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ORIGINAL ARTICLE

Prevalence and predictors of sleep-disordered breathing in chronic heart failure: the SchlaHF-XT registry

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Abstract

Aims Heart failure with preserved ejection fraction (HFpEF) is a condition with increasing prevalence. Sleep-disordered breathing (SDB) is an important co-morbidity in HFpEF. The SchlaHF-XT registry evaluated the sex-specific prevalence and predictors of SDB, including obstructive (OSA) and central sleep apnoea, in patients with HFpEF compared with heart failure with mildly reduced (HFmrEF) or reduced (HFrEF) ejection fraction.

Methods and results Consecutive adults with chronic heart failure treated according to current guidelines were enrolled. The presence of moderate-to-severe SDB (apnoea–hypopnoea index ≥15/h) was determined using Type 3 polygraphic devices. Of 3289 patients included, 2032 had HFpEF, 559 had HFmrEF, and 698 had HFrEF, of whom 34, 21, 23, and 42%, respectively, were female. Prevalence of SDB in HFpEF was high, but significantly lower than in HFmrEF or HFrEF (36% vs. 41 and 48%, respectively). Rates of SDB in males and females were 41 and 28% in HFpEF, 44 and 30% in HFmrEF, and 50 and 40% in HFrEF. The proportion of males and females with SDB who had OSA was significantly greater in those with HFpEF vs. HFrEF. Male sex, older age, higher body mass index, and New York Heart Association functional Class III/IV were significant predictors of moderate-to-severe SDB in HFpEF patients.

Conclusions Prevalence of SDB in HFpEF was high, but lower than in patients with HFmrEF or HFrEF. Moderate-to-severe SDB occurred more frequently in males than in females across the whole spectrum of heart failure. In both sexes, the proportion of OSA in SDB patients with HFpEF was higher than in those with HFrEF.

Keywords Heart failure with preserved ejection fraction; Heart failure; Obstructive sleep apnoea; Central sleep apnoea; Prevalence; Predictors

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Introduction

Heart failure (HF) is a chronic disease characterized by periods of stability with intermittent episodes of worsening. Common symptoms include shortness of breath and fatigue.[1] The number of individuals developing HF over coming years is expected to increase markedly due to the fact that the risk of developing HF increases with age and the overall ageing population demographic.[2,3]

Based on European guideline and position papers, HF is categorized based on left ventricular ejection fraction (LVEF) as HF with reduced ejection fraction (HFrEF), HF with mildly reduced ejection fraction (HFmrEF), or HF with preserved ejection fraction (HFpEF).[1,3] The proportion of HF patients with HFpEF is increasing, and HFpEF is becoming the dominant form of HF.[4] The lifetime risk of developing HFpEF ranges from 9.7 to 10.7%,[5] and 5-year survival rates for patients with HFpEF are estimated to be 55–74%.[6] In Europe,

there are 0.5 million hospitalizations per year due to HFpEF.[7] These figures and trends are concerning because treatment options to reduce morbidity and mortality in patients with HFpEF are currently scarce.[3] Therefore, attention has been directed towards co-morbidities of HFpEF and to interventions aimed at improving quality of life.[3]

A promising co-morbidity to treat in patients with HFpEF is sleep-disordered breathing (SDB). Both obstructive sleep apnoea (OSA) and central sleep apnoea (CSA) occur in patients with HFpEF.[8] OSA is characterized by repetitive collapse of the upper airway during sleep due to anatomical and functional factors, whereas ventilatory control instability plays a minor role.[9] In contrast, CSA in HF patients is generally the product of an unstable ventilatory control system (high loop gain) usually due to increased controller gain (high hypercapnic responsiveness).[9] CSA in patients with HFrEF is often associated with a periodic breathing pattern (Hunter–Cheyne–Stokes breathing) that can also be observed during daytime wakefulness.[10] In patients with HFrEF, both OSA and CSA, as well as periodic breathing during the daytime, are associated with increased mortality rates after accounting for HF severity.[10,11] Patients with CSA and periodic breathing have the worse outcome.[10] To date, treatment of CSA in HFrEF with positive airway pressure cannot be recommended because it may be associated with increased mortality.[12] However, treatment of OSA in patients with HFpEF provides an opportunity to improve quality of life[13] and exercise capacity[14] and has the potential to prevent progression of HFpEF via reduction in arterial blood pressure and cardiac workload, as well as prevention of cardiac remodelling.[15,16] Due to the different pathophysiology, prognostic impact and implications, and treatment modalities, it is essential to distinguish between HF patients with predominant OSA or CSA.[17]

Currently available data on SDB in HF focus primarily on HFrEF,[3] whereas data on SDB and HFpEF are limited. Moderate-to-severe SDB appears to be a common co-morbidity in HFpEF, affecting 37–58% of patients.[8,18] However, previous studies have a number of important limitations, including small sample size and single-centre design,[8,18–23] lack of a control group,[20,21] and no differentiation between OSA and CSA[19,21] (*Table 1*).

Therefore, the objective of this analysis of the SchlaHF-XT registry was to evaluate the sex-specific prevalence and predictors of SDB (both OSA and CSA) in patients with HFpEF vs. those with HFmrEF or HFrEF.

Methods

Study design

A total of 108 cardiology and sleep centres in Germany (64 practices, 44 hospital departments) enrolled patients into the prospective SchlaHF-XT registry (NCT02301689) (see Supporting Information for a full list of sites and investigators). The first patient was enrolled in February 2013 and enrolment continued until November 2015. The registry received central ethics committee approval from the Ethics committee of the Ruhr University Bochum for Germany (No. 16/2014), and all patients provided written informed consent prior to inclusion. All aspects of the registry were conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice.

Table 1 Studies reporting the prevalence of sleep-disordered breathing in heart failure with preserved ejection fraction

				SDB			
					Prevalence, %		
Study	Design	Patients with HFpEF (*n*)	Control groups (*n*)	Diagnosis and Definition	SDB	OSA	CSA
Arzt et al., 2021 (present study)	Prospective, multicentre	2032	HFmrEF (559) HFrEF (698)	Polygraphy AHI ≥15/h	36%	29%	7%
Borrelli et al., 2019[8]	Prospective, single centre	175 HFpEF	HFmrEF (117) HFrEF (408)	Polygraphy AHI ≥15/h	58%	30%	28%
Bitter et al., 2009[20]	Prospective, single centre	244	n.a.	Polygraphy AHI ≥5/h (AHI ≥15/h data not available)	69.3%	39.8%	29.5%
Sekizuka et al., 2013[18]	Prospective	19	HFmrEF/HFrEF (82)	Polygraphy AHI ≥15/h	37	11	26
Herrscher et al., 2011[23]	Prospective, single centre	44	HFrEF (71)	AHI >5/h	79.5	61.4	18.2
Gupta et al., 2020[22]	Observational, case–control, single centre	25 (HFpEF and HFmrEF)	Healthy controls (25)	Polysomnography AHI >5/h	64%	52%	12%
Chan et al., 1997[21]	Prospective, single centre	20	n.a.	Polysomnography AHI >10/h	85%	-	-

AHI, apnoea–hypopnoea index; CSA, central sleep apnoea; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; OSA, obstructive sleep apnoea; SDB, sleep-disordered breathing.

Participants

Eligibility criteria included age ≥18 years and diagnosis of chronic HF at least 3 months previously, regardless of LVEF. Patients receiving positive airway pressure or long-term oxygen therapy, and pregnant or breastfeeding women were excluded. Enrolled patients were treated according to current guidelines and international therapy standards.[3] Therapeutic approaches were individualized for each patient by their treating physician.

Diagnosis and classification of heart failure

HF was diagnosed by each patient's physician based on contemporary European guidelines.[3,24] Patients with chronic HF were classified as having HFpEF, HFmrEF, or HFrEF (LVEF ≥50, 40–49, and <40%, respectively) according to current European guideline and position papers.[1,3]

Assessment of SDB

Overnight SDB monitoring was performed using Type 3 polygraphic devices (PG; ApneaLink Plus, ResMed, Sydney, Australia, 90%; seven-channel PG 10%). PGs were scored by trained medical staff. Apnoea was defined as a ≥90% decrease in airflow for ≥10 s, hypopnoea as a ≥30–90% decrease in airflow vs. baseline for ≥10 s, and desaturation as a ≥3% decrease in oxygen saturation.[25,26] The apnoea–hypopnoea index (AHI) is expressed as the frequency of apnoea or hypopnoea events per hour recording time; AHI ≥ 15/h was the cut-off for diagnosing SDB. As previously described,[12] an obstructive or central apnoea was defined in the presence or absence of thoracoabdominal excursions, respectively. If the central component of an apnoea already satisfied the definition of a central apnoea (i.e. ≥10 s), three consecutive obstructive breaths were needed to classify that event as an obstructive apnoea. Just one or two obstructed breaths at the end of an apnoea did not change the classification as a central apnoea. Patients with SDB and >50% of apnoeas as central apnoeas were classified into the CSA group, and patients with ≥50% of apnoeas as obstructive apnoeas were classified into the OSA group.[27,28]

Statistical analysis

Data are presented using descriptive statistics: absolute and relative frequency, mean ± standard deviation (SD) or median ± interquartile range, whichever is appropriate. To describe the characteristics of patients with HFpEF, HFmrEF, or HFrEF, metric variables were compared via independent samples *t*-test, and categorical variables were compared using a two samples *Z* test. In both cases, Bonferroni adjustment for multiple testing was applied. Prevalence data are unadjusted.

A multivariable binary logistic regression analysis was used to determine the risk of having SDB (AHI ≥ 15/h vs. <15/h; dependent variable), with potential clinical risk factors [sex, age, body mass index (BMI), New York Heart Association (NYHA) class, and the presence of atrial fibrillation] as the independent variables and to determine the risk factors for having OSA vs. CSA. Extended multivariable binary logistic regression models adding chronic obstructive pulmonary disease (COPD), hypertension, diabetes mellitus, and ischaemic heart disease as independent variables were performed.

A sensitivity analysis was conducted to analyse data when diagnosis of HFpEF and HFmrEF was calculated strictly based on 2016 European Society of Cardiology (ESC) guideline criteria[3] using available data rather than the physician-based diagnosis that was used according to the study protocol for classification in the SchlaHF-XT registry.

Statistical significance was defined as $P < 0.05$. Statistical analysis was performed with SPSS 22.0 (SPSS Inc., Chicago, USA) and R Version 3.6.0 (Copyright 2019, The R Foundation for Statistical Computing).

Results

Participants

A total of 3289 patients were included (*Figure 1*); 698 had HFrEF, 559 had HFmrEF, and 2032 had HFpEF (*Table 2*), of whom 34, 21, 23, and 42%, respectively, were female. As expected, there were several significant differences between patients with different types of HF, including younger age, lower LVEF, higher NYHA functional class, more frequent left atrial enlargement, and a higher symptom burden in patients with HFrEF compared with the other groups (*Table 2*). HF medications also differed by HF category (*Table 2*). A minority of the SchlaHF-XT patients used opioids (4%) or hypnotics (4%).

Overall prevalence of SDB and OSA and CSA

Mean AHI in the total population was 16 ± 15/h and was lowest in patients with HFpEF ($P < 0.05$ vs. HFmrEF and HFrEF) (*Table 3*). In addition, patients with HFpEF had a significantly lower oxygen desaturation index and central apnoea index compared with patients with either HFmrEF or HFrEF (*Table 3*).

The prevalence of moderate-to-severe SDB (AHI ≥ 15/h) in patients with HFpEF was high (at 36%), but significantly lower than in those with HFmrEF or HFrEF (41 and 48%, respectively; $P < 0.001$ for both comparisons) (*Figure 2A* and *Table S1*). Overall SDB prevalence rates at different AHI cut-off values are reported in *Table S1*.

Figure 1 Patient flow in the SchlaHF-XT registry. AHI, apnoea–hypopnoea index; BMI, body mass index; LVEF, left ventricular ejection fraction; HF, heart failure.

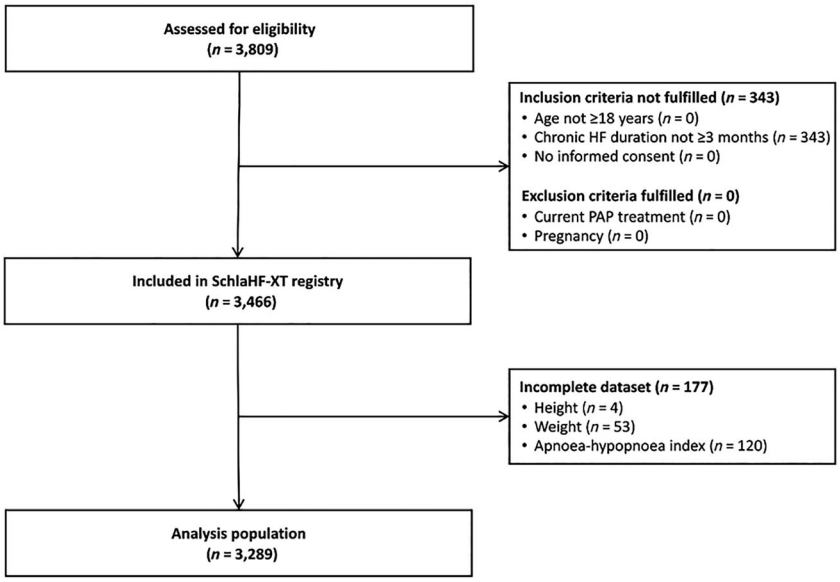


Table 2 Baseline demographic and clinical data in the overall population and by type of heart failure

Characteristics	Total (n = 3289)	HFrEF (n = 698)	HFmrEF (n = 559)	HFpEF (n = 2032)
Age, years	68 ± 11	67 ± 12*	69 ± 11	68 ± 11
Female, *n* (%)	1132/3289 (34)	147/698 (21)	129/559 (23)**	856/2032 (42)***
Body mass index, kg/m^2	29 ± 5	28 ± 5*	29 ± 5	29 ± 6***
ESS score ≥11, *n* (%)	404/2940 (14)	89/621 (14)	58/481 (12)	257/1838 (14)
NYHA Class III/IV, *n* (%)	986/2998 (33)	377/650 (58)*	182/523 (35)**	427/1811 (24)***
LVEF[a], %	51 ± 15	29 ± 7*	43 ± 3**	62 ± 8***
LAD[a], mm	43 ± 10	48 ± 10*	44 ± 10**	42 ± 9 ***
LAE, *n* (%)	1667/2469 (68)	428/517 (83)*	317/433 (73)**	922/1519 (61)***
Diastolic dysfunction, *n* (%)	1368/2038 (67)	211/403 (52)	188/350 (54)**	969/1285 (75)***
HF symptoms, *n* (%)	972/3289 (32)	307/698 (52)*	185/559 (36)	480/2032 (25)***
≥3 nocturia episodes, *n* (%)	402/2998 (13)	117/641 (18)	85/503 (17)**	200/1854 (11)***
Atrial fibrillation, *n* (%)	592/3226 (18)	156/680 (23)	125/544 (23)**	311/2002 (16)***
Hypertension, *n* (%)	2594/3222 (81)	482/678 (71)*	423/542 (78)**	1689/2002 (84)***
Diabetes, *n* (%)	880/3215 (27)	217/675 (32)	156/548 (29)	507/1992 (26)***
COPD, *n* (%)	374/3193 (12)	105/669 (16)	72/544 (13)	197/1980 (10)***
HF medication, *n* (%)				
ACEi and/or ARB	2531/3289 (77)	601/698 (86)	463/559 (83)**	1467/2032 (72)***
β-Blockers	2503/3233 (77)	631/686 (92)*	464/551 (84)**	1408/1996 (71)***
Loop diuretics	1486/3190 (47)	519/677 (77)*	276/542 (51)**	691/1971 (35)
MR antagonists	754/3169 (24)	418/675 (62)*	163/538 (30)**	173/1956 (9)
Ivabradine	71/3097 (2)	28/645 (4)	14/523 (3)	29/1929 (2)
Digitalis	198/3150 (6)	198/3150 (6)	74/656 (11)**	40/533 (8)**
Calcium antagonists	783/2123 (25)	88/641 (14)*	126/535 (24)**	569/1947 (29)***
Antiarrhythmics	408/3156 (13)	408/3156 (13)	117/656 (18)	74/538 (14)
Opioids, *n* (%)	18/646 (3)	18/646 (3)	18/646 (3)	18/646 (3)
Hypnotics, *n* (%)	112/3197 (4)	31/614 (5)	19/504 (4)	62/3197 (3)***

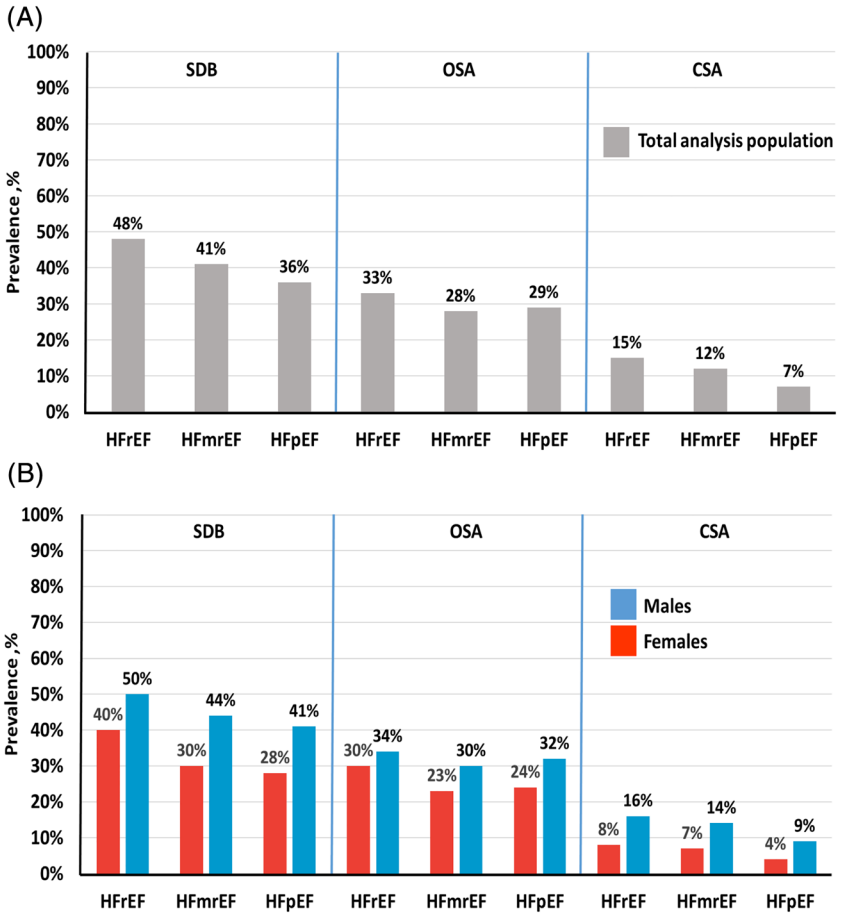
ESS, Epworth Sleepiness Scale; HF, heart failure; LAD, left atrial diameter; LAE, left atrial enlargement; LVEF, left ventricular ejection fraction; MR, mineralocorticoid; NYHA, New York Heart Association.
Values are mean ± standard deviation, or number of patients (%). Denominator is number of patients with available data; age and body mass index data were available for all patients.
[a]Data available for 2469 patients.
*$P < 0.05$ vs. HFmrEF.
**$P < 0.05$ vs. HFpEF.
***$P < 0.05$ vs. HFrEF (two-sample t-test for metric variables and two-sample Z test for categorical variables).

Table 3 Polygraphy findings

	N	Total	HFrEF	HFmrEF	HFpEF
AHI, /h	3289	11 [5, 23]	14 [6, 28]	11 [5, 24]**	10 [4, 2]***
AI, /h	3248	3 [1, 10]	4 [1, 14]*	3 [1, 10]	2 [0, 9]***
cAI/AI, %	3248	19 ± 30	25 ± 35*	20 ± 32**	16 ± 28***
ODI, /h	3220	11 [5, 22]	15 [7,29]*	11 [5, 23]**	10 [4, 21]***
Minimum SaO_2, %	3206	80 ± 9	79 ± 10	80 ± 9	80 ± 9***
Mean SaO_2, %	3215	92 ± 6	92 ± 7	91 ± 5	92 ± 6
Time with $SaO_2 < 90\%$, min	3090	21 ± 26	21 ± 25	21 ± 26	20 ± 26
Supplemental oxygen used, *n* (%)	3288	24 (1)	8 (1)	2 (0)	14 (1)
Respiratory rate, breaths/min	3051	16 ± 4	16 ± 4	16 ± 4	15 ± 3
Heart rate, beats/min	3181	64 ± 13	66 ± 12	65 ± 13	63 ± 13***

AHI, apnoea–hypopnoea index; AI, apnoea index; cAI, central apnoea index; ODI, oxygen desaturation index; SaO_2, oxygen saturation.
Values are mean ± standard deviation or median [interquartile range].
*$P < 0.05$ vs. HFmrEF.
**$P < 0.05$ vs. HFpEF.
***$P < 0.05$ vs. HFrEF (all two-sample *t*-test).

Figure 2 Overall prevalence of sleep-disordered breathing (SDB; apnoea–hypopnoea index ≥15/h) and prevalence of obstructive (OSA) and central (CSA) sleep apnoea in patients with different heart failure phenotypes in the total population (A) and in males and females (B). HFpEF, heart failure with preserved ejection fraction; HFmrEF, heart failure with mildly-reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction.



With respect to type of SDB, the prevalence of at least moderate CSA (AHI ≥ 15/h) was lowest in patients with HFpEF and highest in those with HFrEF; nevertheless, a small proportion of patients in the HFpEF group (7%) did have CSA (*Figure 2A* and *Table S1*). The proportion of SDB patients with OSA was significantly

higher in the HFpEF vs. HFrEF group (*Figure 3* and *Table S2*).

Sensitivity analysis

For this analysis, definition of HFmrEF and HFpEF was based on the 2016 ESC guidelines[3] and calculated with the available data. Rates of SDB, OSA, and CSA in the revised HFmrEF (n = 178) and HFpEF (n = 446) groups were consistent with those in the main analysis ($P > 0.05$ for all comparisons) (*Table S3*).

Sex-specific prevalence of SDB and OSA and CSA

The SchlaHF-XT population includes 1132 (34%) women, who were significantly older and had significantly more often HFpEF (*Table S4*). Consistent with the overall population, the unadjusted prevalence of moderate-to-severe SDB (AHI $\geq$ 15/h) in both males (*Figure 2B* and *Table S5*) and females (*Figure 2B* and *Table S6*) with HFpEF was high, but rates were significantly lower than in males and females with HFrEF ($P < 0.005$ for both comparisons). Sex-specific SDB prevalence rates at different AHI cut-off values are reported in *Tables S5* and *S6*.

Across all types of HF, the prevalence of at least moderate SDB (AHI $\geq$ 15/h) and of CSA was significantly higher in men vs. women (*Figure 2B* and *Table S7*). Similar to the total sample, the proportion of men and women with OSA was significantly greater in patients with HFpEF vs. HFrEF ($P < 0.001$ for both), whereas the proportion of males vs. females with OSA did not differ significantly within each HF phenotype group (*Table S2*).

Predictors of SDB and OSA

In patients with HFpEF, male sex, older age, higher BMI, and NYHA functional Class III/IV were significant predictors of at least moderate SDB (*Figure 4A*). Atrial fibrillation was not significantly associated with SDB (*Figure 4A*). Predictors of SDB were similar in patients with HFrEF or HFmrEF, apart from no significant association between NYHA functional Class III/IV and SDB in HFmrEF group (*Figure 4B* and *4C*).

SDB patients with HFpEF were significantly more likely to have predominant OSA vs. CSA if they were female, had a higher BMI, or were in NYHA Class I/II (*Figure 5A*). In patients with HFmrEF or HFrEF, only higher BMI was a significant predictor of predominant OSA (*Figure 5B* and *5C*). Use of either opioids or hypnotics was not associated with an increased prevalence of SDB or with a specific type of SDB.

In extended models, COPD, hypertension, diabetes mellitus, and ischaemic heart disease were added as independent variables. Diabetes was significantly associated with SDB in HFrEF, but not in HFpEF or HFmrEF (*Figure S1*). COPD, hypertension, and ischaemic heart disease were not significantly associated with SDB (*Figure S1*), CSA, or OSA (*Figure S2*) after accounting for established risk factors for SDB, CSA, and OSA.

Discussion

SchlaHF-XT is a large prospective multicentre registry to determine the sex-specific prevalence of SDB, and its sub-types OSA and CSA, in patients with HFpEF, HFmrEF, or HFrEF. The prevalence of at least moderate SDB in patients with HFpEF was high at 36%, but was significantly lower than in patients with HFmrEF or HFrEF. In addition, the proportion of SDB patients with OSA was significantly higher in HFpEF vs. HFrEF. In this first study to report sex-specific SDB prevalence in patients with HFpEF and HFmrEF, males had a higher overall prevalence of SDB than females across all types of HF, and the proportion of OSA in both male and female SDB patients

Figure 3 Proportion of patients with obstructive sleep apnoea (OSA) as a percentage of the total sleep-disordered breathing (SDB) population by heart failure phenotype in the total population and in males and females.

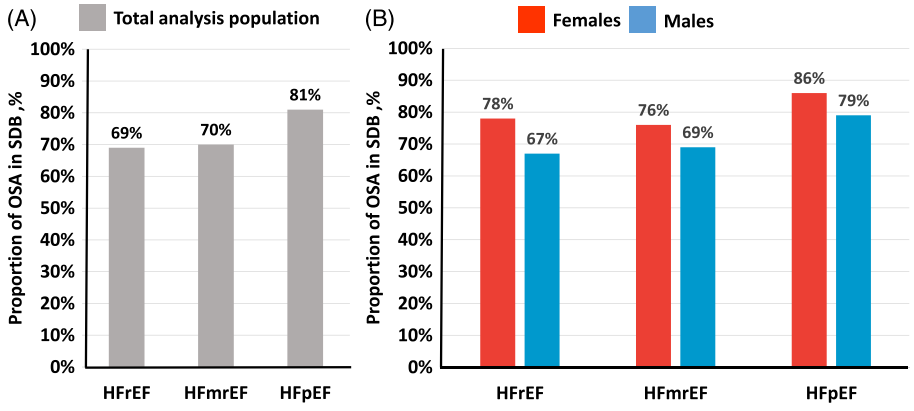


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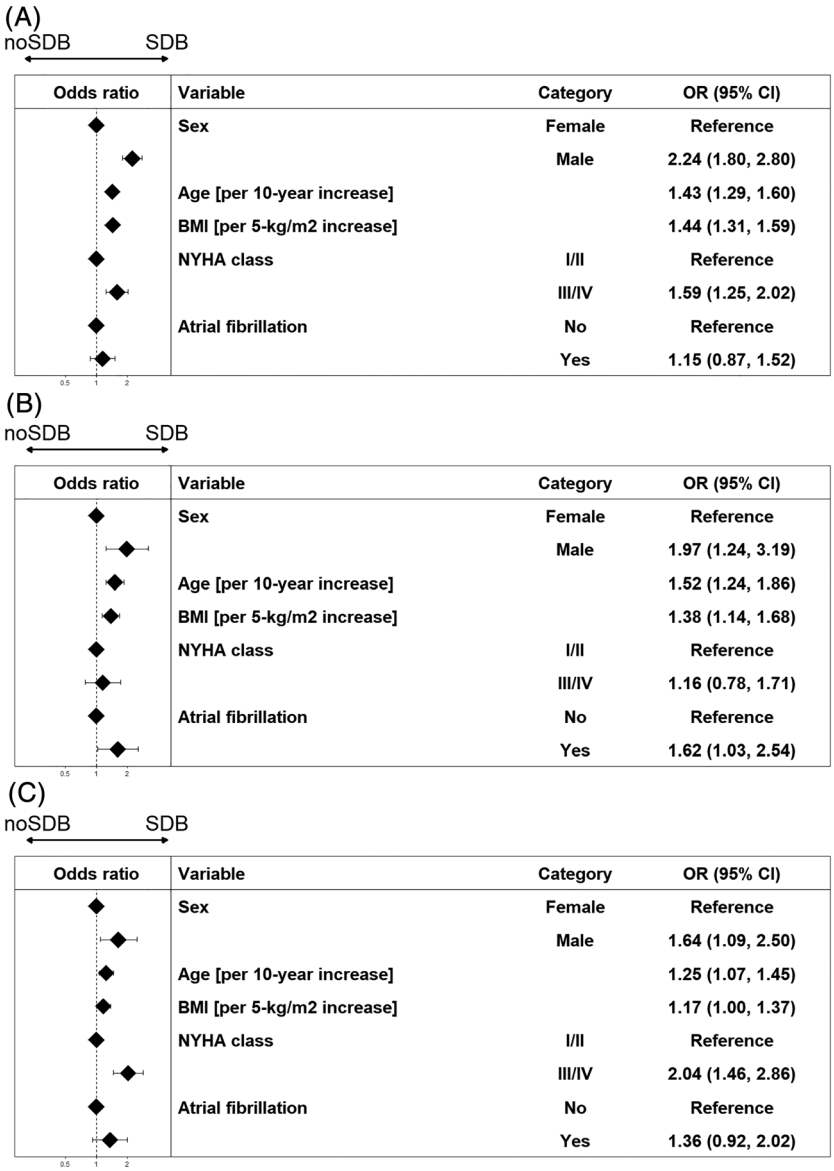
Figure 4 Predictors of sleep-disordered breathing (SDB; apnoea–hypopnoea index ≥15/h vs. <15/h) in patients with heart failure with preserved ejection fraction (HFpEF; A), heart failure with mildly-reduced ejection fraction (HFmrEF; B) or heart failure with reduced ejection fraction (HFrEF; C). BMI, body mass index; *CI*, confidence interval; OR, odds ratio.

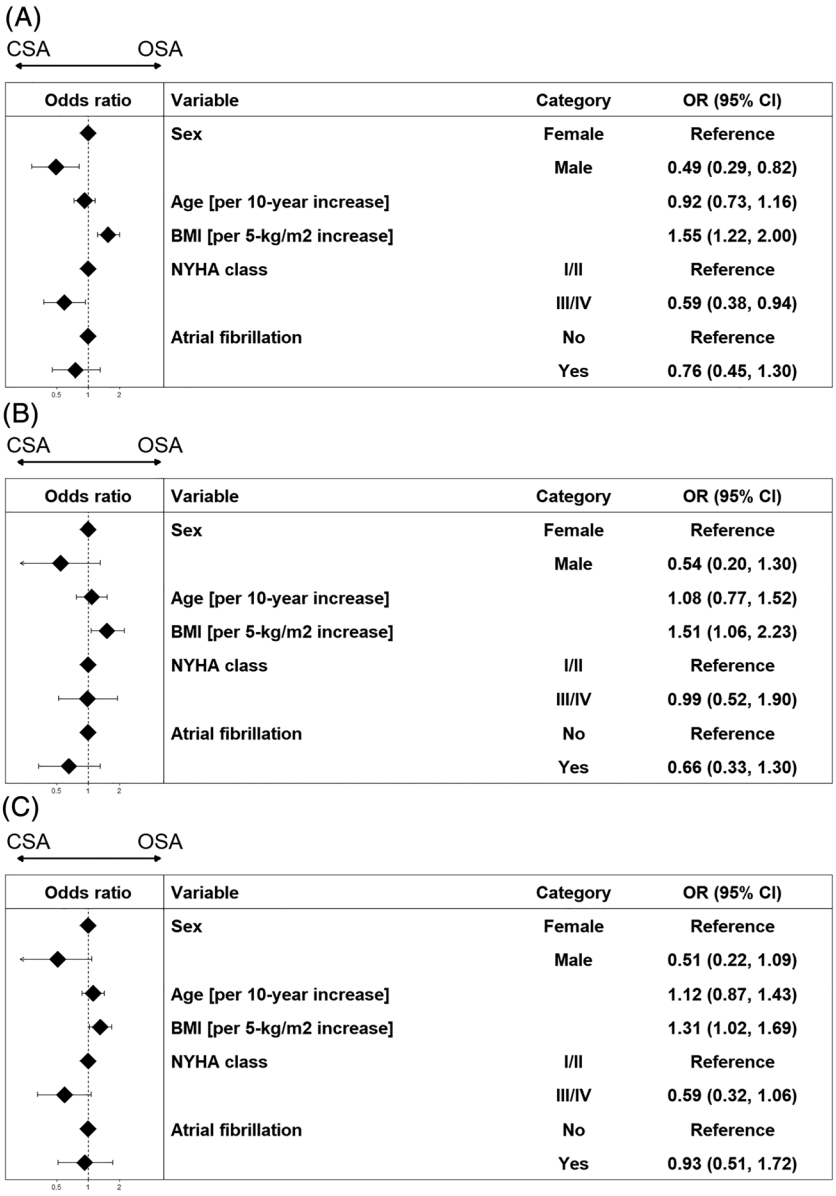


was higher in those with HFpEF compared with other HF phenotypes.

The published data most similar to our study come from Borelli et al. who used polygraphy to evaluate SDB in patients with HFpEF, HFmrEF, or HFrEF from a single-centre in Italy[8] and included a population that was demographically comparable with the SchlaHF-XT cohort. Prevalence rates for moderate-to-severe nocturnal SDB in the Borelli study were higher (58, 50, and 60%, respectively, in the three HF groups) than in our multicentre study (36, 41, and 48%, respectively). In patients with HFpEF, rates of moderate-to-severe OSA and CSA were 37 and 20%, respectively.[8] The prevalence of moderate-to-severe OSA was similar to our SchlaHF-XT registry data, but the prevalence of CSA was higher.

Although there were design similarities between our study and the one by Borelli and colleagues, the SchlaHF-XT registry has important strengths compared with previous publications, complementing previous findings. In addition to the multicentre vs. single-centre design, our sample size was much larger than that of Borelli et al., including 3289 vs. 700 patients overall and 2032 vs. 175 patients with HFpEF. This provides sufficient patient numbers to allow the development of robust multivariable models and improves statistical power. Furthermore, our study is the first to provide data

Figure 5 Predictors of having obstructive (OSA) vs. central (CSA) sleep apnoea in patients with heart failure with preserved ejection fraction (HFpEF; A), heart failure with mildly-reduced ejection fraction (HFmrEF; B) or heart failure with reduced ejection fraction (HFrEF; C). BMI, body mass index; CI, confidence interval; OR, odds ratio.



on the sex-specific prevalence of SDB, OSA, and CSA in patients with HFmrEF or HFpEF.

Sex hormones have significant effects on the pathophysiology of SDB. For example, pre-menopausal women have higher upper airway patency (anatomical and functional) and lower chemosensitivity to carbon dioxide compared with men,[29] factors which protect against the development of OSA and CSA, respectively. However, women from the present SchlaHF-XT cohort were predominantly in the post-menopausal age group. This may explain why the SDB prevalence ratio for women and men in the HF groups ranged from 4:5 to 3:4, compared with a ratio of approximately 1:2 in younger community samples without known heart disease.[30,31] Similarly, the SDB prevalence ratio in women vs. men with HFrEF has been reported to be approximately 1:2 in the group aged 18–50 years, but closer to 1:1 in older age groups.[32] These data are highly clinically relevant because rates of SDB differ between men and women with HF, and women are less likely to develop CSA, and represent a large proportion of the HFpEF population.

Other previous studies reporting the prevalence of SDB in HFpEF (*Table 1*)[18,20–23] also have significant limitations, in-

cluding small sample size, lack of data on CSA, and/or defining AHI using a cut-off value of 5/h, which is of uncertain clinical significance in patients with HF. In addition, patients enrolled in older studies were not being treated with current optimal medical therapy for HFrEF.[3]

There is increasing recognition of the importance of patient phenotyping among patients with HFpEF.[33] For example, one HFpEF phenotype that has been described includes obesity, diabetes, and OSA; this group had the worst left ventricular relaxation compared with the other two phenotypes groups defined by clinical characteristics, invasive haemodynamics, and outcomes.[34] In those HFpEF patients, treatment of OSA has the potential to improve quality of life, exercise capacity, and prevent disease progression, as has been described previously.[13,14,16,35]

Co-morbidities in HFpEF are of special interest due to the lack of current therapies with proven benefit to treat this form of HF. Therefore, management of co-morbidities is an achievable therapeutic goal and has the potential to increase patient quality of life and perhaps also to improve outcomes. Current HF guidelines highlight the importance of identifying non-cardiovascular co-morbidities in patients with HFpEF.[3]

Although the use of positive airway pressure in patients with HFrEF and CSA has failed to improve objective clinical endpoints in randomized controlled trials,[36] there is a relative lack of corresponding data in patients with HFpEF and OSA. Treatment with adaptive servo-ventilation (ASV) may have beneficial effects in patients with HFpEF and moderate-to-severe SDB.[37] These include improved diastolic function and decreased natriuretic peptide levels and arterial stiffness. In addition, 6-month event-free survival was significantly better in the ASV-treated group compared with non-ASV controls (94.4% vs. 61.1%; $P < 0.05$).[37]

Key strengths of our study are the inclusion of the largest population of patients with HFpEF and SDB studied to date and determination of SDB prevalence rates separately for males and females. Inclusion of patients receiving contemporary guideline-recommended therapy is another strength of the study because older studies[18,20,21,23] do not reflect current clinical management and treatment options. Furthermore, SchlaHF-XT had a multicentre design and included a range of HFpEF, HFmrEF, and HFrEF patients from cardiology and sleep practices, plus hospital cardiology and sleep departments, increasing the external validity of the findings.

Despite these strengths, there are limitations that need to be considered when interpreting our findings.

Data were mostly collected during routine clinical practice, which meant there were limited datasets for some parameters. The lack of data with respect to biomarkers of HF and other important markers such as left ventricular hypertrophy or mitral regurgitation is one such limitation of the registry. In the SchlaHF-XT registry, the diagnosis of HF was physician based. Thus, a sensitivity analysis was performed and provided similar results in a subset of patients in whom the diagnosis of HFpEF and HFmrEF was determined based on guideline criteria[3] using available data. Another limitation is that we determined SDB prevalence using Type 3 polygraphic devices instead of gold standard polysomnography.[32] Type 3 polygraphic devices have been compared with polysomnography in several studies, which reported an excellent correlation between the results obtained with the two devices by PSG and Type 3 polygraphic devices.[32,38–40] The results of a validation study in a subset of HFrEF patients from the SchlaHF registry suggest that Type 3 polygraphic devices might underestimate the AHI.[32] This is plausible because the number of apnoeas and hypopnoeas are reported as the proportion of total recording time with Type 3 polygraphic devices compared with total sleep time for PSG.[32] Thus, use of Type 3 polygraphic devices is likely to result in conservative prevalence estimates.[32] In addition, the use of Type 3 polygraphy devices means that only apnoeas, but not hypopnoeas, could be classified as central and obstructive.

Conclusions

Data from the SchlaHF-XT registry showed that the prevalence of SDB in HFpEF was high (36%) but lower than in patients with HFmrEF or HFrEF. Moderate-to-severe SDB occurred more frequently in males than in females across the whole spectrum of HF. In both sexes, the proportion of OSA in SDB patients with HFpEF was higher than in HFrEF. Additional studies are needed to determine the effects of treating OSA on clinical outcomes in patients with HFpEF.

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Conflict of interest

M.A. has received consulting fees from ResMed, Philips Respironics, Boehringer Ingelheim, NRI, Novartis, JAZZ Pharmaceuticals, Bayer, Inspire, and Bresotec and grant support from ResMed Foundation, ResMed, Philips Respironics, and Else-Kroehner Fresenius Foundation (2018_A159), outside the submitted work. H.W., H.T., C.S., and O.O. have received research grants, consulting fees, and lecture fees from ResMed. E.E. has received consulting fees from ResMed. A. G. and J.S. are employees of ResMed, Germany.

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Supporting information

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

Table S1. Overall prevalence of sleep-disordered breathing (SDB), obstructive sleep apnoea (OSA) and central sleep apnoea (CSA) in patients with heart failure with preserved ejection fraction (HFpEF), heart failure with mildly-reduced ejection fraction (HFmrEF) or heart failure with reduced ejection fraction (HFrEF) using different apnoea-hypopnoea index (AHI) thresholds.

Table S2. Proportion of patients with obstructive sleep apnoea as a percentage of the overall number of patients with sleep-disordered breathing in the total population and by sex in patients with heart failure with preserved ejection fraction (HFpEF), heart failure with mildly-reduced ejection fraction (HFmrEF) or heart failure with reduced ejection fraction (HFrEF).

Table S3. Sensitivity analysis: overall prevalence of moderate-to-severe sleep-disordered breathing (SDB), obstructive sleep apnoea (OSA) and central sleep apnoea (CSA) (all apnoea-hypopnoea index ≥15/h) in patient subgroups based on type of heart failure when heart failure with preserved ejection fraction (HFpEF) and heart failure with mildly-reduced ejection fraction (HFmrEF) were diagnosed based on the European Society of Cardiology (ESC) guideline criteria based on the available data rather than physician decision (note: criteria for physician diagnosis of heart failure with reduced ejection fraction [HFrEF] matched those of the ESC guidelines).

Table S4. Baseline demographic and clinical data in the overall population and by sex.

Table S5. Sex-specific prevalence of sleep-disordered breathing (SDB), obstructive sleep apnoea (OSA) and central sleep apnoea (CSA) in male patients with heart failure with preserved ejection fraction (HFpEF), heart failure with mildly-reduced ejection fraction (HFmrEF) or heart failure with reduced ejection fraction (HFrEF) using different apnoea-hypopnoea index (AHI) thresholds.

Table S6. Sex-specific prevalence of sleep-disordered breathing (SDB), obstructive sleep apnoea (OSA) and central sleep apnoea (CSA) in female patients with heart failure with preserved ejection fraction (HFpEF), heart failure with mildly-reduced ejection fraction (HFmrEF) or heart failure with reduced ejection fraction (HFrEF) using different apnoea-hypopnoea index (AHI) thresholds.

Table S7. Prevalence of moderate-to-severe (apnoea-hypopnoea index ≥15/h) sleep-disordered breathing (SDB), obstructive sleep apnoea (OSA) and central sleep apnoea (CSA) in male and female patients with heart failure with preserved ejection fraction (HFpEF), heart failure with mildly-reduced ejection fraction (HFmrEF) or heart failure with reduced ejection fraction (HFrEF).

Figure S1. Predictors of sleep-disordered breathing (SDB; apnoea-hypopnoea index ≥15/h vs <15/h) in patients with heart failure with preserved ejection fraction (HFpEF; **A**), heart failure with mildly-reduced ejection fraction (HFmrEF; **B**) or heart failure with reduced ejection fraction (HFrEF; **C**). Extended multivariable binary logistic regression models adding chronic obstructive pulmonary disease (COPD), hypertension, diabetes mellitus and ischaemic heart disease as independent variables are shown. BMI, body mass index; CI, confidence interval; OR, odds ratio.

Figure S2. Predictors of having obstructive (OSA) versus central (CSA) sleep apnoea in patients with heart failure with preserved ejection fraction (HFpEF; **A**), heart failure with mildly-reduced ejection fraction (HFmrEF; **B**) or heart failure with reduced ejection fraction (HFrEF; **C**). Extended multivariable binary logistic regression models adding chronic obstructive pulmonary disease (COPD), hypertension, diabetes mellitus and ischaemic heart disease as independent variables are shown. BMI, body mass index; CI, confidence interval; OR, odds ratio.

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