, leading the authors to conclude that the associations between sleep duration and estimated bone mineral density are rather explained by unmeasured confounders than causality (Chen et al., 2021). Confounding might therefore contribute to explain the difference between the present and previous study results.

4.3 | Sleep characteristics and self-reported osteoporosis

In our data, associations of all PSG variables and all examined questionnaire scores with ultrasound-based stiffness index were absent after full adjustment. Concurrently, higher ISI and PSQI scores as well as moderate-or-severe OSA were related to increased odds of self-reported osteoporosis. This apparent contradiction may be attributable to peculiarities of the outcome variable 'self-reported osteoporosis'. It must be noted that this variable is a weak instrument due to the diagnostic gap in osteoporosis (Rausch et al., 2018). We assume that the SHIP-TREND participants who reported a respective diagnosis (43/1037 [4.2%]) are those with more serious disease and that an unknown number of participants with less serious disease was misclassified as healthy. Thus, the observed associations may be restricted to individuals with advanced osteoporosis. The quantitative ultrasound-based stiffness index, which better reflects bone strength in the whole study population, was not associated with any of the examined sleep characteristics, supporting this notion.

4.4 | Sensitivity analyses

Only one third of the SHIP-TREND participants underwent PSG. It is unclear whether individuals with sleep disorders had more or less often taken part in PSG. On the one side, the use of CPAP machines during PSG was not allowed, which might have restrained participants with moderate or severe OSA from participation. However, information on regular CPAP use was not collected. On the other side, individuals with subjective sleep disorders might have been highly interested in participating. Either or both may have caused a selection bias in our analyses. Yet, the first sensitivity analysis, that included weights to account for the large number of excluded participants, confirmed our main results. We, therefore, assume that although our study population is not representative of the whole SHIP-TREND population, the results of the associations between sleep characteristics and bone turnover or strength are valid for the whole population.

In the SHIP-TREND, the blood sampling conditions, i.e., the timing and fasting status, were not optimal for the determination of CTX. While P1NP is little affected by the time of day and fasting status, CTX is subject to a circadian rhythm and drops postprandially (Eastell et al., 2018). It is therefore recommended to measure CTX in samples taken in the mornings from fasting participants. In our second sensitivity analysis, we observed that the positive associations of ISI and PSQI scores with CTX concentrations in women were restricted to fasting women ($n = 285$). Effect directions and sizes were quite similar in non-fasting women, but respective associations were not statistically significant. Yet, the number of non-fasting women was low ($n = 63$), which may have prevented us from detecting respective associations in that group. In men, fasting status did not impact on our results; there were no associations between any of the sleep characteristics and CTX in the fasting or non-fasting state. We are therefore confident, that our results for CTX were not significantly biased by the inclusion of non-fasting participants.

4.5 | Strengths and limitations

Our study has several strengths and limitations. Strengths include the large population-based sample with standardised PSG measurements. This allowed us to collect objective information about the participant's sleep behaviour and to define OSA. Additional sleep characteristics were obtained using standardised and validated questionnaires. Moreover, we adjusted our analyses for several common confounders that affect OSA and osteoporosis such as age, sex, BMI, smoking, alcohol consumption, and physical inactivity. Limitations include the fact that PSG data were collected in a single night to maximise participation. It would have been favourable to obtain PSG measurements from 2 consecutive nights to allow the participants to get accustomed to the examination (Stubbe et al., 2016). Second, the response rate in the baseline SHIP-TREND examination was low at only 50.1%. This observation and its implications have been discussed previously (Völzke et al., 2015). In short, from a non-responder questionnaire it is known that non-participants were older, more often female, more often had diabetes, were less well educated, and had subjectively worse general health than participants (Völzke et al., 2015). However, as only 31% of non-participants answered the questionnaire, we refrained from performing further non-responder analyses. The generalisability of the present study results to a more morbid population or individuals with disturbed circadian rhythm, e.g., shift workers, may not be given. This may be particularly relevant to CTX, which exhibits a marked circadian rhythm. Moreover, our study sample was restricted to Caucasian adults, further limiting the generalisability of the study results. Third, we performed quantitative ultrasound instead of dual-energy X-ray absorptiometry (DXA) measurements, the latter being the 'gold standard' in osteoporosis diagnosis. In a population-based setting, the use of non-invasive quantitative ultrasound measurements without ionising radiation was, however, more appropriate. Moreover, previous studies demonstrated that fracture risk prediction by quantitative ultrasound is comparable to that of DXA (Moayyeri et al., 2009). Fourth, the cross-sectional design of the present analyses prohibits determining the causality of the observed associations. Thus, whether the relations between the ISI or PSQI scores and the bone turnover markers in women are causal remains to be further elucidated.

4.6 | CONCLUSION

Overall, our large study including adult men and women from the general adult population provides limited evidence for a relation between sleep characteristics and bone strength and turnover independent of common risk factors for OSA and osteoporosis. Nevertheless, female patients reporting poor sleep or insomnia in combination with risk factors for osteoporosis might benefit from an evaluation of bone health.

AUTHOR CONTRIBUTIONS

Kathrin Rassow: Methodology, Investigation, Writing–original draft, Writing–review and editing; Anne Obst: Formal analysis, Data curation, Writing–review and editing; Matthias Nauck: Resources, Writing–review and editing; Henry Völzke: Resources, Writing–review and editing; Beate Stubbe: Data curation, Writing–review and editing; Ingo Fietze: Data curation, Writing–review and editing; Thomas Penzel: Data curation, Writing–review and editing; Ralf Ewert: Resources, Data curation, Writing–review and editing; Anke Hannemann: Methodology, Data curation, Formal analysis, Writing–review and editing. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

Restrictions apply to the availability of data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. Data can be applied for following a standardized procedure: http://www2.medizin.uni-greifswald.de/cm/fv/ship/daten-beantragen/.

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SUPPORTING INFORMATION

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