Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study

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Summary

Background The effect of obstructive sleep apnoea-hypopnoea as a cardiovascular risk factor and the potential protective effect of its treatment with continuous positive airway pressure (CPAP) is unclear. We did an observational study to compare incidence of fatal and non-fatal cardiovascular events in simple snorers, patients with untreated obstructive sleep apnoea-hypopnoea, patients treated with CPAP, and healthy men recruited from the general population.

Methods We recruited men with obstructive sleep apnoea-hypopnoea or simple snorers from a sleep clinic, and a population-based sample of healthy men, matched for age and body-mass index with the patients with untreated severe obstructive sleep apnoea-hypopnoea. The presence and severity of the disorder was determined with full polysomnography, and the apnoea-hypopnoea index (AHI) was calculated as the average number of apnoeas and hypopnoeas per hour of sleep. Participants were followed-up at least once per year for a mean of 10·1 years (SD 1·6) and CPAP compliance was checked with the built-in meter. Endpoints were fatal cardiovascular events (death from myocardial infarction or stroke) and non-fatal cardiovascular events (non-fatal myocardial infarction, non-fatal stroke, coronary artery bypass surgery, and percutaneous transluminal coronary angiography).

Findings 264 healthy men, 377 simple snorers, 403 with untreated mild-moderate obstructive sleep apnoea-hypopnoea, 235 with untreated severe disease, and 372 with the disease and treated with CPAP were included in the analysis. Patients with untreated severe disease had a higher incidence of fatal cardiovascular events (1·06 per 100 person-years) and non-fatal cardiovascular events (2·13 per 100 person-years) than did untreated patients with mild-moderate disease (0·55, p=0·02 and 0·89, p<0·0001), simple snorers (0·34, p=0·0006 and 0·58, p<0·0001), patients treated with CPAP (0·35, p=0·0008 and 0·64, p<0·0001), and healthy participants (0·3, p=0·0012 and 0·45, p<0·0001). Multivariate analysis, adjusted for potential confounders, showed that untreated severe obstructive sleep apnoea-hypopnoea significantly increased the risk of fatal (odds ratio 2·87, 95%CI 1·17–7·51) and non-fatal (3·17, 1·12–7·51) cardiovascular events compared with healthy participants.

Interpretation In men, severe obstructive sleep apnoea-hypopnoea significantly increases the risk of fatal and non-fatal cardiovascular events. CPAP treatment reduces this risk.

Introduction

Obstructive sleep apnoea-hypopnoea affects 4% of middle-aged men and 2% of middle-aged women.[1,2] This disorder is widely accepted to be associated with high rates of morbidity and mortality, mostly due to cardiovascular disease and traffic accidents.[3–10] However, the epidemiological studies that provided evidence for this association[3–5] had important methodological limitations. These studies were either retrospective[3,4] or did not take into account the role of potential confounding factors, such as the presence of comorbidity.[3–5] In fact, after adjustment for age and obesity, studies have not been able to show such increased risk.[6,7,11] Whether there is a link between the severity of obstructive sleep apnoea-hypopnoea and cardiovascular risk; whether simple snoring (ie, snoring without the presence of obstructive sleep apnoea-hypopnoea) increases this risk; and whether effective treatment of the disorder with continuous positive airway pressure (CPAP) can modify or eventually normalise this risk is unclear. These questions have important social and economic implications for public health.[12,13] We did an observational study to address these issues, since a randomised controlled trial, although ideal, would be unethical because the available evidence on the effectiveness of CPAP on symptom control precludes the possibility of withholding treatment for the time needed for the study.[14–18]

Since 1992, we have followed up a cohort of patients with obstructive sleep apnoea-hypopnoea and have recorded carefully the incidence of new fatal and non-fatal cardiovascular events. Although all patients with severe obstructive sleep apnoea-hypopnoea were initially offered treatment with CPAP, a substantial proportion refused it; because these individuals were nonetheless followed up in the clinic regularly, they provide information on the natural history of untreated, severe obstructive sleep apnoea-hypopnoea.

Methods

Patients

We recruited men with obstructive sleep apnoea-hypopnoea or simple snorers from those referred to our

sleep unit between Jan 1, 1992, and Dec 31, 1994. During this inclusion period, in keeping with the guidelines of the Spanish Society of Pneumology and Thoracic Surgery,[19] nasal CPAP was recommended to all patients who had more than 30 episodes of apnoea or hypopnoea per hour of sleep (ie, apnoea-hypopnoea index [AHI] >30).[19] CPAP was also recommended if the AHI was between 5 and 30 and the patient complained of severe daytime sleepiness that interfered with daily activities or if there was coexistent polycythaemia or cardiac failure.[19] Patients not treated with nasal CPAP received conservative advice: weight loss, avoidance of alcohol and sedatives, stopping smoking, avoidance of sleep deprivation, and, if appropriate, restriction of sleep position. Snorers with an AHI less than 5 were defined as simple snorers.

Healthy men were recruited from the database of the Zaragoza Sleep Apnoea Prevalence Study,[20] a population-based study carried out during 1991 and 1992. In that study, participants were visited at home where they completed a general health and a specific sleep questionnaire, and were later invited to come to our hospital for a polysomnographic study. For the purpose of the current investigation, we selected men who did not have excessive daytime somnolence during active situations (eg, reading, working, or driving) and who did not snore, as reported by a close relative (usually their wife). We studied the first one or two individuals from the database who fulfilled the matching criteria (age within 3 years and body-mass index [BMI] within 2 kg/m^2) for each patient with severe untreated obstructive sleep apnoea-hypopnoea (AHI >30).

The ethics committee of our institution approved the study and all participants gave their written informed consent.

Data collection

The same physician (JMM) assessed all patients at baseline and during follow-up. Clinical data were recorded at each outpatient visit with the same standardised questionnaire used in the epidemiological study mentioned previously.[20] Current smoking was defined as daily smoking of any number of cigarettes, cigars, or pipes. Alcohol use was defined as the consumption of an alcoholic beverage (1 unit) at least three times per week. The initial assessment also included routine blood tests and 12-lead electrocardiography. Blood pressure was measured in the right arm after 10 min of rest. Hypertension was defined as one or more of: resting systolic blood pressure of at least 140 mm Hg, resting diastolic blood pressure of at least 90 mm Hg, or treatment with antihypertensive medication.[21] We obtained medical records from hospital and family practitioners and recorded cardiovascular risk factors. We regarded cardiovascular disease as present when there was documented hospital admission for myocardial infarction, unstable angina, stroke, coronary bypass surgery, or coronary angioplasty. We recorded a lipid disorder as present if serum lipids were higher than the upper normal limit or if the patient was taking lipid-lowering medication at recruitment, or both. The diagnosis of diabetes mellitus and other prevalent chronic diseases was recorded according to the clinical history and use of specific medication, as revealed by the patient or chart review.

We did a full polysomnographic study of all participants at study entry. This investigation consisted of: continuous polygraphic recording of two electroencephalographic leads (C3/O1, C3/A2); right and left electro-oculographic leads; and chin electromyography for sleep staging. Ribcage and abdominal motion were monitored by inductive plethysmography (Respitrace Systems, Respitrace, Ardsley, NY, USA), airflow by thermistor (Ambulatory monitoring, Ardsley, NY, USA), and arterial oxyhaemoglobin saturation by finger pulse oximetry (Ohmeda Biox 3700, Ohmeda, Boulder, CO, USA). Sleep-stage scoring was done for 30-s intervals by trained technicians according to standard criteria.[22] Apnoea was defined as the complete cessation of airflow, and hypopnoea as a discernible reduction in airflow or thoracoabdominal excursion lasting for 10 s or more, accompanied by a decrease in oxygen saturation of at least 4%. AHI was defined as the total number of apnoeas and hypopnoeas per hour of electroencephalographic sleep. Patients with obstructive sleep apnoea-hypopnoea who accepted CPAP treatment had a second full sleep study for nasal CPAP titration. Optimum CPAP pressure was defined as the pressure value that abolished all respiratory events, arousals, and oxyhaemoglobin desaturation episodes.

Follow-up

Patients with obstructive sleep apnoea-hypopnoea and simple snorers attended our clinic yearly. Additionally, patients treated with CPAP visited the clinic at 3 and 6 months after starting treatment, and yearly thereafter. During these visits, compliance with CPAP treatment was assessed with the timer built into each CPAP device. We regarded mean daily use of more than 4 h per day as necessary to maintain the CPAP prescription. Otherwise, if after a reinforcement period of 3 additional months the patient still used the CPAP for less than 4 h per night, treatment was stopped and an alternative was offered. During the last quarter of 2003, all participants were contacted by telephone or letter and invited to visit the clinic for examination and to update medical information.

Endpoints

The main endpoints of our study were fatal and non-fatal cardiovascular events. Fatal events were defined as death from myocardial infarction or stroke. Non-fatal events included the occurrence of non-fatal myocardial infarction, stroke, and acute coronary insufficiency that needed coronary artery bypass surgery or percutaneous

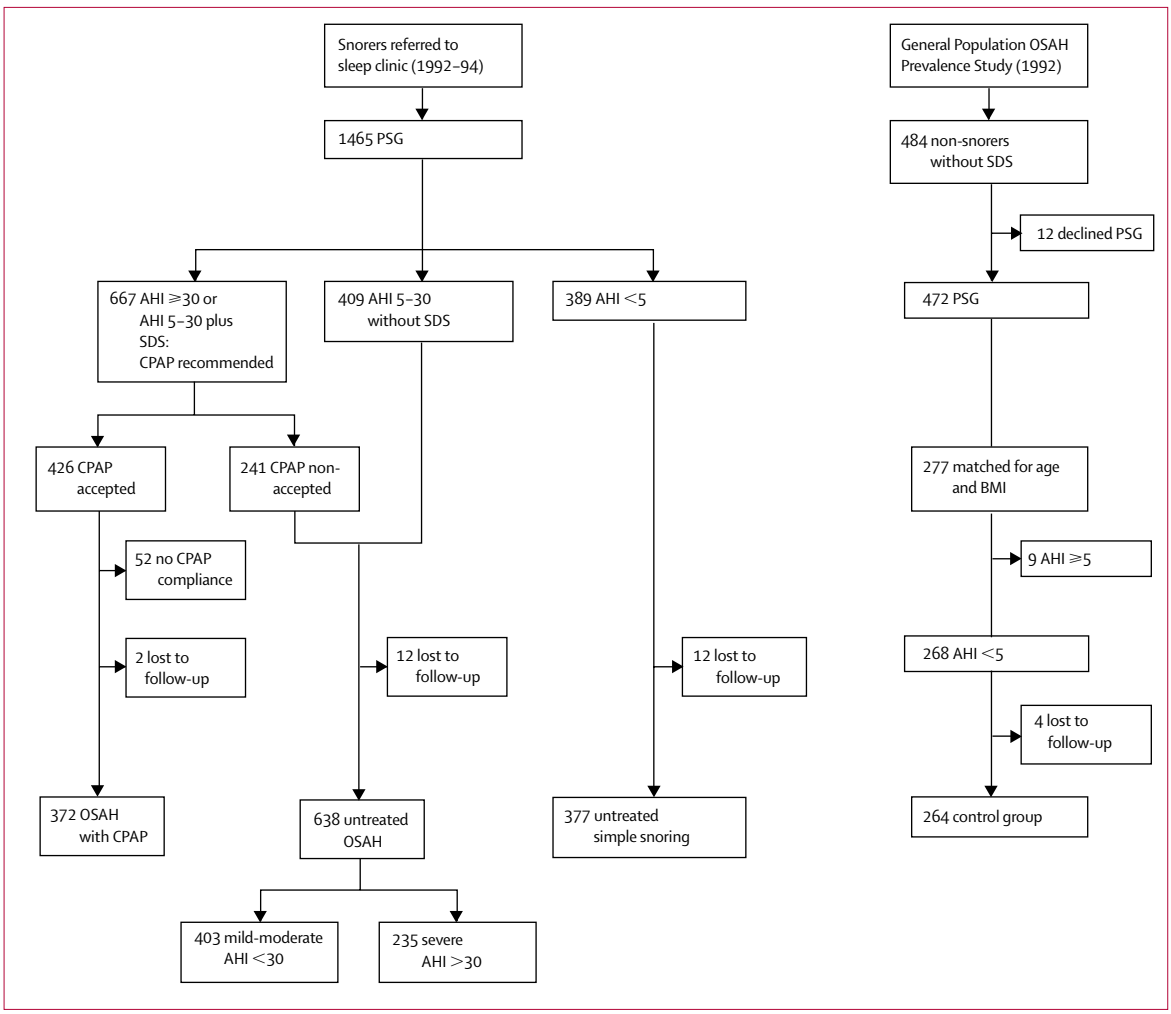


Figure 1: **Cohort profile**
PSG=polysomnogram; OSAH=obstructive sleep apnoea-hypopnoea; SDS=severe daytime sleepiness; CPAP=continuous positive airway pressure; AHI=apnoea-hypopnoea index.

transluminal coronary angiography, or both. The occurrence of cardiovascular death was ascertained from medical records of the patients who died in hospital, and from death certificates and direct contact with the local physicians or patients' relatives in the remaining cases. Vital status was further checked against the Social Security Death Index. Non-fatal cardiovascular events were confirmed through medical records, and episodes of myocardial infarction and stroke were ascertained with WHO criteria.[23,24]

Statistical analysis

Data analysis was done with SPSS (version 7.0). For analysis, we subdivided untreated patients with obstructive sleep apnoea-hypopnoea into mild-moderate (AHI 5–30) and severe (AHI >30) disease. We assessed differences between groups using the χ^2 test and ANOVA, and then post-hoc contrasts (*t* test) as appropriate. Survival was calculated by the Kaplan-Meier product limited method as the time from the initial sleep study to the cardiovascular event, with data censored at the time of the last medical assessment. The Mantel-Haenszel (or log-rank) test was used to assess differences between groups and we used Cox's proportional hazard regression model to identify independent predictors of fatal and non-fatal cardiovascular events.[25] In the univariate analysis, we regarded the following variables as potential prognostic factors: age; BMI; presence of cardiovascular diseases—ie, ischaemic heart disease, congestive heart disease, or cerebrovascular diseases; associated clinical conditions—ie, hypertension, diabetes mellitus, hyperlipidaemia, smoking, alcohol use, or use of antihypertensives, lipid-lowering agents, and antidiabetic agents; and diagnostic group—ie, healthy individuals, simple snorers, untreated patients with mild-moderate disease, untreated patients with severe disease, and patients treated with CPAP. Variables with a significant unadjusted association with cardiovascular

	Healthy men (n=264)	Snorers (n=377)	Untreated mild-moderate OSAH (n=403)	Untreated severe OSAH (n=235)	OSAH treated with CPAP (n=372)
Age (years)	49·6 (8·1)	49·9 (9·1)	50·3 (8·1)	49·9 (7·2)	49·9 (8·5)
Body-mass index (kg/m²)	29·8 (4·4)	26·1 (3·6)*	27·5 (4·4)*	30·3 (4·2)	30·7 (4·4)†
Hypertension (%)	14·8	17·7	24·8‡	34·9*	35·1*
Diabetes (%)	6·1	7·5	8·5	9·9	11·3†
Lipid disorders (%)	6·8	7·2	7·4	7·7	7·9
Current smoker (%)	22·9	23·1	24·3	25·1	25·2
Alcohol use (%)	27·7	28·2	28·3	29·1	29·2
Cardiovascular disease (%)	2·6	3·4	5·2	8·2†	8·5‡
Total cholesterol (mmol/L)	6·41 (0·28)	6·44 (0·09)	6·45 (0·13)†	6·47 (0·31)†	6·46 (0·17)†
Triglycerides (mmol/L)	1·31 (0·09)	1·31 (0·05)	1·32 (0·03)	1·32 (0·11)	1·32 (0·03)
Systolic blood pressure (mm Hg)	121·3 (1·8)	121·7 (0·8)§	122·7 (0·6)*	124·7 (1·7)*	124·8 (1·1)*
Diastolic blood pressure (mm Hg)	75·3 (1·1)	75·4 (0·5)	76·1 (0·4)*	78·8 (1·4)*	78·9 (0·7)*
Plasma glucose (mmol/L)	5·33 (0·12)	5·34 (0·05)	5·36 (0·08)§	5·38 (0·05)*	5·39 (0·03)*
Apnoea-hypopnoea index	1·2 (0·3)	3·5 (0·8)	18·2 (3·5)*	43·3 (5·7)*	42·4 (4·9)*

OSAH=obstructive sleep apnoea-hypopnoea syndrome; CPAP=continuous positive airway pressure. Data are mean (SD). *p<0·0001 versus healthy men; †p<0·05, ‡p<0·01, §p<0·001.

Table 1: **Baseline characteristics of participants**

events were entered into a forward stepwise Cox model after forcing the entry of diagnostic group as a variable. The p-to-enter value had to be lower than 0·1 and the p-to-remove value greater than 0·1.

Role of the funding source

The sponsors of the study had no role in study design, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility to submit for publication.

Results

We enrolled 277 age-matched and BMI-matched healthy men, 389 men with simple snoring, 409 patients with mild-moderate obstructive sleep apnoea-hypopnoea, and 667 patients with severe disease (or mild-moderate disease plus severe daytime sleepiness [n=38]). CPAP was declined by 241 patients, and 52 patients (43 with AHI >30, and nine with AHI 5–30) were judged non-compliant with CPAP treatment and were excluded from the final analysis (figure 1). However, mean age, BMI, and AHI for this subgroup were similar to that of the CPAP compliant group. 14 patients with obstructive sleep apnoea-hypopnoea, 12 snorers, and four healthy men were lost for follow-up. In the final analysis, we therefore studied 372 patients who were compliant with CPAP (349 with an AHI >30 and 23 with an AHI 5–30), 638 patients with untreated CPAP (235 with an AHI >30 and 403 with an AHI of 5–30), 377 simple snorers, and 264 healthy men.

Patients with untreated severe obstructive sleep apnoea-hypopnoea and patients treated with CPAP were of similar age and did not differ for BMI, AHI, and prevalence of cardiovascular risk factors; both groups had higher BMI (p<0·001), AHI (p<0·001), and prevalence of hypertension (p<0·001) than did snorers and patients with mild-moderate disease. Healthy individuals were of a similar age and had much the same BMI as patients with severe disease (by design), but a lower prevalence of hypertension, diabetes, lipid disorders, cardiovascular disease, smoking, and alcohol use (table 1).

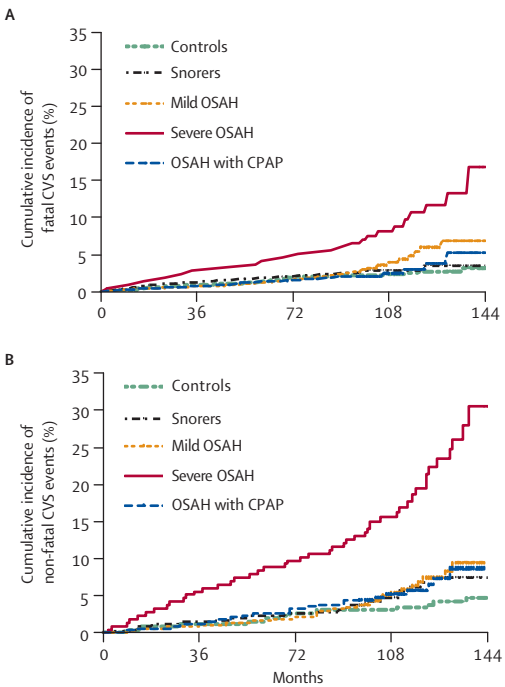
The incidence of non-fatal cardiovascular events per 100 people during 10 years' follow-up was significantly higher in patients with untreated severe disease than in healthy men, as was the incidence of cardiovascular death due to fatal myocardial infarction or stroke (table 2). The type and frequency of the different cardiovascular events did not differ between study groups. The 52 patients who were not compliant with CPAP (and who were therefore excluded from the analysis) were followed up at the clinic and received alternative treatment options—uvulopalatopharongoplasty, n=13; mandibular advancement, n=11; septoplasty, n=9; pharmacotherapy, n=8; or no specific treatment, n=11. The 10-year incidence of fatal and non-fatal cardiovascular events was 0·9 and 1·9 events per 100 people per year, respectively. These figures are similar to those recorded in the untreated group of patients with severe obstructive sleep apnoea-hypopnoea.

Patients with severe obstructive sleep apnoea-hypopnoea had the worst outlook, whereas outlook was

	Healthy men (n=264)	Simple snorers (n=377)	Untreated mild-moderate OSAH (n=403)	Untreated severe OSAH (n=235)	OSAH treated with CPAP (n=372)
Non-fatal cardiovascular events					
Number of events	12	22	36	50	24
Events per 100 person years	0·45	0·58	0·89	2·13*	0·64
Cardiovascular death					
Number of events	8	13	22	25	13
Events per 100 person years	0·3	0·34	0·55	1·06†	0·35

OSAH=obstructive sleep apnoea-hypopnoea syndrome; CPAP=continuous positive airway pressure. *p<0·0001 versus healthy men; †p=0·0012.

Table 2: **Incidence of cardiovascular events during the 10-year follow-up in healthy men, snorers, and patients untreated and treated for OSAH**



Numbers at risk

Controls	264	262	259	258
Snorers	377	372	361	232
Mild OSAH	403	401	392	264
Severe OSAH	235	229	221	167
OSAH with CPAP	372	364	361	229

Figure 2: **Cumulative percentage of individuals with new fatal (A) and non-fatal (B) cardiovascular events in each of the five groups studied**

best (and not significantly different from that seen in healthy participants) in patients treated with CPAP and in snorers (figure 2). Patients with mild-moderate untreated disease had an intermediate rate for cardiovascular events (figure 2). When patients with mild-moderate obstructive sleep apnoea-hypopnoea were further subdivided into those with mild (AHI 5–15) or moderate disease (AHI 16–30), the difference between them with respect to fatal and non-fatal cardiovascular outcomes was not significant. Furthermore, cardiovascular events (both fatal and non-fatal) were closely similar in mild-moderate untreated obstructive sleep apnoea-hypopnoea (n= 403; 0·55 fatal and 0·89 non-fatal cardiovascular events per 100 people per year) and mild-moderate disease treated with CPAP (n=23; 0 fatal and 0·86 non-fatal cardiovascular events per 100 people per year).

Tables 3 and 4 show the results of the logistic regression analysis used to obtain the unadjusted and adjusted odds ratios for cardiovascular death and non-fatal cardiovascular events. Age was the best predictor of increased risk for fatal and non-fatal cardiovascular events. The presence of cardiovascular disease at baseline was also a strong predictor of cardiovascular death and a mild predictor of new non-fatal cardiovascular events. Systolic blood pressure, which was regarded as a continuous variable, and current smoking at baseline were mild predictors for non-fatal cardiovascular events. Patients with untreated severe obstructive sleep apnoea-hypopnoea showed an increased risk of both cardiovascular death and non-fatal cardiovascular events. Patients with simple snoring, untreated mild-moderate obstructive sleep apnoea-hypopnoea, or those under CPAP treatment had an adjusted odds ratio for either fatal or non-fatal cardiovascular events that did not differ significantly from 1·0, suggesting that these groups have closely similar cardiovascular mortality and morbidity rates to healthy individuals. Further adjustment for total cholesterol, tryglicerides, diabetes, alcohol use, and current use of antihypertensives, antidiabetics, or lipid-lowering agents did not change the results significantly.

Discussion

We have shown that incidence of fatal and non-fatal cardiovascular events in untreated patients with severe obstructive sleep apnoea-hypopnoea is significantly higher than in healthy participants recruited from the general population matched individually for age and BMI. Furthermore, there seems to be a dose-effect relation for this association. Treatment with CPAP significantly reduces cardiovascular risk in patients with severe obstructive sleep apnoea-hypopnoea. Simple snoring does not significantly increase this risk.

	Unadjusted odds ratio (95% CI)	p	Part adjusted odds ratio (95% CI)	p	Fully adjusted odds ratio (95% CI)	p
Age, years	1·09 (1·06–1·11)	<0·0001	1·09 (1·05–1·11)	0·0005	1·09 (1·04–1·12)	0·001
Diagnostic group						
Snoring	1·04 (0·51–1·34)	0·61	1·03 (0·41–1·46)	0·74	1·03 (0·31–1·84)	0·88
Untreated mild-moderate OSAH	1·19 (0·74–1·89)	0·09	1·16 (0·55–2·11)	0·59	1·15 (0·34–2·69)	0·71
Untreated severe OSAH	3·98 (1·74–6·13)	0·003	3·02 (1·44–7·33)	0·015	2·87 (1·17–7·51)	0·025
CPAP	1·06 (0·55–1·91)	0·45	1·05 (0·45–2·09)	0·65	1·05 (0·39–2·21)	0·74
Cardiovascular disease	3·66 (1·98–4·07)	<0·0001			2·54 (1·31–4·99)	0·005

OSAH=obstructive sleep apnoea-hypopnoea; CPAP=continuous positive airway pressure. Variables included in the fully adjusted model were age, diagnostic group, presence of cardiovascular disease, hypertension, diabetes, lipid disorders, smoking status, alcohol use, systolic and diastolic blood pressure, blood glucose, total cholesterol, triglycerides, and current use of antihypertensive, lipid-lowering, and antidiabetic drugs. Variables included in the part adjusted model were those included in the fully adjusted model except hypertension and presence of cardiovascular disease.

Table 3: **Unadjusted, part adjusted, and fully adjusted odds ratio for cardiovascular death associated with clinical variables and diagnosis status, according to the logistic-regression analysis**

	Unadjusted odds ratio (95% CI)	p	Part adjusted odds ratio (95% CI)	p	Fully adjusted odds ratio (95% CI)	p
Age, years	1·11 (1·07–1·14)	<0·0001	1·09 (1·06–1·13)	0·0008	1·09 (1·05–1·13)	0·001
Diagnostic group						
Snoring	1·52 (0·88–2·11)	0·12	1·23 (0·71–2·86)	0·25	1·32 (0·64–3·01)	0·38
Mild-moderate OSAH	1·77 (0·91–2·76)	0·07	1·62 (0·65–3·01)	0·19	1·57 (0·62–3·16)	0·22
Severe OSAH	5·65 (1·92–6·52)	<0·001	3·32 (1·24–7·41)	0·005	3·17 (1·12–7·52)	0·001
CPAP	1·44 (0·61–2·80)	0·24	1·42 (0·53–3·29)	0·28	1·42 (0·52–3·40)	0·29
Cardiovascular disease	2·68 (1·13–2·57)	<0·0001			1·77 (1·03–3·09)	0·02
SBP, mm Hg	1·83 (1·24–5·52)	0·003			1·57 (1·04–4·09)	0·04
Current smoker	1·97 (1·42–6·71)	0·002	1·62 (1·06–6·12)	0·02	1·51 (1·02–5·88)	0·04

OSAH=obstructive sleep apnoea-hypopnoea; CPAP=continuous positive airway pressure; SBP=systolic blood pressure. Variables included in the fully adjusted model were age, diagnostic group, presence of cardiovascular disease, hypertension, diabetes, lipid disorders, smoking status, alcohol use, systolic and diastolic blood pressure, blood glucose, total cholesterol, tryglicerides and current use of antihypertensive, lipid-lowering and antidiabetic drugs. Variables included in the part adjusted model were those included in the fully adjusted model except hypertension and presence of cardiovascular disease.

Table 4: **Unadjusted, part adjusted, and fully adjusted odds ratio for non-fatal cardiovascular events associated with clinical variables and diagnosis status, according to the logistic-regression analysis**

Many previous studies have suggested that obstructive sleep apnoea-hypopnoea significantly increases cardiovascular morbidity and mortality, especially in patients with pre-existing cardiovascular disease.[26,27] However, these studies were methodologically limited by either their retrospective design[3,4] or the lack of adjustment for potential confounding factors.[3–5] When these factors have been taken into account, such increased risk is small.[6,7] Peker and colleagues[28] reported heightened risk of cardiovascular disease in middle-aged patients with obstructive sleep apnoea-hypopnoea and a positive effect of treatment on this risk. However, no polysomnography was done at entry; the number of patients included was relatively small; the control group was not matched for age or BMI; and important predictors of cardiovascular disease, such as cholesterol or fasting blood glucose concentrations, were not determined.[28] These limitations were overcome in our study because: (1) we recorded cardiovascular morbidity and mortality in a large cohort of untreated patients that was followed up prospectively for an extended period; (2) we compared the incidence of both fatal and non-fatal cardiovascular events in untreated patients with that in healthy participants recruited from the general population, matched for age and BMI; and, (3) we investigated the effect of potential confounding factors in the multivariate analysis.

The association of mild obstructive sleep apnoea-hypopnoea and simple snoring with risk of cardiovascular disease has been investigated in cross-sectional epidemiological studies with both positive[9,29] and negative results,[11] in case-control studies after the development of cardiovascular disease,[30,31] and in population-based studies with positive[32,33] and negative results also.[34,35] Again, most of these studies did not take into account potential confounders for risk of cardiovascular disease. In our study, the fact that the group of untreated patients with obstructive sleep apnoea-hypopnoea included patients with different disease severities allowed us to stratify them in two groups (mild-moderate or severe) according to number of apnoea-hypopnoea events recorded during sleep (less or more than 30 per h, respectively). We also followed up a large cohort of simple snorers, which allowed us to make appropriate comparisons. Our study, therefore, has enabled us to address our aim in a prospective and controlled manner, taking into account potential confounders. By contrast with patients with severe obstructive sleep apnoea-hypopnoea, untreated patients with mild-moderate disease were not at a higher risk than were healthy participants (tables 3 and 4). We cannot exclude the possibility, however, that if sample size was bigger or follow-up longer, differences between mild-moderate disease and healthy participants might have reached significance. Our results also suggest that simple snoring does not significantly increase cardiovascular risk by itself.

To further investigate the relation between obstructive sleep apnoea-hypopnoea and cardiovascular risk, we compared the cardiovascular event rates seen in our study with those predicted by the Framingham data.[36] To do so, we used the average age, blood pressure, and cholesterol concentration for all of our study groups, as well as smoking history and diabetes status. We showed that the predicted cardiovascular event rates by the Framingham data were similar to those recorded in our study for healthy individuals (3·8—2·4% *vs* 4·1–3·2%, respectively; the two figures correspond to those calculated in the presence or absence of smoking and diabetes), simple snorers (4·8–2·5% *vs* 5·1–2·9%, respectively), and mild-moderate disease (4·9–2·6% *vs* 5·9–2·9%, respectively). By contrast, those seen in untreated severe obstructive sleep apnoea-hypopnoea seem to be much higher in our study (10·8–6·8%) than in the Framingham study (5·2–3·2%). Although, compared with ours, the Framingham study has several fundamental differences in its design (general population *vs* clinical cohort), size, and participants' sex (men and women *vs* men only), ethnic origin, baseline variables, and diet (American *vs* Mediterranean), among others; we think that this comparison reinforces our own observations and interpretation.

Although CPAP is regarded as the cornerstone of treatment for obstructive sleep apnoea-hypopnoea,[14,37–39] its

effects on cardiovascular morbidity and mortality in these patients is not fully understood. A study has indicated that treatment of the disorder in patients with pre-existing cardiovascular disease is associated with a decrease in new cardiovascular events during a 7-year follow-up period.[40] However, few patients were treated with CPAP or upper airway surgery in that study and many potential confounders were not adequately controlled for.[40] By contrast, the design of our study allowed us to compare the incidence of fatal and non-fatal cardiovascular events in a large cohort of untreated patients with severe obstructive sleep apnoea-hypopnoea, patients effectively treated with CPAP, and healthy participants of similar age and BMI, irrespective of their previous cardiovascular history.

These strengths, however, should be balanced with some potential weaknesses. The most obvious concern is that our study was not a randomised controlled trial and, in cohort observational studies like ours, baseline characteristics could differ between groups for reasons other than chance. Thus patients who refused treatment might be less adherent to treatment for reasons such as presence of comorbidities. Yet, this did not seem to be the case in our study because comorbidity was equally present in patients untreated for obstructive sleep apnoea-hypopnoea and those treated with CPAP. As happens with most cohort studies, the potential cardiovascular risk factors were measured at baseline, and changes over time have not been modelled. Furthermore, this study was not formally randomised because, ethically, the available evidence on the effect of CPAP precludes the possibility of withholding treatment. The alternative chosen here, however, is a reliable compromise between the ideal experimental design and the possibility to implement it in the real world.[17,18]

In our study, 36% of patients with severe obstructive sleep apnoea-hypopnoea refused treatment with CPAP. This figure is probably higher than that seen in most sleep units today, where 10–20% would be the normal failure rate (unpublished); and the current failure rate in our unit is 18%. We think that this difference is probably due to the technological improvements that occurred in the 10 years since our study began (better nasal interfaces, auto-adjusting CPAP, and heated CPAP humidifiers, etc), as well as to the enhanced medical and social awareness of obstructive sleep apnoea-hypopnoea. Other potential limitations of our study are that we studied only men, so our results cannot be readily extrapolated to women with the disease in whom additional factors, such as sex hormones, can also play an important part in the pathogenesis of cardiovascular disease. Yet, the fact that we included only men reduces the variability of the results. Likewise, although ischaemic and non-ischaemic heart failure,[41] transient ischaemic attacks,[42] and stroke[43,44] have been associated with obstructive sleep apnoea-hypopnoea, we did not specifically report heart failure and transient ischaemic attacks in our study because of the logistical difficulties involved in confirming these diagnoses. Additionally, since the group treated with CPAP received more intensive follow-up during the first year after diagnosis (two additional visits), outcome could be improved in this group independently of the CPAP treatment. With these caveats in mind, our results suggest that treatment with CPAP for at least 4 h per night significantly reduces the raised cardiovascular risk reported in untreated patients with obstructive sleep apnoea-hypopnoea.

We used AHI as a descriptor of disease severity because this is almost universal in the field. However, other descriptors of the abnormal sleep of these patients, such as the desaturation index or the number of arousals per hour of sleep, could also predict cardiovascular morbidity and mortality in obstructive sleep apnoea-hypopnoea since most apnoeic episodes are followed by oxygen desaturation and an arousal. In fact, Peker and co-workers[26] reported a rise in the incidence of cardiovascular disease in patients with obstructive sleep apnoea-hypopnoea using the desaturation index as a surrogate of the AHI. Our study was not designed to investigate the mechanism underlying our observations; however, it is consistent with the mechanisms proposed to explain both the increased cardiovascular risk in obstructive sleep apnoea-hypopnoea (namely hypertension,[45] nocturnal hypoxaemia,[46] endothelial dysfunction,[47] and platelet aggregation[48]) and the physiological effects of nasal CPAP (including normalisation of blood pressure in hypertensive patients, avoidance of nocturnal hypoxaemia, and correction of endothelial and coagulation abnormalities).[49–51]

In conclusion, the results of this large, long-term, prospective controlled study suggest that in untreated men with severe obstructive sleep apnoea-hypopnoea, the risk of fatal and non-fatal cardiovascular events is increased. There is a relation between the severity of this disease and cardiovascular risk, but effective treatment with nasal CPAP significantly reduces the cardiovascular outcomes associated with this medical condition. Simple snoring is not a significant cardiovascular risk factor.

Conflict of interest statement

We declare that we have no conflict of interest.

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