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SLEEP

Mortality and morbidity in obstructive sleep apnoea–hypopnoea syndrome: results from a 30-year prospective cohort study

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ABSTRACT

Background: Obstructive sleep apnoea–hypopnoea syndrome (OSAHS) carries substantial negative health consequences. This study examines factors affecting mortality and morbidity according to continuous positive airway pressure (CPAP) use and predictors affecting CPAP adherence in a longitudinal cohort of OSAHS patients.

Materials and methods: This prospective, cohort study comprised 4502 patients who were diagnosed with OSAHS at a tertiary sleep disorders centre between 1982 and 2003. Of these, 1174 patients completed follow-up in 2012. Data collected included anthropometric, sleep and demographic characteristics, including comorbidities, ongoing medications and CPAP adherence. Patients were followed up for an average of 14.8±3.7 years.

Results: Imputation analysis showed that long-term CPAP users (>5 years) were 5.63 times more likely to be alive at study end than non-CPAP users (95% CI: 4.83–6.58, p<0.001) and 1.74-times more likely than short-term CPAP users (⩽5 years) (95% CI: 1.49–2.02, p<0.001). Females had a significantly higher mortality rate during the follow-up period (26.8% *versus* 19.6%, p<0.001). Respiratory mortality was more common in patients with OSAHS, in particular those who did not use CPAP, compared to the general population (17.2% *versus* 12.2%, p=0.002 respectively), whereas deaths from cancer were less common compared to the general population (16.2% *versus* 25.6%, p<0.001). Compared to CPAP users, non-CPAP-users had a significantly increased incidence of type II diabetes mellitus (DMII) (27.9% *versus* 18.7%, p=0.003), ischaemic heart disease (IHD) (25.5% *versus* 12.7%, p<0.001) and myocardial infarction (MI) (14.7% *versus* 4.2%, p<0.001) at long-term follow-up.

Conclusions: Long-term CPAP use in men and women with OSAHS reduces mortality and decreases the incidence of DMII and cardiovascular disease.

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In this first long-term prospective cohort study to use imputation analysis in OSAHS patients, all-cause morbidity and mortality were significantly reduced in long-term CPAP users (>5 years), and equivalent for both males and females https://bit.ly/3cKL2HK

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Introduction

Obstructive sleep apnoea–hypopnea syndrome (OSAHS) affects 3–7% of the population and is characterised by excessive sleepiness and neurocognitive impairment [1]. Continuous positive airway pressure (CPAP) therapy, the current gold-standard treatment for moderate-to-severe OSAHS, provides a constant stream of pressurised air, maintaining the upper airway during sleep.

OSAHS is considered an independent risk factor for all-cause mortality and morbidity. Severe obstructive sleep apnoea has been associated with a 1.9-times increased risk in all-cause mortality and 2.65-times increased risk of cardiovascular mortality [2]. Previous cohort studies have shown female patients to have a lower morbidity and mortality rate than males [3, 4]. CPAP has been shown to improve survival in male patients [5], but less so in females [4].

Patients with severe, untreated OSAHS have been shown to have a higher incidence of cardiovascular events compared to normal controls, and those treated with CPAP [5]. When compared with the general population, OSAHS is more common in patients with existing coronary artery disease, with a reported prevalence of 38–65% [6]. A large cohort study in Denmark showed negative predictors for survival to be male sex, age ⩾60 years, no CPAP treatment, increased comorbidity burden (calculated using the Charlson comorbidity index) and low educational level [4]. Another study also showed increasing age and comorbid illness, namely cardiovascular, COPD and type II diabetes mellitus (DMII), to be predictors of mortality in OSAHS patients [7].

The aim of the present study was to assess determinants of morbidity and mortality in a 30-year, prospective cohort study of patients diagnosed with treatable OSAHS. We also hypothesised that lower CPAP use would raise the risk of mortality and morbidity.

Material and methods

Study design

A single-centre prospective cohort study was carried out between 1982 and 2012. Follow-up took place for a minimum of 7.5 years and a maximum of 30 years (average=14.8±3.7 years). All research was conducted in accordance with the Declaration of Helsinki [8]. Mortality data were traced by the General Register Office for Scotland [9].

Study subjects

A total of 6473 patients who had a sleep study at a tertiary sleep disorders centre between 1982 and 2003 were enrolled at baseline. Between 2010 and 2012, a follow-up questionnaire was sent to 5530 patients (943 patients had died during the intervening period). Of 5530 questionnaires, 2857 (51.7%) were not returned at all; 1047 (18.9%) were sent back due to a change of address; in 73 cases (1.3%) the patient was unable to return the questionnaire and 25 patients refused to participate in the study (0.5%). In total, 1528 questionnaires were returned and were valid for analysis (27.6%). By 2012, the last year of the study, 68 more patients had died, raising the total number of deaths to 1011 patients.

Prior to analysis, all patients receiving noninvasive ventilation (NIV) or a mandibular repositioning splint (MRS) were removed from the baseline database (n=94). Twelve patients were removed due to a diagnosis of myotonic dystrophy. All patients with type II respiratory failure receiving bilevel ventilation (n=25) and all patients with conditions implicating type II respiratory failure were removed (kyphoscoliosis (n=12), myasthenia gravis (n=4), polio (n=6)). Another 1818 patients were removed due to a diagnosis of a sleep disorder other than OSAHS. Thus, the baseline cohort of the study comprised 4502 OSAHS patients and 1174 at follow-up (questionnaire responders).

Methods

Data included basic demographic information and results of a clinical questionnaire completed prior to the initial sleep clinic appointment. This questionnaire has been used routinely in the department for over 30 years and asks about age at presentation, height, weight, collar size, occupation, marital status, number of children, smoking and alcohol, the three major reasons for attendance, comorbidities, current medications, previous surgery of the upper airways and nose, the Epworth sleepiness score (ESS) [10], driving history, symptoms consistent with sleep apnoea, impact on bed-mates of snoring and breathing pauses, other symptoms consistent with sleep disorders, weight changes and sex life. In the majority of patients (n=3481), OSAHS was diagnosed using polysomnography (PSG), while in the remaining cases, it was diagnosed using ambulatory polygraphy (PG) (n=1021). PSG comprised electroencephalogram (EEG), electrooculogram (EOC), chin electromyogram (EMG), nasal manometry, chest and abdominal wall movements, oxygen saturation, snoring recording, body position and video monitoring during sleep, whereas limited study comprised nasal manometry, chest and abdominal wall movements, oxygen saturation and heart rate [10, 11]. OSAHS was diagnosed as an apnoea–hypopnoea index (AHI) of ⩾5 or

an apnoea+hypopnoea per hour in bed (A+H) of ⩾25 plus an ESS of ⩾11 [10]. PSGs and PGs were scored by experienced sleep physiologists according to the respective guidelines during the study period [12, 13]. During the questionnaire follow-up phase (2010–2012) patients were sent a postal questionnaire to assess health status. The questionnaires included questions regarding current height, weight, smoking/alcohol history, comorbidities (including new medical, sleep and psychiatric conditions that had developed since last review), medications currently prescribed, questions regarding driving and sleepiness and what type of license the patient was using, subjective CPAP use in hours per night, which was verified objectively using records as far as possible and questions regarding issues with CPAP irrespective of whether the patients was still using or not. Patients who were no longer on CPAP were asked to respond as to why they had stopped. Patients were also asked to complete an ESS.

Analysis

Analysis was carried out using SPSS Statistics 24.0 software (IBM Corp, Armonk, NY, USA). Continuous variables are presented as a mean±SD and categorical variables as number and percentage. To separate parametric from nonparametric variables, normality tests, using the Kolmogorov–Smirnov test, were

TABLE 1 Baseline characteristics of the obstructive sleep apnoea–hypopnoea syndrome (OSAHS) cohort and cause of death split by sex

Characteristic	Males (n=3580, 79.5%)	Females (n=922, 20.5%)	p-value
Length of follow-up years	14.8±3.7 (3579)	14.7±3.6 (920)	0.20
Age years	50.5±11.3 (3558)	51.8±13.8 (917)	**0.001**
Weight kg	97.2±21.4 (2485)	85.6±23.7 (644)	**<0.001**
BMI kg·m^{-2}	31.8±6.7 (2466)	33.6±9.4 (635)	**0.001**
Smoking[#] cigarettes per day	14.7±15.8 (2250)	11.5±12.9 (576)	**<0.001**
Alcohol units per week	12.4±14.3 (2284)	3.8±6.4 (567)	**<0.001**
ESS n/24	13.2±4.9 (3069)	13.7±5.1 (778)	0.004
Partner-reported ESS n/24	7.3±4.8 (941)	8.8±5.7 (168)	0.003
AHI	38.9±36.5 (2758)	27.9±30.9 (736)	**<0.001**
A+H	45.0±21.9 (473)	38.4±24.2 (89)	0.003
CPAP[¶] hours per night	4.6±2.9 (2282)	3.9±3.2 (471)	**<0.001**
OSAHS severity			
Mild	734 (20.5%)	347 (37.6%)	**<0.001**
Moderate	809 (22.6%)	206 (22.3%)	0.97
Severe	1688 (47.2%)	272 (29.5%)	**<0.001**
CPAP use	2064 (57.7%)	409 (44.3%)	**<0.001**
Mortality	702 (19.6%)	247 (26.8%)	**<0.001**
Cause of death			
Cardiovascular	280 (39.9%)	80 (32.4%)	0.037
Respiratory	114 (16.2%)	49 (19.8%)	0.20
Cancer	116 (16.5%)	38 (15.4%)	0.68
Accident/violent	14 (2.0%)	1 (0.4%)	0.13
Dementia	3 (0.4%)	3 (1.2%)	0.19
Other	62 (8.8%)	30 (12.2%)	0.13
Unknown	113 (16.1%)	46 (18.6%)	0.36

Data are presented as mean±SD (n) or n (%), unless otherwise stated. Statistical significance is at p<0.05/25=0.002). OSAHS: obstructive sleep apnoea–hypopnoea syndrome; BMI: body mass index; ESS: Epworth sleepiness scale; AHI: apnoea–hypopnoea index; A+H: apnoea+hypopnoea per hour in bed; CPAP: continuous positive airway pressure. [#]: Current plus ex-smokers; [¶]: Data are downloaded from CPAP machine.

performed. Categorical variables were analysed using the Chi-squared test, whereas continuous variables were analysed using the independent samples t-test for parametric variables and the Mann–Whitney U-test for nonparametric variables. All tests were two-tailed and analysis for multiple comparisons was undertaken. Significance was taken at $p<0.05/n$ (n=number of groups, or when there were two groups, n=number of comparisons). To search for variables affecting survival or adherence to CPAP treatment, a univariate analysis was initially performed between the dependent variable and each independent variable separately, followed by a multivariate backward regression analysis using the dependent variable and all the independent variables that were statistically significant in univariate regression analysis. Kaplan–Meier survival curves were used to analyse survival likelihood. For morbidity and mortality analyses we divided the cohort in two groups: 1) those who had used CPAP continuously since their diagnosis (CPAP arm); and 2) those who refused CPAP use plus those who initially used CPAP but eventually stopped using it (No-CPAP arm).

Baseline data were further analysed using imputation analysis to emulate a randomised controlled trial with full adherence, thereby removing immortal time bias [14]. Patients were initially assigned to CPAP *versus* non-CPAP users at t=0. Clones were then assigned to either 'short-term' (CPAP use for ⩽5 years) or 'long-term' (CPAP use for >5 years) groups in order to look at the effects of CPAP use on long-term mortality. This grouping was carried out on the basis of trends discovered within the dataset, and comparison with parameters set by similar cohort studies [15]. Artificial censoring ensures that clones follow the assigned strategy through follow-up. Selection bias was eliminated by inverse probability weighting [14]. Data were then used to calculate a relative risk ratio comparing patient mortality across the three patient groups.

Results

A total of 4502 patients with a mean age of 50.8±11.8 years were included for analysis at baseline. Of them, 3580 (79.5%) were male and 922 (20.5%) were female. Females were older and had a higher body mass index (BMI), whereas males had a higher AHI, consumed more alcohol and smoked more. Of the initial 4502 patients, 949 were known to have died by 2012. Despite males having significantly higher rates of severe OSAHS, females had a significantly higher mortality rate during the follow-up period (26.8% *versus* 19.6%, $p<0.001$). Women used CPAP significantly less compared to males, both as a percentage of total and as hours per night (table 1).

Cardiovascular and respiratory events were more common causes of death in OSAHS patients compared to the general Scottish population. For respiratory causes, the difference was statistically significant ($p=0.002$) (table 2). Deaths from cancer were significantly less common in OSAHS patients compared to the general population (16.2% *versus* 25.6%, $p<0.001$). During the follow-up period, 95.2% (n=903) of the deaths occurred in the No-CPAP arm of the study, whereas 4.8% (n=46) occurred in the CPAP arm ($p<0.001$) (table 2). Among causes of death, respiratory mortality was significantly higher in the No-CPAP arm compared to the CPAP arm (17.9% *versus* 2.2%, $p=0.006$) (table 2).

The strongest predictor of mortality in both sexes was non-CPAP use (OR=16.8, $p<0.001$ for males, OR=11, $p<0.001$ for females) (table 3). The coexistence of DMII at OSAHS diagnosis was also significant

TABLE 2 Cause of death split by CPAP use and comparison with the general Scottish population between 1982–2012

Cause of death	OSAHS population (n=4502)				General Scottish population	p-value
	On CPAP (n=2473, 54.9%)	No CPAP (n=2029, 45.1%)	p-value	Total deaths (n=949)	Total deaths (n≈1.5 million)	
Cardiovascular	14 (30.4%)	346 (38.3%)	0.28	37.9%	35.9%	0.37
Respiratory	1 (2.2%)	162 (17.9%)	**0.006**	17.2%	12.2%	**0.002**
Cancer	5 (10.9%)	149 (16.5%)	0.31	16.2%	25.6%	**<0.001**
Accident/violent	0 (0.0%)	15 (1.7%)	1.00	1.6%	2.8%	0.06
Dementia	0 (0.0%)	6 (0.7%)	1.00	0.6%	2.4%	**0.001**
Other	4 (8.7%)	88 (9.8%)	1.00	9.7%	21.1%	**<0.001**
Unknown	22 (47.8%)	137 (15.2%)	**<0.001**	16.8%	–	n/a
Total	46 (4.8%)	903 (95.2%)	**<0.001**	100%	100%	n/a

Data are presented as n (%). Statistical significance is at $p<0.05/8=0.0063$. CPAP: continuous positive airway pressure; OSAHS: obstructive sleep apnoea–hypopnoea syndrome; n/a: not applicable.

(OR=2.8, p=0.015 for males, OR=6.7, p=0.004 for females) (table 3). Age and AHI were also predictors of mortality for both sexes. BMI, alcohol consumption and CPAP compliance were predictors of mortality only for males, whereas smoking was a predictor of mortality only for females (table 3).

Figure 1 shows the cumulative survival of patients over long-term follow-up (years), split by CPAP use. No observable difference in survival was noted until t=10 years. After this point, there was a steep decline in survival in the non-CPAP group. Results were similar for each sex separately (supplementary figure 1a and b). The survival curve split by OSAHS severity revealed a significant difference in survival between patients with severe OSAHS, not on CPAP compared to less severe OSAHS (p<0.001) (figure 2). There was no difference in survival between mild, moderate and severe OSAHS in patients on CPAP treatment (p=0.92) (figure 3). These findings were consistent for both males and females (supplementary figures 2a and b and 3a and b).

A significant association was found between CPAP use and length of survival (p<0.001). Those who used CPAP for >5 years were 5.6-times more likely to survive than those not on CPAP (p<0.001). Similarly, the mortality risk ratio showed that those who used CPAP for ⩽5 years were 3.1-times more likely to survive than those in the non-CPAP arm (p<0.001). A statistically significant difference was also found in relative mortality risk between those on long-term and short-term CPAP (RR=1.7, p<0.001) (table 4).

On follow-up, males were more likely to continue using CPAP compared to females (p<0.001) (table 5). Patients not using CPAP were more likely to develop DMII (p=0.003), ischaemic heart disease (IHD) (p<0.001) and suffer myocardial infarction (MI) (p<0.001) (table 5). Weight, BMI, AHI, A+H and OSAHS severity were the most significant predictors of incident DMII, with BMI being a significant predictor for both sexes (supplementary table 6). No significant predictors were identified for hypertension (HTN) incidence (supplementary table 7), whereas age, smoking and CPAP compliance were significant predictors of incident IHD in males (supplementary table 8).

Multivariate logistic regression analysis demonstrated that higher AHI was a significant predictor of adherence to CPAP treatment (OR=1.02, 95% CI: 1.01–1.03, p=0.001) (supplementary table 9). Patients with inability to fall asleep because of CPAP use were 2.99-times less likely to adhere to CPAP treatment (95% CI: 1.64–5.48, p<0.001) (supplementary table 10). Mask issues led to 3.17-times less adherence to CPAP treatment (95% CI: 1.68–5.99, p<0.001), while the strongest predictor of nonadherence was a bed partner's annoyance at the noise of the CPAP machine, with lowered adherence of 4.39-times (95% CI: 2.13–9.07, p<0.001) (supplementary table 10). No comorbidity increased CPAP treatment adherence. However, respiratory comorbidity and MI lower adherence 1.46 (95% CI: 1.22–1.76, p<0.001) and 2.17 (95% CI: 1.59–2.98, p<0.001) times respectively (supplementary table 11).

TABLE 3 Results of logistic regression analysis affecting survival split by sex

Variable	Males			Females		
	OR	95% CI	p-value	OR	95% CI	p-value
Age years	1.10	1.07–1.13	**<0.001**	1.12	1.06–1.18	**<0.001**
Weight kg	1.00	0.97–1.03	0.97	1.00	0.97–1.04	0.79
BMI kg·m^{-2}	1.05	1.01–1.10	**0.034**	1.00	0.82–1.23	0.97
Smoking cigarettes per day	1.00	0.98–1.02	0.97	1.03	1.01–1.06	**0.037**
Alcohol units per week	1.02	1.01–1.04	**0.010**	1.01	0.91–1.12	0.86
ESS (n/24)	1.01	0.97–1.06	0.58	1.09	0.99–1.19	0.07
AHI (n)	1.02	1.01–1.03	**0.014**	1.02	1.01–1.03	**0.012**
OSAHS severity (mild/moderate/severe)	2.11	0.91–4.93	0.07	1.94	0.41–9.21	0.21
CPAP use (yes/no)	16.77	6.21–45.32	**<0.001**	10.94	3.16–37.82	**<0.001**
CPAP hours per night	1.31	1.19–1.44	**<0.001**	1.13	0.94–1.36	0.18
Type II diabetes mellitus (yes/no)	2.74	1.22–6.19	**0.015**	6.71	1.83–24.60	**0.004**
Respiratory condition (yes/no)	1.36	0.76–2.42	0.30	1.18	0.41–3.39	0.77
Depression/anxiety (yes/no)	1.36	0.68–2.74	0.39	1.22	0.37–3.99	0.74
Angina (yes/no)	2.56	0.66–9.85	0.17	4.33	0.67–28.09	0.12
Hypertension (yes/no)	1.18	0.67–2.08	0.56	1.36	0.47–3.93	0.57
Myocardial infarction (yes/no)	1.04	0.44–2.45	0.92	1.68	0.23–12.46	0.62

OR: odds ratio; CI: confidence intervals; BMI: body mass index; ESS: Epworth sleepiness scale; AHI: apnoea–hypopnoea index; OSAHS: obstructive sleep apnoea–hypopnoea syndrome; CPAP: continuous positive airway pressure.

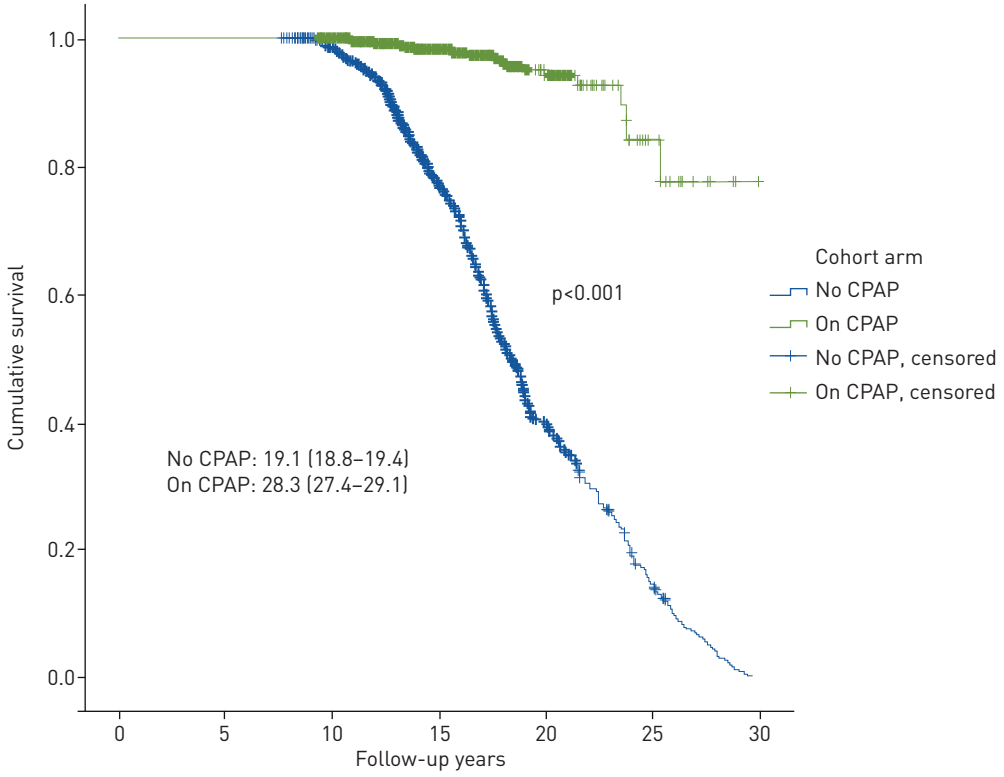

FIGURE 1 Survival curve showing cumulative survival in years, split by continuous positive airway pressure (CPAP) use.

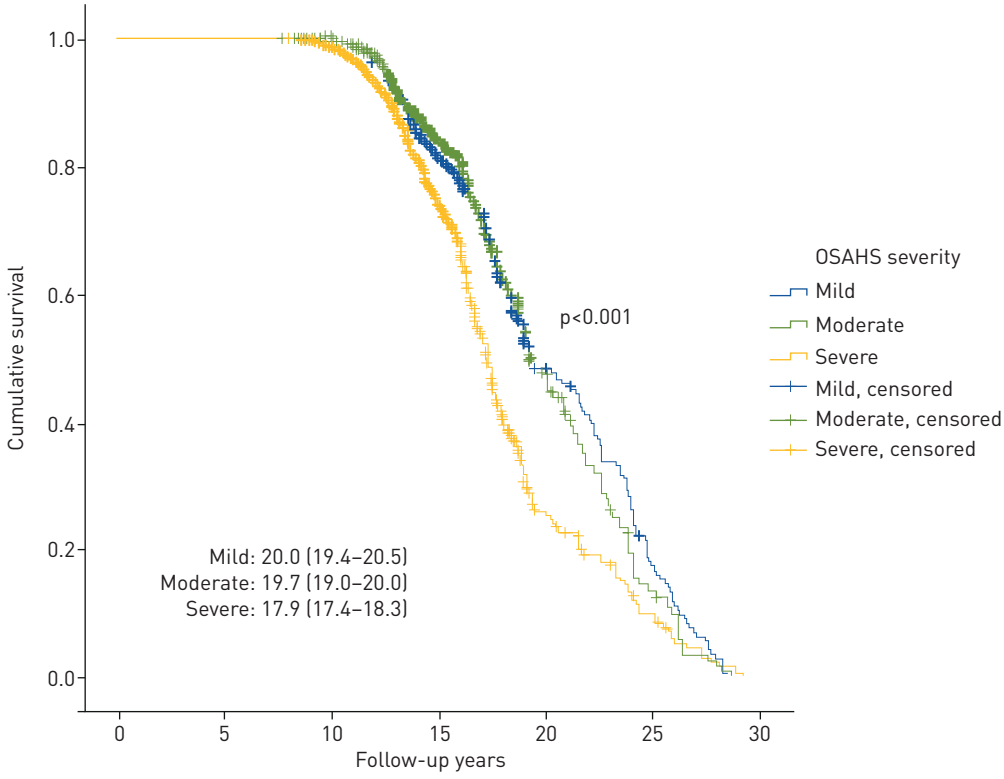

FIGURE 2 Survival curve showing cumulative survival in years, split by obstructive sleep apnoea–hypopnoea syndrome (OSAHS) severity in patients who were not on treatment with continuous positive airway pressure (CPAP).

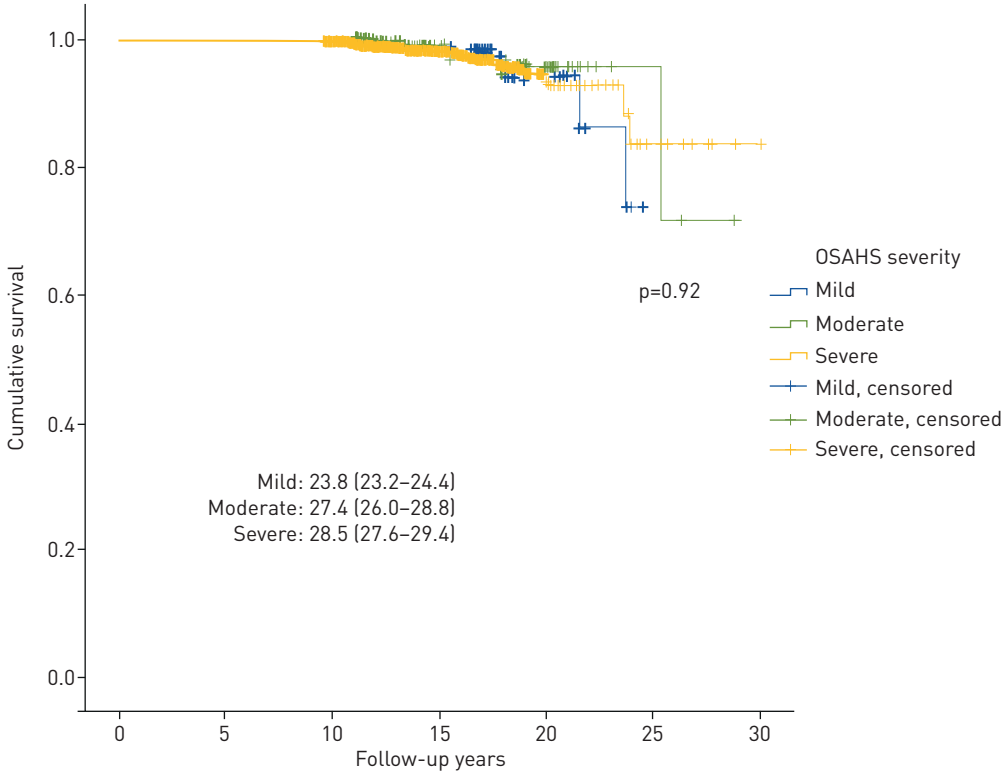

FIGURE 3 Survival curve showing cumulative survival in years, split by obstructive sleep apnoea–hypopnoea syndrome (OSAHS) severity in patients under continuous positive airway pressure (CPAP) treatment.

Discussion

This study investigated factors affecting morbidity, mortality and adherence to CPAP treatment in a cohort of OSAHS patients over an average follow-up period of 14.8±3.7 years. The main outcome was that CPAP use reduced mortality and had a protective role in the incidence of DMII and cardiovascular comorbidities. These observations have been well established by several previous cohort studies [3–5, 15–18]. Nevertheless, our study is the first to use imputation analysis in order to emulate a randomised, controlled trial. This allows for removal of biases, namely immortal time bias on follow-up, a common flaw in previous cohort studies.

We demonstrated that both long-term (>5 years) and short-term (⩽5 years) CPAP use substantially reduced risk of death compared to non-CPAP use. Moreover, long-term CPAP use was significantly more protective, regarding the risk of death, when compared to short-term use. This suggests that the benefits of CPAP increase with longer-term use. The protective role of CPAP was evidenced by the fact that 95.2% of deaths during the study period were in the No-CPAP arm of the cohort. CPAP use was a very strong predictor for mortality in both males (OR=16.8) and females (OR=11).

TABLE 4 Results of imputation analysis of CPAP use and long-term survival in 4502 patients

CPAP use ratio	Relative risk of mortality ratio	Lower 95% CI	Upper 95% CI	p-value
No use/short-term use	3.14	2.69	3.66	**<0.001**
No use/long-term use	5.63	4.83	6.58	**<0.001**
Short-term use/long-term use	1.74	1.49	2.02	**<0.001**

No use is defined as: patients who refused CPAP treatment (n=447). Short-term use is defined as: patients who used CPAP for ⩽5 years. Long-term use is defined as: patients who used CPAP for > 5 years CPAP: continuous positive airway pressure, CI: confidence interval.

TABLE 5 Comparison of comorbidities at follow-up by CPAP use and by sex

Comorbidities	On CPAP (n=895, 76.2%)			No CPAP (n=279, 23.8%)			p-value
	Male (n=774, 86.5%)	Female (n=121, 13.5%)	p-value	Male (n=215, 77.1%)	Female (n=64, 22.9%)	p-value	**<0.001**
Type II diabetes mellitus	121/649 (18.6%)	20/105 (19.1%)	0.50	45/168 (26.8%)	17/54 (31.5%)	0.92	**0.003**
Hypertension	138/621 (22.2%)	15/80 (18.8%)	0.48	37/186 (19.9%)	14/59 (23.7%)	0.53	0.74
Ischaemic heart disease	82/659 (12.4%)	14/98 (14.3%)	0.61	47/161 (29.2%)	5/43 (11.6%)	0.20	**<0.001**
Angina	65/655 (9.9%)	13/97 (13.4%)	0.29	16/138 (11.6%)	2/40 (5.0%)	0.22	0.92
Myocardial infarction	29/659 (4.4%)	3/102 (2.9%)	0.49	35/198 (17.7%)	3/60 (5%)	0.02	**<0.001**
Heart failure	26/698 (3.7%)	4/107 (3.7%)	1.00	9/187 (4.8%)	0/57 (0.0%)	0.09	0.98
Atrial fibrillation	65/480 (13.5%)	6/67 (9.0%)	0.30	28/141 (19.9%)	7/41 (17.1%)	0.69	0.04
Stroke	43/721 (6.0%)	13/113 (11.5%)	0.03	23/204 (11.3%)	4/60 (6.7%)	0.30	0.06
Transient ischaemic attack	77/733 (10.5%)	12/108 (11.1%)	0.85	27/205 (13.2%)	5/60 (8.3%)	0.31	0.50
Smoking	44/312 (14.1%)	6/48 (12.5%)	0.77	18/99 (18.2%)	1/26 (3.9%)	0.07	0.72
Asthma	35/650 (5.4%)	10/81 (12.4%)	0.01	8/179 (4.5%)	5/47 (10.6%)	0.11	0.82

Data are presented as n/N (%). Statistical significance is at p<0.05/12=0.004. CPAP: continuous positive airway pressure.

Previous cohort studies have shown female patients to have a lower morbidity and mortality rate than males [3, 4], while CPAP use has been shown to improve survival in male patients but not in females [4, 5]. The results of our study demonstrate that females with OSAHS are at least as much at risk of death as males and that CPAP use has a protective role in females too. Our findings mirror those reported by Campos-Rodriguez *et al.* [17] reporting exclusively on females. A significant contributor to that could be the fact that our cohort included a notable proportion of professional drivers who were mainly males and had higher rates of adherence to CPAP treatment.

Cardiovascular and respiratory events were the main causes of death among OSAHS patients, more common compared to the general population. The relationship between OSAHS and cardiovascular mortality has been demonstrated in previous studies [3, 5, 15–18]. However, many previous studies were methodologically limited, only including observational data and retrospective study designs. In this study, the creation of clones allowed study participants to be compared against 'healthy controls'. CPAP use in OSAHS has a protective role against all-cause mortality as shown in this study and by others [19–21]. In our study, respiratory events were a statistically significant more common cause of death among OSAHS patients compared to the general population and CPAP use seemed to play a protective role (p=0.006). We speculate that referral bias would have played a strong role in this observation, as the sleep centre was initially a respiratory clinic, established in 1982, gradually evolving over the following decades. Changes in lifestyle, health behaviour and the absence of many guidelines for positive pressure ventilation in respiratory patients in the past may have also contributed to these results. By contrast, death from cancer was significantly less common in OSAHS patients, a finding inconsistent with the results of several studies published in the last 5 years [22–26].

At baseline, mean BMI was 31.8 $kg \cdot m^{-2}$ and 33.6 $kg \cdot m^{-2}$ in males and females respectively, indicating obesity. Obesity has been linked to incident DMII, HTN and cardiovascular disease [27]. DMII was significantly more prevalent in OSAHS patients not receiving CPAP therapy. Males and females who developed diabetes were significantly heavier and had a higher mean AHI than those who did not develop diabetes at follow-up. The mean BMI of all patients who developed DMII at follow-up and those who did not were both in the obese range, which suggests there are more complex factors at play, including baseline genetic and epigenetic risks, lifestyle, exercise and ethnic differences. Previous studies have shown a dose–response relationship between OSAHS severity and blood pressure [28, 29]. In this cohort, no significant predictors were identified for HTN incidence.

There is limited evidence in the literature for the association between smoking and OSAHS [30]. However, smoking is a well-known risk factor for cardiovascular disease, such as IHD. As OSAHS greatly increases a patient's cardiovascular risk, it can be speculated that smoking may add to and interact with this increased risk. This was confirmed in the present study which demonstrated that smoking was an independent predictor of mortality for females with OSAHS and a predictor of developing IHD in patients with OSAHS, both male and female. Marin *et al.* [5] first reported increased cardiovascular mortality risk with severe OSAHS, which normalised with CPAP therapy. Our cohort reflects these results, as OSAHS patients without CPAP therapy had a significantly greater incidence of IHD and MI. In this cohort, no significant association was found between OSAHS and risk of stroke. Current understanding of this association is unclear, with CPAP treatment of OSAHS in stroke patients remaining controversial [31].

With regard to CPAP adherence, a higher AHI and fewer comorbidities were significantly more likely to predict better long-term use in both males and females.

Proportionally, fewer women were entered into the study than men, which may have skewed some of the comparative findings between the sexes. Recruitment was undertaken during a period when sleep medicine was just climbing out of its infancy and general awareness may not have been so great, particularly among females as well as referring doctors. Therefore, conclusions drawn from these results may be potentially less reliable. Since patients cannot ethically be randomised to the non-CPAP group, we relied upon refusal of treatment to create the 'No-CPAP' variable. This created a smaller sample size than the CPAP group, possibly decreasing the reliability of our results by introducing type 2 errors. This could have also introduced participant bias as non-CPAP users may have different needs, lifestyle choices, personality types compared to CPAP users. It has been shown in previous studies that personality type may play a significant role in CPAP adherence [32]. More specifically, patients with type D personality, assessed using a 14-item questionnaire, the Type D Scale (DS14) [33], have poor compliance with treatment in general [33], and particularly in the case of OSAHS, patients with type D personality are less likely to adhere to CPAP and mandibular advancement devices (MADs) compared to those who do not have type D personality [34, 35]. Patients with OSAHS with type D personality use their CPAP less than non-type D personality OSAHS patients by 2 h per night (4 h *versus* 6 h) and are 45% less likely to use their MAD treatment [34–36]. It has also been shown that OSAHS patients with higher scores on the depression and hypochondriasis scales of the Minnesota Multiphasic Personality Inventory have lower adherence to CPAP treatment [37]. Incomplete questionnaires and potential recall bias meant that not all variables were available for each patient making sample sizes smaller than anticipated and occasionally not adequately powered. Responder bias cannot be excluded from the follow-up cohort due to the low response rate for the follow-up questionnaires (26%).

In conclusion, CPAP use is a significant predictor of long-term mortality and morbidity in the OSAHS population. This was confirmed using imputation analysis, to allow for immortal time bias removal. Emphasising the importance of diagnosing OSAHS and adherence to CPAP, in the form of public health initiatives may be beneficial in reducing cardiometabolic disease burden in the community.

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Data availability: We are happy to share data upon written request and on the approval of the corresponding author.

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