Increased Incidence of Cardiovascular Disease in Middle-aged Men with Obstructive Sleep Apnea

A 7-Year Follow-up

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The incidence of a cardiovascular disease (CVD) was explored in a consecutive sleep clinic cohort of 182 middle-aged men (mean age, 46.8 ± 9.3; range, 30–69 years in 1991) with or without obstructive sleep apnea (OSA). All subjects were free of hypertension or other CVD, pulmonary disease, diabetes mellitus, psychiatric disorder, alcohol dependency, as well as malignancy at baseline. Data were collected via the Swedish Hospital Discharge Register covering a 7-year period before December 31, 1998, as well as questionnaires. Effectiveness of OSA treatment initiated during the period as well as age, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP) at baseline, and smoking habits were controlled. The incidence of at least one CVD was observed in 22 of 60 (36.7%) cases with OSA (overnight oxygen desaturations of 30 or more) compared with in 8 of 122 (6.6%) subjects without OSA ($p < 0.001$). In a multiple logistic regression model, significant predictors of CVD incidence were OSA at baseline (odds ratio [OR] 4.9; 95% confidence interval [CI], 1.8–13.6) and age (OR 23.4; 95% CI, 2.7–197.5) after adjustment for BMI, SBP, and DBP at baseline. In the OSA group, CVD incidence was observed in 21 of 37 (56.8%) incompletely treated cases compared with in 1 of 15 (6.7%) efficiently treated subjects ($p < 0.001$). In a multiple regression analysis, efficient treatment was associated with a significant risk reduction for CVD incidence (OR 0.1; 95% CI, 0.0–0.7) after adjustment for age and SBP at baseline in the OSA subjects. We conclude that the risk of developing CVD is increased in middle-aged OSA subjects independently of age, BMI, SBP, DBP, and smoking. Furthermore, efficient treatment of OSA reduces the excess CVD risk and may be considered also in relatively mild OSA without regard to daytime sleepiness.

Keywords: sleep apnea; cardiovascular; hypertension; risk factor

Obstructive sleep apnea (OSA) affects 24% of middle-aged men and 9% of women in the United States, but the treatment criterion, daytime sleepiness, is reported by 17 and 22% of these subjects, respectively (1). There is growing research evidence for an independent association between OSA and cardiovascular disease (CVD), mainly hypertension (2) and coronary artery disease (CAD) (3). However, a causal link has not yet been convincingly documented. Some previous studies addressing the long-term cardiovascular outcome in patients with OSA were entirely retrospective and lacked adequate control for coexisting known cardiovascular risk factors (4, 5). In follow-up studies performed on retrospectively selected cohorts of OSA patients (6, 7), documentation of outcome was mainly questionnaire-based, and loss of subjects to follow-up was considerable (6). More than half of the study population had at least one CVD diagnosis already at baseline (7). Moreover, these studies were performed selectively in OSA patients and lacked a control group. Inadequate adjustment for confounding factors such as age, sex, obesity, and smoking, as well as the lack of objective assessment of OSA treatment effectiveness, may additionally have contributed to the skepticism against the proposed relationship between OSA and CVD (8).

To explore better the possibility of a causal link between OSA and CVD, we performed a follow-up study on a retrospectively selected consecutive population of middle-aged men with and without OSA. Subjects were free of hypertension and any other concomitant CVD, pulmonary disease, diabetes mellitus, psychiatric disorder, alcohol dependency, or malignancy at baseline. Moreover, the impact of OSA treatment initiated during the follow-up period as well as potential confounding factors such as age, body mass index (BMI), smoking habits, and blood pressure were controlled.

METHODS

Study Population

In 1991, 370 consecutive cases with a history of snoring and/or witnessed apneas were investigated in the sleep laboratory of the Department of Pulmonary Medicine, University Hospital of Gothenburg (Gothenburg, Sweden) for a cross-sectional study addressing the influence of age, BMI, and OSA on blood pressure and hypertension prevalence (9). By review of baseline data of this sample, 20 young (age of less than 30 years) and 17 older (age of more than 69 years) subjects, as well as 15 individuals who had moved abroad or could not be identified and/or located in the Population Register of the National Tax Board of Sweden were excluded (Figure 1). For the remaining 318 middle-aged (30–69 years old) subjects, besides baseline recordings in clinic charts, complementary information on health status was obtained from the Swedish Hospital Discharge Register (SHDR) via the Center for Epidemiology, National Board of Health and Welfare. At least one concomitant CVD, defined as *International Classification of Diseases* (ICD)-9 codes (10) 401–445, was identified at baseline in 74 and a concomitant other disorder (diabetes mellitus, pulmonary disease, psychiatric disorder, or alcohol dependency) in 13 cases. Among the remaining 231 middle-aged otherwise healthy subjects, 49 women were analyzed separately. Finally, 182 middle-aged, otherwise healthy men, were identified for this study (Figure 1). The patients were enrolled independently of a history of associated excessive daytime sleepiness. A 7-year period following the baseline investigation within the time span January 1, 1991, to December 31, 1998, was defined for each subject. Death certificates for the deceased patients were obtained from the National Cause of Death Registry. In parallel, a postal questionnaire was sent to the survivors. Moreover, objective data on therapy effectiveness of the OSA subjects during the follow-up period were obtained. Consequently, 182 men (mean age, 46.8 ± 9.3 years) were analyzed in two groups, depending on absence or presence of OSA at baseline (Table 1) as well as in subgroups depending on treatment effectiveness in the OSA patients (Table 2). The study protocol was approved by the Ethics Committee of the Medical Faculty of the University of Gothenburg.

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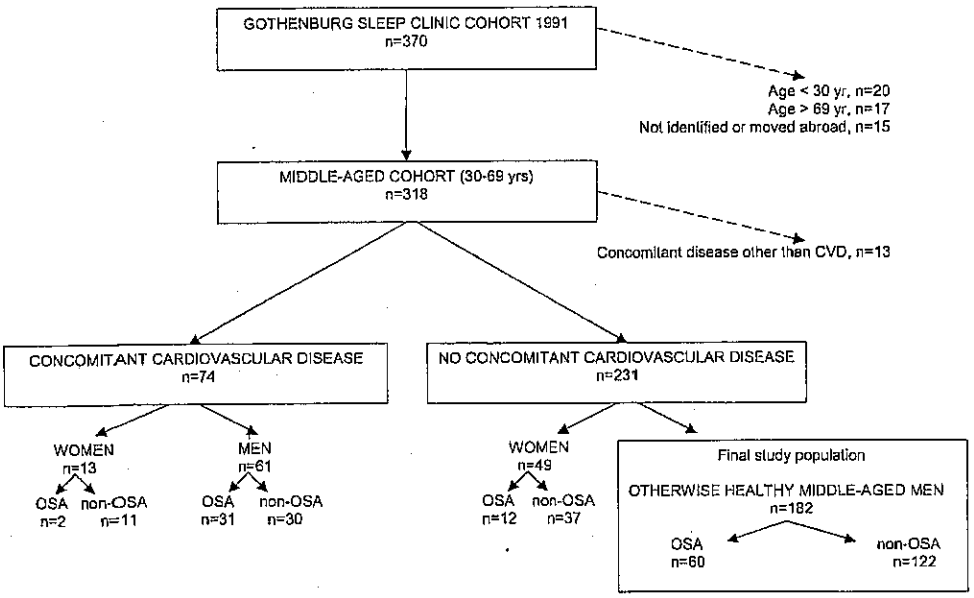

Figure 1. Patient log demonstrating the study cohort and the different subgroups.

Baseline Investigations

Sleep studies, blood pressure recordings, and other measurements at baseline have been described in detail elsewhere (9). In brief, the subjects underwent an overnight sleep study in the sleep laboratory, and investigations were initiated at approximately 11:00 P.M. and were terminated at 6:00 A.M., allowing for 7 hours of sleep. Lights out and lights on were recorded, and the subjective sleep quality as well as subjective sleep duration was documented. Patients with a self-reported sleep duration of shorter than 5 hours were reinvestigated. The average estimated sleep time was empirically chosen to be 6 hours. The sleep study included a continuous recording of transcutaneous arterial oxygen saturation via a finger probe (BIOX 3700; Ohmeda, Louisville, CO), nasal and oral airflow recorded via a thermistor, and respiration and body movement monitored via a static charge-sensitive bed (Bio-matt; Biorec Inc., Raisio, Finland). Signals were amplified and recorded on a filter pen recorder (Kipp and Zonen, Delft, Holland). A sleep-related obstructive event (apnea) was scored when oxygen saturation dropped by at least 4% from the immediately preceding baseline simultaneously with absence of nasal and oral airflow as well as the presence of chest movements for more than 10 seconds. Scoring was made manually from each recording strip by trained technicians unrelated to the study itself. The total number of significant oxygen desaturations (ODs) as well as the minimal OD reached during the overnight recording (sat. min) was determined. An overnight OD of 30 or more was defined as OSA. This value was based on previously established diagnostic criteria (11) of an apnea index (AI) of five or more for the sleep apnea syndrome, which was accepted at the time of the baseline investigations. Additionally, the OD index (ODI) was applied as the average number of OD per hour of self-estimated sleep in each case.

Height and weight were obtained. Blood pressure was measured with an appropriate arm cuff in the left or right arm after a minimum of a 15-minute supine rest in each patient on the evening before the onset of the sleep study according to the routine clinical procedure in the sleep laboratory. Cases with ongoing hypertensive medication, and/or an SDP of 160 or more, and/or diastolic blood pressure (DBP) of 95 mm Hg or more were qualified for the diagnosis of hypertension based on the definition used at the time of the investigation (12). A second definition of hypertension was applied using an SDP of 140 or more and/or a DBP of 90 mm Hg or more in agreement with current World Health Organization (WHO) criteria (13). BMI was calculated according to the formula body weight divided by the square of the height. Data on smoking habits were also documented in the routine questionnaire at baseline.

TABLE 1. BASELINE CHARACTERISTICS OF THE OTHERWISE HEALTHY MIDDLE-AGED MEN IN 1991 AS WELL AS THE INCIDENCE OF CVD AT FOLLOW-UP*

Variable	OSA (*n = 60*)	non-OSA (*n = 122*)	p Value
Age, years	50.0 ± 8.8	45.2 ± 9.2	0.001
BMI, kg/m^2	27.9 ± 3.4	25.6 ± 3.1	0.001
SBP, mm Hg	132.3 ± 6.9	125.5 ± 13.7	< 0.001
DBP, mm Hg	80.3 ± 6.7	76.6 ± 7.7	0.002
OD, n/6 h	88.4 ± 89.0	8.8 ± 8.1	< 0.001
ODI, n/h	16.5 ± 15.3	1.6 ± 1.6	< 0.001
Sat. min, %	80.7 ± 7.8	89.0 ± 3.8	< 0.001
Current smokers, n (%)	22 (36.7)	51 (41.8)	NS
Subjects with CVD incidence, n (%)	22 (36.7)	8 (6.6)	< 0.001

Definition of abbreviations: BMI = body mass index; CVD = cardiovascular disease; DBP = diastolic blood pressure; NS = nonsignificant; OD = oxygen desaturations ≥ 4%; ODI = oxygen desaturation index; OSA = obstructive sleep apnea; Sat. min = minimal oxygen saturation; SBP = systolic blood pressure.

* Continuous variables are expressed as mean ± SD, statistics by unpaired student's *t* test, comparison of groups by chi-squared test.

SHDR

The SHDR covers all public in-patient care since 1987. The number of cases not reported to the register was estimated to between 1 and 2% according to a data quality check (14). In the SHDR, there are four different types of information: patient-related data (personal identification number, sex, age, place of residence), hospital-related data (county council, hospital, department), administration-related data (date of admission, discharge, length of stay, acute or planned admission, admitted from, discharged to), and medical data (main diagnosis, secondary diagnoses, external cause of injury and poisoning, surgical procedures). For classification of diseases, ICD-9 codes were used until 1997, and ICD-10 codes were used thereafter. To identify cases without any CVD diagnosis or other concomitant diseases at baseline, and to control for psychiatric disorders and alcohol dependency, data from the SHDR were obtained for a 3-year extension period before the baseline investigation. The main outcome measure in the subsequent evaluation was the incidence of at least one CVD during the follow-up period. A further analysis of the CVD event permitted subclassification into the diagnosis groups of hypertension, CAD (angina pectoris or myocardial infarction), and cardiovascular event (stroke or myocardial infarction or cardiovascular death) during the follow-up period. Cardiac arrhythmias and congestive heart failure were considered as a CVD event. Cases with more than one CVD diagnosis and/or more than one hospital admission with the same CVD diagnosis were considered only once in the reporting of overall CVD to avoid bias with increased CVD in the study population.

TABLE 2. BASELINE AND FOLLOW-UP CHARACTERISTICS OF THE OSA PATIENTS IN SUBGROUPS BASED ON EFFECTIVENESS OF TREATMENT*

Variable	Incompletely Treated ($n = 37$)	Efficiently Treated ($n = 15$)	p Value
Age at baseline, years	52.9 ± 7.7	46.6 ± 8.6	0.013
BMI 1991, kg/m^2	28.3 ± 3.9	27.5 ± 2.5	NS
BMI 1998, kg/m^2	29.0 ± 4.5	27.6 ± 2.6	NS
SBP 1991, mm Hg	134.6 ± 11.6	130.7 ± 12.1	NS
DBP 1991, mm Hg	80.7 ± 6.7	79.7 ± 7.9	NS
OD 1991, n/6 h	68.8 ± 32.6	124.7 ± 158.9	0.044
OD at follow-up, n/6 h	—	11.2 ± 7.0	—
ODI 1991, n/h	13.4 ± 8.6	21.4 ± 23.8	NS
ODI at follow-up, n/h	—	2.0 ± 1.3	—
Sat. min 1991, %	82.3 ± 5.4	78.7 ± 10.9	NS
Sat. min at follow-up, %	—	88.8 ± 2.8	—
Current smokers 1991, n (%)	11 (29.7)	6 (40.0)	NS
Current smokers 1998, n (%)	9 (24.3)	3 (20.0)	NS
Responder to questionnaire, n (%)	31 (83.8)	14 (93.3)	NS
Subjects with CVD incidence, n (%)	21 (56.8)	1 (6.7)	< 0.001
Drug treatment at follow-up			not done
ASA or Warfarin, (%)	7 (18.9)	0	
β-blockers, n (%)	11 (29.7)	0	
Nitrates, n (%)	2 (5.4)	0	
Calcium antagonists, n (%)	1 (2.7)	0	
Diuretics, n (%)	6 (16.2)	1 (6.7)	
ACE inhibitors, n (%)	4 (10.8)	1 (6.7)	
Angiotensin II antagonists, n (%)	2 (5.4)	0	
α-blockers, n (%)	2 (5.4)	0	

Definition of abbreviations: ACE = angiotensin-converting enzyme; ASA = acetyl salicylic acid; BMI = body mass index; CVD = cardiovascular disease; DBP = diastolic blood pressure; NS = nonsignificant; OD = oxygen desaturations ≥ 4%; ODI = oxygen desaturation index; Sat. min = minimal oxygen saturation; SBP = systolic blood pressure.

* Continuous variables are expressed as mean ± SD, statistics by unpaired Student's *t* test. Comparison of groups by chi-squared test. Eight subjects receiving treatment without objective data on therapy effectiveness at follow-up excluded (*see* text).

Questionnaires

Postal questionnaires sent to the 177 survivors in the beginning of 1999 included questions regarding current weight, history of smoking, and if relevant, hospital admissions with CVD, ongoing medication, and treatment for snoring or OSA during the follow-up period. Drugs that were registered include those listed within the anatomical therapeutic chemical classification system codes C01–C08 (15).

Treatment of OSA

OSA treatment was initiated by different physicians according to the clinical routines depending on severity of the sleep-related breathing disorder, the extent of excessive daytime sleepiness, and social aspects of loud snoring. Patients with excessive daytime sleepiness were offered either treatment with continuous positive airway pressure (CPAP), surgery (uvulopalatopharyngoplasty [UPPP]), or oral appliance. Surgically treated cases were invited for renewed sleep study recordings for evaluation of effectiveness of the treatment and were offered CPAP or oral appliance in case of remaining symptomatic OSA despite treatment. Therapeutic CPAP titration was performed according to the prevailing manual standardized procedure using a full-night evaluation in a laboratory setting including a CPAP nasal pressure monitoring. The therapeutic effect of CPAP was routinely reinvestigated at 3 and 12 months after initiation of treatment, and an individual follow-up procedure was applied in each case depending on compliance with and effectiveness of CPAP. Objective evaluation of CPAP use was estimated by time counter of the devices (hours divided by days gone between the last two recordings). OSA patients without any treatment, or with remaining OSA despite treatment with UPPP, or oral device or daily CPAP run time of less than 50% of estimated sleep time were regarded as incompletely treated cases. Efficiently treated patients were defined as the cases with an OD below 30 at the renewed sleep study after UPPP or on treatment with oral device (subjective use for at least 50% of estimated sleep hours) or on CPAP with an objective daily CPAP run time at least 50% of estimated sleep hours. Evaluation of compliance data was done by two observers blinded to the incidence of CVD diagnoses.

Statistics

The groups were compared using Student's *t* test for variables measured on a continuous scale, and where appropriate, Fisher's exact test (two-tailed) or chi-squared test for categorical variables. A univariate logistic regression (STATISTICA; StatSoft Inc., Tulsa, OK) was used to calculate odds ratios (ORs) for the relationships between OSA, OD, ODI, sat. min, UPPP, CPAP, efficient treatment of OSA as well as age, systolic blood pressure (SBP), DBP, BMI, and the outcome measures (incidence of hypertension, CAD, cardiovascular event, and overall CVD, respectively.) All significant variables that correlated with the outcome measures in the univariate analyses were subsequently included in a multiple logistic regression model, and corrected ORs were calculated from the regression coefficients. All ORs are presented with their 95% confidence intervals. Continuous values are given as means ± SD. A p value (two sided) of 0.05 or less was regarded as statistically significant.

RESULTS

As shown in Figure 1, a concomitant CVD was prevalent at baseline in 23.3% of the middle-aged sleep clinic cohort. Almost 51% of men and 15% of women had OSA diagnosis in this group.

In middle-aged otherwise healthy women, OSA was found in 12 (25%) subjects (mean age, 57.6 ± 8.7; range, 42–68 years). Women without OSA were almost 10 years younger than those with OSA ($p = 0.006$). CVD incidence was observed in 4 of 12 cases with OSA (33.3%) compared with in 4 of 37 (10.8%) subjects with non-OSA ($p = 0.069$). No CVD was observed in the subgroup of four women with efficiently treated OSA. None of the studied variables predicted CVD incidence in multivariate analysis in this cohort of 49 otherwise healthy women at baseline.

There were five deaths (2.7%) in the final study group of middle-aged otherwise healthy men at baseline. Two of these were of cardiovascular origin and occurred in the incompletely treated OSA group (5.4%). One deceased patient in

the efficiently treated OSA group had a cancer diagnosis. Two deaths in the non-OSA group (1.6%) were due to malignancy and central neurologic disorder, respectively. Overall mortality was not addressed in the final statistical analysis, whereas cardiovascular death was classified as one event.

In the final study population of middle-aged otherwise healthy men, OSA was found in almost one-third of the cohort (Figure 1). Compared with subjects without OSA at baseline, the OSA patients were significantly older and had a higher BMI, SBP, DBP, OD, and ODI and a lower sat. min, whereas the relative proportion of smokers did not differ significantly (Table 1).

As shown in Table 2, incompletely treated OSA patients were almost 5 years older than those treated efficiently but with fewer desaturations at baseline. BMI, SBP, DBP, and proportion of smokers did not differ significantly between groups.

During follow-up, treatment of OSA was initiated with CPAP (n = 14) and/or UPPP (n = 22) and/or oral device (n = 4), whereas no active treatment was considered in 19 patients (36.5%) due to either mild OSA and/or a lack of excessive daytime sleepiness. Among the CPAP-treated OSA patients, nine cases (64.3%) returned the device or had low treatment compliance at follow-up. Approximately 50% of subjects undergoing UPPP still had OSA at the follow-up recording even if some nonsignificant reduction of desaturations was achieved (ODI 15 ± 10 before and 12 ± 6 after the surgery). The first follow-up recordings were done 1–2 years after surgery within the first 4 years of the observation period (ODI 2.0 ± 1.3 in the efficiently UPPP-treated subjects) but were not renewed later, as these subjects did not report symptoms. Only one out of four subjects treated with an oral device was considered as an efficiently treated case.

Eight OSA subjects (one treated with CPAP and seven with UPPP) with a lack of objective sleep study recordings at follow-up were excluded from the final statistical analysis when comparing the subgroups based on the effectiveness of treatment (Table 2). However, none of these subjects had ongoing medication according to questionnaire reports, and no CVD diagnosis was documented in the SHDR. ICD's definitions of CVD covered hypertension, angina pectoris, myocardial infarction, atrial fibrillation, cardiomyopathy, cardiac failure, and stroke. Drug treatment regimens at follow-up in OSA patients are shown in Table 2. None of the subjects in this study were receiving drug at baseline.

As illustrated in Figure 2, more than 50% of the patients with incompletely treated OSA received at least one CVD diagnosis during the follow-up period. In fact, when the CVD was classified as hypertension, CAD, or cardiovascular event (stroke or myocardial infarction or cardiovascular death), the incidences were consistently more frequent in the incompletely treated OSA subjects. With application of the current definition of hypertension (13), that is, excluding subjects with borderline hypertension at baseline in 1991, a new CVD occurred in 7 of 17 cases (41.2%) with incompletely treated OSA compared with in 3 of 87 (3.5%) subjects without OSA ($p < 0.001$). None of the subjects with efficiently treated OSA (n = 8) experienced a CVD during the follow-up period. Without regard to OSA treatment during the follow-up period, age, OSA, SBP, DBP, and BMI at baseline were all significantly predictive of at least one CVD incident with ORs ranging from 8.3 to 41.9 in the univariate logistic regression analysis. However, only age and OSA (OR 23.4 and 4.9, respectively) remained as significant predictors in the multiple logistic regression model (Table 3). After exclusion of subjects with borderline hypertension at baseline, OSA and age were significantly predictive of at least one CVD in the univariate analysis. Only OSA at baseline remained significant in the multivariate analysis with an OR of 6.7 (Table 3). A separate analysis revealed ODI as well as sat. min at baseline as significant predictors of CVD (ORs 40.9 and 0.04, respectively) without regard to OSA treatment during the observation period. Interestingly, when analyzing the subgroup of non-OSA subjects, CVD incidence was observed in 4 of 22 (18.2%) cases with an overnight OD between 15–29 compared with in 4 of the remaining 100 non-OSA subjects with OD below 15 ($p = 0.015$).

Univariate predictors of CVD incidence in the study population with regard to OSA treatment during the observation period were incompletely treated OSA, age, SBP, DBP, and BMI at baseline with ORs ranging from 10.3 to 46.9. However, only age and incompletely treated OSA (OR 15.2 and 11.1, respectively) remained as significant predictors in the multiple logistic regression model (Table 4). Independent predictors of separate CVD diagnosis were identified as SBP at baseline and incompletely treated OSA (adjusted ORs 30.1 and 3.7, respectively). CAD, as well as cardiovascular event (stroke or myocardial infarction or cardiovascular death), was predicted by age, SBP, and incompletely treated OSA in univariate analysis but only incompletely treated OSA in multivariate (ORs 5.4 for CAD and 7.8 for cardiovascular event).

A separate analysis of the OSA group revealed age and SBP at baseline as predictors of CVD, whereas treatment with UPPP was associated with a risk reduction in univariate logistic regression model. However, this reduction was age-dependent and no longer significant in multivariate analysis (Table 5). Intervention with CPAP without regard to treatment effec-

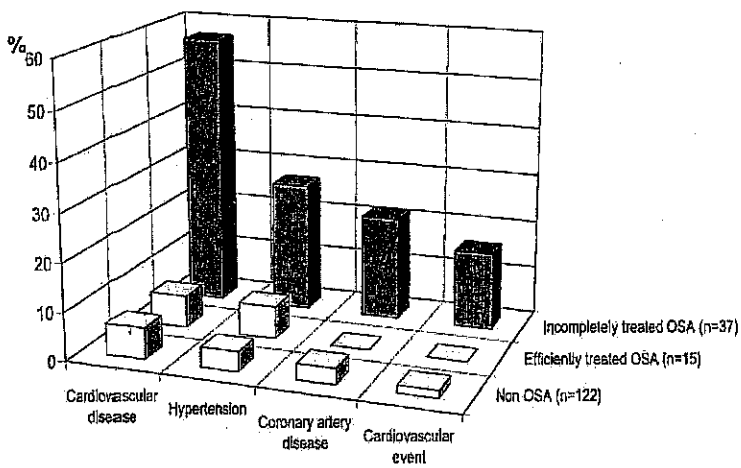

Figure 2. Incidence of CUD during a 7-year follow-up in otherwise healthy middle-aged men at baseline. Proportion of individuals with incidence of cardiovascular event, CAD, hypertension, and CVD in incompletely treated OSA, efficiently treated OSA, and non-OSA.

TABLE 3. BASELINE PREDICTORS OF CARDIOVASCULAR DISEASE INCIDENCE IN MIDDLE-AGED MEN WITHOUT REGARD TO OSA TREATMENT DURING THE FOLLOW-UP PERIOD*

	Odds Ratio	95% CI	p Value
SBP of less than 160, DBP of less than 95 mm Hg at baseline			
Age	23.4	2.7–197.5	0.004
OSA	4.9	1.8–13.6	0.002
SBP	4.9	0.5–49.7	NS
DBP	4.3	0.3–62.3	NS
BMI	2.3	0.2–31.5	NS
SBP of less than 140, DBP of less than 90 mm Hg at baseline			
Age	11.4	0.6–199.8	NS
OSA	6.7	1.5–28.8	0.012

Definition of abbreviations: BMI = body mass index; CI = confidence interval; DBP = diastolic blood pressure; NS = nonsignificant; OSA = obstructive sleep apnea; SBP = systolic blood pressure.
* Multiple logistic regression model including the significant univariate predictors.

tiveness was not associated with a risk reduction in these patients. However, effective treatment of OSA was associated with a significant risk reduction for CVD incidence (OR 0.1) after adjustment for age and SBP at baseline.

DISCUSSION

This study has demonstrated a markedly increased incidence of a CVD in previously healthy, middle-aged men with OSA during a follow-up period of 7 years. Without regard to treatment, OSA was associated with an almost fivefold increase in risk for development of CVD independent of age, BMI, SBP, DBP, and current smoking. When OSA was incompletely treated, the independent risk for CVD turned out to increase up to 11-fold, whereas efficient treatment of OSA significantly reduced this excess risk for CVD in OSA patients.

To our knowledge, this is the first long-term, clinic-based, epidemiologic investigation of the development of CVD in middle-aged men free of hypertension and other concomitant CVD at baseline. The strength of this study is the construction of an inception cohort with known OSA status, free of outcome measures at baseline as well as the use of SHDR from a well-organized public epidemiologic center providing reliable and complete data on diagnoses related to hospitalization episodes (14). The main weakness of this study is the lack of polysomnography for a fully accurate diagnosis of OSA. However, an overnight OD of 30 or more was defined as OSA based on previously established diagnostic criteria (11), which was accepted at the time of the baseline investigations in 1991. Although the diagnosis was mainly based on the oximetry results, it was supported by data from oro-nasal thermistors as well as respiratory and body movements. The specificity and sensitivity of static charge-sensitive bed combined with pulse oximetry for an AI of more than 5 verified by polysomnograpy have previously been shown to vary between 67 to 100% (16). Although apnea events were counted, hypopneas could not be adequately detected at baseline in this study. This diagnostic procedure might explain the relatively low proportion of OSA (33%) in this sleep clinic cohort from 1991. On the other hand, this may also be related to the selection criteria (free from outcome at baseline), as OSA was more prevalent (51%) in subjects with a concomitant CVD at baseline. Moreover, many "otherwise healthy subjects" were referred from the Department of Otorhinolaryngology to the sleep laboratory for screening before surgical treatment of habitual snoring was considered. This may also explain the relatively high proportion of the sleep apneics that underwent surgery. However, as we may have missed OSA subjects with mainly hypopneas and/or without desaturations, our results apply to desaturating OSA subjects. On the other hand, as recently discussed in an extensive article by Leung and Bradley (17), apnea–hypopnea index (AHI) may not accurately reflect the most relevant

TABLE 4. PREDICTORS OF CARDIOVASCULAR DISEASE INCIDENCE IN MIDDLE-AGED MEN WITH REGARD TO OSA TREATMENT DURING THE FOLLOW-UP PERIOD*

	Odds Ratio	95% CI	p Value
Overall CVD			
Incompletely treated OSA	11.1	3.9–32.3	< 0.001
Age at baseline	15.2	1.5–160.0	0.023
SBP at baseline	4.2	0.4–47.8	NS
DBP at baseline	3.8	0.2–64.4	NS
BMI at baseline	1.2	0.1–18.0	NS
Hypertension			
Incompletely treated OSA	3.7	1.1–13.1	0.044
Age at baseline	5.1	0.3–82.9	NS
SBP at baseline	30.1	1.4–662.2	0.031
DBP at baseline	4.2	0.1–120.1	NS
BMI at baseline	4.2	0.2–88.8	NS
Coronary artery disease			
Incompletely treated OSA	5.4	1.4–20.6	0.014
Age at baseline	8.1	0.4–160.7	NS
SBP at baseline	7.5	0.4–137.6	NS
Cardiovascular event†			
Incompletely treated OSA	7.7	1.4–43.3	0.021
Age at baseline	9.4	0.2–375.9	NS
SBP at baseline	5.4	0.2–181.8	NS

Definition of abbreviations: BMI = body mass index; CI = confidence interval; DBP = diastolic blood pressure; NS = nonsignificant; OSA = obstructive sleep apnea; SBP = systolic blood pressure.
* Multiple logistic regression model including the significant univariate predictors.
† Cardiovascular event = stroke or myocardial infarction or cardiovascular death.

TABLE 5. PREDICTORS OF CARDIOVASCULAR DISEASE INCIDENCE IN OSA PATIENTS WITH REGARD TO TREATMENT DURING THE FOLLOW-UP PERIOD*

	Odds Ratio	95% CI	p Value
UPPP			
Age at baseline	15.3	1.0–234.3	0.049
SBP at baseline	7.6	0.6–100.2	NS
UPPP at follow-up	0.4	0.1–1.6	NS
CPAP			
CPAP at follow-up	1.7	0.5–5.9	NS
Efficient treatment†			
Age at baseline	7.8	0.3–179.7	NS
SBP at baseline	7.9	0.5–129.1	NS
Efficient OSA treatment at follow-up	0.1	0.0–0.7	0.021

Definition of abbreviations: CI = confidence interval; CPAP = continuous positive airway pressure; NS = nonsignificant; OSA = obstuctive sleep apnea; SBP = systolic blood pressure; UPPP = uvulopalatopharyngoplasty.
* Multiple logistic regression model, including the significant univariate predictors.
† CPAP, UPPP, or oral appliance.

pathophysiologic aspect of OSA contributing to CVD. Some combinations such as frequency and duration of apneas, as well as frequency and degree of desaturations were suggested to provide a better overall index of the cardiovascular burden of OSA (17). In this study, despite the low absolute number of the cases with CVD incidence in the non-OSA group, it is noteworthy that the development of CVD was proportionally more prevalent in the subgroup with "borderline OSA." In other words, assuming that we had missed OSA subjects with dominantly hypopneas relying on the absence of significant desaturations at baseline, the subjects in this age group were still free of a CVD at a follow-up period of 7 years. These findings might therefore have some implications in consideration of intermediate- or long-term randomized trials of the subgroup of OSA subjects with regard to cardiovascular morbidity.

Incidence of CVD was high also in middle-aged otherwise healthy women with OSA compared with women without OSA in this sleep-clinic cohort. However, as the sample size of women was small, and as there were considerable differences in baseline characteristics in the subgroups, we did not include these subjects in the final study population. As this study mainly addressed the causality issue, we focused on the middle-aged men without a pre-existing CVD and could thereby avoid confounding impact of the baseline characteristics of women as well as the gender factor *per se*.

It may be argued that a randomized study design of the OSA subjects would provide a better understanding of a possible causal relationship between OSA and CVD and that observed differences at follow-up in this study might reflect a difference in baseline health status of the groups. However, when considering the serious hemodynamic changes associated with OSA, it appears to be unethical to randomize OSA patients to nontreatment for any longer time period. Not only would randomization of OSA patients to nontreatment mean a potentially increased risk for cardiovascular morbidity, but it would also imply withholding of quality of life improvement due to reduced hypersomnolence in these patients. After a careful selection of the otherwise healthy subjects in our sleep-clinic cohort, the baseline health status was comparable in the OSA subgroups in terms of BMI, current smoking, and blood pressure measurements at baseline. Incompletely treated OSA subjects were 5 years older, but this was statistically adjusted for in the multivariate analysis. In fact, the more severe OSA in terms of ODs was found in the "efficiently treated" group, and this would actually lead a potential underestimation of the therapy effect.

It should also be kept in mind that these results refer to gross clinical abnormalities, but our patients may have had more subtle abnormalities at baseline, including impaired glucose tolerance and elevated fasting cholesterol and/or triglyceride levels (18). Consequently, it is likely that the CVD process might have begun but not yet manifested as clinically diagnosable CVD in many of the men with severe OSA. Although those with apparent CVD were eliminated from the baseline sample, it is likely that occult CVD was present. For instance, SBP and DBP values were significantly higher in OSA subjects at baseline even if the subjects were classified as normotensives according to the WHO criteria of 1991. In other words, the criteria for definition of hypertension used at baseline may have lead to inadvertent inclusion of cases with borderline hypertension. However, a separate analysis including only cases fulfilling adopted WHO criteria did not change the mainstream outcome of the study. Indeed, exclusion of subjects with borderline hypertension at baseline resulted in an even higher OR for CVD in cases with incompletely treated OSA.

Regarding the relatively high proportion of the surgically treated OSA subjects in this cohort, it may be argued that even if the initial result of UPPP was positive, the subjects may have had developed OSA after a few years. However, the first follow-up recordings were done 1–2 years after surgery within the first 4 years of the observation period and demonstrated a 100% treatment effectiveness in the "efficiently treated" group. Assuming that some of these subjects developed OSA later than 4 years, the overall impact of effectiveness of UPPP during the entire observation period may be compared with the compliance defined by CPAP use of at least 50% of the sleep time. In fact, even if half of the OSA population treated with UPPP still had OSA at follow-up, the relative reduction of the obstructive events may have contributed to a favorable impact on prognosis, especially in the younger group of this middle-aged cohort. Assuming that all OSA subjects (even "efficiently treated") were in fact "not efficiently treated," OSA seems to be an independent risk factor for CVD. Nevertheless, some "efficient treatment" does exist and seems to reduce the risk of incidence of CVD in the OSA subjects (Table 5). However, the small number of OSA subjects treated with CPAP in this study and the relatively high proportion of subjects not tolerating CPAP at long-term highlight the difficulties in the clinical setting for treatment selection in otherwise healthy subjects, especially if they do not have daytime sleepiness.

Mechanisms related to increased cardiovascular morbidity in OSA patients have been discussed in detail elsewhere (3). Repeated nocturnal hypoxemia (19) as well as sympathetic activation (20), disturbed endothelial function (19, 21), depressed baroreflex sensitivity (22), increased platelet aggregability (23), and increased vasoconstrictor sensitivity to angiotensin II (24) are some of the proposed mediating mechanisms, whereas to our knowledge, there has been no research evidence suggesting that OSA occurs as a consequence of CVD.

Much of the previous research evidence for a possible causal relationship between OSA and CVD has been focused on hypertension. Indeed, available evidence uniformly demonstrates a moderately strong independent relationship between OSA and hypertension after adjustment for confounding factors (2, 25–28). There is evidence of a dose–response relationship in clinic-based cross-sectional studies, suggesting that more severe OSA has the strongest link to hypertension (9). There is also evidence that OSA may be particularly common among patients with poorly controlled hypertension (29) as well as among those with nondipping hypertension, a marker related with poor prognosis in hypertension (30). Moreover, effective OSA treatment with CPAP was demonstrated to reduce blood pressure in hypertensive OSA patients (31). It is also important to remember that hypertension, if well managed, may be associated with a relative favorable prognosis (32). The time span to secondary complications of OSA may be extended, which may explain the low overall mortality in this study population. Interestingly, these data show that not only hypertension but also other CVD, such as CAD, were associated with OSA. Thus, the causative link between OSA and CVD may not necessarily be mediated by hypertension. Future research needs to take this aspect into account when designing prospective studies. These data strongly support previous smaller studies suggesting a causal relationship between OSA and CAD. In a matched case-control study of 62 CAD patients, OSA represented a threefold increased risk for CAD prevalence after risk factor adjustment (3). At a 5-year follow-up of this CAD group, the Respiratory Disturbance Index was the only independent predictor of cardiovascular mortality (33). The prevalence of electrocardiographically verified myocar-

dial ischemia during sleep was common in OSA patients without a history of CAD, and ischemic episodes were reversed on CPAP treatment (34). Moreover, OSA was found in the patients with severely disabling nocturnal angina, and ischemic episodes were reduced on CPAP treatment (35).

An increased incidence of CVD in incompletely treated OSA subjects clearly advocates that active treatment should be readily considered in sleep-disordered breathing. Treatment may also be rewarding to relatively mild OSA as encountered in this study. In fact, it appeared that even 50% effectiveness of OSA treatment may have a favorable impact on prognosis in this population with more frequent and severe desaturations at baseline. Moreover, this study cohort had no recognizable CVD at baseline. It is possible that OSA contributes as an additive or even synergistic risk factor in patients with co-existing cardiovascular risk factors (18). The frequent occurrence of OSA in patients with hypertension, central obesity, insulin resistance, or dyslipidemia should stimulate to future research in this area (36).

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