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Risk factors for, and prevalence of, sleep apnoea in cardiac rehabilitation facilities in Germany: The Reha-Sleep registry

Erik Skobel[1], Wolfram Kamke[2], Gerd Bönner[3], Bernd Alt[4], Hans-Christian Purucker[5], Bernhard Schwaab[6], Hans-Peter Einwang[7], Klaus Schröder[8], Eike Langheim[9], Heinz Völler[10,11], Alexandra Brandenburg[12], Andrea Graml[13], Holger Woehrle[13] and Stefan Krüger[14]

Abstract

Aim: To determine the prevalence of, and the risk factors for, sleep apnoea in cardiac rehabilitation (CR) facilities in Germany.

Methods: 1152 patients presenting for CR were screened for sleep-disordered breathing with 2-channel polygraphy (ApneaLink™; ResMed). Parameters recorded included the apnoea–hypopnoea index (AHI), number of desaturations per hour of recording (ODI), mean and minimum nocturnal oxygen saturation and number of snoring episodes. Patients rated subjective sleep quality on a scale from 1 (poor) to 10 (best) and completed the Epworth Sleepiness Scale (ESS).

Results: Clinically significant sleep apnoea (AHI $\geq$15/h) was documented in 33% of patients. Mean AHI was 14 $\pm$ 16/h (range 0–106/h). Sleep apnoea was defined as being of moderate severity in 18% of patients (AHI $\geq$15–29/h) and severe in 15% (AHI $\geq$30/h). There were small, but statistically significant, differences in ESS score and subjective sleep quality between patients with and without sleep apnoea. Logistic regression model analysis identified the following as risk factors for sleep apnoea in CR patients: age (per 10 years) (odds ratio (OR) 1.51; $p < 0.001$), body mass index (per 5 units) (OR 1.31; $p = 0.001$), male gender (OR 2.19; $p < 0.001$), type 2 diabetes mellitus (OR 1.45; $p = 0.040$), haemoglobin level (OR 0.91; $p = 0.012$) and witnessed apnoeas (OR 1.99; $p < 0.001$).

Conclusions: The findings of this study indicate that more than one-third of patients undergoing cardiac rehabilitation in Germany have sleep apnoea, with one-third having moderate-to-severe SDB that requires further evaluation or intervention. Inclusion of sleep apnoea screening as part of cardiac rehabilitation appears to be appropriate.

Keywords

Cardiac rehabilitation, sleep apnoea, sleep-disordered breathing

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[1]Clinic for Cardiac and Pulmonary Rehabilitation, Rosenquelle, Aachen, Germany
[2]MediClin Rehabilitation Centre of Spreewald, Burg/Spreewald, Germany
[3]Park Klinikum, Bad Krozingen, Germany
[4]Park-Klinik Bad Hermannsborn, Bad Driburg, Germany
[5]Teutoburger Wald Clinic, Rothenfelde, Germany
[6]Curschmann Clinic, Timmendorfer Strand, Germany
[7]Clinic Hohenried, Department of Cardiology, Bernried, Germany
[8]ZAR, Stuttgart, Germany
[9]Clinic for Cardiac Rehabilitation DRV, Teltow/Seehof, Germany
[10]Clinic for Cardiac Rehabilitation Rüdersdorf, Germany
[11]Center of Rehabilitation Research University of Potsdam, Germany
[12]Clinical Trial Center Aachen, University Hospital Aachen, Aachen, Germany
[13]ResMed Science Center, Martinsried, Munich, Germany
[14]University Hospital Aachen, RWTH, Internal Medicine I, Cardiology, Pulmonology & Vascular Medicine, Aachen, Germany

Corresponding author:
Erik Skobel, Clinic for Cardiac and Pulmonary Rehabilitation, Kurbrunnenstraße 5, Rosenquelle, 52077 Aachen, Germany.
Email: erik.skobel@rosenquelle.de

Introduction

Sleep-disordered breathing (SDB) has been shown to be an independent risk factor for cardiovascular diseases.[1–3] Obstructive sleep apnoea (OSA) is the most prevalent type of SDB. It is defined as repetitive episodes of partial or complete cessation of airflow in the upper airways during sleep. The number of people in the USA estimated to be affected by OSA is 3–7%[4,5] and, according to the US National Commission of Sleep Disorders Research, OSA contributes to 38,000 cardiovascular deaths annually.[6] In Europe, a Spanish study reported that 7% of women and 15% of men aged 30–70 years had OSA, defined as an apnoea–hypopnoea index (AHI) of $\geq$15/h.[7]

Patients with OSA typically present with symptoms such as disruptive snoring, witnessed apnoeas or gasping, excessive daytime sleepiness, morning headache, sleep disturbance and cognitive dysfunction.[8,9] Diagnosis of OSA can be made using polysomnography (PSG) or at-home polygraphy. Although the American Academy of Sleep Medicine (AASM) recommends PSG for the evaluation and diagnosis of SDB,[10] many centres do not have this type of facility and polygraphy is a feasible and validated alternative.[11–19] According to AASM Task Force definitions,[10] an AHI of $\geq$5/h defines the presence of OSA, although the AHI cut-off for diagnosing OSA varies between studies. An AHI cut-off value of $\geq$15/h is clinically significant, and benefits from the use of nasal continuous positive airway pressure (nCPAP) therapy.[20,21]

OSA has been associated with increases in cardiovascular morbidity and mortality.[22–24] The most important mechanisms that cause myocardial damage are increased sympathetic activity, heart rate variability, endothelial dysfunction, systemic inflammation, oxidative stress, platelet activation and metabolic abnormalities.[8,25–33] Cardiovascular conditions associated with OSA include hypertension, cardiac hypertrophy, heart failure, stroke, arrhythmias, myocardial infarction (MI), pulmonary arterial hypertension and end-stage renal disease.[8,34–36]

Although OSA could be a modifiable cardiovascular risk factor, it appears to be under-diagnosed in patients with coronary artery disease (CAD).[37,38] In addition, available data on the prevalence of sleep apnoea in patients undergoing cardiac rehabilitation (CR) are very limited. The aim of this study was to evaluate the feasibility of implementing a screening programme for OSA in patients enrolled in early CR and to investigate the prevalence and predictors of SDB.

Methods

This project was designed as a quality-improvement programme by the working group for sleep disorders of the German Society of Cardiac Prevention and Rehabilitation (DGPR®). Physicians who were members of this group were invited to participate in the study, which was approved by the Regional Ethical Review Board at the University of Aachen. In addition, the registry was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to inclusion in the study, including permission to gather electronic data from medical files. All patients who gave their consent to participate in medical record-based research were included in the final analysis.

Patient characteristics

Consecutive patients enrolled in early CR in nine CR facilities (eight inpatient, one outpatient) in Germany from September 2011 to September 2012 were eligible for inclusion.

Indications for CR included MI, coronary artery bypass graft surgery (CABG), valve repair or replacement surgery, percutaneous coronary intervention (PCI), stable chronic heart failure, peripheral arterial disease, or other forms of cardiovascular disease (including cardiac resynchronization therapy, implantable cardioverter defibrillator implantation or conservative treatment for CAD; see Table 1 for details). All patients who presented for CR were asked to participate in the registry. The main reasons for non-inclusion were not wanting to be part of a registry, poor language skills and dementia.

Assessments

The primary indication for rehabilitation – history of hypertension, presence of diabetes, smoking habits, family history of CAD, atrial fibrillation, lipid metabolism disorders, stroke, peripheral arterial occlusive disease and presence of chronic obstructive pulmonary disease (COPD) – were determined for each patient. In addition, body mass index (BMI), current medication, New York Heart Association (NYHA) class, and levels of haemoglobin (Hb) (g/dl) and serum creatinine (mg/dl) were evaluated and glomerular filtration rate (GFR) was calculated based on the Cockroft and Gault method. The indication for CR and the specific intervention were also recorded. The severity of CAD was evaluated by reporting the extent of vessel involvement (1-, 2- or 3-vessel disease) before rehabilitation determined using coronary angiography, as provided by the treating hospital. Echocardiography was used to determine left ventricular ejection fraction (LVEF), left atrial dimension, right ventricular systolic pressure (PASP) and the interventricular septal dimension. All patients were questioned by the physician to determine

Table 1. Patient demographic data and characteristics for all patients, and for patients with versus without clinically significant sleep apnoea (apnoea–hypopnoea index [AHI] <15/h vs ≥15/h).

	All patients ($n=1152$)	AHI <15/h ($n=773$)	AHI ≥15/h ($n=379$)
Age, years	60 ± 12	59 ± 12	64 ± 10[a]
Male, %	79	77	82[a]
Body mass index, kg/m^2	28.3 ± 5.2	28.0 ± 5.2	28.9 ± 5.0[a]
Disease history, %			
Coronary artery disease	87	87	86
Hypertension	78	75	83[a]
Atrial fibrillation	11	10	11
Familial coronary disease	41	42	38
NYHA class, %			
I	65	67[a]	60
II	24	23	25
III/IV	12	10	15[a]
LVEF, %	55 ± 11	55 ± 10	54 ± 11
Normal LVEF, %	75	78	72[a]
LVEF <50%, %	23	21	26
LVEF <30%, %	2	1	2
LA diameter, mm	40 ± 9	39 ± 9	40 ± 9
Comorbid conditions, %			
Type 1 diabetes	1	1	1
Type 2 diabetes	20	17	27[a]
Lipid metabolism disorders	86	87	86
Peripheral arterial occlusive disease	8	7	9
Stroke	3	3	3
Current smoker, %	48	53	40[a]
Smoking pack-years	38 ± 72	37 ± 75	41 ± 62
COPD, %	12	11	16[a]
Heart rhythm (ECG), %			
Sinus rhythm	92	92	90
Atrial fibrillation	5	5	6
Pacing	3	3	4
GFR (ml/min)	59 ± 8	59 ± 6	59 ± 11
Hb (mmol/l)	8 ± 5	8.1 ± 1.2	7.8 ± 1.3
Creatinine (mmol/l)	1.0 ± 0.5	1.0 ± 0.5	1.0 ± 0.5
Indication for cardiac rehabilitation[b], %			
PCI	57	61[a]	50
CABG	19	16	27[a]
Myocardial infarction	50	53[a]	45
Valve replacement surgery	13	11	18[a]
CRT implantation	1	1	1
ICD implantation	3	3	2
Conservative therapy	7	9[a]	3
Medication[c], %			
ACE inhibitors or AR blockers	85	84	87
Calcium channel blockers	17	16	19
Diuretics	44	39	52[a]
ß-blockers	92	90	95[a]
Digitalis	2	2	3

(continued)

Table 1. Continued

	All patients ($n = 1152$)	AHI <15/h ($n = 773$)	AHI ≥ 15/h ($n = 379$)
HMG-CoA reductase inhibitors	88	89	88
Ivabradine	3	3	3
Amiodarone	4	4	5
Hypnotics	4	4	5
Antidepressants	5	4	4
Diabetes medications	18	15	23

Values are mean ± standard deviation, unless otherwise stated.

ACE, angiotensin converting enzyme; AHI, apnoea–hypopnoea index; AR, angiotensin receptor; CABG, coronary artery bypass graft surgery; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; ECG, electrocardiogram; GFR, glomerular filtration rate; Hb, haemoglobin; ICD, implantable cardioverter defibrillator; LA, left atrial; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

[a] $p < 0.05$ vs patients with AHI <15/h.

[b] There was >1 indication for cardiac rehabilitation in some patients.

[c] Most patients were receiving >1 medication.

whether they were snoring and had witnessed apnoeas, and asked to rate subjective sleep quality on a scale from 1 (poor) to 10 (best). Patients also completed the Epworth Sleepiness Scale (ESS) and the SF12 questionnaire. A 12-lead electrocardiogram was used to assess heart rhythm to evaluate rhythm at the time of sleep analysis. All data were stored electronically in a central database.

Diagnosis of sleep apnoea

ApneaLink™ (ResMed) was used to screen for sleep apnoea. The device measures air flow, heart rate and oxygen saturation by pulse oximetry but does not differentiate between obstructive or central apnoea events. It has been shown to have high diagnostic accuracy for SDB compared with simultaneous PSG; using an AHI cut-off value of 15/h, ApneaLink™ had a pooled sensitivity of 91.4% and a pooled specificity of 93.8%.[11–19,39]

Diagnosis was determined in the first week after the start of rehabilitation. Parameters recorded included the AHI, apnoea index, hypopnoea index, oxygen desaturation index, number of desaturations during the recording, mean nocturnal oxygen saturation, lowest nocturnal oxygen saturation, and numbers of episodes of Cheyne-Stokes respiration (CSR) sleep apnoea and snoring.

Statistical methods

Data are presented as mean ± SD. Differences between groups were analysed using a t-test after testing for normal distribution. Single or multiple logistic regression analysis was performed. Values of $p < 0.05$ were considered statistically significant. Patients were divided into two groups based on the AHI (AHI <15/h: no relevant sleep apnoea; AHI ≥ 15/h: sleep apnoea present); patients with an AHI ≥ 15/h were considered to have a high probability of having clinically-important SDB. Sleep apnoea was graded by severity (AHI 5–14/h, not significant; AHI 15–29/h, moderate; AHI ≥ 30/h, severe). An AHI cut-off value 15/h was used to differentiate between no/mild apnoea and moderate/severe sleep apnoea based on the association between AHI values ≥ 15/h and worse cardiovascular outcomes.[40–43] All statistical analyses were performed using IBM SPSS Statistics 20.

Results

A total of 1293 patients gave informed consent to participate in the registry; approximately 5–10% of patients eligible for inclusion in the registry declined to be part of the registry. At baseline, 22 patients (1.8%) had known sleep apnoea and 14 (1.2%) were receiving treatment for sleep apnoea. Details of patient demographic data and characteristics are shown in Table 1 and patient flow is detailed in Figure 1.

Sleep quality and snoring

Mean ESS score was 5.7 ± 3.7 (range 0–19). Subjective sleep quality rating was 6.1 ± 2.2 points; 73% of all patients reported snoring and 28% reported witnessed apnoeas during sleep (Table 2).

Sleep apnoea screening

Sleep apnoea screening data were available in 1152 patients (92.4%). The main reason for missing

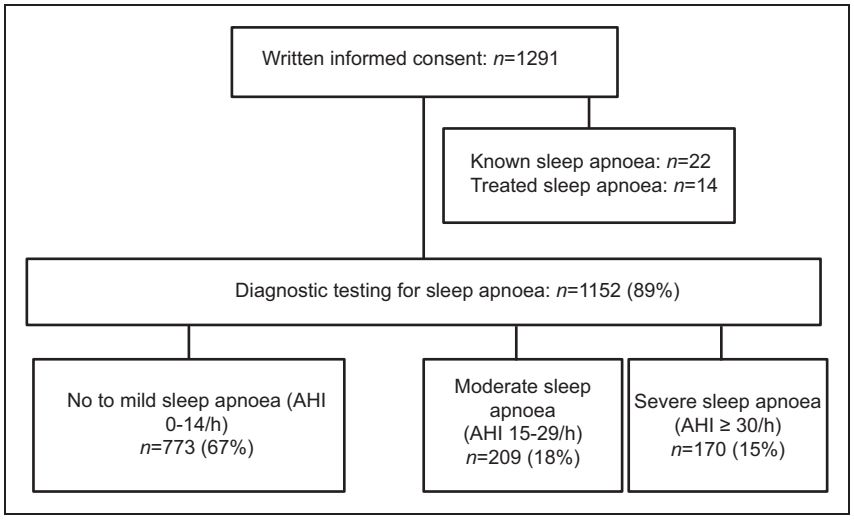

Figure 1. Flow chart of patient inclusion.

data was refusal of patients to undergo sleep apnoea testing. Significant sleep apnoea (AHI ≥5/h) was documented in 68% of screened patients. Mean AHI was 14 ± 16/h (range 0–106/h). Information on the presence of CSR was available for 1123 patients (97.5%), of whom 203 (18.1%) had at least one episode of CSR.

Comparison of patient groups

Differentiating groups by SDB severity, 369 (32%) patients had no sleep apnoea (AHI 0–4/h), 209 (18%) had moderate apnoea (AHI 15–29/h) and 170 (15%) had severe sleep apnoea (AHI ≥30/h) (Figure 1). Patients with no clinically significant apnoea (AHI <15/h) were compared with those who had clinically-relevant sleep apnoea (AHI ≥15/h), based on validation of the screening tool being made for an AHI value of >15/h. Demographic and clinical data for the two patient groups are compared in Table 1. There were no statistically significant differences between patient groups for age, presence of CAD, haemoglobin, creatinine, GFR, lipid metabolism disorders, peripheral arterial occlusive disease, history of stroke, history of atrial fibrillation, family history of CAD, presence of atrial fibrillation on ECG or left atrial dimension; patients with clinically significant sleep apnoea were older, more likely to be male and/or obese, had a higher NYHA class, and were more likely to have type 2 diabetes, hypertension, reduced LVEF, COPD and/or a history of CABG or valve surgery whereas those with an AHI <15/h were more likely to have MI and/or to have undergone PCI. Patients with versus without clinically significant SBD had a higher rate of ß-blocker and diuretic use, but use of all other medications did not differ significantly between the two patient groups.

Table 2. Sleep data for patients with no or mild sleep apnoea (AHI <15/h) versus those with moderate-to-severe sleep apnoea (AHI ≥15/h).

	AHI	
	<15/h (*n* = 773)	≥15/h (*n* = 379)
Witnessed apnoea, n (%)	170 (23%)	137 (38%)[a]
Snoring, n (%)	527 (71%)	281 (78%)[a]
ESS score	5.5 ± 3.7	6.0 ± 3.7[a]
Subjective sleep quality score	6.2 ± 2.2	5.9 ± 2.1
Short Form-12:		
MCS	47 ± 12	48 ± 12
PCS	38 ± 10	37 ± 10
AHI, /h	5 ± 4	32 ± 16[a]
AI, /h	2 ± 2	18 ± 16[a]
HI, /h	4 ± 3	13 ± 9[a]
ODI, /h	6 ± 5	25 ± 17[a]
CSR epochs, /h	1 ± 4	10 ± 19[a]
Mean SaO_2, %	93.4 ± 1.9	92.7 ± 2.0[a]
Minimum SaO_2, %	82.6 ± 5.8	79.7 ± 5.5[a]

Values are mean ± standard deviation, unless otherwise stated.
AHI, apnoea–hypopnoea index; AI, arousal index; CSR, Cheyne-Stokes respiration; ESS, Epworth Sleepiness Scale; HI, hypopnoea index; MCS, mental component score; ODI, oxygen desaturation index; PCS, physical component score; SaO_2, arterial oxygen saturation.
[a]$p < 0.05$ vs patients with AHI <15/h.

Sleep analysis (Table 2) showed that SDB patients had more witnessed apnoeas, were more likely to have a history of snoring and had more CSR with lower

Table 3. Echocardiographic assessments for patients with no or mild sleep apnoea (AHI <15/h) versus those with moderate-to-severe sleep apnoea (AHI ≥15/h), based on NYHA class (I versus >I).

	AHI <15/h		AHI ≥15/h	
	NYHA class I	NYHA class ≥I	NYHA class I	NYHA class ≥I
N (% patients)	518 (67)	255 (33)	229 (60)	150 (40)
LVEF, %	56.8 ± 8.5[a]	52.5 ± 12.7	55.1 ± 10.2[b]	52.5 ± 12.3
LA diameter, mm	39 ± 8	40 ± 10	40 ± 7	41 ± 11
PASP (mmHg)	22 ± 15[a]	26 ± 17	24 ± 15	26 ± 17
Septum (mm)	10.4 ± 2.6	10.6 ± 3.1	10.7 ± 2.8[b]	11.5 ± 3.9

LA, left atrial; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PASP, right ventricular systolic pressure.
[a]$p < 0.05$ vs patients with AHI <15/h; [b]$p < 0.05$ patients with NHYA = I vs NHYA ≥I for AHI ≥15.

minimum oxygen saturation, whereas ESS score and subjective sleep quality only differed slightly between groups (although these differences did reach statistical significance). Quality of life, as measured by the Short Form-12 (SF-12) mental component score (MCS) and physical component score (PCS), did not differ between patients with and without clinically significant SDB.

Table 3 details comparative echocardiographic data, NYHA class and AHI. Patients in both groups who had a higher NYHA class showed impaired LVEF and higher PASP. The septum diameter was higher in patients with significant SBD and higher NYHA class.

Sleep apnoea risk factors

Univariate analysis showed significant correlations between AHI and age (per 10 years) (odds ratio (OR) 1.45; $p < 0.001$), body mass index (per 5 units) (OR 1.26; $p = 0.001$), male sex (OR 1.61; $p = 0.009$), type 2 diabetes mellitus (OR 2.07; $p < 0.001$), COPD (OR 1.58; $p = 0.021$), haemoglobin level (g/dl) (OR 0.89; $p < 0.001$), CABG (OR 1.80; $p < 0.001$), hypertension (OR 1.74; $p = 0.003$), NYHA class III/IV (OR 1,73; $p = 0{,}008$), MI (OR 0.75; $p = 0.041$) and witnessed apnoeas (OR 1.94; $p < 0.001$) (Table 4).

The stepwise backward model selection (multivariate analysis) revealed age (per 10 years) (OR 1.51; $p < 0.001$), BMI (per 5 units) (OR 1.31; $p = 0.001$), male gender (OR 2.19; $p < 0.001$), type 2 diabetes (OR 1.45; $p = 0.040$), lower haemoglobin values (g/dl) (OR 0.91; $p = 0.012$) and witnessed apnoeas (OR 1.99; $p < 0.001$) as independent risk factors for SDB (Table 5).

Table 4. Univariate logistic regression analysis.

Variable	Estimate	Odds ratio	95% CI	*p* value
Age (per 10 years)	0.37	1.45	1.28, 1.64	<0.001
Body mass index (per 5 kg/m^2)	0.23	1.26	1.10, 1.45	0.001
Male	0.48	1.61	1.12, 2.30	0.009
Type 2 diabetes	0.73	2.07	1.49, 2.86	<0.001
COPD	0.46	1.58	1.07, 2.32	0.021
Haemoglobin (g/dl)	−0.12	0.89	0.83, 0.95	<0.001
Creatinine (mg/dl)	0.22	1.25	0.95, 1.65	0.119
GFR (ml/min)	−0.02	0.98	0.96, 1.01	0.132
Hypertension	0.55	1.74	1.21, 2.49	0.003
Coronary artery disease	−0.12	0.89	0.60, 1.32	0.548
CABG	0.59	1.80	1.33, 2.45	<0.001
Valvular heart disease	0.27	1.31	0.97, 1.77	0.074
NYHA class III/IV	0.55	1.73	1.15, 2.60	0.008
Atrial fibrillation	0.17	1.19	0.77, 1.83	0.427
Myocardial infarction	−0.29	0.75	0.57, 0.99	0.041
ESS score	0.03	1.03	0.99, 1.06	0.187
Short Form-12 score:				
MCS	0.00	1.00	0.99, 1.01	0.640
PCS	−0.01	0.99	0.98, 1.00	0.141

COPD, chronic obstructive pulmonary disease; CABG, coronary artery bypass graft surgery; ESS, Epworth Sleepiness Scale; GFR, glomerular filtration rate; NYHA, New York Heart Association; MCS, mental component score; PCS, physical component score.

Discussion

The main findings of our large registry are as follows: patients presenting for CR in Germany show a high prevalence of sleep apnoea; sleep apnoea in these patients has been previously diagnosed in only a minority of patients; patients with and without sleep apnoea showed only slight differences in SBD-associated symptoms as measured by sleep quality and ESS; and the main risk factors for sleep apnoea in these patients are age, BMI, male sex, anaemia and diabetes. To the best of our knowledge, our registry is by far the largest of its kind investigating SDB in CR patients.

The prevalence of sleep apnoea in this unselected patient cohort was very high – 33%. This corresponds to the 39% prevalence of sleep apnoea in CR patients

Table 5. Final logistic regression model (multivariate).

Variable	Estimate	Odds ratio	95% CI	*p* value
Age (per 10 years)	0.41	1.51	1.31, 1.74	<0.001
Body mass index (per 5 kg/m^2)	0.27	1.31	1.12, 1.52	0.001
Male	0.78	2.19	1.48, 3.23	<0.001
Type 2 diabetes	0.37	1.45	1.02, 2.08	0.040
Haemoglobin (g/dl)	−0.10	0.91	0.84, 0,98	0.012
Witnessed apnoea	0.69	1.99	1.44, 2.74	<0.001

reported by researchers from the USA.[44] They took a different approach and first used the Berlin questionnaire to screen 383 patients undergoing outpatient CR for diabetes (20%), hypertension (65%) and/or recent MI (58%). This classified 52% of patients as being at high risk for sleep apnoea, almost 80% of whom were recommended for further evaluation. Sleep laboratory studies showed that 39% of patients had sleep apnoea, with OSA being the most prevalent form of SDB (90% of patients). In another study, the Berlin Questionnaire was used in a CR setting.[45] That study reported that 44% of patients had a high probability of sleep apnoea, which is comparable to the proportion of patients in this study who had clinically relevant SBD. As a consequence, screening for sleep apnoea seems to be justified in all CR patients and not only in those presenting with several risk factors or severe clinical symptoms.[46]

The Berlin Questionnaire has also been used in other studies to show independent associations between OSA, hypertension and CAD.[47,48] This is in accordance with the findings of the current study, in which more patients had hypertension, CABG, valve replacement or type 2 diabetes, corresponding to data showing a link between severity of SDB and extent of coronary atherosclerosis.[49] However, caution needs to be exercised when using the Berlin Questionnaire because a high prevalence of obesity and hypertension has been shown to limit the ability of this tool to discriminate between post-myocardial infarction patients with or without SDB.[50]

The results from our registry showed that symptoms or indicators of sleepiness are only slightly different and may not differentiate between the presence or absence of SDB in patients with CAD, as has been reported in other studies.[51–55] Similar conclusions have been made by the authors of a study on heart failure patients, who had less subjective daytime sleepiness associated with OSA than patients without heart failure.[52] Furthermore, a high prevalence of sleep apnoea has been documented in patients with transient ischaemic attacks and stroke.[56]

The presence of only minor daytime sleepiness as a symptom of underlying OSA highlights the importance of screening patients with CAD for sleep apnoea even if some of the traditional symptoms are absent. However, the use of the ESS score showed some significance between the groups, whereas snoring or sleep quality did not.[57] Another study showed an inverse relationship between subjective daytime sleepiness and daytime muscle sympathetic nervous system activity in patients with heart failure and OSA, which may in fact be associated with a worse prognosis in these patients.[58] In addition, short sleep duration has been linked with a greater risk of developing or dying of CAD.[59]

Univariate analysis identified age, BMI, male gender, type 2 diabetes, COPD, haemoglobin level, hypertension, CABG, MI and higher NYHA class as risk factors for SBD. It is not entirely clear why the factors that remained significant in the multivariate analysis were only age, body mass index, male gender, type 2 diabetes mellitus, haemoglobin level and a history of witnessed apnoeas. Diabetes as a risk factor can be explained by the fact that this disease is more common in obese patients and the risk of sleep apnoea increases with age. However, it is less clear why lower haemoglobin levels are associated with SBD (OR <1.0). One possible explanation is the higher incidence of SDB in patients after CABG, who have lower haemoglobin levels after surgery. It is also unclear why MI was more common in patients without SDB in this study. It is possible that the higher rate of MI compared with PCI and CABG played some role. As Areias et al. and other studies found a high incidence (43.1%) of sleep apnoea in patients admitted to a coronary intensive care unit with acute coronary syndromes this is possibly based on acute coronary syndrome, which was more common in the PCI group. Further evaluation is needed here.[22,60] However, similar assessments at one and six months documented a decline in AHI over time, indicating the possibility that sleep apnoea may be transient in these patients and specifically associated with the acute phase of CAD.[61]

Certainly, rapidly accumulating evidence showing links between SDB and a variety of cardiovascular conditions, along with poor outcomes in those with both cardiovascular disease and SDB, confirm the potential for SDB to worsen outcomes during and after cardiac rehabilitation,[62,63] because patients with OSA have daytime sleepiness, fatigue and, as a result, reduced physical activity and find it more difficult to lose weight than those without OSA. Moreover OSA may cause angina and/or atrial fibrillation that could potentially interfere with the success of a rehabilitation programme.[37] OSA is associated with depression, obesity and impaired physical activity, conditions that could affect adherence to a rehabilitation programme.

Indeed, these risk factors have been associated with worse outcomes in CR.[64–66] Furthermore, sleepiness associated with OSA can lead to cognitive impairment. In turn, cognitive impairment has been identified as a predictor of exercise trainability in CR and impairments can reduce the effectiveness of rehabilitation.[67,68]

Since CR reduces total and cardiovascular mortality, risk factors and hospital admissions,[69,70] it has been suggested that incorporation of strategies to diagnose and treat sleep apnoea as part of CR could improve compliance with the rehabilitation programme.

The CR patients in our registry were only screened for SDB; the effect of rehabilitation on the presence and severity of sleep apnoea was not assessed. However, it is possible that CR has the potential to have a positive long-term effect not only on cardiovascular performance but also on sleep apnoea in these patients. Levels of inflammatory cytokines, which are increased in patients with OSA[71] and are markers of cardiovascular complications,[72] are decreased after 4 weeks of CR.[73] In our opinion, studying the combined effects of definitive diagnosis and treatment of sleep apnoea during the CR phase in combination with classical CR is a very interesting area for future investigation. However, the effect of treating SDB in patients with cardiovascular disease has yet to be clearly defined using data from randomized, controlled clinical trials. The ongoing SERVE-HF study is currently investigating the effect of adaptive servo-ventilation (ASV) treatment on morbidity and mortality in patients with heart failure, and will add to the body of knowledge in this area.[74]

A limitation of our study is the missing data on sleep. PSG is not a standard tool in CR facilities and therefore an alternative screening tool – 2-channel polygraphy – was used in this study. This is likely to provide greater flexibility and patient acceptability but could underestimate the severity of SDB in patients with impaired sleep quality.[61]

In conclusion, the findings of our registry indicate that more than two-thirds of patients undergoing CR in Germany probably have sleep apnoea that requires further evaluation or intervention, with one-third of the patients experiencing moderate-to-severe SDB. The presence of sleep apnoea was associated with age, weight, male sex, diabetes, other cardiovascular risk factors, severity of CAD and atrial fibrillation, whereas symptoms of daytime sleepiness and impaired sleep quality were only slightly impaired. As a result, inclusion of screening for sleep apnoea as part of the CR process appears to be warranted.

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Conflicts of interest

ES received grants and personal fees from ResMed for lectures during the study, and he received personal fees from Philips and Medtronic outside the submitted work. HPE and SK report grants from ResMed during the study period. HW and AG were employed by ResMed for the duration of the study and outside the submitted work. K. Schroeder reports personal fees from Novartis Pharma outside the submitted work. WK, BA, HV, AB, GB, EL and HCP have no conflicts to declare.

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References

1. Brown DL. Sleep disorders and stroke. *Semin neurol* 2006; 26: 117–122.
2. Jean-Louis G, Brown CD, Zizi F, et al. Cardiovascular disease risk reduction with sleep apnea treatment. *Expert Rev Cardiovasc Ther* 2010; 8: 995–1005.
3. Lanfranchi PA, Braghiroli A, Bosimini E, et al. Prognostic value of nocturnal Cheyne-Stokes respiration in chronic heart failure. *Circulation* 1999; 99: 1435–1440.
4. Punjabi NM. The epidemiology of adult obstructive sleep apnea. *Proc Am Thorac Soc* 2008; 5: 136–143.
5. Stradling JR and Davies RJ. Sleep. 1: Obstructive sleep apnoea/hypopnoea syndrome: definitions, epidemiology, and natural history. *Thorax* 2004; 59: 73–78.
6. Research. TNCoSD. *Wake up America: a national sleep alert*. Washington DC: US Government Printing Office, 2002.
7. Duran J, Esnaola S, Rubio R, et al. Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. *Am J Respir Crit Care Med* 2001; 163: 685–689.
8. Somers VK, White DP, Amin R, et al. 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. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). *Circulation* 2008; 118: 1080–1111.
9. Parati G, Lombardi C, Hedner J, et al. Position paper on the management of patients with obstructive sleep apnea and hypertension: joint recommendations by the European Society of Hypertension, by the European Respiratory Society and by the members of European COST (COoperation in Scientific and Technological research) ACTION B26 on obstructive sleep apnea. *J Hypertens* 2012; 30: 633–646.

10. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med* 2012; 8: 597–619.
11. Wang Y, Teschler T, Weinreich G, et al. [Validation of microMESAM as screening device for sleep disordered breathing]. *Pneumologie* 2003; 57: 734–740.
12. Baisch A, Afshar S, Hormann K, et al. [Use of a screening device for sleep apnea in clinical practice]. *HNO* 2007; 55: 90–92.
13. Erman MK, Stewart D, Einhorn D, et al. Validation of the ApneaLink for the screening of sleep apnea: a novel and simple single-channel recording device. *J Clin Sleep Med* 2007; 3: 387–392.
14. Ng SS, Chan TO, To KW, et al. Validation of a portable recording device (ApneaLink) for identifying patients with suspected obstructive sleep apnoea syndrome. *Intern Med J* 2009; 39: 757–762.
15. Chen H, Lowe AA, Bai Y, et al. Evaluation of a portable recording device (ApneaLink) for case selection of obstructive sleep apnea. *Sleep Breath* 2009; 13: 213–219.
16. Clark AL, Crabbe S, Aziz A, et al. Use of a screening tool for detection of sleep-disordered breathing. *J Laryngol Otol* 2009; 123: 746–749.
17. Weinreich G, Armitstead J, Topfer V, et al. Validation of ApneaLink as screening device for Cheyne-Stokes respiration. *Sleep* 2009; 3: 553–557.
18. Ragette R, Wang Y, Weinreich G, et al. Diagnostic performance of single airflow channel recording (ApneaLink) in home diagnosis of sleep apnea. *Sleep Breath* 2010; 14: 109–114.
19. Nigro CA, Dibur E, Malnis S, et al. Validation of ApneaLink Ox for the diagnosis of obstructive sleep apnea. *Sleep Breath* 2013; 17: 259–266.
20. Kushida CA, Littner MR, Morgenthaler T, et al. Practice parameters for the indications for polysomnography and related procedures: an update for 2005. *Sleep* 2005; 28: 499–521.
21. Buchner NJ, Sanner BM, Borgel J, et al. Continuous positive airway pressure treatment of mild to moderate obstructive sleep apnea reduces cardiovascular risk. *Am J Respir Crit Care Med* 2007; 176: 1274–1280.
22. Correia LC, Souza AC, Garcia G, et al. Obstructive sleep apnea affects hospital outcomes of patients with non-ST-elevation acute coronary syndromes. *Sleep* 2012; 35: 1241–125A.
23. Mooe T, Franklin KA, Holmstrom K, et al. Sleep-disordered breathing and coronary artery disease: long-term prognosis. *Am J Respir Crit Care Med* 2001; 164: 1910–1913.
24. Jilek C, Krenn M, Sebah D, et al. Prognostic impact of sleep disordered breathing and its treatment in heart failure: an observational study. *Eur J Heart Fail* 2011; 13: 68–75.
25. Galletti F, Barbato A, Versiero M, et al. Circulating leptin levels predict the development of metabolic syndrome in middle-aged men: an 8-year follow-up study. *J Hypertens* 2007; 25: 1671–1677.
26. Minoguchi K, Yokoe T, Tazaki T, et al. Increased carotid intima-media thickness and serum inflammatory markers in obstructive sleep apnea. *Am J Respir Crit Care Med* 2005; 172: 625–630.
27. Kourembanas S, Marsden PA, McQuillan LP, et al. Hypoxia induces endothelin gene expression and secretion in cultured human endothelium. *Journal Clin Invest* 1991; 88: 1054–1057.
28. Meier-Ewert HK, Ridker PM, Rifai N, et al. Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk. *J Am Coll Cardiol* 2004; 43: 678–683.
29. Vgontzas AN, Papanicolaou DA, Bixler EO, et al. Elevation of plasma cytokines in disorders of excessive daytime sleepiness: role of sleep disturbance and obesity. *J Clin Endocrinol Metab* 1997; 82: 1313–1316.
30. Prabhakar NR. Sleep apneas: an oxidative stress? *Am J Respir Crit Care Med* 2002; 165: 859–860.
31. Schulz R, Mahmoudi S, Hattar K, et al. Enhanced release of superoxide from polymorphonuclear neutrophils in obstructive sleep apnea. Impact of continuous positive airway pressure therapy. *Am J Respir Crit Care Med* 2000; 162: 566–570.
32. Suzuki YJ, Jain V, Park AM, et al. Oxidative stress and oxidant signaling in obstructive sleep apnea and associated cardiovascular diseases. *Free Radic Biol Med* 2006; 40: 1683–1692.
33. von Kanel R, Loredo JS, Ancoli-Israel S, et al. Association between polysomnographic measures of disrupted sleep and prothrombotic factors. *Chest* 2007; 131: 733–739.
34. Baguet JP, Barone-Rochette G, Tamisier R, et al. Mechanisms of cardiac dysfunction in obstructive sleep apnea. *Nat Rev Cardiol* 2012; 9: 679–688.
35. Lopez-Jimenez F, Sert Kuniyoshi FH, Gami A, et al. Obstructive sleep apnea: implications for cardiac and vascular disease. *Chest* 2008; 133: 793–804.
36. Latina JM, Estes 3rd NA and Garlitski AC. The relationship between obstructive sleep apnea and atrial fibrillation: a complex interplay. *Pulm Med* 2013; 2013: 621736.
37. Konecny T, Kuniyoshi FH, Orban M, et al. Under-diagnosis of sleep apnea in patients after acute myocardial infarction. *J Am Coll Cardiol* 2010; 56: 742–743.
38. Jaffe LM, Kjekshus J and Gottlieb SS. Importance and management of chronic sleep apnoea in cardiology. *Eur Heart J* 2013; 34: 809–815.
39. Nigro CA, Serrano F, Aimaretti S, et al. Utility of ApneaLink for the diagnosis of sleep apnea-hypopnea syndrome. *Medicina* 2010; 70: 53–59.
40. Dong JY, Zhang YH and Qin LQ. Obstructive sleep apnea and cardiovascular risk: meta-analysis of prospective cohort studies. *Atheroscler* 2013; 229: 489–495.
41. Ge X, Han F, Huang Y, et al. Is obstructive sleep apnea associated with cardiovascular and all-cause mortality? *PloS One* 2013; 8: e69432.
42. Martinez-Garcia MA, Campos-Rodriguez F, Catalan-Serra P, et al. Cardiovascular mortality in obstructive sleep apnea in the elderly: role of long-term continuous positive airway pressure treatment: a prospective

observational study. *Am J Respir Crit Care Med* 2012; 186: 909–916.
43. Campos-Rodriguez F, Martinez-Garcia MA, de la Cruz-Moron I, et al. Cardiovascular mortality in women with obstructive sleep apnea with or without continuous positive airway pressure treatment: a cohort study. *Ann Intern Med* 2012; 156: 115–122.
44. Sert-Kuniyoshi FH, Squires RW, Korenfeld YK, et al. Screening for obstructive sleep apnea in early outpatient cardiac rehabilitation: feasibility and results. *Sleep Med* 2011; 12: 924–927.
45. Sharma S and Parker AT. Prevalence of obstructive sleep apnea in a patient population undergoing cardiac rehabilitation. *J Cardiopulm Rehabil Prev* 2011; 31: 188–192.
46. Glantz H, Thunstrom E, Herlitz J, et al. Occurrence and predictors of obstructive sleep apnea in a revascularized coronary artery disease cohort. *Ann Am Thorac Soc* 2013; 10: 350–356.
47. Gus M, Goncalves SC, Martinez D, et al. Risk for obstructive sleep apnea by Berlin Questionnaire, but not daytime sleepiness, is associated with resistant hypertension: a case-control study. *Am J Hyperten* 2008; 21: 832–835.
48. Massierer D, Martinez D, Fuchs SC, et al. Obstructive sleep apnea, detected by the Berlin Questionnaire: an associated risk factor for coronary artery disease. *Cad Saude Publica* 2012; 28: 1530–1538.
49. Inami T, Seino Y, Otsuka T, et al. Links between sleep disordered breathing, coronary atherosclerotic burden, and cardiac biomarkers in patients with stable coronary artery disease. *J Cardiol* 2012; 60: 180–186.
50. Sert Kuniyoshi FH, Zellmer MR, Calvin AD, et al. Diagnostic accuracy of the Berlin Questionnaire in detecting sleep-disordered breathing in patients with a recent myocardial infarction. *Chest* 2011; 140: 1192–1197.
51. Javaheri S, Parker TJ, Liming JD, et al. Sleep apnea in 81 ambulatory male patients with stable heart failure. Types and their prevalences, consequences, and presentations. *Circulation* 1998; 97: 2154–2159.
52. Arzt M, Young T, Finn L, et al. Sleepiness and sleep in patients with both systolic heart failure and obstructive sleep apnea. *Arch Intern Med* 2006; 166: 1716–1722.
53. Kaneko Y, Floras JS, Usui K, et al. Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea. *N Engl J Med* 2003; 348: 1233–1241.
54. Rao A, Georgiadou P, Francis DP, et al. Sleep-disordered breathing in a general heart failure population: relationships to neurohumoral activation and subjective symptoms. *J Sleep Res* 2006; 15: 81–88.
55. Simon R, Chirakalwasan N, Teerapraipruk B, et al. Severity of obstructive sleep apnea in patients with and without cardiovascular-related diseases. *Respir Care* 2012; 57: 1476–1482.
56. Mohsenin V. Sleep-disordered breathing: implications in cerebrovascular disease. *Preventive Cardiol* 2003; 6: 149–154.
57. Feng J, He QY, Zhang XL, et al. Sleep Breath Disorder Group SoRM. Epworth Sleepiness Scale may be an indicator for blood pressure profile and prevalence of coronary artery disease and cerebrovascular disease in patients with obstructive sleep apnea. *Sleep Breath* 2012; 16: 31–40.
58. Taranto Montemurro L, Floras JS, Millar PJ, et al. Inverse relationship of subjective daytime sleepiness to sympathetic activity in patients with heart failure and obstructive sleep apnea. *Chest* 2012; 142: 1222–1228.
59. Cappuccio FP, Cooper D, D'Elia L, et al. Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. *Eur Heart J* 2011; 32: 1484–1492.
60. Areias V, Romero J, Cunha K, et al. Sleep apnea-hypopnea syndrome and acute coronary syndrome – an association not to forget. *Rev Port Pneumol* 2012; 18: 22–28.
61. Schiza SE, Simantirakis E, Bouloukaki I, et al. Sleep disordered breathing in patients with acute coronary syndromes. *J Clin Sleep Med* 2012; 8: 21–26.
62. Levy P, Ryan S, Oldenburg O, et al. Sleep apnoea and the heart. *Eur Respir Review* 2013; 22: 333–352.
63. Monahan K and Redline S. Role of obstructive sleep apnea in cardiovascular disease. *Curr Opin Cardiol* 2011; 26: 541–547.
64. Caulin-Glaser T, Maciejewski PK, Snow R, et al. Depressive symptoms and sex affect completion rates and clinical outcomes in cardiac rehabilitation. *Prev Cardiol* 2007; 10: 15–21.
65. Gunstad J, Luyster F, Hughes J, et al. The effects of obesity on functional work capacity and quality of life in phase II cardiac rehabilitation. *Prev Cardiol* 2007; 10: 64–67.
66. Zhang JP, Pozuelo L, Brennan DM, et al. Association of SF-36 with coronary artery disease risk factors and mortality: a PreCIS study. *Prev Cardiol* 2010; 13: 122–129.
67. Kakos LS, Szabo AJ, Gunstad J, et al. Reduced executive functioning is associated with poorer outcome in cardiac rehabilitation. *Prev Cardiol* 2010; 13: 100–103.
68. Franklin BA. Cognitive impairment: a new predictor of exercise trainability and outcomes in cardiac rehabilitation? *Prev Cardiol* 2010; 13: 97–99.
69. Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013; 34: 2949–3003.
70. Kelley GA and Kelley KS. Efficacy of aerobic exercise on coronary heart disease risk factors. *Prev Cardiol* 2008; 11: 71–5.
71. Ohga E, Tomita T, Wada H, et al. Effects of obstructive sleep apnea on circulating ICAM-1, IL-8, and MCP-1. *J App Physiol* 2003; 94: 179–184.
72. Teramoto S, Yamamoto H and Ouchi Y. Increased C-reactive protein and increased plasma interleukin-6 may synergistically affect the progression of coronary atherosclerosis in obstructive sleep apnea syndrome. *Circulation* 2003; 107: E40–E40.

73. Parker AT and Sharma S. Effect of cardiac rehabilitation on inflammatory markers in patients with high risk for obstructive sleep apnea: a pilot study. *J Interferon Cytokine Res* 2011; 31: 527–531.
74. Cowie MR, Woehrle H, Wegscheider K, et al. Rationale and design of the SERVE-HF study: treatment of sleep-disordered breathing with predominant central sleep apnoea with adaptive servo-ventilation in patients with chronic heart failure. *Eur J Heart Fail* 2013; 15: 937–943.