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Original research

Cardiovascular outcomes in obstructive sleep apnoea and implications of clinical phenotyping on effect of CPAP treatment

Pei-Hang Xu,[1,2] Daniel Y T Fong,[3] Macy M S Lui,[2] David C L Lam,[2] Mary Sau Man Ip [ID] [2,4]

[1]Division of Pulmonary and Critical Care Medicine, the First Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China
[2]Division of Respiratory and Critical Care Medicine, Department of Medicine, LKS Faculty of Medicine, Queen Mary Hospital, University of Hong Kong, Hong Kong, China
[3]School of Nursing, LKS Faculty of Medicine, University of Hong Kong, Hong Kong, China
[4]Division of Respiratory Medicine, Department of Medicine, University of Hong Kong-Shenzhen Hospital, Shenzhen, China

Correspondence to
Professor Mary Sau Man Ip, Division of Respiratory and Critical Care Medicine, Department of Medicine, LKS Faculty of Medicine, Queen Mary Hospital, University of Hong Kong, Hong Kong, China; msmip@hkucc.hku.hk

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ABSTRACT

Background There is a growing awareness of the heterogeneity of obstructive sleep apnoea (OSA). Clinical trials of CPAP treatment on cardiovascular protection have been mostly negative. We aimed to assess the association between polysomnographic parameters and incident major adverse cardiovascular events (MACEs), and to investigate if the CPAP effect could be better delineated among clinical subgroups.

Methods This sleep cohort study was conducted using a clinical database and territory-wide electronic health administration data in Hong Kong. Cox regressions were used to calculate HRs. Latent class analysis was used to cluster patients with OSA according to clinical and polysomnographic features.

Results Of 1860 eligible Chinese subjects who underwent polysomnography (2006–2013), 1544 (83%) had OSA. Over median follow-up of 8.3 years, 278 (14.9%) experienced MACEs. Apnoea–hypopnoea index (AHI) did not predict MACEs (HR: 0.95; 95% CI 0.76 to 1.17), whereas sleep time with oxygen saturation <90% (TST90) (HR: 1.41; 95% CI 1.10 to 1.81) was an independent predictor of MACEs, as were wake and nocturnal heart rate. In moderate–severe OSA (n=1108) who were indicated for CPAP treatment, regular CPAP was not associated with reduction of incident MACEs. Further cluster analysis identified a subgroup (n=333) who was younger, more obese, had more severe OSA (higher AHI and TST90) and more cardiovascular risks, in whom regular CPAP was associated with a lower risk of MACEs (HR:0.49, 95% CI 0.25 to 0.95).

Conclusions OSA-related TST90 and mean heart rate, but not AHI, were robust predictors of MACEs. A clinical phenotype subgroup who demonstrated beneficial effect of CPAP treatment was identified.

Key messages

What is the key question?
⇒ Can routine polysomnographic (PSG) data independently predict cardiovascular endpoints, and would long-term CPAP treatment of obstructive sleep apnoea (OSA) according to widely used PSG and/or other clinical parameters be associated with lower risk of adverse cardiovascular events?

What is the bottom line?
⇒ Sleep-apnoea related hypoxia and mean heart rate, but not apnoea–hypopnoea index (AHI) are likely to be dominant predictors of adverse cardiovascular outcomes. Not all patients with moderate–severe OSA according to AHI criteria benefited uniformly from regular CPAP therapy, but those who were younger with greater nocturnal hypoxaemia, higher AHI and other concurrent cardiovascular risk factors demonstrated a lower incidence of cardiovascular events with regular CPAP treatment.

Why read on?
⇒ Data from clinical trials has been controversial and largely negative regarding cardiovascular protection, and this study addresses the prognostication ability of different sleep indices as well as differential patient cluster response to CPAP therapy in terms of incident major cardiovascular events using a sleep clinic population.

INTRODUCTION

Untreated obstructive sleep apnoea (OSA) is believed to lead to a cluster of serious adverse health sequelae, particularly in the context of cardiovascular morbidity and mortality.[1] Many OSA cohorts studying cardiovascular endpoints have drawn positive conclusions or at least in some OSA subgroups.[2–6] However, the modifying effect of CPAP treatment of OSA on cardiovascular outcomes is highly controversial. Several large randomised controlled trials (RCTs) have reported negative results, in terms of either primary or secondary cardiovascular prevention by treatment of OSA with CPAP.[7–10]

To date, the apnoea–hypopnoea index (AHI) remains the key parameter on which severity of OSA is categorised, in turn guiding physician prescription for CPAP therapy. However, it has long been observed that the pathophysiology downstream of sleep disordered breathing resulting in adverse health outcomes may not be adequately reflected by AHI on polysomnograms (PSG).[11] Furthermore, due to the heterogeneity among OSA subjects, it is increasingly recognised that the effect of CPAP on health outcomes may not be uniform across the entire spectrum of OSA population. The aims of the

current study were to determine the association between various polysomnographic measures of OSA and incident major adverse cardiovascular events (MACEs) in a sleep clinic cohort, and to evaluate the impact of CPAP therapy which has been prescribed per usual criteria in consensus recommendations, based on consideration of AHI, symptoms and background cardiovascular disease (CVD) risks.[12]

METHODS

Study design and subjects

This was a clinic-based retrospective cohort study. The target cohort was drawn from those seen at the Department of Medicine, and received first diagnostic sleep studies between 1 January 2006 and 31 December 2013 at the Ho Ting Sik Sleep Disorders Centre, Queen Mary Hospital. Subjects were excluded if they had non-Chinese ethnicity; sleep disorders other than OSA; invalid or incomplete record; treatment other than CPAP; or conditions with known effect on OSA.

Data sources

Baseline clinical data were derived from protocolised questionnaires implemented as part of clinical routine to all subjects undergoing sleep studies (see online supplemental materials for details of variables).

Follow-up data were drawn from the Hong Kong Hospital Authority (HA) Clinical Management System up to the day of data entry. This territory-wide system covers all electronic patient records (ePR) of those who attend HA healthcare facilities (hospitals and clinics). CPAP adherence data were extracted from both the ePR and paper records which would contain periodic objective data from CPAP device and protocolised nurse evaluation of CPAP usage. The details of data acquisition regarding this historical cohort have been published previously.[13]

Overnight PSG data have been stored on electronic files and were manually scored or rescored according to American Academy of Sleep Medicine 2012 criteria.[14]

CPAP compliance

For this study, CPAP compliance was dichotomised into regular use or not. Regular use was defined as average use ≥4 hours/night for >70% of the follow-up period, or on average of >4 hours per night (for CPAP devices which only provided cumulative hours of use), and these patients were classified as 'treated'. Others with no or less than regular use, or defaulted CPAP clinic follow-up, were classified as 'untreated'.

Study outcome

The primary outcome was time from the baseline diagnostic PSG to the first confirmed (adjudicated) event of the MACE composite endpoint. Fatal MACEs were deaths from CVDs. Non-fatal MACEs were defined as the first hospitalisation due to acute coronary syndrome (acute myocardial infarction and unstable angina), revascularisation procedures (percutaneous coronary intervention and coronary artery bypass grafting), stroke or exacerbation of congestive heart failure. Censoring occurred on the day of data entry for those who did not develop the outcome of interest, or last clinical visit for those lost to follow-up or the date of death whichever occurred first.

Statistical analysis

Sleep and other measures were summarised using summary statistics. Bonferroni adjustment for multiple tests was applied for comparison within cluster groups. Multiple imputation was

conducted to handle missing data. Cox regression models were constructed to assess the association between OSA and MACEs in the entire dataset and the untreated subgroup. Multivariable models were estimated with adjustment for known cardiovascular risk factors captured in the study (see table 1 and online supplemental material).

To investigate the effect of CPAP therapy on MACEs, Cox regression on CPAP compliance, with and without adjustment of potential confounders was conducted. We further used the latent class analysis (LCA)[15] to cluster the patients with moderate–severe OSA into subgroups based on the most informative indicators which were selected from least absolute shrinkage and selection operator (LASSO) regression.[16]

Sensitivity analyses included the following: Fine and Gray regressions were processed to treat 96 competing deaths rather than censoring; landmark analyses were performed at half year and 1 year (landmark time) to avoid the potential immortal time bias introduced by CPAP compliance; the associations between PSG parameters and MACEs was evaluated in the subgroup of non-obese OSA subjects and the outcome of non-fatal MACEs; for a unified presentation of the results, the findings were shown by a single imputed dataset. Analyses in different multiple-imputed datasets or complete-data analysis were also conducted.

Results from Cox regression were presented as HR with 95% CI. All statistical analyses were conducted using R (V.3.4.3). Details of statistical analysis are provided in the online supplemental file.

RESULTS

Sample characteristics

From 2006 to 2013, 2880 cases underwent PSG at our sleep clinic, and 1860 subjects meeting the criteria were included in the analysis (figure 1). Clinical characteristics of the sample are summarised in table 1. A total of 1236 (66.5%) were men, with a mean age of 52.4±12.2 years, mean BMI of 27.7±5.3 kg/m^2 (obesity is defined as BMI ≥25 kg/m^2 for subjects in Hong Kong), and median AHI of 21.7/hour. The amount of missing PSG data ranged from 0.16% (Min SpO$_2$) to 3.8% (AHI during rapid eye movement sleep (REM-AHI)). Over a median follow-up of 100 months (IQR, 71–123 months), 278 (14.9%) subjects developed fatal and non-fatal MACEs, giving an incidence rate of 1.95 (95% CI 1.73 to 2.19) per 100 person years.

Of these 278 cases who developed incident MACEs, 56 (20.1%) had acute coronary syndrome, 87 (31.3%) had revascularisation procedure, 54 (19.4%) had stroke, 54 (19.4%) had congestive heart failure and 27 (9.7%) died due to cardiovascular-related cause. Besides, 96 subjects died due to other reasons.

AHI as a predictor of MACEs

The incidence rates of MACEs per 100 person years with (95% CI) in patients with no, mild, moderate or severe OSA were 1.19 (0.82 to 1.66), 1.83 (1.42 to 2.33), 1.93 (1.47 to 2.50) and 2.40 (2.01 to 2.84), respectively, but the risk of MACEs in severe OSA by category was no longer different from no OSA after adjustment. AHI as a continuous variable was significantly associated with incident outcomes in the univariable Cox model (table 2), but the magnitude was reduced after adjustment for age (HR: 1.22, 95% CI 1.23 to 1.46) and was not significant after adjustment for gender, BMI and other cardiovascular confounders (HR: 0.95, 95% CI 0.76 to 1.17).

Table 1 Characteristics of study patients in total and by incident major adverse cardiovascular events (MACEs) (n=1860)

Variables	Total (n=1860)	Incident case (n=278)	Event free (n=1582)	P for difference
Demographics				
Male, n (%)	1236 (66.5%)	200 (71.9%)	1036 (65.5%)	0.042
Age, year	52.4 (12.2)	59.0 (12.2)	51.2 (11.9)	<0.001
Symptom and measures				
BMI, kg/m^2	27.7 (5.3)	28.0 (5.0)	27.7 (5.4)	0.367
Neck circumference, cm	38.4 (4.0)	39.3 (4.7)	38.3 (3.9)	0.001
Waist circumference, cm	93.1 (12.4)	95.2 (11.2)	92.7 (12.6)	<0.001
Hip circumference, cm	99.3 (9.8)	98.5 (9.1)	99.4 (9.9)	0.130
Epworth Sleepiness Scale	8.7 (5.4)	8.4 (5.5)	8.7 (5.3)	0.307
Polysomnogram				
TST, min	422.0 (371.5–458.5)	407.5 (356.0–455.0)	423.0 (373.6–459.0)	0.039
AHI, /hour	21.7 (8.0–46.9)	28.3 (10.3–52.9)	20.5 (7.5–45.8)	0.003
REM-AHI, /hour	30.9 (11.2–54.3)	36.9 (15.0–57.2)	30.0 (10.8–54.0)	0.052
3% ODI, /hour	16.4 (4.8–41.0)	22.9 (8.5–49.3)	15.6 (4.4–39.0)	<0.001
Mean SpO$_2$, %	95.0 (93.7–96.0)	94.7 (93.1–96.0)	95.0 (93.8–96.1)	<0.001
Min SpO$_2$, %	81.0 (71.0–87.0)	79.0 (68.0–86.0)	81.0 (72.0–87.0)	0.005
TST90, min	6.8 (0.7–36.4)	17.1 (1.9–56.9)	5.8 (0.6–30.7)	<0.001
Arousal Index, /hour	19.0 (11.8–31.0)	21.8 (14.0–36.2)	18.4 (11.3–30.2)	<0.001
Mean AHD, s	22.5 (18.9–26.8)	22.2 (18.8–26.4)	22.5 (18.9–26.8)	0.553
Nocturnal MHR, /min	63.8 (58.5–70.1)	65.7 (58.3–71.9)	63.8 (58.5–69.8)	0.048
Wake MHR, /min	69.2 (63.0–75.7)	71.0 (62.9–79.1)	68.9 (63.0–75.3)	0.016
History				
Prior hypertension, n (%)	1187 (63.8%)	229 (63.8%)	958 (60.6%)	<0.001
Prior diabetes, n (%)	586 (31.5%)	138 (31.5%)	447 (28.3%)	<0.001
Fasting glucose, mmol/L	5.4 (4.9–6.5)	5.9 (5.0–7.7)	5.4 (4.9–6.4)	<0.001
Prior hyperlipidaemia, n (%)	614 (33.0%)	116 (33.0%)	498 (31.5%)	0.001
Total cholesterol, mmol/L	4.9 (4.2–5.6)	4.8 (4.1–5.5)	4.9 (4.3–5.6)	0.262
Triglycerides, mmol/L	1.6 (1.1–2.2)	1.6 (1.2–2.3)	1.6 (1.1–2.2)	0.110
Prior CVDs, n (%)	232 (12.5%)	77 (27.7%)	155 (9.8%)	<0.001
Statin use, n (%)	442 (23.8%)	92 (33.1%)	350 (22.1%)	<0.001
Beta blocker use, n (%)	442 (23.8%)	118 (42.4%)	324 (20.5%)	<0.001
Family history of CVD, n (%)	466 (25.1%)	75 (25.1%)	391 (24.7%)	0.467
Cigarette smoking, n (%)				<0.001
No	1262 (67.8%)	161 (57.9%)	1101 (69.6%)	
Former	263 (14.1%)	47 (16.9%)	216 (13.7%)	
Current	332 (17.8%)	69 (24.8%)	263 (16.6%)	
Alcohol use, n (%)				0.014
No	1411 (75.8%)	198 (71.2%)	1213 (76.7%)	
Former	314 (16.9%)	49 (17.6%)	265 (16.8%)	
Current	127 (6.8%)	30 (10.8%)	97 (6.1%)	
Physical activity, n (%)				0.028
Low	1199 (64.5%)	198 (71.2%)	1001 (63.3%)	
Medium	542 (29.1%)	63 (22.7%)	479 (30.3%)	
High	101 (5.4%)	14 (5.0%)	87 (5.5%)	
Education level, n (%)				<0.001
Primary or below	501 (26.9%)	109 (39.2 %)	392 (24.8%)	
Secondary	827 (44.5%)	111 (39.9%)	716 (45.3%)	
Tertiary	529 (28.4%)	57 (20.5%)	472 (29.8%)	

Table 1 Continued

Variables	Total (n=1860)	Incident case (n=278)	Event free (n=1582)	P for difference
Body weight change*, kg	1.4 (6.4)	0.8 (6.2)	1.5 (6.5)	0.127
Regular CPAP use, n (%)	293 (15.8%)	42 (15.1%)	251 (15.9%)	0.818
Follow-up time, months	99.5 (70.6–122.9)	53.9 (26.0–75.7)	104.2 (80.3–125.6)	<0.001

Data are given as mean (SD), median (IQR) or n (%).

Numbers may not add to total because of missing values.

*Body weight change was defined as body weight at endpoint or censoring minus baseline body weight.

AHD, apnoea–hypopnoea duration; AHI, apnoea–hypopnoea index; BMI, body mass index; CVDs, cardiovascular diseases; MACEs, major adverse cardiovascular events; MHR, mean heart rate; ODI, oxygen desaturation index; OSA, obstructive sleep apnoea; REM-AHI, apnoea–hypopnoea index during rapid eye movement sleep; SpO$_2$, peripheral capillary oxygen saturation; TST90, sleep time with oxygen saturation below 90; TST, total sleep time.

Other PSG parameters as predictors of MACEs

Sleep time with oxygen saturation below 90% (TST90), mean heart rate (MHR), oxygen desaturation index (ODI), REM-AHI and arousal index were significant predictors of MACEs in the univariable Cox models. To allow for the non-linear association between TST90 and its HR of MACEs (figure 2). Cubic spline transformations were conducted. TST90, wake MHR and nocturnal MHR remained as independent predictors in the fully adjusted multivariable models, with HR of 1.41 (95% CI 1.10 to 1.81), 1.30 (95% CI 1.12 to 1.50) and 1.27 (95% CI 1.10 to 1.46), respectively (table 2). With additional adjustment in the final model for hip circumference, family history of CVD, educational level, beta blocker and statin use, the risk from TST90 was only marginally attenuated (HR: 1.40, 95% CI 1.09 to 1.80). TST90 did not show any significant interactions with gender and age (p=0.104 and 0.537, respectively), as were MHRs.

To further investigate the impact of PSG parameters on non-fatal MACEs, we performed additional analyses in the entire dataset and CPAP untreated subset (online supplemental table E1). TST90 was a robust significant predictor for non-fatal MACEs (HR: 1.43, 95% CI 1.11 to 1.85). Similar to wake MHR, nocturnal MHR during the PSG study was also predictive of MACEs after full adjustment (HR: 1.25, 95% CI 1.08 to 1.45). The effects of TST90 and MHR in competing risk models had similar HRs to those from the Cox regressions (online supplemental table E2); TST90 and wake MHR were significant predictors for incident MACEs when restricted to non-obese subjects (BMI <25 kg/m^2) (online supplemental table E3).

Association between TST90 and AHI

AHI showed a higher density between 0 and 25/hour with a wide range of TST90 values. On the other hand, TST90 values close
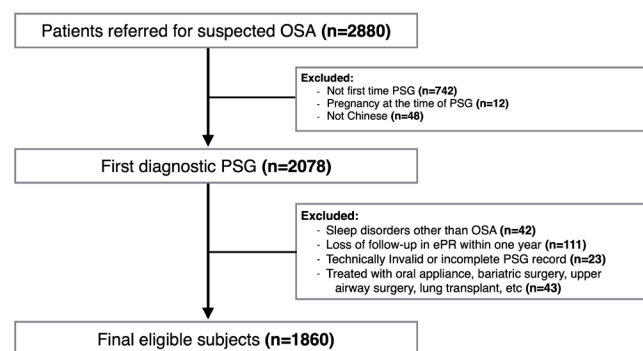
to zero were often seen in combination with a wide range of AHI values (online supplemental figure E1). Further Pearson correlation analysis showed only a mild association between TST90 and AHI (r=0.65, 95% CI 0.62 to 0.68). In multivariable Cox model, entering both TST90 and AHI simultaneously, TST90

Table 2 Cox regression analysis: associations of polysomnographic parameters and incident MACEs

PSG parameters	Univariable model HR (95% CI)	Multivariable model* HR (95% CI)
Total dataset (n=1860)		
AHI (46.9 vs 8.0)	**1.24 (1.05 to 1.45)**	0.95 (0.76 to 1.17)
REM-AHI (54.4 vs 11.1)	1.19 (0.98 to 1.44)	1.03 (0.80 to 1.31)
3% ODI (41.3 vs 4.9)	**1.24 (1.07 to 1.44)**	1 (0.82 to 1.22)
Mean AHD (26.8 vs 18.9)	1.02 (0.88 to 1.18)	0.96 (0.82 to 1.13)
TST90† (36.4 vs 0.7)	**1.10 (1.05 to 1.16)**	**1.41 (1.10 to 1.81)**
Mean SpO$_2$ (96.0 vs 93.7)	0.89 (0.83 to 0.96)	0.99 (0.89 to 1.10)
Min SpO$_2$ (87.0 vs 71.0)	0.86 (0.75 to 0.97)	0.99 (0.85 to 1.15)
Arousal index (30.9 vs 11.8)	**1.18 (1.06 to 1.32)**	1.03 (0.90 to 1.17)
Nocturnal MHR (70.2 vs 58.5)	**1.21 (1.05 to 1.40)**	**1.27 (1.10 to 1.46)**
Wake MHR (75.7 vs 63.1)	**1.24 (1.07 to 1.42)**	**1.30 (1.12 to 1.50)**
Untreated subset (n=1567)		
AHI (39.4 vs 6.3)	**1.31 (1.12 to 1.52)**	0.99 (0.81 to 1.22)
REM-AHI (51.0 vs 8.9)	**1.27 (1.04 to 1.56)**	1.06 (0.82 to 1.38)
3% ODI (34.0 vs 3.8)	**1.29 (1.12 to 1.47)**	1.03 (0.86 to 1.24)
Mean AHD (26.5 vs 18.7)	0.97 (0.83 to 1.14)	0.93 (0.78 to 1.11)
TST90† (25.4 vs 0.3)	**1.09 (1.05 to 1.13)**	**1.46 (1.14 to 1.86)**
Mean SpO$_2$ (96.2 vs 9.0)	0.89 (0.82 to 0.95)	0.99 (0.89 to 1.11)
Min SpO$_2$ (88.0 vs 74.0)	0.82 (0.73 to 0.92)	0.96 (0.83 to 1.10)
Arousal index (27.4 vs 11.0)	**1.23 (1.11 to 1.37)**	1.08 (0.95 to 1.22)
Nocturnal MHR (70.0 vs 58.6)	**1.29 (1.12 to 1.49)**	**1.33 (1.15 to 1.54)**
Wake MHR (75.7 vs 63.0)	**1.33 (1.15 to 1.54)**	**1.38 (1.19 to 1.61)**

These PSG parameters were modelled separately. The PSG variables are compared by 75th versus 25th percentiles.

Bold font indicates statistical significance.

*Multivariable models adjusted for age, gender, body mass index, neck circumference, waist circumference, body weight change, Epworth sleepiness scale, total sleep time, cigarette smoking, alcohol use, physical activity, prior hypertension, prior cardiovascular disease, prior hyperlipidaemia and prior diabetes.

†TST90 with non-linearity was transformed using restricted cubic spline transformation with three knots at default 0.1, 0.5 and 0.9 quantiles.

AHD, apnoea–hypopnoea duration; AHI, apnoea–hypopnoea index; BMI, body mass index; HR, hazard ratio; MACEs, major adverse cardiovascular events; MHR, mean heart rate; ODI, oxygen desaturation index; OSA, obstructive sleep apnoea; PSG, polysomnography; REM-AHI, apnoea–hypopnoea index during rapid eye movement sleep; SpO$_2$, peripheral capillary oxygen saturation; TST90, sleep time with oxygen saturation below 90%; TST, total sleep time.

Patients referred for suspected OSA **(n=2880)**

Excluded:
- Not first time PSG **(n=742)**
- Pregnancy at the time of PSG **(n=12)**
- Not Chinese **(n=48)**

First diagnostic PSG **(n=2078)**

Excluded:
- Sleep disorders other than OSA **(n=42)**
- Loss of follow-up in ePR within one year **(n=111)**
- Technically invalid or incomplete PSG record **(n=23)**
- Treated with oral appliance, bariatric surgery, upper airway surgery, lung transplant, etc **(n=43)**

Final eligible subjects **(n=1860)**

Figure 1 Flow chart of the study cohort. ePR, electronic patient record; OSA, obstructive sleep apnoea; PSG, polysomnography.
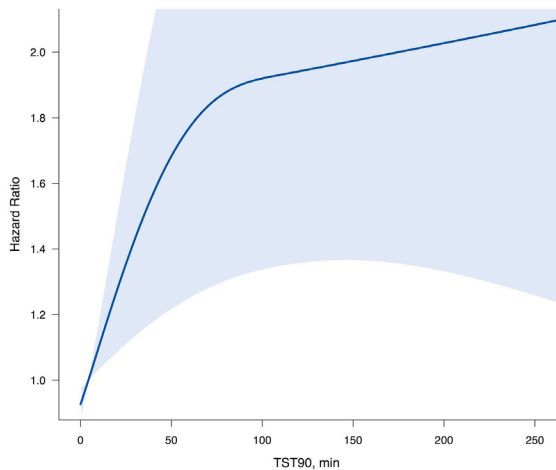
Figure 2 TST90 and its HR with incident MACEs. The model was derived from the fully adjusted Cox regression including a restricted cubic spline term with three knots, restricted to untreated subgroup. The blue shaded curve represents 95% CI. MACEs, major adverse cardiovascular events; TST90, sleep time with oxygen saturation below 90%.

was still a robust predictor of MACEs with a HR of 1.89 (95% CI 1.39 to 2.57), while the HR of AHI was not significant.

Role of CPAP in the incidence of MACEs

Among 1544 patients with AHI≥5/hour, 293 patients had regular long-term CPAP compliance (CPAP-treated group), of which 252 were evaluated for primary prevention, and 41 for secondary prevention. A total of 265 out of 1108 patients with moderate–severe OSA (AHI≥15/hour) were classified as CPAP-treated group. Subjects with regular long-term CPAP compliance were more likely to have higher baseline AHI and more prior diabetes, other baseline characteristics were balanced between CPAP treated and untreated groups (online supplemental table E4).

Compared with the no-OSA (AHI <5/hr) group, a lower hazard risk was observed in patients with moderate–severe OSA who were adherent to CPAP treatment. However, the difference was attenuated after adjustments, with HR of 0.93 (95% CI 0.56 to 1.56) in treated group versus HR of 1.02 (95% CI 0.67 to 1.55) in untreated group (Log-rank test, p=0.20) (table 3). The model was refitted with exclusion of those who defaulted sleep clinic follow-up (n=134) and those with irregular CPAP use (n=164), and results did not change significantly.

Secondary analysis by a two-stage LASSO-LCA algorithm was conducted for cluster profile identification, which followed by Cox regression to interrogate the response of CPAP treatment on different clusters for the outcome of MACEs. The first stage LASSO using all patients' characteristics identified nine robust indicators (online supplemental figure E2). Three additional cardiovascular risk factors (AHI, BMI and waist circumference) were considered based on published literature, thus finalising on 12 indicators for further clustering analysis. LCA revealed that models with four distinct clusters had the best fit (BIC=116 995.2). These subgroups were distinguished notably by age, gender, obesity, OSA severity and comorbidities. The radar chart graphically showed that cluster 1 (n=333, 30% of the moderate–severe OSA cohort) was characterised by significantly younger patients with obesity, with the highest severity of OSA and more comorbidities (table 4 and figure 3). In this cluster, compared with the untreated group, the CPAP-treated group was significantly associated with reduced risk of incident MACEs (HR: 0.49, 95% CI 0.25 to 0.95) in the univariable Cox model. The effect was tenable after adjustments, with the HR of 0.45 (95% CI 0.23 to 0.90) and the statistical power of 87% (table 5). The finding of differential response to CPAP also had been validated in view of fully adjusted model with interactions between CPAP and by OSA subphenotype (p=0.01). The other three clusters with relatively lower risks did not demonstrate any significant benefit from CPAP treatment. To avoid immortal time bias, landmark analyses were conducted by excluding patients who developed incident MACEs or censored within 6 months and 12 months, similar results were observed (online supplemental table E5).

Table 3 Cox regression analysis: the effect of CPAP on fatal and non-fatal MACEs (n=1860)

	No OSA	Mild OSA	Untreated moderate–severe OSA	Treated moderate–severe OSA
Incident MACEs				
No. of subjects	316	436	843	265
Incident MACEs, n (%)	31 (9.8%)	63 (14.4%)	146 (17.3%)	38 (14.3%)
Unadjusted HR	Ref	1.48 (0.97 to 2.28)	1.90 (1.29 to 2.80)	1.52 (0.95 to 2.45)
Partially adjusted HR*	Ref	1.10 (0.71 to 1.69)	1.06 (0.70 to 1.60)	0.88 (0.53 to 1.45)
Fully adjusted HR†	Ref	1.10 (0.71 to 1.70)	1.02 (0.67 to 1.55)	0.93 (0.56 to 1.56)
Incident non-fatal MACEs				
No. of subjects	316	436	843	265
Incident MACEs, n (%)	29 (9.2%)	60 (13.8%)	138 (16.4%)	38 (14.3%)
Unadjusted HR	Ref	1.51 (0.97 to 2.35)	1.92 (1.28 to 2.86)	1.63 (1.01 to 2.64)
Partially adjusted HR*	Ref	1.13 (0.72 to 1.76)	1.09 (0.71 to 1.67)	0.96 (0.58 to 1.60)
Fully adjusted HR†	Ref	1.13 (0.72 to 1.77)	1.05 (0.68 to 1.63)	1.03 (0.61 to 1.75)

*Partially adjusted for age, gender, body mass index.
†Fully adjusted for age, gender, body mass index, waist circumference, body weight change, Epworth sleepiness scale, total sleep time, cigarette smoking, alcohol use, physical activity, prior hypertension, prior cardiovascular disease, prior hyperlipidaemia and prior diabetes.
CPAP, continuous positive airway pressure; HR, hazard ratio; MACEs, major adverse cardiovascular events; OSA, obstructive sleep apnoea.

Table 4 Characteristics of patients in moderate–severe OSA by clusters (n=1108)

Variables	Cluster 1 (n=333, 30%)	Cluster 2 (n=265, 24%)	Cluster 3 (n=271, 24%)	Cluster 4 (n=239, 22%)	P for difference*
Demographics					
Male, n (%)	258 (77.5%)	168 (63.4%)	224 (82.7%)	177 (74.1%)	<0.001
Age, year	49.6 (12.2)	55.6 (11.5)	52.5 (12.0)	58.0 (11.2)	<0.001
Symptom and measurements					
BMI, kg/m^2	34.7 (5.4)	25.1 (2.8)	30.0 (2.3)	25.5 (2.3)	<0.001
Neck circumference, cm	42.8 (4.2)	36.9 (2.7)	40.8 (2.3)	37.5 (2.3)	<0.001
Waist circumference, cm	108.7 (12.0)	87.4 (6.8)	100.1 (5.4)	88.2 (5.7)	<0.001
Polysomnogram					
AHI, /hour	68.2 (53.7–82.3)	23.1 (18.8–28.4)	35.3 (25.4–46.5)	49.2 (37.8–61.0)	<0.001
TST90, min	111.3 (50.3–200.6)	3.8 (1.4–8.0)	15.6 (6.8–27.5)	40.4 (21.7–68.0)	<0.001
Mean heart rate, /min	69.0 (63.1–75.0)	62.5 (57.5–68.3)	63.6 (57.5–70.5)	64.0 (58.9–70.7)	<0.001
History					
Prior hypertension, n (%)	262 (78.7%)	157 (59.2%)	202 (74.5%)	168 (70.3%)	<0.001
Prior diabetes, n (%)	113 (33.9%)	76 (28.7%)	91 (33.6%)	69 (28.9%)	0.362
Prior CVDs*, n (%)	62 (18.6%)	26 (9.8%)	46 (17.0%)	34 (14.2%)	0.020
Cigarette smoking, n (%)					<0.001
No	229 (73.4%)	200 (74.3%)	160 (74.1%)	241 (59.4%)	
Former	41 (13.1%)	26 (9.7%)	23 (10.6%)	77 (19.0%)	
Current	42 (17.1%)	43 (14.3%)	33 (17.0%)	88 (18.0%)	
Regular CPAP use, n (%)	100 (30.0%)	43 (16.2%)	54 (19.9%)	68 (28.5%)	0.083
Incident MACEs, n (%)	57 (17.1%)	38 (14.3%)	46 (17.0%)	43 (18.0%)	<0.001
Follow-up time, months	93.9 (66.4–117.1)	100.4 (73.3–123.4)	97.7 (69.3–118.0)	94.0 (67.6–119.2)	0.705

Data are given as mean (SD), median (IQR) or n (%).
Characteristics among clusters were compared by analysis of variance or Kruskal-Wallis test for continuous variables and χ^2 test for categorical variables.
*Bonferroni corrected for multiple comparisons (p ≤ (0.05/12)=p ≤ 0.004).
AHI, apnoea–hypopnoea index; BMI, body mass index; CPAP, continuous positive airway pressure; CVDs, cardiovascular diseases; MACEs, major adverse cardiovascular events; OSA, obstructive sleep apnoea; TST90, sleep time with oxygen saturation below 90%.
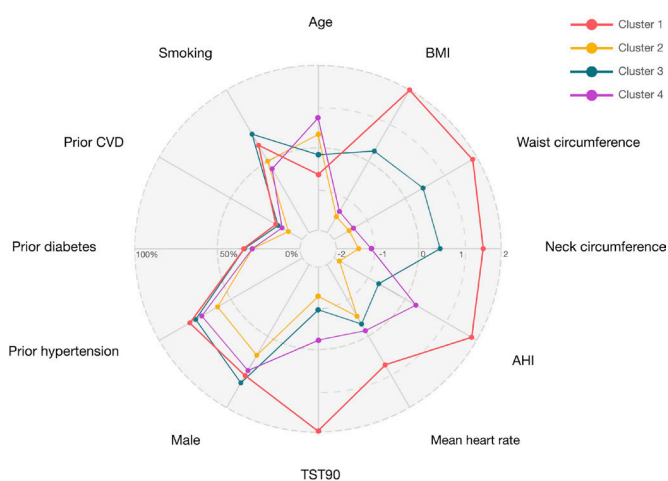

Figure 3 Radar chart comparing 12 characteristics of patients with moderate–severe OSA in each of the four clusters. Since these 12 indicators have different ranges, z-standardised scores were plotted for quantitative variables and proportions for categorical variables to simplify the interpretation of the chart. AHI, apnoea–hypopnoea index; BMI, body mass index; CVDs, cardiovascular diseases; OSA, obstructive sleep apnoea; TST90, sleep time with oxygen saturation below 90%.

Finally, statistical models in other multiple-imputed datasets or complete-case analysis did not change the results significantly. The Cox regression models all satisfied the proportional hazards assumption.

DISCUSSION

In a clinic-based cohort of middle-aged OSA subjects, AHI was not significantly associated with incident MACEs after adjustment for potential confounders. In contrast, TST90 and MHR were independent and significant predictors of the occurrence of fatal and non-fatal MACEs. Regular CPAP treatment was not associated with a lower rate of MACEs, but cluster analysis based on baseline clinical and PSG features identified a high-risk subgroup who could benefit from regular CPAP treatment. The prognostication ability of different sleep indices as well as potential differential patient benefit from CPAP therapy on long-term cardiovascular burden should be elaborated in future OSA studies and clinical practice.

The severity of oxygen desaturation and event duration may vary widely among patients with similar AHI and influence outcomes. In our study, for a TST90 from 0 to 1 min, the AHI ranged from 0 to 76/hour. This broad range and weak correlation represent the diversity of OSA characterisation. TST90 measures the depth and the duration of event-related hypoxia that may not be captured by AHI or ODI. One study suggested

Table 5 Cox regression analysis: the effect of CPAP on MACEs in patients with moderate–severe OSA by clusters (n=1108)

	Cluster 1	Cluster 2	Cluster 3	Cluster 4
No. of subjects	333	265	271	239
Incident MACEs, n (%)	57 (17.1%)	38 (14.3%)	46 (17.0%)	43 (18.0%)
Crude HR	0.49 (0.25 to 0.95)	0.85 (0.33 to 2.19)	0.94 (0.45 to 1.95)	1.18 (0.62 to 2.27)
Adjusted HR*	0.44 (0.22 to 0.85)	0.85 (0.33 to 2.19)	0.85 (0.41 to 1.77)	1.57 (0.79 to 3.13)
Adjusted HR†	0.45 (0.23 to 0.90)	0.79 (0.30 to 2.12)	0.68 (0.31 to 1.45)	1.40 (0.67 to 2.91)

*Adjusted for age, gender and body mass index.
†Adjusted for age, gender, body mass index, waist circumference, neck circumference, AHI, TST90 and mean heart rate.
AHI, apnoea–hypopnoea index; MACEs, major adverse cardiovascular events; OSA, obstructive sleep apnoea; TST90, sleep time with oxygen saturation below 90%.

that nocturnal desaturation, but not the frequency of apnoea, corresponded with the haemodynamic stress in patients with heart failure and had a bearing on cardiovascular outcomes.[17] Similar evidence came from a large clinic cohort in Canada, where the findings endorsed a relationship between the TST90 (but not AHI) and composite cardiovascular events.[18] The 'hypoxic burden' of OSA with the innovative measurement of sleep-event-related area under the oxygen desaturation curve predicted stroke and cardiovascular morbidity more consistently than AHI and ODI.[19–21] On the other hand, a low prognostic value of both AHI and ODI for cardiovascular events was reported in a *post-hoc* analysis of the SAVE study.[22]

AHI is subject to a number of measurement challenges. The choice of oxygen desaturation cut-offs (set at ≥4% or≥3%) to identify hypopnoea could influence the association analyses with clinical outcomes. The Sleep Heart Health Study (SHHS) found that only ≥4%, but not ≥3% desaturation-defined hypopnoea index were associated with hypertension and CVD.[23] Another Spanish cohort found that AHI by either ≥4% or≥3% hypopnoea criterion was appropriate to identify cardiovascular mortality risk in women and elderly, but the AHI definition with ≥3% oxyhaemoglobin desaturation or event-related arousal failed to predict increased risk in the elderly.[24]

The incidence rate of MACEs was 1.95 per 100 person years in our cohort, which is close to the rates from other clinic-based studies with similar cardiovascular outcomes.[2 18] The source of patients, especially the selection of the reference group, might account for the negative associations with AHI in clinic studies. Compared with community cohorts,[4 6 25–28] the control group in clinic cohorts usually have a greater prevalence of concomitant chronic medical conditions and this could attenuate the estimation of exposure-disease association. Furthermore, health literacy and intention to seek medical care of clinic cohort controls tend to be higher than that of community ones, which would render a narrower gap of hospitalisation between severe OSA group and no-OSA controls.

Multiple studies have demonstrated that resting heart rate, one of the simplest measurements, is associated with CVD in the general population.[29 30] Daytime heart rate is susceptible to fluctuations of emotion and activity, whereas nocturnal heart rate has been found to be more related to MACEs,[31 32] which might reflect sympathetic activation and a loss of cardiac reserve in patients with OSA. Sleep-related heart rate variability predicted incident stroke in a French cohort.[21] An increased night-time heart rate through increased sympathetic tone may injure the vascular endothelium and predispose to cardiac arrhythmias.[33 34] In this study, nocturnal hypoxia (TST90) and MHR derived from PSG were the only two significant predictors of long-term risk of MACEs. Our finding has been observed previously in the SHHS, in which the subgroup of patients with OSA with higher

sleep apnoea-specific heart rate response had higher cardiovascular morbidity and mortality, and the hypoxic burden was also particularly high in this subgroup.[35]

The effect of CPAP therapy may provide a viable surrogate for the adverse impact of OSA on cardiovascular endpoint, but results of studies have been limited and inconsistent. The Spanish Zaragoza cohort in men with ten years' follow-up suggested a dramatic modifying effect from CPAP treatment of OSA on CVDs.[2] In contrast, large RCTs of CPAP intervention did not demonstrate a significant cardiovascular risk prevention.[7–10] This discrepancy has stimulated scrutiny of the current understanding of OSA and its health sequelae. It is progressively recognised that OSA is a heterogenous disease and the OSA population even more so with highly variable symptom presentations or comorbidities[36–38]; hence, the adverse health impacts and their prevention by treating OSA may not be uniform across the entire patient spectrum despite the same OSA severity categorised by AHI.

This clinical cohort was prescribed CPAP therapy per consensus recommendations along with international guidelines, thus heavily biased towards those with AHI≥15/hour. As a group, no beneficial effect of regular CPAP treatment on incident MACEs could be demonstrated. However, based on 24 clinical and PSG parameters, further cluster analysis helped to identify one subtyped group of patients with moderate–severe OSA who were clinically indicated for CPAP, and who had a significantly lower incident risk of MACEs over a median of 8 years' CPAP use. Among four clusters of subjects, this group was comparatively younger, more obese, had higher AHI and greater oxygen desaturation (TST90), and had more background comorbidities such as CVD and hypertension. Our findings may reflect that severe OSA with hypoxaemia would be of greater detriment to those with prior cardiovascular comorbidities who would thus also derive more benefit from treatment.[39 40] OSA is a disease of insidious onset, and there is no information regarding prior incubation period. It is plausible that the adverse impact in older subjects is not as well reversed through CPAP use compared with younger counterparts. Much research is needed to delineate the mechanisms of potential adverse cardiovascular impact in the heterogenous OSA population.

Phenotypic characterisation of patients with OSA may identify treatment-responsive clusters, allowing refinement of the therapeutic approach. Our findings of the protective CPAP effect on CVD outcomes in only a phenotypic subgroup of patients resonate with that of the few studies along the same theme. In the SHHS cohort, the excessively sleepy subtype was significantly associated with increased risk of coronary heart disease or heart failure compared with other subtypes, and compared with individuals without OSA (AHI <5/hour), the sleepy subtype had a significantly increased risk for both prevalent and incident

cardiovascular events.[41] The SAVE study did not find a beneficial effect of CPAP therapy in secondary prevention of MACEs over a 3.7 years follow-up,[8] while the post-hoc analyses of the dataset classified four phenotypes based on patients' clinical characteristics, and the subgroups with comorbid diabetes had better response to CPAP compared with those without.[42] In the US veteran cohort study, seven clusters were identified on baseline polysomnographic data, with the 'periodic limb movement in sleep', 'hypopnoea and hypoxia', and 'combined severe' subgroups showing significantly increased risk of adverse cardiovascular outcomes,[43] and the risk of adverse events for regular versus non-regular CPAP use was significantly lower among the first two subgroups.

A single centre for sleep apnoea related data has the benefit of meticulous protocolised collection of demographic, anthropometric and clinical history at first presentation to the sleep clinic and which were all available for the study analysis. We have body weight measurements at both baseline and endpoint (or very close to endpoint) as the surrogate measure of on lifestyle behaviour changes during the follow-up period. In addition, our sample consisted of a considerable number of non-obese OSA subjects, with 34% of subjects (n=624) having BMI <25 kg/m^2, the threshold for defining obesity in this study population. Although adjustments for obesity (BMI) and central obesity (waist circumference) removed much of the OSA signal, nocturnal hypoxia still emerged as an independent predictor for incident MACEs. Further exploration of TST90 by the continuous spectrum showed a non-linear dose–response curve with incident MACEs. This finding could help clinicians for better clinical decision-making according to risk-targeted management.

This study has the limitation of using historical data. The retrospective nature is compensated by abundance of data captured by the comprehensive electronic healthcare record system. In particular, MACEs have the unique advantage of being significant and clearly defined healthcare events and thus very well captured and accurately coded in this territory-wide healthcare administration system. Through the ePR, we have also been able to collect data about beta blocker and statin use, fasting glucose, and lipid profile that may affect the incidence of MACEs. Treatment was non-randomised as expected of a clinical cohort follow-up study, we addressed this issue by fully adjusting our models and further cluster analysis. CPAP usage data were collected with protocolised assessment at clinic follow-up, and given the long course of years of nightly treatment, CPAP adherence was defined by simple dichotomization of an average of greater or less than 4 hours/per night while one should not take this as a rigid cut-off number. Although we have 133 untreated patients with OSA with TST90 >100 min, the limited amount of cases at the tail end resulted in a wide CI of the non-linear dose–response curve.

In conclusion, in a clinic cohort presenting for suspected OSA, AHI in the baseline PSG was not significantly associated with incident MACEs over the median of 8 years follow-up. On the other hand, nocturnal hypoxaemia and mean heart rate documented on the sleep study were better measures regarding the subsequent risk of CVD consequences in this OSA cohort. CPAP treatment of OSA was not associated with risk reduction of incident major cardiovascular events in all those who were treated, but only in a subgroup of moderate–severe OSA characterised by younger age, higher obesity, higher AHI and greater oxygen desaturation, and more baseline CVD risks. The findings further support that awareness of the heterogeneity of OSA would allow for better identification of those at risk of specific adverse health outcomes and those who are most likely to benefit from CPAP treatment.[44]

ORCID iD
Mary Sau Man Ip http://orcid.org/0000-0002-8692-6933

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Supplemental material

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Thorax

Online Data Supplements

Cardiovascular outcomes in obstructive sleep apnoea and implications of clinical phenotyping on effect of continuous positive airway pressure treatment

Pei-Hang Xu; Daniel Yee-Tak Fong; Macy Mei-Sze Lui; David Chi-Leung Lam and Mary Sau-Man Ip

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Thorax

1 **Materials and Methods**

2 **CPAP treatment**

3 Per clinical indication criteria, continuous positive airway pressure (CPAP) therapy

4 was recommended for treatment of moderate to severe obstructive sleep apnoea

5 (OSA) or mild OSA with symptoms or other significant risks [E1]. Patients were

6 followed up at the specialist sleep clinics, usually at 3 and 6 months after CPAP

7 titration, and yearly thereafter, at which both objective (machine-reported) and

8 subjective (self-reported) compliance were assessed.

9

10 **Variables**

11 Available variables were derived from the cohort database for the research purpose:

12 1) Demographics — age and gender; 2) Anthropometric parameters — body mass

13 index (BMI), neck/waist/hip circumferences and body weight change; 3) Epworth

14 sleepiness scale (ESS) scores; 4) Medical history — prior hypertension, prior

15 diabetes, prior hyperlipidaemia, prior cardiovascular disease (CVD),family history of

16 CVD, statin use and beta blocker use; 5) Baseline blood samples — fasting glucose,

17 total cholesterol, triglycerides; 6) Lifestyle behaviour — cigarette smoking, alcohol

18 use, physical activity and educational level; 7) Polysomnographic parameters —

19 apnoea-hypopnoea index (AHI), apnoea-hypopnoea index during rapid eye

20 movement sleep (REM-AHI), total sleep time (TST), sleep time with oxygen

21 saturation below 90% (TST90), oxygen desaturation index (ODI), minimum oxygen

22 saturation (SpO_2), mean SpO_2, nocturnal and wake mean heart rate (MHR), mean

23 apnoea-hypopnoea duration (AHD) and arousal index; 8) CPAP compliance.

24

25 **Statistical analysis**

1   Distribution of covariates and sleep measures were summarized by outcome status.

2   The association between AHI and TST90 was explored with scatter plot with marginal

3   histograms. Mid-*P* test [E1] was used to calculate the 95%CI of incidence rate.

4

5   A series of Kaplan-Meier plots and Cox regression models were constructed to assess

6   the association between OSA and major adverse cardiovascular events (MACEs) in

7   entire dataset and untreated subgroup. To avoid arbitrary cut-off, PSG parameters

8   were modelled as continuous variables, comparing by 75th vs. 25th percentiles.

9   Covariates were chosen *a priori*. Models were estimated with and without adjusting for

10   these covariates. As a secondary endpoint, we analysed the association with

11   incidence of non-fatal MACEs as well.

12

13   To investigate the effect of CPAP therapy on MACEs, Cox regression on CPAP

14   compliance, with and without adjustment of potential confounders, was conducted. We

15   further proposed a two-stage least absolute shrinkage and selection operator

16   (LASSO)-latent class analysis (LCA) algorithm. LASSO regression was used to

17   determine the optimal features for this OSA cohort, which removed redundant and

18   irrelevant features to provide important feature information by penalizing some

19   regression coefficients to zero [E2]. Twenty-four variables had been entered into this

20   selection process in the first stage, including age, gender, BMI, neck circumference,

21   waist circumference, body weight change, ESS, TST, cigarette smoking, alcohol use,

22   physical activity, prior hypertension, prior cardiovascular disease, prior

23   hyperlipidaemia, prior diabetes and PSG parameters (AHI, ODI, TST90, heart rate,

24   REM-AHI, $MinSpO_2$, $MeanSpO_2$, Mean AHD and arousal index). The indicators in

25   cluster analysis were finally selected by the overall consideration. LCA models based

1   on selected features was constructed in the second stage to uncover the hidden

2   clusters with different treatment response [E3]. The "depmixS4" package in R was

3   used to run the data-driven LCA cluster analyses from two to five clusters, and the

4   number of clusters was chosen based on Bayesian Information Criteria and law of

5   parsimony [E4]. In each identified subgroup, Cox models were refitted with additional

6   adjustment for CPAP compliance.

7

8   Multiple imputation was conducted to handle missing data. For a unified presentation

9   of the results, the findings were shown by a single imputed dataset. Analyses in

10   other multiple datasets or complete-data analysis were conducted. Results from

11   Cox-regression were presented as hazard ratio (HR) with 95% confidence interval

12   (CI). *P* values were determined using 2-tailed tests and significance level was set at

13   0.05. All statistical analyses were conducted using R statistical software, version

14   3.4.3 (https://www.r-project.org).

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Table E1. Associations of polysomnographic parameters and incident non-fatal MACEs

PSG parameters	Univariate Model		Multivariable Model*	
	HR (95%CI)		HR (95%CI)	
Total dataset (n=1860)				
AHI (46.9 vs 8.0)	**1.24**	**(1.05-1.47)**	0.97	(0.78-1.21)
REM-AHI (54.4 vs 11.1)	1.17	(0.96-1.43)	1.02	(0.80-1.32)
3% ODI (41.3 vs 4.9)	**1.25**	**(1.08-1.46)**	1.03	(0.84-1.26)
Mean AHD (26.8 vs 18.9)	1.04	(0.90-1.21)	0.99	(0.84-1.16)
TST90[†] (36.4 vs 0.7)	**1.11**	**(1.05-1.16)**	**1.43**	**(1.11-1.85)**
Mean SpO$_2$ (96.0 vs 93.7)	0.89	(0.82-0.96)	0.97	(0.87-1.07)
Min SpO$_2$ (87.0 vs 71.0)	0.84	(0.74-0.96)	0.96	(0.83-1.12)
Arousal index (30.9 vs 11.8)	**1.18**	**(1.05-1.33)**	1.04	(0.90-1.19)
Nocturnal MHR (70.2 vs 58.5)	**1.20**	**(1.04-1.39)**	**1.25**	**(1.08-1.45)**
Wake MHR (75.7 vs 63.1)	**1.22**	**(1.05-1.41)**	**1.27**	**(1.09-1.48)**
Untreated subset (n=1567)				
AHI (39.4 vs 6.3)	**1.31**	**(1.12-1.53)**	1.01	(0.82-1.25)
REM-AHI (51.0 vs 8.9)	**1.25**	**(1.01-1.54)**	1.06	(0.81-1.38)
3% ODI (34.0 vs 3.8)	**1.29**	**(1.12-1.48)**	1.06	(0.87-1.28)
Mean AHD (26.5 vs 18.7)	1.00	(0.85-1.17)	0.95	(0.79-1.15)
TST90[†] (25.4 vs 0.3)	**1.09**	**(1.05-1.13)**	**1.47**	**(1.15-1.88)**
Mean SpO$_2$ (96.2 vs 9.0)	0.88	(0.81-0.95)	0.97	(0.87-1.08)
Min SpO$_2$ (88.0 vs 74.0)	0.81	(0.72-0.92)	0.93	(0.81-1.08)
Arousal index (27.4 vs 11.0)	**1.23**	**(1.11-1.37)**	1.09	(0.95-1.24)
Nocturnal MHR (70.0 vs 58.6)	**1.28**	**(1.11-1.49)**	**1.31**	**(1.12-1.53)**
Wake MHR (75.7 vs 63.0)	**1.32**	**(1.13-1.53)**	**1.35**	**(1.16-1.59)**

These parameters were modelled separately. The PSG variables are compared by 75th vs. 25th percentiles.

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*Multivariable models adjusted for age, gender, body mass index, neck circumference, waist circumference, body weight change, Epworth sleepiness scale, total sleep time, cigarette smoking, alcohol use, physical activity, prior hypertension, prior cardiovascular disease, prior hyperlipidaemia and prior diabetes.

†TST90 with non-linearity was transformed using restricted cubic spline transformation with 3 knots at default 0.1, 0.5 and 0.9 quantiles.

Definition of abbreviations: AHD, apnoea-hypopnoea duration; AHI, apnoea-hypopnoea index; BMI, body mass index; PSG, polysomnography; HR, hazard ratio; MACEs, major adverse cardiovascular events; MHR, mean heart rate; ODI, oxygen desaturation index; OSA, obstructive sleep apnoea; REM-AHI, apnoea-hypopnoea index during rapid eye movement sleep; SpO_2, peripheral capillary oxygen saturation; TST, total sleep time; TST90, sleep time with oxygen saturation below 90%.

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Table E2. Multivariate regression analyses: associations of polysomnographic parameters and incident MACEs (n=1860)

PSG parameters	Cox survival model*		Competing risk survival model*	
	HR (95% CI)		HR (95% CI)	
Total dataset (n=1860)				
AHI (46.9 vs 8.0)	0.95	(0.76-1.17)	0.94	(0.76-1.18)
REM-AHI (54.4 vs 11.1)	1.03	(0.80-1.31)	1.04	(0.80-1.36)
3% ODI (41.3 vs 4.9)	1.00	(0.82-1.22)	0.99	(0.80-1.22)
Mean AHD (26.8 vs 18.9)	0.96	(0.82-1.13)	0.99	(0.84-1.16)
TST90[†] (36.4 vs 0.7)	**1.41**	**(1.10-1.81)**	**1.37**	**(1.07-1.43)**
Mean SpO_2 (96.0 vs 93.7)	0.99	(0.89-1.10)	0.99	(0.89-1.10)
Min SpO_2 (87.0 vs 71.0)	0.99	(0.85-1.15)	1.00	(0.86-1.16)
Arousal index (30.9 vs 11.8)	1.03	(0.90-1.17)	1.04	(0.91-1.19)
Nocturnal MHR (70.2 vs 58.5)	**1.27**	**(1.10-1.46)**	**1.21**	**(1.03-1.42)**
Wake MHR (75.7 vs 63.1)	**1.30**	**(1.12-1.50)**	**1.26**	**(1.08-1.48)**
Untreated subset (n=1567)				
AHI (39.4 vs 6.3)	0.99	(0.81-1.22)	0.99	(0.80-1.23)
REM-AHI (51.0 vs 8.9)	1.06	(0.82-1.38)	1.08	(0.81-1.43)
3% ODI (34.0 vs 3.8)	1.03	(0.86-1.24)	1.02	(0.84-1.25)
Mean AHD (26.5 vs 18.7)	0.93	(0.78-1.11)	0.95	(0.79-1.13)
TST90[†] (25.4 vs 0.3)	**1.46**	**(1.14-1.86)**	**1.35**	**(1.10-1.42)**
Mean SpO_2 (96.2 vs 9.0)	0.99	(0.89-1.11)	1.00	(0.89-1.12)
Min SpO_2 (88.0 vs 74.0)	0.96	(0.83-1.10)	0.97	(0.84-1.12)
Arousal index (27.4 vs 11.0)	1.08	(0.95-1.22)	1.09	(0.95-1.24)
Nocturnal MHR (70.0 vs 58.6)	**1.33**	**(1.15-1.54)**	**1.29**	**(1.09-1.53)**
Wake MHR (75.7 vs 63.0)	**1.38**	**(1.19-1.61)**	**1.35**	**(1.14-1.60)**

These parameters were modelled separately. The PSG variables are compared by 75th vs. 25th percentiles.

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*Models adjusted for age, gender, body mass index, neck circumference, waist circumference, body weight change, Epworth sleepiness scale, total sleep time, cigarette smoking, alcohol use, physical activity, prior hypertension, prior cardiovascular disease, prior hyperlipidaemia and prior diabetes.

[†]TST90 with non-linearity was transformed using restricted cubic spline transformation with 3 knots at default 0.1, 0.5 and 0.9 quantiles.
Definition of abbreviations: AHD, apnoea-hypopnea duration; AHI, apnoea-hypopnea index; BMI, body mass index; PSG, polysomnography; HR, hazard ratio; MACEs, major adverse cardiovascular events; MHR, mean heart rate; ODI, oxygen desaturation index; OSA, obstructive sleep apnoea; REM-AHI, apnoea-hypopnea index during rapid eye movement sleep; SpO_2, peripheral capillary oxygen saturation; TST, total sleep time; TST90, sleep time with oxygen saturation below 90%.

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Table E3. Associations of polysomnographic parameters and incident MACEs in patients with BMI <25kg/m² (n=624)

PSG parameters	Univariate Model		Multivariable Model*	
	HR (95%CI)		HR (95%CI)	
AHI (26.8 vs 3.6)	**1.35**	**(1.05-1.73)**	0.96	(0.72-1.29)
REM-AHI (34.2 vs 4.07)	1.32	(0.97-1.79)	0.96	(0.69-1.36)
3% ODI (17.7 vs 1.6)	**1.26**	**(1.07-1.50)**	0.98	(0.81-1.19)
Mean AHD (28.4 vs 19.9)	0.91	(0.69-1.20)	0.85	(0.61-1.17)
TST90 (8.62 vs 0.0)	**1.07**	**(1.04-1.10)**	**1.03**	**(1.00-1.07)**
Mean SpO₂ (97.0 vs 95.0)	0.70	(0.55-0.89)	0.96	(0.73-1.26)
Min SpO₂ (91.0 vs 79.0)	0.87	(0.69-1.10)	1.14	(0.84-1.55)
Arousal index (30.9 vs 11.8)	**1.18**	**(1.05-1.33)**	1.04	(0.90-1.19)
Nocturnal MHR (68.1 vs 57.6)	1.21	(0.95-1.55)	1.24	(0.97-1.57)
Wake MHR (73.6 vs 62.6)	**1.38**	**(1.09-1.75)**	**1.34**	**(1.06-1.69)**

These parameters were modelled separately. The PSG variables are compared by 75th vs. 25th percentiles.

*Multivariable models adjusted for age, gender, body mass index, neck circumference, waist circumference, body weight change, Epworth sleepiness scale, total sleep time, cigarette smoking, alcohol use, physical activity, prior hypertension, prior cardiovascular disease, prior hyperlipidaemia and prior diabetes.

Definition of abbreviations: AHD, apnoea-hypopnoea duration; AHI, apnoea-hypopnoea index; BMI, body mass index; PSG, polysomnography; HR, hazard ratio; MACEs, major adverse cardiovascular events; MHR, mean heart rate; ODI, oxygen desaturation index; OSA, obstructive sleep apnoea; REM-AHI, apnoea-hypopnoea index during rapid eye movement sleep; SpO₂, peripheral capillary oxygen saturation; TST, total sleep time; TST90, sleep time with oxygen saturation below 90%.

Table E4. Characteristics of CPAP-treated and untreated patients with moderate-severe OSA (n=1108)

Variables	Moderate-severe OSA (AHI≥15/hr)		*p* for difference
	CPAP Untreated (n=843, 76%)	CPAP Treated (n=265, 24%)	
Demographics			
Male, n (%)	617 (73.2%)	210 (79.2%)	0.058
Age, year	53.8 (12.5)	52.9 (11.2)	0.305
Symptom and measures			
BMI, kg/m^2	29.3 (5.6)	29.1 (4.8)	0.566
Neck circumference, cm	39.7 (4.1)	39.9 (3.6)	0.564
Waist circumference, cm	97.1 (12.6)	97.2 (11.2)	0.903
Hip circumference, cm	101.7 (10.4)	101.7 (8.7)	0.945
Epworth sleepiness scale	8.7 (5.4)	9.4 (5.4)	0.060
Polysomnogram			
TST, min	417.5 (367.0-457.5)	424.5 (382.0-459.5)	0.047
AHI, /hr	37.2 (24.6-60.0)	50.4 (35.6-66.7)	<0.001
REM-AHI, /hr	48.5 (29.2-63.4)	52.1 (41.5-65.8)	<0.001
3% ODI, /hr	30.4 (18.0-55.1)	44.8 (27.3-65.2)	<0.001
Mean SpO$_2$, %	94.3 (92.9-95.7)	93.7 (92.0-94.9)	<0.001
Min SpO$_2$, %	76.0 (66.0-82.0)	72.0 (60.0-79.0)	<0.001
TST90, min	20.2 (5.8-58.2)	40.9 (12.2-112.7)	<0.001
Arousal Index, /hr	25.1 (15.6-39.0)	32.3 (21.6-49.4)	<0.001
Mean AHD, sec	22.1 (18.8-26.0)	23.4 (20.3-27.9)	<0.001
Nocturnal MHR, /min	65.2 (59.1-71.5)	65.2 (58.4-71.1)	0.664
Wake MHR, /min	70.2 (63.3-76.8)	70.1 (63.3-77.3)	0.848
History			
Prior hypertension, n (%)	610 (72.4%)	179 (67.5%)	0.152
Prior diabetes, n (%)	290 (34.4%)	59 (22.3%)	<0.001
Fasting glucose, mmol/L	5.5(5.0-6.6)	5.6(5.0-6.2)	0.439
Prior hyperlipidaemia, n (%)	314 (37.2%)	96 (36.2%)	0.820
Total cholesterol, mmol/L	4.9(4.2-5.6)	4.9(4.2-5.4)	0.864
Triglycerides, mmol/L	1.7(1.2-2.3)	1.7(1.2-2.3)	0.983
Prior CVDs, n (%)	130 (15.4%)	38 (14.3%)	0.741
Statin use, n (%)	232 (27.5%)	71 (26.8%)	0.878
Beta blocker use, n (%)	234 (27.8%)	70 (26.4%)	0.728
Family history of CVD, n (%)	198 (23.5%)	78 (29.4%)	0.061
Cigarette smoking, n (%)			0.235
No	527(62.5%)	181(68.3%)	
Former	134(15.9%)	34(12.8%)	
Current	180(21.4%)	50(18.9%)	
Alcohol use, n (%)			0.690
No	614(72.8%)	188(70.9%)	

Former	161(19.1%)	57(21.5%)	
Current	64(7.6%)	19(7.2%)	
Physical activity, n (%)			0.323
Low	553(65.6%)	165(62.3%)	
Medium	235(27.9%)	84(31.7%)	
High	48(5.7%)	11(4.2%)	
Education level, n (%)			0.011
Primary or below	247 (29.3%)	60 (22.6 %)	
Secondary	379 (45.0%)	113 (42.6%)	
Tertiary	216 (25.6%)	91 (34.3%)	
Body weight change[*], kg	1.0 (7.0)	1.9 (6.4)	0.059
Follow-up time, months	97.4 (67.4-118.4)	97.6 (71.3-123.4)	0.251
Incident MACEs, n (%)	146 (17.3%)	38 (14.3%)	0.297

*Body weight change was defined as body weight at endpoint or censoring minus baseline body weight.

Data are given as mean (SD), median (IQR) or n (%). Numbers may not add to total because of missing values.

Definition of abbreviations: AHD, apnoea-hypopnoea duration; AHI, apnoea-hypopnoea index; BMI, body mass index; CVDs, cardiovascular diseases; PSG, polysomnography; MACEs, major adverse cardiovascular events; ODI, oxygen desaturation index; MHR, mean heart rate; OSA, obstructive sleep apnoea; REM-AHI, apnoea-hypopnoea index during rapid eye movement sleep; SpO$_2$, peripheral capillary oxygen saturation; TST, total sleep time; TST90, sleep time with oxygen saturation below 90%.

Table E5. Landmark analysis: the effect of CPAP on MACEs in moderate-severe OSA patients by clusters

	Cluster 1		Cluster 2		Cluster 3		Cluster 4	
Subset of follow-up more than 0 days (n=1108)								
No. of subjects	333		265		271		239	
Incident MACEs, n (%)	57 (17.1%)		38 (14.3%)		46 (17.0%)		43 (18.0%)	
Unadjusted HR	**0.49**	**(0.25 - 0.95)**	0.85	(0.33 - 2.19)	0.94	(0.45 - 1.95)	1.18	(0.62 - 2.27)
Partially adjusted HR*	**0.44**	**(0.22 - 0.85)**	0.85	(0.33 - 2.19)	0.85	(0.41 - 1.77)	1.57	(0.79 - 3.13)
Fully adjusted HR†	**0.45**	**(0.23 - 0.90)**	0.79	(0.30 - 2.12)	0.68	(0.31 - 1.45)	1.40	(0.67 - 2.91)
Subset of follow-up more than 180 days (n=1098)								
No. of subjects	330		263		269		236	
Incident MACEs, n (%)	54 (16.4%)		36 (13.7%)		44 (16.4%)		41 (17.4%)	
Unadjusted HR	**0.46**	**(0.23 - 0.92)**	0.86	(0.34 - 2.23)	0.99	(0.48 - 2.06)	1.14	(0.58 - 2.23)
Partially adjusted HR*	**0.41**	**(0.21 - 0.83)**	0.90	(0.35 - 2.33)	0.90	(0.43 - 1.89)	1.48	(0.73 - 3.01)
Fully adjusted HR†	**0.42**	**(0.21 - 0.86)**	0.84	(0.31 - 2.26)	0.74	(0.34 - 1.60)	1.27	(0.59 - 2.72)
Subset of follow-up more than 365 days (n=1084)								
No. of subjects	324		260		276		233	
Incident MACEs, n (%)	50 (15.4%)		33 (12.7%)		43 (15.6%)		39 (16.7%)	
Unadjusted HR	0.51	(0.25 - 1.01)	0.74	(0.26 - 2.11)	1.02	(0.49 - 2.13)	1.23	(0.62 - 2.42)
Partially adjusted HR*	**0.46**	**(0.23 - 0.92)**	0.75	(0.26 - 2.13)	0.93	(0.44 - 1.94)	1.65	(0.80 - 3.38)
Fully adjusted HR†	**0.47**	**(0.23 - 0.95)**	0.75	(0.25 - 2.24)	0.75	(0.35 - 1.63)	1.47	(0.67 - 3.22)

* Adjusted for age, gender and body mass index.

† Adjusted for age, gender, body mass index, waist circumference, neck circumference, AHI, TST90 and mean heart rate.

Definition of abbreviations: CPAP, continuous positive airway pressure; HR, hazard ratio; MACEs, major adverse cardiovascular events; OSA, obstructive sleep apnoea.
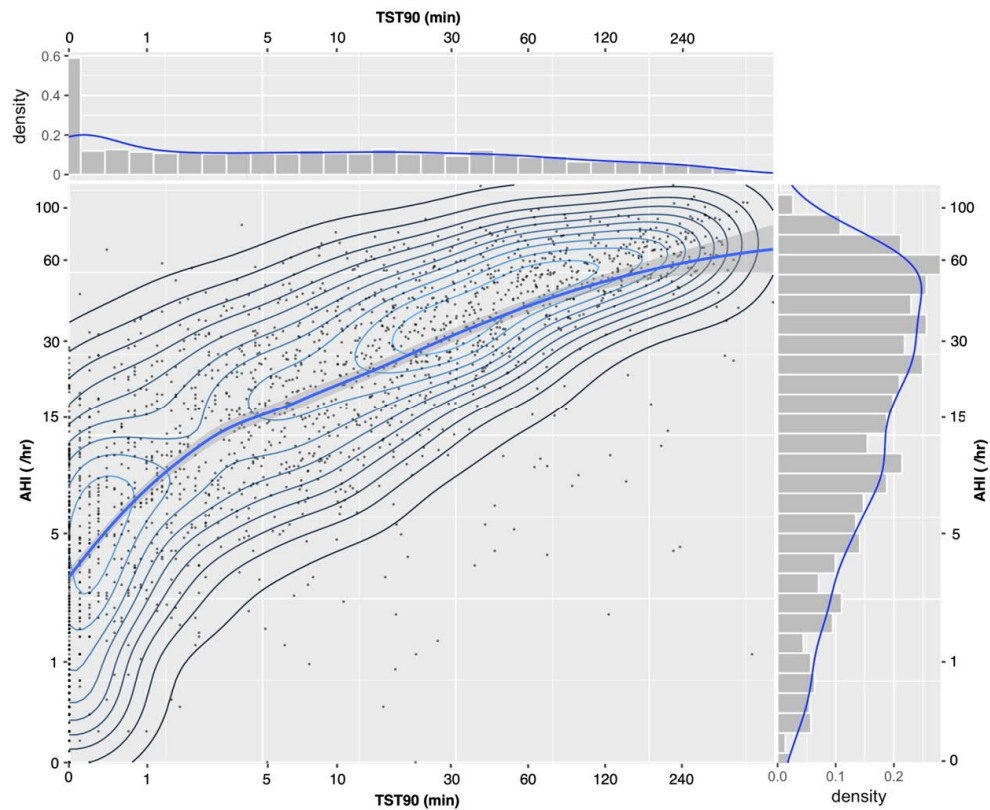
Figure E1. Scatter plot with marginal histograms of AHI and TST90

The contour reflects their distribution and the smoothing curve with 95%CI indicates their association. The log-transformation was used as $log_2(TST90+1)$ and $log_2(AHI+1)$, 1 was added in the arguments to allow for analysis of many zero values. Two OSA measures are mildly correlated, and variability is high. A short duration of TST90 near zero is frequently observed in combination with a wide range of AHI values. AHI, apnoea-hypopnoea index; TST90, sleep time with oxygen saturation below 90%.
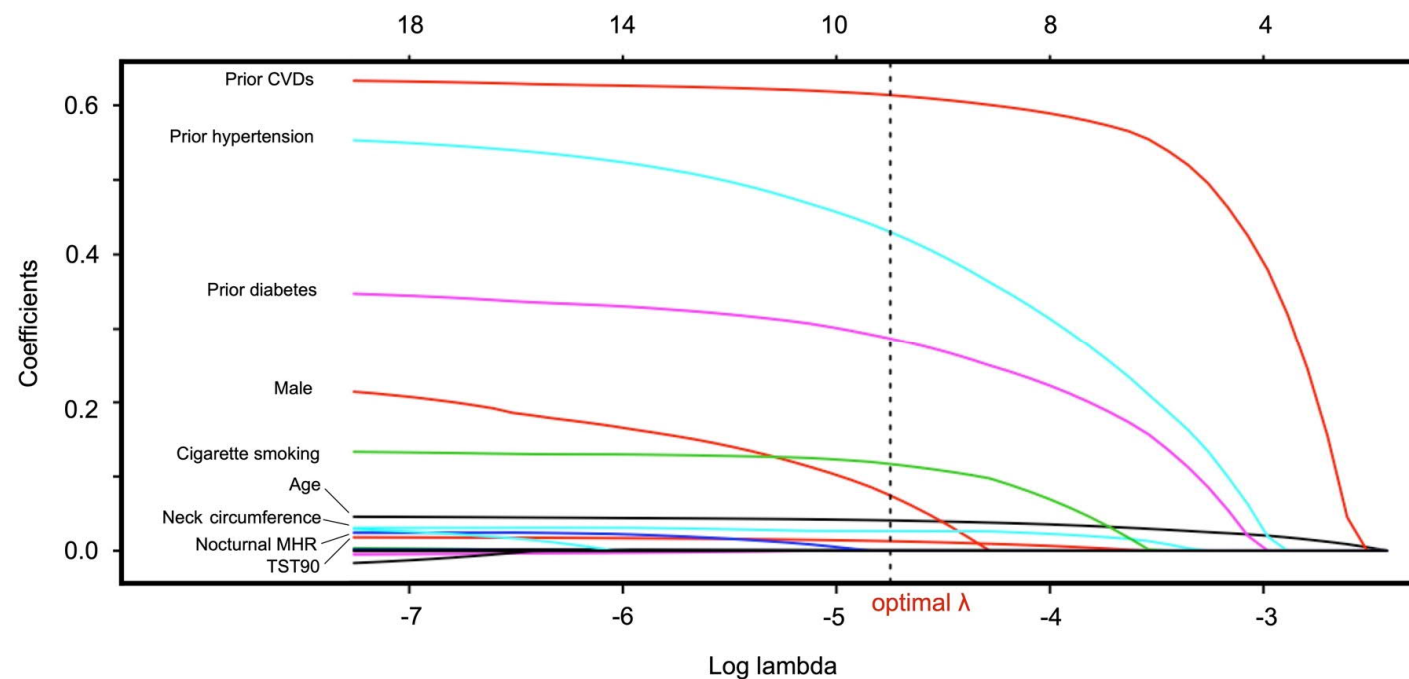
Figure E2. Coefficient progression of the LASSO regression model (n=1860)

Tuning log(lambda) sequence in the LASSO model used 10-fold cross-validation via minimum MSE (dotted vertical line). The most distinguishing indicators were determined according to the minimum MSE criteria, where optimal lambda resulted in 9 non-zero coefficients. Together with *a priori* selection of AHI, BMI and waist circumference, we finalized 12 indicators for further cluster profile identification. AHI, apnoea-hypopnoea index; BMI, body mass index; CVDs, cardiovascular diseases; LASSO, least absolute shrinkage and selection operator; MHR, mean heart rate; MSE, mean squared error; TST90, sleep time with oxygen saturation below 90%.