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REGULAR RESEARCH PAPER

Prevalence and association analysis of obstructive sleep apnea with gender and age differences – Results of SHIP-Trend

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Abstract

Identification of obstructive sleep apnea and risk factors is important for reduction in symptoms and cardiovascular risk, and for improvement of quality of life. The population-based Study of Health in Pomerania investigated risk factors and clinical diseases in a general population of northeast Germany. Additional polysomnography was applied to measure sleep and respiration with the objective of assessing prevalence and risk factors of obstructive sleep apnea in a German cohort. One-thousand, two-hundred and eight people between 20 and 81 years old (54% men, median age 54 years) underwent overnight polysomnography. The estimated obstructive sleep apnea prevalence was 46% (59% men, 33% women) for an apnea–hypopnea index ≥5%, and 21% (30% men, 13% women) for an apnea–hypopnea index ≥ 15. The estimated obstructive sleep apnea syndrome prevalence (apnea–hypopnea index ≥5; Epworth Sleepiness Scale >10) was 6%. The prevalence of obstructive sleep apnea continuously increased with age for men and women with, however, later onset for women. Gender, age, body mass index, waist-to-hip ratio, snoring, alcohol consumption (for women only) and self-reported cardiovascular diseases were significantly positively associated with obstructive sleep apnea, whereas daytime sleepiness was not. Diabetes, hypertension and metabolic syndrome were positively associated with severe obstructive sleep apnea. The associations became non-significant after adjustment for body mass. Women exhibited stronger associations than men. The prevalence of obstructive sleep apnea was high, with almost half the population presenting some kind of obstructive sleep apnea. The continuous increase of obstructive sleep apnea with age challenges the current theory that mortality due to obstructive sleep apnea and cardiovascular co-morbidities affect obstructive sleep apnea prevalence at an advanced age. Also, gender differences regarding obstructive sleep apnea and associations are significant for recognizing obstructive sleep apnea mechanisms and therapy responsiveness.

KEYWORDS
diabetes, epidemiology, hypertension, obstructive sleep apnea, polysomnography, sleep-disordered breathing

1 | INTRODUCTION

Obstructive sleep apnea (OSA) – a common form of chronic sleep-disordered breathing caused by recurrent upper-airway collapse during sleep – is an increasingly prevalent public health problem. Older age, male gender and obesity are risk factors. Snoring and daytime sleepiness are the main symptoms (Senaratna et al., 2016). Sleep questionnaires such as the Epworth Sleepiness Scale (ESS) are used to assess symptom severity. However, not all patients with OSA present with these symptoms (Rosenthal & Dolan, 2008). A reliable diagnosis requires overnight polysomnography (PSG) in which sleep is recorded, breathing events scored and the apnea–hypopnea index (AHI) calculated to define the severity of sleep-disordered breathing (Iber, Ancoli-Israel, Chesson, & Quan, 2007). The prevalence of OSA is high, but estimates vary greatly based on the time of study, sample size, age, techniques, scoring criteria and population (Senaratna et al., 2016). The prevalence has increased over the years due to more sensitive recording techniques, change of scoring definitions, increased obesity prevalence and longer life expectancy (Flegal, Carroll, Kit, & Ogden, 2012; World Mortality Report, 2013). The Swiss HypnoLaus study has until now presented the highest prevalence estimate (72%, AHI $\geq$ 5; Heinzer et al., 2015).

Obstructive sleep apnea is associated with car accidents, depression, diabetes, metabolic syndrome, atherosclerosis, hypertension, stroke, arrhythmias and heart failure. While studies have shown that untreated OSA increases morbidity and mortality risks (Heinzer et al., 2015; Newman et al., 2001), recent studies have also shown that the most common treatment of OSA (i.e. use of a continuous positive airway pressure mask) might not reduce cardiovascular risk (McEvoy et al., 2016; Yu et al. 2017). Nevertheless, several studies have shown a positive effect of OSA treatment on cardiovascular disease (CVD) and, especially, early diagnosis and treatment of OSA have been shown to reduce symptoms and cardiovascular risk (Maurer, 2008). However, assessment of OSA with PSG is expensive and time-consuming. In at least 80% of cases, OSA remains undiagnosed (Peppard et al., 2013). International comparisons identified a high prevalence of risk factors, including hypertension, obesity, diabetes and metabolic syndrome in Germany (Meisinger et al., 2006; Schipf et al., 2012; Wolf-Maier et al., 2003). The Study of Health in Pomerania (SHIP) is a population-based project, designed to assess prevalence, incidence and associations of common risk factors, subclinical disorders and clinical diseases in northeast Germany (Völzke et al., 2011). While the initial cohort (SHIP-0, 1997–2001) did not investigate sleep, the second cohort (SHIP-Trend), conducted between 2008 and 2012, included laboratory-based PSG (Stubbe et al., 2016).

The goals of the SHIP-Trend sleep study were to estimate OSA prevalence in a population-based cohort, and to investigate associations with risk factors and CVDs. We expected to find a high prevalence of OSA owing to the prevailing great incidence of major risk factors.

2 | MATERIALS AND METHODS

2.1 | Participants and recruitment

SHIP-Trend conducted a series of interviews and examinations, including laboratory, medical and magnetic resonance imaging (MRI) data (for a complete list of examinations, see Völzke et al., 2011). For SHIP-Trend, a stratified sample of 10,000 people was randomly selected from local population registries in the German Federal State of Mecklenburg-West Pomerania. Stratification variables included age, sex and city/county of reference. At the time of recruitment, participants were required to be primary residents of Western Pomerania, and to be German citizens aged 20–79 years. After exclusion of deceased and relocated subjects, a net sample of 8,826 persons remained. Of these, 4,420 persons participated in SHIP-Trend (response rate: 50%; Stubbe et al., 2016). These SHIP-Trend participants were invited – through written invitations, phone calls and directly during other SHIP examinations – to additionally take part in a PSG subproject. Of the 4,420 SHIP-Trend participants, 1,264 took part in the PSG examination (PSG response rate of SHIP-Trend participants: 29%). The main reason for non-participation was the requirement of staying overnight. PSG participants received breakfast, a short medical report, €20 compensation, and free transport to the examination centre and back. The study was conducted over 4 years (2008–2012), and was approved by the Institutional Ethics and Scientific Review Committee of the University Hospital Greifswald, Germany. Participants gave written informed consent. No additional selection criteria were applied to balance a bias based on sleep-study participation, but we addressed a possible bias in our statistical analysis.

2.2 | Procedure

After completing baseline examinations (medical examinations and interview, including five sleep questions), participants attended a single-night, laboratory-based PSG (Alice 5 System, Philips Respironics, Eindhoven, The Netherlands) at a study site in Greifswald, Germany (Stubbe et al., 2016). On average, participants completed PSG examinations 9 days (median; interquartile range: 0–32 days) after the baseline examinations. Sensor placement began at about 20:00 hours, and was performed in compliance with 2007 American Academy of Sleep Medicine (AASM) rules that were current at the time of study design (Iber et al., 2007). Recordings included electroencephalogram (F4-M1, C4-M1, O2-M1, F3-M2, C3-M2, O1-M2), electrooculogram, electromyogram (chin and tibialis muscles), electrocardiogram, nasal pressure sensor and thermistor, inductance plethysmography to detect thoracic and abdominal efforts, body position sensor, pulse oximetry for arterial oxygen saturation, and microphone to detect snoring (Stubbe et al., 2016). We aspired a total bedtime of 8 hr, with a minimum requirement of 5 hr (median: 462 min; interquartile range: 431–490 min). Participants completed four sleep questionnaires after arrival: ESS; Insomnia Severity Index; Pittsburgh Sleep Quality Index; and Restless Legs Syndrome

Diagnostic Index. To assure quality control, personnel were trained and certified, with annual revision, by sleep experts from the Charité Universitätsmedizin Berlin (Lüdemann et al., 2000).

2.3 | Scoring of sleep and respiration

Visual scoring of sleep and respiration was performed according to AASM 2007 criteria and was subjected to strict quality control (Iber et al., 2007). A sleep event was scored as apnea if there was a drop in peak signal excursion by ≥ 90% for at least 10 s, and with at least 90% of the event duration showing such amplitude reduction. It was scored a hypopnea if there was either flow drop of ≥ 30% for at least 10 s with ≥ 4% oxygen desaturation, or flow drop of ≥ 50% with ≥ 3% oxygen desaturation, or an arousal. The AHI (events per hr) with clinically recognized thresholds was used to define OSA severity (no OSA: AHI < 5; mild-to-severe OSA: AHI ≥ 5; moderate-to-severe OSA: AHI ≥ 15; severe OSA: AHI ≥ 30). At the start of our study, it was common to distinguish between OSA and OSA syndrome, the latter of which included a daytime symptom such as excessive daytime sleepiness. For our study, we defined excessive daytime sleepiness as reflected by an ESS score > 10.

2.4 | Statistical analyses

Statistical analyses were performed with SAS 9.4 (SAS Institute, Cary, NC, USA). A *p*-value below .05 was considered statistically significant. Results were presented in three parts. In part one, the sample was described. Continuous variables were presented as medians with interquartile range and categorical variables, as proportions (%). For group comparisons, the Mann-Whitney *U*-test and chi-squared tests were employed. Part two presented AHI prevalence. A significant proportion of SHIP-Trend participants did not participate in the PSG examination. To correct for a possible selection bias (Table S1), inverse probability weighting according to Li, Shen, Li, and Robins (2013) was performed. We used multivariable logistic regression models to examine whether certain risk factors associated with OSA had a significant influence on participation. The factors that we considered included age, gender, body mass index (BMI), hypertension, smoking, alcohol, as well as hours of sleep per day and snoring. Based on the results, inverse probability weights were calculated and used to estimate OSA prevalence. The AHI was presented either as a continuous variable in terms of medians with 95% confidence interval (CI), or as a categorical variable in terms of relative frequency with 95% CI. For the analysis of age and gender, differences in prevalence, quantile regression (continuous AHI) and Poisson regression (categorical AHI) were applied. In part three, associations between OSA severity and risk factors and between OSA severity and clinical variables were evaluated for the sample without inverse probability weights. Logistic regression models with odds ratios (ORs) and 95% CI were used. For the association analysis of OSA and risk factors, OSA severity was categorized as mild-to-severe OSA (AHI ≥ 5) and moderate-to-severe OSA (AHI ≥ 15). Risk factors included age, BMI, waist-to-hip ratio, ESS, self-reported snoring and self-reported previous CVD. Although studies have shown an association between OSA and CVD, the causality of such an association is still unclear, and CVD has been considered an outcome as well as a risk factor for OSA (Somers et al., 2008). As the variable "previous CVD" was assessed only subjectively through self-reporting during the initial medical interview, we included it as a risk factor and not as an outcome variable. For the association analysis of OSA and clinical variables, OSA severity was assessed by AHI quartiles (Q1 = quartile one, reference group). Clinical variables included objectively assessed diagnoses of diabetes, hypertension and metabolic syndrome. The full logistic regression models were additionally adjusted for gender, age, alcohol, smoking, BMI and waist-to-hip ratio (Table S2).

3 | RESULTS

3.1 | Sample

Of 4,420 SHIP-Trend participants, 1,264 (29%) underwent PSG. It was necessary to exclude one participant from analysis due to the usage of a continuous positive airway pressure mask during PSG, and 56 participants owing to missing or incomplete data, technical problems, low-quality recordings or recording time less than 300 min. The final analysis was performed with 1,208 participants between the ages of 20 and 81 years. The PSG sample (Table S1) consisted of 54% men, and had a median age of 54 years and a median BMI of 28 kg m^{-2}. Approximately 11% had a diagnosis of diabetes, 49% of hypertension, 29% of metabolic syndrome and 20% of self-reported previous CVD, with men being slightly more affected than women.

3.2 | Prevalence estimates

The estimated median AHI score was 4.1 (95% CI = 3.5–4.7) events per hr. An estimated 46% (95% CI = 44.4–47.4) of the population-based sample exhibited mild-to-severe OSA (AHI ≥ 5), 21% (20.0–22.4) moderate-to-severe OSA (AHI ≥ 15), and 8% (6.9–8.5) severe OSA (AHI ≥ 30). AHI scores and prevalence were significantly higher for men than for women (AHI ≥ 15: men = 29.7%, 27.8–31.6 versus women = 13.2%, 11.8–14.6), and significantly higher for participants aged 60 years or older than for participants under 60 years. Prevalence differences between gender and age categories were more pronounced for greater AHI severity (Table 1). For men, estimated AHI scores increased continuously and reached as high as 15.2 (11.7–18.7) among those 70 years and older. For women, AHI scores did not begin to increase until the age of 50 years and older (Figure 1). Prevalence estimates of OSA increased continuously with age for both men and women (Figure S1). Mild-to-severe OSA was prevalent in men aged 20 years, and continuously increased to 80% (74.7–84.3) for men aged 70 years and older. In women, mild-to-severe OSA did not begin until age 30 years, with an estimated prevalence of 1.7% (0.1–3.3). Moderate-to-severe OSA started at age 40 years, with an estimated prevalence of 3.1% (1.6–4.5). Gender differences decreased with increasing age. Only a few participants

TABLE 1 Prevalence estimates of OSA and OSA syndrome, by gender and age

OSA/OSA syndrome severity	Total	Gender			Age		
	All	Men	Women	*p*	<60 years	≥60 years	*p*
AHI (median)	4.1 (3.5; 4.7)	7.5 (6.5; 8.5)	2.2 (1.8; 2.6)	**<0.001**	2.5 (2.0; 3.0)	9.4 (7.9; 10.9)	**<0.001**
AHI ≥ 5 (%)	45.9 (44.5; 47.4)	59.4 (57.3; 61.4)	33.2 (31.3; 35.2)	**<0.001**	35.0 (33.3; 36.8)	67.6 (65.2; 70.0)	**<0.001**
AHI ≥ 15 (%)	21.2 (20.0; 22.4)	29.7 (27.8; 31.6)	13.2 (11.8; 14.6)	**<0.001**	13.4 (12.2; 14.7)	36.6 (34.2; 39.1)	**<0.001**
AHI ≥ 30 (%)	7.7 (6.9; 8.5)	11.6 (10.3; 13.0)	4.1 (3.3; 4.9)	**0.009**	4.3 (3.6; 5.1)	14.5 (12.7; 16.3)	**<0.001**
AHI ≥ 5+ ESS score > 10 (%)	6.3 (5.6; 7.0)	9.7 (8.5; 11.0)	3.0 (2.3; 3.7)	**0.024**	6.3 (5.4; 7.1)	6.4 (5.1; 7.6)	0.977
AHI ≥ 15+ ESS score > 10 (%)	2.8 (2.3; 3.3)	4.3 (3.5; 5.2)	1.3 (0.8; 1.7)	0.308	2.2 (1.6; 2.7)	4.0 (3.0; 5.1)	0.555
AHI ≥ 30+ ESS score > 10 (%)	0.9 (0.7; 1.2)	1.4 (0.9; 1.9)	0.5 (0.2; 0.8)	0.754	0.8 (0.5; 1.2)	1.1 (0.6; 1.7)	0.925

Presented are estimated medians or percentages with 95% confidence interval (CI).
All analyses are weighted with inverse probability of participation weights, *p*-values for prevalence differences (quantile regression for continuous variables; Poisson regression for dichotomous variables) under .05 are considered statistically significant and highlighted (bold).
OSA, obstructive sleep apnea; AHI, apnea–hypopnea index; AHI ≥ 5: mild-to-severe OSA; AHI ≥ 15: moderate-to-severe OSA; AHI ≥ 30: severe OSA; ESS, Epworth Sleepiness Scale; AHI ≥ 5+ ESS score > 10: mild-to-severe OSA syndrome; AHI ≥ 15+ ESS score > 10: moderate-to-severe OSA syndrome; AHI ≥ 30+ ESS score > 10: severe OSA syndrome.

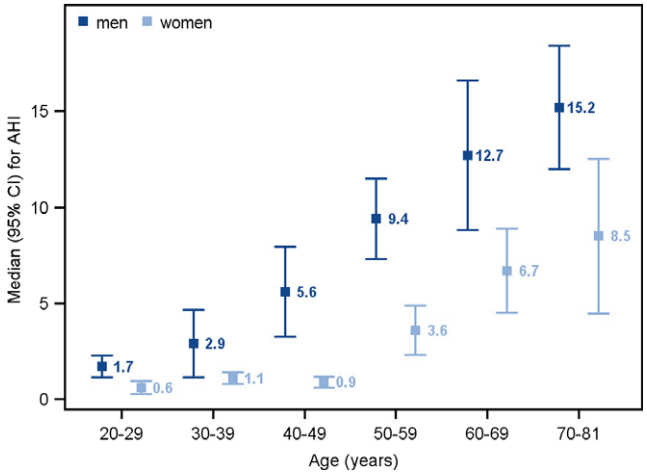

FIGURE 1 Estimated AHI median for age by 10-year increments, separated for gender. AHI, apnea–hypopnea index, defining obstructive sleep apnea (OSA) severity. Boxes represent estimated median scores and whiskers 95% confidence interval (CI)

exhibited OSA syndrome with excessive daytime sleepiness (ESS score > 10; Table 1). The estimated mild-to-severe OSA syndrome prevalence was 6% (5.6–7.0), with men exhibiting greater prevalence than women. The use of inverse probability weights had only marginal impact on our results. The prevalence within our sample without inverse probability weights showed similar results with slightly greater prevalence (Table S3). In our sample, 71% of the respiratory events were apnea (55% obstructive apnea, 11% central apnea, 4% mixed apnea) and 29% hypopnea. The weighted prevalence of mild-to-severe AI and HI was 33% (31.5–34.3) and 19% (18.3–20.6); of moderate-to-severe AI and HI, 13% (12.2–14.2) and 3% (2.8–3.8), respectively.

3.3 | Association analysis within sample

As weighted and unweighted prevalence (Tables 1 and S3) did not show substantial differences, we conducted the association analysis for the sample without inverse probability weights. A logistic regression analysis revealed a highly significant gender effect (mild-to-severe OSA: OR = 3.26; 95% CI = 2.36–4.16; $p < .001$; moderate-to-severe OSA: 2.60; 2.06–3.29; $p < .001$). Both men and women, showed significant positive associations between OSA and age, BMI, waist-to-hip ratio, self-reported snoring and self-reported previous CVD (Table 2). Additionally, women presented a significant positive association of alcohol consumption with AHI. Associations were stronger with greater AHI. With the exception of previous CVD, women presented stronger positive associations than men, especially regarding associations with high BMI and self-reported snoring. Daytime sleepiness assessed with ESS score > 10 was not significantly associated with AHI. Only 81 participants (13%) with mild-to-severe OSA ($n = 604$), 37 participants (13%) with moderate-to-severe OSA ($n = 287$) and 13 participants (12%) with severe OSA ($n = 105$) also reported an ESS score above 10. The ESS was also significantly associated with neither the AI nor the HI. Association analysis with AHI as a continuous variable revealed similar results.

In order to assess associations between OSA and diabetes, hypertension and metabolic syndrome, we adjusted logistic regression models to account for potential confounding risk factors. AHI severity was assessed by AHI quartiles (Q1: 0–1.3 events per hr; Q2: 1.4–4.9; Q3: 5.0–13.9; Q4: >14.0) with reference to the first quartile. For models 1 (adjusted for age and gender) and 2 (adjusted additionally for smoking and alcohol), significant positive associations between AHI and diabetes, hypertension and metabolic syndrome became apparent (Figure 2). Associations were stronger for the upper quartiles. After adjusting for BMI in model 3, the associations became non-significant for all quartiles. Only metabolic syndrome showed a significant *p*-trend across all quartiles for model 3 (*p*-trend = .031). No further changes were detected after adjusting for waist-to-hip ratio in model 4. Analyses repeated for women and men separately showed similar results (Table S4). However, while women showed no significant associations in model 3, men showed a significant association of metabolic syndrome with higher AHI quartiles (*p*-trend = .010 with Q3: OR = 2.3, 95% CI = 1.2–4.3/Q4: 2.2, 1.1–4.2).

TABLE 2 Associations between AHI and risk factors, by severity and gender

	Men (n = 649/n = 395)		Women (n = 559/n = 209)		Interaction[a]
AHI ≥ 5	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	***p***
Age (per 10-year increment)	1.77 (1.56–2.02)	**<0.001**	2.79 (2.29–3.40)	**<0.001**	**<0.001**
BMI (kg m^{-2})					
25–30 (versus < 25)	2.52 (1.64–3.89)	**<0.001**	3.43 (2.02–5.82)	**<0.001**	**<0.001**
> 30 (versus < 25)	6.38 (3.92–10.37)	**<0.001**	9.41 (5.57–15.90)	**<0.001**	**<0.001**
Waist-to-hip ratio[b]					0.705
Category 2 (versus Q1)	2.63 (1.66–4.16)	**<0.001**	1.84 (0.99–3.39)	0.052	
Category 3 (versus Q1)	4.37 (2.71–7.05)	**<0.001**	4.26 (2.32–7.82)	**<0.001**	
Category 4 (versus Q1)	7.12 (4.36–11.61)	**<0.001**	7.41 (4.05–13.53)	**<0.001**	
Alcohol use (yes versus no)	1.16 (0.64–2.11)	0.630	2.84 (1.59–5.07)	**<0.001**	**0.035**
ESS score (> 10 versus ≤ 10)	1.08 (0.70–1.68)	0.718	0.61 (0.35–1.06)	0.082	0.111
Snoring (yes versus no)	3.47 (2.21–5.43)	**<0.001**	4.69 (2.89–7.61)	**<0.001**	0.370
Previous CVD (yes versus no)	2.49 (1.64–3.78)	**<0.001**	1.83 (1.92–2.92)	**0.006**	0.358
AHI ≥ 15	**Men (n = 456/n = 202)**		**Women (n = 435/n = 85)**		**Interaction**
	OR (95% CI)	***p***	**OR (95% CI)**	***p***	***p***
Age (per 10-year increment)	1.94 (1.66–2.27)	**<0.001**	3.20 (2.41–4.25)	**<0.001**	**0.003**
BMI (kg m^{-2})					
25–30 (versus < 25)	3.25 (1.78–5.95)	**<0.001**	4.64 (1.84–11.71)	**0.001**	**<0.001**
> 30 (versus < 25)	10.38 (5.49–19.60)	**<0.001**	16.82 (6.94–40.80)	**<0.001**	**<0.001**
Waist-to-hip ratio[b]					**<0.001**
Category 2 (versus Q1)	2.71 (1.48–4.96)	**0.001**	2.31 (0.72–7.38)	0.159	
Category 3 (versus Q1)	5.44 (2.98–9.90)	**<0.001**	8.48 (2.84–25.32)	**<0.001**	
Category 4 (versus Q1)	9.35 (5.13–17.02)	**<0.001**	16.27 (5.55–47.71)	**<0.001**	
Alcohol use (yes versus no)	1.05 (0.52–2.14)	0.889	4.20 (2.12–8.30)	**<0.001**	0.953
ESS score (> 10 versus ≤ 10)	0.97 (0.57–1.64)	0.906	0.65 (0.29–1.43)	0.281	**<0.001**
Snoring (yes versus no)	4.60 (2.49–8.49)	**<0.001**	9.77 (3.84–24.88)	**<0.001**	**<0.001**
Previous CVD (yes versus no)	3.32 (2.10–5.25)	**<0.001**	2.38 (1.35–4.21)	**0.003**	**<0.001**

AHI, apnea–hypopnea index; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; ESS, Epworth Sleepiness Scale; OR, odds ratio. A p-value under .05 is considered statistically significant and highlighted (bold).

[a]Interaction displays the gender difference for each riskfactor separately on a .05 signifcance level (for waist-to-hip ratio, the continuous waist-to-hip ratio was used due to the gender-specific different categories).

[b]The gender-specific cut-off points for waist-to-hip ratio are based on quartiles, and are 0.90, 0.95, 0.99 for men and 0.78, 0.83, 0.87 for women. Presented are ORs with 95% CI. Statistical analysis by logistic regression models.

Women exhibited stronger associations with diabetes and hypertension than did men, and men demonstrated a slightly stronger association with metabolic syndrome. Gender differences were most pronounced for the association with diabetes.

4 | DISCUSSION

A large-scale PSG study was conducted in a general German population with a wide age range (20–81 years). Considering the characteristics of Europe, and especially of northeast Germany (Meisinger et al., 2006; Schipf et al., 2012; Wolf-Maier et al., 2003), i.e. a region with high hypertension, diabetes and obesity prevalence, known risk factors for OSA, we expected to find high OSA prevalence. With a prevalence of diabetes (11%), hypertension (49%), metabolic syndrome (29%) and obesity (35% with BMI > 30 kg m^{-2}), our sample matched these characteristics. The OSA prevalence by our study was indeed high, with almost half the population experiencing at least mild OSA, and one-fifth having at least moderate OSA. The prevalence of OSA rose as high as 80% for men aged 70 years and older, with a median AHI as high as 15.2 events per hr. With such high prevalence especially in older people, there is the implication that OSA (at least in its milder form) may be part of the typical aging process without reflecting a specific pathology. The Swiss HypnoLaus study assessed with a prevalence of 72% for mild-to-severe OSA in people 40 years and older the highest prevalence until now, and concluded that almost every person that age has some degree of sleep-disordered breathing (Heinzer et al., 2015). Further research is needed to explore this question, and to possibly adapt definitions and restrictions. While we did not confirm the extremely high prevalence that HypnoLaus found, our high prevalence was in line with

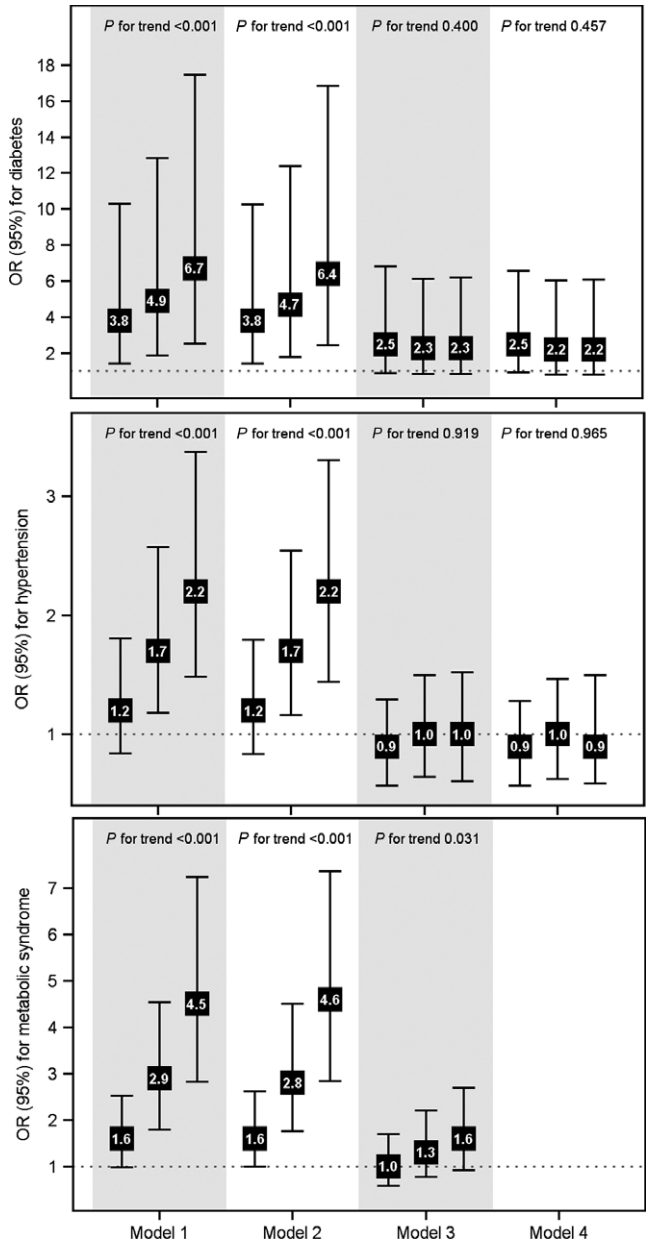

FIGURE 2 Association between AHI and diabetes, hypertension and metabolic syndrome. AHI, apnea–hypopnea index; CI, confidence interval; OR, odds ratio. Boxplots represent AHI quartiles. Squares represent the OR and whiskers 95% CI. Association is not significant when bars cross the dotted line at 1.0. Quartiles for AHI are as follows: Q1: 0–1.3 events per hr (median: 0.5); Q2: 1.4–4.9 (2.7); Q3: 5.0–13.9 (8.7); Q4: 14.0–91.8 (24.6). Q1 was used as reference group. Model 1 is adjusted for age and sex, model 2 additionally for alcohol (continuous variable) and smoking (categorical variable yes/no), model 3 additionally for body mass index (BMI), model 4 additionally for waist-to-hip ratio. There was no model 4 for metabolic syndrome as waist-to-hip ratio was part of its definition

several recent studies (Franklin, Sahlin, Stenlund, & Lindberg, 2013; Gabbay & Lavie, 2012; Weinreich et al., 2013), indicating a trend of rising prevalence. However, comparing prevalence between sleep studies is difficult due to different study populations and methods (Bixler et al., 2001; Duran, Esnaola, Rubio, & Iztueta, 2001; Ip et al., 2001; Senaratna et al., 2016; Shahar et al., 2001; Tufik, Santos-Silva, Taddei, & Bittencourt, 2010; Young et al., 1993). While HypnoLaus used home PSG and did not investigate persons under 40 years, we conducted laboratory-based PSG with participants as young as 20 years. Also, in the HypnoLaus sample, 75% of the sleep-disordered breathing events were hypopnea; in our sample, we had more apnea events (71%). Furthermore, HypnoLaus applied the more liberal 2012 AASM scoring criteria. They rescored with the 2007 criteria. Here, their median AHI sank from 9.9 to 4.3, which was, interestingly, in accordance with our results (4.1).

We additionally found a positive linear association of AHI severity and prevalence with age for men as well as for women. OSA increased continuously until age 80 years. However, women had a later onset of OSA, and AHI severity did not increase until age 50 years and older. These gender differences decreased with age. Studies have suggested that hormonal changes that women experience during menopause may be responsible for an increased AHI in women of menopausal age. Menopause may even represent a more important determinant than age for prevalence changes (Heinzer et al., 2015; Huang et al., 2018). Contrary to our results, previous studies suggested a non-linear association of OSA and age, with prevalence reaching a maximum at approximately age 65 years, and then levelling off or even decreasing (Huang et al., 2018; Young, Peppard, & Gottlieb, 2002). The explanation was that mortality due to OSA and its association with cardiovascular co-morbidities may increase with age, resulting in levelled or decreased OSA prevalence ("healthy survivor effect"; Huang et al., 2018; Marshall, Wong, Cullen, Knuiman, & Grunstein, 2014). Our results question this theory. However, we cannot completely rule out the effects of a possible selection bias. Also, further analysis needs to separate the effects of menopause from age.

While estimated OSA prevalence was high, OSA syndrome prevalence (defined by including excessive daytime sleepiness) was low. With an estimated 10%, men had a higher OSA syndrome prevalence than did women, with 3%. These results are in line with other studies (Punjab, 2008). However, many patients with OSA are asymptomatic (Arnardottir, Bjornsdottir, Olafsdottir, Benediktsdottir, & Gislason, 2016; Kapur, Baldwin, Resnick, Gottlieb, & Nieto, 2005). Only 13% of our participants with OSA also self-reported excessive daytime sleepiness. As in other studies, we did not find a significant association between AHI and sleepiness assessed by ESS (Arnardottir et al., 2016; Franklin et al., 2013). Despite its insufficient predictive capabilities, the ESS is widely used in clinical practice as an OSA screening tool (Rosenthal & Dolan, 2008; Vana, Silva, & Goldberg, 2013). Other tools to assess daytime sleepiness may be more effective. One of our interview questions regarding daytime napping showed a significantly higher AHI for participants that did nap during the day than for those who did not. Also, studies using objective measures for sleepiness found a greater association (Seneviratne & Puvanendran, 2004). Fatigue may also need more consideration in OSA screening. Excessive fatigue was associated with more severe dysfunction than was high sleepiness (Bailes et al., 2011; Shahid,

Shen, & Shapiro, 2010). The ESS as a screening tool and the reliance on sleepiness alone as a conclusive symptom for OSA diagnosis may not be warranted.

Our association analysis furthermore disclosed important gender-specific differences regarding several risk factors and co-morbidities. There is little evidence of gender-specific differences regarding associations to underlying factors. However, differences in symptoms and anatomy between men and women (including hormonal changes and differences in body composition and fat distribution) suggest differences regarding the pathogenesis of and treatment effectiveness for OSA. Our study revealed that women exhibited stronger positive associations than did men regarding hypertension, diabetes, age, BMI, waist-to-hip ratio, snoring and alcohol use. A recent study on sex differences also determined a stronger association of OSA and hypertension for women. Contrary to our results, they found no gender differences regarding BMI, snoring and diabetes, but differences for daytime sleepiness. However, they assessed OSA only on the basis of self-reports and daytime sleepiness not by applying the ESS but by asking certain similar sleep-related questions (Huang et al., 2018). The positive association of OSA with hypertension, diabetes and metabolic syndrome was present only for higher AHI levels, in contrast to other studies (Duran et al., 2001; Heinzer et al., 2015). This association also disappeared when adjusting for BMI. Some studies stated that there may not be a causal relationship between OSA and hypertension (Cano-Pumarega et al., 2011), while other studies found no influence of the BMI on these associations (Carlson, Hedner, Ejnell, & Peterson, 1994). Recent studies introduced the cluster analysis approach, forming subtypes based on clinical symptoms to account for OSA heterogeneity (Lacedonia et al., 2016; Ye et al., 2014). They found that the association to CVDs depended on clusters (Ye et al., 2014).

One limitation of our study was the possible selection bias. Only one-third of SHIP-Trend participants underwent PSG. Most declined due to the overnight requirement. Also, studies have shown general decreasing willingness to participate in population studies (Völzke et al., 2015). Our results indicated that it was participants with subjective sleep problems who especially committed to the overnight PSG (Table S1). The similarity of weighted prevalence estimates (Table 1) and unweighted prevalence (Table S3) suggests that the selection bias may not have been critical.

Our study is a unique German sleep-monitoring study, representative of European populations, using PSG with a population-based cohort. Although the OSA level was high, we could not confirm the most recent extremely high Swiss prevalence (Heinzer et al., 2015). We also revealed that women with OSA exhibited greater prevalence than did men regarding common risk factors, cardiovascular and metabolic co-morbidities. These findings emphasize the importance of thorough phenotype evaluation regarding possible gender-specific differences in OSA pathogenesis, mechanism and susceptibility. Additionally, the linear increase of OSA with age questions how far mortality due to OSA and its co-morbidities may indeed affect and reduce OSA prevalence in age as previously assumed. We also confirmed once more that the ESS is an insufficient tool for OSA symptom evaluation. In a next step, we recommend further investigation of the influence of age and menopause on OSA prevalence, as well as possible application of a cluster analysis approach. It is becoming more and more important to investigate not only OSA defined purely by the AHI but also OSA syndrome and its symptoms as the apparent disease. They do have an effect not only on therapy responsiveness but also on co-morbidities such as cardiovascular morbidity (Ye et al., 2014). Therefore, it is highly relevant (especially considering the high prevalence) to improve definitions and therapy strategies.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

HV, RE, SF., SG, CS, BS designed the SHIP-Trend study. IF, TP, SZ, MG designed the sleep study and supervised sleep-related data collection. AO performed the required data analysis. IF, TP, NL, CG, AO interpreted sleep data, discussed findings, and linked sleep findings to clinical data from SHIP-Trend. NL, AO, IF, TP wrote the manuscript. All authors critically reviewed the manuscript.

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REFERENCES

Arnardottir, E. S., Bjornsdottir, E., Olafsdottir, K. A., Benediktsdottir, B., & Gislason, T. (2016). Obstructive sleep apnoea in the general population: Highly prevalent but minimal symptoms. *European Respiratory Journal*, *47*(1), 194–202.

Bailes, S., Libman, E., Baltzan, M., Grad, R., Kassissia, I., Creti, L., … Fichten, C. S. (2011). Fatigue: The forgotten symptom of sleep apnea. *Journal of Psychosomatic Research*, *70*, 346–354. https://doi.org/10.1016/j.jpsychores.2010.09.009

Bixler, E., Vgontzas, A., Lin, H.-M., Ten have, T., Rein, J., Vela-bueno, A., & Kales, A. (2001). Prevalence of sleep-disordered breathing in women—Effects of gender. *American Journal of Respiratory and Critical Care Medicine*, *163*, 608–613. https://doi.org/10.1164/ajrccm.163.3.9911064

Cano-Pumarega, I., Durán-Cantolla, J., Aizpuru, F., Miranda-Serrano, E., Rubio, R., Martínez-Null, C., … Fernández-Bolaños, M. (2011).

Obstructive sleep apnea and systemic hypertension: Longitudinal study in the general population: The Vitoria Sleep Cohort. *American Journal of Respiratory and Critical Care Medicine*, *184*(11), 1299–1304.

Carlson, J. T., Hedner, J. A., Ejnell, H., & Peterson, L. E. (1994). High prevalence of hypertension in sleep apnea patients independent of obesity. *American Journal of Respiratory and Critical Care Medicine*, *150*(1), 72–77.

Duran, J., Esnaola, S., Rubio, R., & Iztueta, A. (2001). Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. *American Journal of Respiratory and Critical Care Medicine*, *163*, 685–689.

Flegal, K. M., Carroll, M. D., Kit, B. K., & Ogden, C. L. (2012). Prevalence of obesity and trends in the distribution of body mass index among US Adults, 1999–2010. *The Journal of the American Medical Association*, *307*(5), 491–497.

Franklin, K. A., Sahlin, C., Stenlund, H., & Lindberg, E. (2013). Sleep apnoea is a common occurrence in females. *European Respiratory Journal*, *41*, 610–615. https://doi.org/10.1183/09031936.00212711

Gabbay, I. E., & Lavie, P. (2012). Age- and gender-related characteristics of obstructive sleep apnea. *Sleep and Breathing*, *16*, 453–460. https://doi.org/10.1007/s11325-011-0523-z

Heinzer, R., Vat, S., Marques-Vidal, P., Marti-Soler, H., Andries, D., Tobback, N., … Vollenweider, P. (2015). Prevalence of sleep-disordered breathing in the general population: The HypnoLaus study. *The Lancet Respiratory Medicine*, *3*(4), 310–318.

Huang, T., Lin, B. M., Markt, S. C., Stampfer, M. J., Laden, F., Hu, F. B., … Redline, S. (2018). Sex differences in the associations of obstructive sleep apnoea with epidemiological factors. *European Respiratory Journal*, *51*, 1 702 421. https://doi.org/10.1183/13993003.02421-2017

Iber, C., Ancoli-Israel, S., Chesson, A., & Quan, S. F. (2007). The AASM Manual for the scoring of sleep and associated events: Rules, terminology and technical specifications (1st edn). Westchester, IL: *American Academy of Sleep Medicine*.

Ip, M. S., Lam, B., Lauder, I. J., Tsang, K. W., Chung, K. F., Mok, Y. W., & Lam, W. K. (2001). A community study of sleep-disordered breathing in middle-aged Chinese men in Hong Kong. *Chest*, *119*, 62–69. https://doi.org/10.1378/chest.119.1.62

Kapur, V. K., Baldwin, C. M., Resnick, H. E., Gottlieb, D. J., & Nieto, J. (2005). Sleepiness in patients with moderate to severe sleep-disordered breathing. *Sleep*, *28*(4), 472–477. https://doi.org/10.1093/sleep/28.4.472

Lacedonia, D., Carpagnano, G. E., Sabato, R., Storto, M. M. L., Palmiotti, G. A., Capozzi, V., … Gallo, C. (2016). Characterization of obstructive sleep apnea-hypopnea syndrome (OSA) population by means of cluster analysis. *Journal of Sleep Research*, *25*(6), 724–730.

Li, L., Shen, C., Li, X., & Robins, J. M. (2013). On weighting approaches for missing data. *Statistical Methods in Medical Research*, *22*(1), 14–30.

Lüdemann, J., Piek, M., Wood, W. G., Meyer, S., Greiner, B., John, U., & Hense, H. W. (2000). Methods for quality assurance of medical examination in epidemiological field studies: The "Study of Health in Pomerania" (SHIP). *Gesundheitswesen*, *62*, 234–243.

Marshall, N. S., Wong, K. K., Cullen, S. R., Knuiman, M. W., & Grunstein, R. R. (2014). Sleep apnea and 20-year follow-up for all-cause mortality, stroke, and cancer incidence and mortality in the Busselton Health Study Cohort. *Journal of Clinical Sleep Medicine*, *10*, 355–362. https://doi.org/10.5664/jcsm.3600

Maurer, J. T. (2008). Early diagnosis of sleep related breathing disorders. *GMS Current Topics in Otorhinolaryngology, Head and Neck Surgery*, *7*, 1–20.

McEvoy, R. D., Antic, N. A., Heeley, E., Luo, Y., Ou, Q., Zhang, X., … Chen, G. (2016). CPAP for prevention of cardiovascular events in obstructive sleep apnea. *New England Journal of Medicine*, *375*, 919–931.

Meisinger, C., Heier, M., Völzke, H., Löwel, H., Mitusch, R., Hense, H. W., & Lüdemann, J. (2006). Regional disparities of hypertension prevalence and management within Germany. *Journal of Hypertension*, *24*, 293–299. https://doi.org/10.1097/01.hjh.0000200508.10324.8e

Newman, A. B., Nieto, F. J., Guidry, U., Lind, B. K., Redline, S., Shahar, E., … Quan for the Sleep Heart Health Study Research Group. (2001). Relation of sleep-disordered breathing to cardiovascular disease risk factors. *American Journal of Epidemiology*, *154*(1), 50–59.

Peppard, P. E., Young, T., Barnet, J. H., Palta, M., Hagen, E. W., & Hla, K. M. (2013). Increased prevalence of sleep-disordered breathing in adults. *American Journal of Epidemiology*, *177*, 1006–1014.

Punjab, N. M. (2008). The epidemiology of adult obstructive sleep apnea. *Proceedings of the American Thoracic Society*, *5*, 136–143.

Rosenthal, L. D., & Dolan, D. C. (2008). The Epworth sleepiness scale in the identification of obstructive sleep apnea. *The Journal of Nervous and Mental Disease*, *196*(5), 429–431.

Schipf, S., Werner, A., Tamayo, T., Holle, R., Schunk, M., Maier, W., … Moebus, S. (2012). Regional differences in the prevalence of known Type 2 diabetes mellitus in 45–74 years old individuals: Results from six population-based studies in Germany (DIAB-CORE Consortium). *Diabetic Medicine*, *29*(7), e88–e95.

Senaratna, C. V., Perret, J. L., Lodge, C. J., Lowe, A. J., Campbell, B. E., Matheson, M. C., … Dharmage, S. C. (2016). Prevalence of obstructive sleep apnea in the general population: A systematic review. *Sleep Medicine Reviews*, *34*, 70–81. https://doi.org/10.1016/j.smrv.2016.07.002

Seneviratne, U., & Puvanendran, K. (2004). Excessive daytime sleepiness in obstructive sleep apnea: Prevalence, severity, predictors. *Sleep Medicine*, *5*, 339–343.

Shahar, E., Whitney, C. W., Redline, S., Lee, E. T., Newman, A. B., Javier Nieto, F., … Samet, J. M. (2001). Sleep-disordered breathing and cardiovascular disease—Cross-sectional results of the Sleep Heart Health Study. *American Journal of Respiratory and Critical Care Medicine*, *163*, 19–25. https://doi.org/10.1164/ajrccm.163.1.2001008

Shahid, A., Shen, J., & Shapiro, C. M. (2010). Measurements of sleepiness and fatigue. *Journal of Psychosomatic Research*, *69*, 81–89. https://doi.org/10.1016/j.jpsychores.2010.04.001

Somers, V. K., White, D. P., Amin, R., Abraham, W. T., Costa, F., Culebras, A., … Pickering, T. G. (2008). Sleep apnea and cardiovascular disease: An American Heart Association/American College of Cardiology Foundation scientific statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. *Circulation*, *118*, 1080–1111.

Stubbe, B., Penzel, T., Fietze, I., Obst, A., Garcia, C., Zimmermann, S., … Piontek, M. (2016). Polysomnography in a large population based study – the study of health in Pomerania protocol. *Journal of Sleep Disorders and Management*, *2*, 010. https://doi.org/10.23937/2572-4053.1510010

Tufik, S., Santos-Silva, R., Taddei, J. A., & Bittencourt, L. R. (2010). Obstructive sleep apnea syndrome in the Sao Paulo Epidemiologic Sleep Study. *Sleep Medicine*, *11*, 441–446.

Vana, K. D., Silva, G. E., & Goldberg, R. (2013). Predictive abilities of the STOP-Bang and Epworth Sleepiness Scale in identifying sleep clinic patients at high risk for obstructive sleep apnea. *Research in Nursing & Health*, *36*, 84–94. https://doi.org/10.1002/nur.21512

Völzke, H., Alte, D., Schmidt, C. O., Radke, D., Lorbeer, R., Friedrich, N., … Havemann, C. (2011). Cohort profile: The study of health in Pomerania. *International Journal of Epidemiology*, *40*, 294–307.

Völzke, H., Ittermann, T., Schmidt, C. O., Baumeister, S. E., Schipf, S., Alte, D., … Hoffmann, W. (2015). Prevalence trends in lifestyle-related risk factors—Two cross-sectional analyses with a total of 8728 participants from the Study of Health in Pomerania from 1997 to 2001 and 2008 to 2012. *Deutsches Ärzteblatt International*, *112*, 185–192. https://doi.org/10.3238/arztebl.2015.0185

Weinreich, G., Wessendorf, T. E., Erdmann, T., Moebus, S., Dragano, N., Lehmann, N., … Erbel, R. (2013). Association of obstructive sleep

apnoea with subclinical coronary atherosclerosis. *Atherosclerosis*, *231*, 191–197. https://doi.org/10.1016/j.atherosclerosis.2013.09.011

Wolf-Maier, K., Cooper, R. S., Banegas, J. R., Giampaoli, S., Hense, H. W., Joffres, M., … Stegmayr, B. (2003). Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. *JAMA*, *289*(18), 2363–2369. https://doi.org/10.1001/jama.289.18.2363

World Mortality Report. (2013).United Nations: Population Division, Department of Economic and Social Affairs; c2016 [cited 2018 Feb 13]. Retrieved from: https://www.un.org/en/development/desa/population/publications/mortality/world-mortality-cdrom-2013.shtml

Ye, L., Pien, G. W., Ratcliffe, S. J., Björnsdottir, E., Arnardottir, E. S., Pack, A. I., … Gislason, T. (2014). The different clinical faces of obstructive sleep apnoea: A cluster analysis. *European Respiratory Journal*, *44*(6), 1600–1607.

Young, T., Palta, M., Dempsey, J., Skatrud, J., Weber, S., & Badar, S. (1993). The occurrence of sleep-disordered breathing among middle-aged adults. *New England Journal of Medicine*, *328*(17), 1231–1235.

Young, T., Peppard, P. E., & Gottlieb, D. J. (2002). Epidemiology of obstructive sleep apnea—A population health perspective. *American Journal of Respiratory and Critical Care Medicine*, *165*, 1217–1239. https://doi.org/10.1164/rccm.2109080

Yu, J., Zhou, Z., McEvoy, R. D., Anderson, C. S., Rodgers, A., … Neal, B. (2017). Association of positive airway pressure with cardiovascular events and death in adults with sleep apnea—A systematic review and meta-analysis. *JAMA*, *318*(2), 156–166. https://doi.org/10.1001/jama.2017.7967

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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