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# Increased incidence of coronary artery disease in sleep apnoea: a long-term follow-up

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**ABSTRACT: An increased incidence of cardiovascular disease has previously been reported in middle-aged males during a follow-up period of 7 yrs. The aim of the present study was to address the incidence of coronary artery disease (CAD) in a larger sample without any heart disease at baseline.**

**The population comprised 308 snorers (245 males and 63 females) with a mean±SD age of 49.0±9.9 yrs in 1991. Data were collected *via* the Swedish Hospital Discharge Register, National Cause of Death Registry, clinical charts and questionnaires.**

**Over 7 yrs, CAD was observed in 17 (16.2%) of 105 patients with obstructive sleep apnoea (OSA; overnight (6 h) oxygen desaturations ⩾30 events) compared with 11 (5.4%) of 203 snorers without OSA. OSA diagnosis at baseline was associated with an increased risk of development of CAD in a multivariate model. In the OSA group, CAD was confirmed in 16 (24.6%) of 65 incompletely treated patients compared with one (3.9%) of 26 efficiently treated subjects. Efficient treatment of OSA reduced this risk.**

**It is concluded that middle-aged sleep apnoeics are at high risk of developing coronary artery disease if they are not treated efficiently, which should be considered in cardiovascular disease prevention models.**

**KEYWORDS: Cardiovascular, coronary artery disease, intervention, sleep apnoea**

Obstructive sleep apnoea (OSA) affects 9–24% of the middle-aged population [1], and there is growing awareness of this condition as a potential risk factor for cardiovascular diseases (CVDs), including hypertension, coronary artery disease (CAD) and stroke [2–5]. Epidemiological data suggest that OSA is overrepresented in CAD [6–8], and that the long-term outcome is poor in these patients [9, 10]. A recent follow-up study reported reductions in new cardiovascular events after treatment of OSA in CAD patients [11]. Moreover, people with OSA seem to exhibit a peak in sudden death from cardiac causes during the sleeping hours compared with the nadir of sudden death from cardiac causes during this period in people without OSA and in the general population [12]. However, besides rapidly increasing epidemiological support for an association between OSA and CAD, a causal relationship has not yet been fully confirmed. In general, there is a stronger relationship between OSA and CAD in clinical cohorts compared with the general population because clinical cohort studies are particularly influenced by comorbidity and confounding factors, including obesity, hypertension, smoking and hyperlipidaemia. In this perspective, OSA may provide an additive or synergistic risk factor for the development of CAD.

In order to explore the possibility of a causal relationship between OSA and CVD, the incidence of CVD during a follow-up period of 7 yrs was previously addressed in middle-aged snoring males with or without OSA but free of hypertension and any other concomitant CVD, pulmonary disease, diabetes mellitus, psychiatric disorders, alcohol dependency or malignancy at baseline [13]. A subanalysis of incident CVD revealed increased CAD even in a small sample. In the current study, the aim was to further explore the incidence of CAD in a larger sample of this sleep clinic cohort from 1991, including all middle-aged males and females without any concomitant heart disease at baseline.

## METHODS

### *Study population*

The study population has been described in detail elsewhere [13]. In brief, 370 consecutive

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subjects with a history of snoring and/or witnessed apnoeas were investigated in the sleep laboratory of the Dept of Pulmonary Medicine at the University Hospital of Gothenburg (Gothenburg, Sweden) during 1991. On reviewing the baseline data of this cohort, 20 younger (aged <30 yrs) and 17 elderly subjects (aged >69 yrs), 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 (Stockholm, Sweden), were excluded (fig. 1). For the remaining 318 middle-aged (30–69 yrs) subjects, besides baseline recordings on clinic charts, complementary information on health status was obtained from the Swedish Hospital Discharge Register (SHDR) *via* the Centre for Epidemiology at the National Board of Health and Welfare (Stockholm, Sweden). Ten patients with concomitant heart disease (CAD and/or cardiac failure) at the baseline investigation were excluded. Finally, 308 middle-aged individuals without concomitant heart disease at baseline were identified for the present study (fig. 1). The patients were enrolled independently of a history of associated excessive daytime sleepiness. A 7-yr period following the baseline investigation was defined for each subject within the time span January 1, 1991 to December 31, 1998. Death certificates for patients who died were obtained from the National Cause of Death Registry. In parallel, a postal questionnaire was sent to the survivors. Moreover, objective data were obtained on therapeutic effectiveness in the OSA subjects during the follow-up period. Consequently, 308 subjects (245 males and 63 females; mean±SD age 49.0±9.9 yrs at baseline) were analysed in two groups depending on OSA diagnosis in 1991 (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.

### *Baseline investigations*

Sleep studies, blood pressure recordings and other measurements performed at baseline have been described in detail elsewhere [13]. In brief, the subjects underwent an overnight sleep study in the sleep laboratory; investigations were initiated at ~23:00 h and terminated at 06:00 h, allowing for 7 h of sleep. Lights out and lights on were recorded and subjective sleep quality, as well as subjective sleep duration, was documented. Patients with a self-reported sleep duration of <5 h were reinvestigated. The mean estimated sleep time was empirically chosen to be 6 h. The sleep study included continuous recording of transcutaneous arterial oxygen saturation ($S_{a,O_2}$) *via* a finger probe (BIOX 3700; Ohmeda, Louisville, CO, USA), nasal and oral airflow *via* a thermistor, and respiration and body movement monitored *via* a static-charge-sensitive bed (SCSB; BioMatt; Biorec, Inc., Raisio, Finland). Signals were amplified and recorded on a fibre-tip pen recorder (Kipp & Zonen, Delft, The Netherlands). An apnoeic event was scored when the $S_{a,O_2}$ fell by ⩾4% from the immediately preceding baseline simultaneous with the absence of nasal and oral airflow, as well as presence of chest movements, for >10 s. Scoring was carried out 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 $S_{a,O_2}$ ($S_{a,O_2,min}$) reached, during the overnight recording was determined. An overnight (6 h) OD of ⩾30 events was defined as OSA. This value was based on previously established diagnostic criteria [14] of an apnoea index of ⩾5 events·h$^{-1}$ for sleep apnoea syndrome, which was accepted at the time of the baseline investigations. Additionally, the oxygen desaturation index (ODI) was applied as the mean number of ODs per self-estimated hour of sleep in each case.

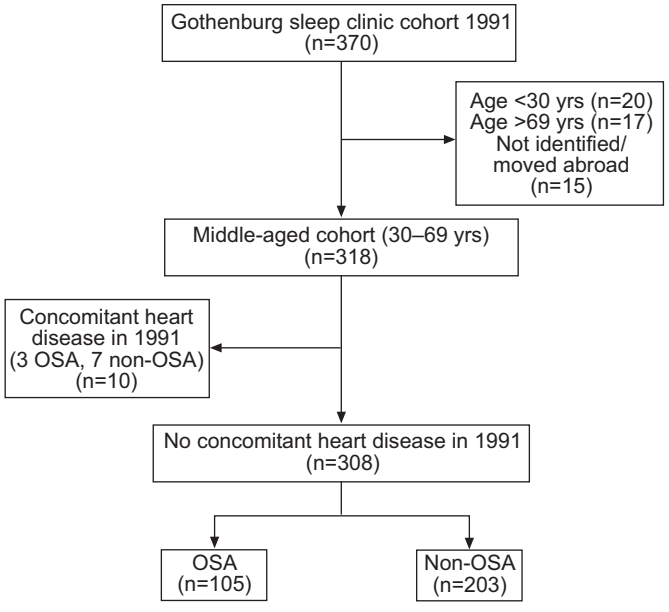


**FIGURE 1.** Flow chart showing study cohort and different subgroups. OSA: obstructive sleep apnoea.

**TABLE 1** Baseline characteristics of the middle-aged sleep clinic cohort without concomitant heart disease in 1991, as well as incidence of coronary artery disease (CAD) at follow-up

| | OSA | Non-OSA | p-value# |
|---|---|---|---|
| **Subjects n** | 105 | 203 | |
| **Age yrs** | 51.8±8.9 | 47.6±10.2 | <0.001 |
| **BMI kg·m$^{-2}$** | 28.6±4.0 | 25.9±3.7 | <0.001 |
| **SBP mmHg** | 138.4±16.3 | 130.1±17.9 | <0.001 |
| **DBP mmHg** | 82.2±9.4 | 78.6±10.3 | 0.003 |
| **OD events·6 h$^{-1}$** | 94.1±86.0 | 8.9±8.3 | <0.001 |
| **ODI events·h$^{-1}$** | 17.8±15.1 | 1.6±1.7 | <0.001 |
| **$S_{a,O_2,min}$ %** | 80.5±7.8 | 88.6±4.2 | <0.001 |
| **Males** | 91 (86.7) | 154 (75.9) | 0.026 |
| **Hypertension** | 30 (28.6) | 33 (16.3) | 0.011 |
| **Diabetes mellitus** | 2 (1.9) | 2 (1.0) | NS |
| **Smokers** | 35 (34.0) | 80 (41.5) | NS |
| **CAD incidence** | 17 (16.2) | 11 (5.4) | 0.003 |
| **Cardiovascular death** | 8 (7.6) | 1 (0.5) | <0.001 |

Data are presented as mean±SD and n (%), unless otherwise indicated. OSA: obstructive sleep apnoea; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; OD: oxygen desaturation ⩾4%; ODI: oxygen desaturation index; $S_{a,O_2,min}$: minimal arterial oxygen saturation; NS: nonsignificant. #: unpaired t-test for continuous variables, Chi-squared test for categorical variables. 1 mmHg=0.133 kPa.

**TABLE 2** Baseline and follow-up characteristics of the obstructive sleep apnoea patients according to effectiveness of treatment[#]

| | Treatment | | p-value[¶] |
|---|---|---|---|
| | Incomplete | Efficient | |
| **Subjects n** | 65 | 26 | |
| **Age at baseline yrs** | 53.2±8.6 | 50.6±8.7 | NS |
| **BMI kg·m$^{-2}$** | | | |
| 1991 | 28.9±4.5 | 27.9±3.2 | NS |
| 1998 | 29.0±4.3 | 28.9±3.9 | NS |
| **SBP 1991 mmHg** | 138.6±15.3 | 141.2±20.1 | NS |
| **DBP 1991 mmHg** | 82.1±8.9 | 83.7±9.5 | NS |
| **OD 1991 events·6 h$^{-1}$** | 76.8±51.0 | 110.9±124.5 | NS |
| **ODI 1991 events·h$^{-1}$** | 14.9±11.2 | 20.8±19.8 | NS |
| **$S_{a,O_2,min}$ 1991 %** | 81.8±6.3 | 78.4±10.5 | NS |
| **Males** | 57 (87.7) | 21 (80.8) | NS |
| **Hypertension 1991** | 20 (30.8) | 7 (26.9) | NS |
| **Diabetes mellitus 1991** | 1 (1.5) | 0 (0.0) | NS |
| **Smoker 1991** | 19 (29.7) | 9 (34.6) | NS |
| **Questionnaire respondent** | 51 (78.5) | 25 (96.2) | 0.040 |
| **CAD incidence** | 16 (24.6) | 1 (3.9) | 0.022 |

Data are presented as mean±SD and n (%), unless otherwise indicated. BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; OD: oxygen desaturation ⩾4%; ODI: oxygen desaturation index; $S_{a,O_2,min}$: minimal arterial oxygen saturation; CAD: coronary artery disease; NS: nonsignificant. [#]: subjects receiving treatment without objective data on therapy effectiveness at follow-up (n=14) were excluded; [¶]: unpaired t-test for continuous variables, Chi-squared test for categorical variables. 1 mmHg=0.133 kPa.

Height and weight were measured. Blood pressure was recorded with an appropriate arm-cuff on the left or right arm after a minimum of 15 min of supine rest in each patient during the evening before the onset of the sleep study according to routine clinical procedure in the sleep laboratory. Patients with ongoing hypertensive medication, a systolic blood pressure (SBP) of ⩾160 mmHg and/or diastolic blood pressure (DBP) of ⩾95 mmHg qualified for a diagnosis of hypertension based on the definition used at the time of the investigation [15]. Body mass index (BMI) was calculated according to the formula body weight divided by height squared. Data on smoking habits were also documented in the routine questionnaire at baseline.

### *Swedish Hospital Discharge Register*

The SHDR covers all public in-patient care since 1987. The number of cases not reported to the register was estimated to be 1–2% by a data quality check [16]. In the SHDR, there are four different types of information, *i.e.* patient-related data (personal identification number, sex, age and place of residence), hospital-related data (county council, hospital and department), administration-related data (date of admission and discharge, duration of stay, whether acute or planned admission, and location admitted from and discharged to) and medical data (main diagnosis, secondary diagnoses, external cause of injury and poisoning, and surgical procedures). For classification of diseases, International Classification of Diseases, ninth revision, codes were used until 1997, and International Statistical Classification of Diseases and Related Health Problems, 10th revision, codes thereafter. In order to identify patients without any cardiac diagnosis and to control for other concomitant diseases at baseline, data were obtained from the SHDR for a 3-yr extension period prior to the baseline investigation. The main outcome measure in the SHDR evaluation was incidence of CAD (angina pectoris or myocardial infarction) requiring hospitalisation. The SHDR does not include information about how the CAD diagnosis was confirmed in each patient. In clinical practice, the diagnosis of angina pectoris is based on standard criteria, *i.e.* prolonged chest pain with typical changes in the ECG, and therapeutic response to nitroglycerine administration, ECG changes on exercise testing, and/or confirmation of coronary artery stenosis by coronary angiography. The diagnosis of myocardial infarction requires standard criteria, *i.e.* prolonged chest pain, a typically evolving ECG and increased levels of cardiac enzymes. Patients with more than one hospitalisation due to angina pectoris or myocardial infarction were considered only once in the reporting of CAD in order to avoid bias with increased CAD in the study population.

### *Questionnaires*

The postal questionnaires, sent to the 299 survivors at the beginning of 1999, included questions regarding current weight, history of smoking, and, if relevant, hospital admissions with CAD, ongoing medication, and treatment for snoring or OSA during the follow-up period. Drugs that were registered include those listed within anatomical therapeutic chemical classification system codes C01–C08 [17]. Data from the questionnaires regarding the CAD diagnosis and hospitalisation were also taken into consideration in the evaluation of the SHDR data.

### *Treatment of obstructive sleep apnoea*

OSA treatment was initiated by different physicians according to clinical routines depending on the severity of the sleep-related breathing disorder, 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 an oral appliance. Surgically treated patients were invited for repeat sleep study recordings for evaluation of the effectiveness of the treatment and offered CPAP or an oral appliance in the case of remaining OSA-symptomatic cases, despite treatment. Therapeutic CPAP titration was performed according to the prevailing manual standardised procedure, using a full-night evaluation in a laboratory setting, including 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 using the time-counter of the devices (hours divided by days passed between the last two recordings). OSA patients not undergoing treatment or with OSA remaining despite treatment with UPPP or an oral device, or a daily CPAP run-time of <50% of the estimated sleep time were regarded as incompletely treated cases. Efficiently treated

patients were defined as those with an OD of <30 events (in 6 h) at the repeat sleep study following UPPP, on treatment with an oral device (subjective use for ⩾50% of estimated sleep time) or on CPAP with an objective daily CPAP run-time of ⩾50% of estimated sleep time. The evaluation of compliance data was performed by two observers blinded to the incidence of CAD diagnosis.

### *Statistics*

The groups were compared using an unpaired t-test for variables measured on a continuous scale, and, where appropriate, Fisher's exact test (two-tailed) or a Chi-squared test for categorical variables. The following variables were analysed: age; sex; BMI; current smoking at baseline; diabetes; hypertension; lung disease; usage of β-blocking agent, calcium channel antagonist, angiotensin-converting enzyme inhibitor or angiotensin II antagonist, and diuretics; SBP; DBP; OSA diagnosis at baseline; OD; ODI; and $S_{a,O_2,min}$. A multivariate Poisson model [18] was used to study the relationship between these variables and the risk of CAD. The variables were chosen one after another on the basis of the lowest p-value until none of the others was significant. The hazard function was assumed to be exp (β0+(β1×OSA diagnosis at baseline)+(β2×time since baseline)+(β3×SBP)+(β4×current age)+(β5×$S_{a,O_2,min}$)). The β coefficient reflected how the risk was changing, depending on the corresponding variable, and βi=0 meant that the risk was not affected at all by the variable. Adjusted risk ratios (taking the other significant variables into account) were calculated from the regression coefficients and presented with their 95% confidence intervals. A separate analysis was performed for OSA patients including treatment of OSA (CPAP, UPPP, oral device and efficient treatment, regardless of treatment modality). In addition, the probability of CAD within different periods was calculated from the Poisson model. Continuous values are presented as mean±SD. A p-value (two-sided) of ⩽0.05 was regarded as significant.

## RESULTS

As shown in figure 1, concomitant heart disease was prevalent at baseline in 10 (3.1%) of the middle-aged sleep clinic cohort. Eight of these patients had previously experienced an acute myocardial infarction, and two had even had cardiac failure. Three showed OSA at baseline. In the final study population of the sleep clinic cohort without concomitant heart disease at baseline, OSA was found in almost a third of the cohort (fig. 1). Compared with subjects without OSA at baseline, the OSA patients were predominantly male and hypertensive and exhibited a higher BMI, whereas the relative proportion of diabetics and smokers did not differ significantly (table 1).

As shown in table 2, incompletely treated OSA patients were slightly older than those efficiently treated but showed fewer desaturations at baseline. BMI, SBP, DBP, and proportion of males, hypertension, diabetes and smokers did not differ significantly between the groups.

During follow-up, treatment of OSA was initiated with CPAP (age 54.4 yrs, ODI 24.1±21.7 events·h$^{-1}$; n=31), UPPP (age 48.4 yrs, ODI 17.0±12.1 events·h$^{-1}$; n=41) and/or an oral device (n=6), whereas no active treatment was considered in 39 (37.1%) patients (age 53.0 yrs, ODI 14.2±9.5 events·h$^{-1}$) due to either mild OSA and/or lack of excessive daytime sleepiness. Among the CPAP-treated OSA patients, 15 (48.4%) cases returned the device or showed low treatment compliance at follow-up. Of subjects undergoing UPPP, ~40% still exhibited OSA at the follow-up recording. However, for the whole UPPP group, there was a significant reduction in ODI from 14.7±8.3 events·h$^{-1}$ at baseline to 6.0±5.7 events·h$^{-1}$ at follow-up (p<0.001). The first follow-up recordings were performed 1–2 yrs following surgery within the first 4 yrs of the observation period but not repeated later as these subjects did not report symptoms. Only two out of six subjects treated with an oral device were considered efficiently treated.

OSA subjects lacking objective sleep study recordings at follow-up (five treated with CPAP and nine with UPPP) were excluded from the final statistical analysis comparing the subgroups based on the effectiveness of treatment (table 2). However, none of these subjects had a history of angina pectoris according to questionnaire reports and no CAD diagnosis was documented in the SHDR.

During the follow-up period, CAD was observed in 17 out of 105 (16.2%) cases with OSA compared with 11 out of 203 (5.4%) snorers without OSA (p=0.003; table 1). The CAD diagnosis was associated with a fatal outcome in nine out of the 28 cases, eight in the OSA group and one in the non-OSA group (p<0.001). When analysing the OSA group with regard to treatment effectiveness, CAD was confirmed in 16 out of 65 (24.6%) incompletely treated cases compared with one out of 26 (3.9%) efficiently treated subjects (p=0.022; table 2).

On multivariate analysis, it was found that OSA diagnosis at baseline, SBP, current age, time since baseline and $S_{a,O_2,min}$ were the variables that were of significant importance for CAD. None of the other variables were significantly important (table 3). Disregarding treatment during the follow-up period, OSA at baseline was associated with an increased relative risk (RR) of 4.6 (95% confidence interval (CI) 1.8–11.6) for the development of CAD (p=0.001). Figure 2 illustrates the probability of CAD in the sleep clinic cohort, calculated from the Poisson model, for an example for whom age is 49 yrs at baseline, with an SBP of 133 mmHg and $S_{a,O_2,min}$ of 86%, and disregarding treatment during the follow-up period. When analysing the OSA group, efficient treatment of OSA was associated with a reduced risk of CAD (RR 0.3, 95% CI 0.1–0.8;

**TABLE 3** Poisson model significant predictors of incidence of coronary artery disease in a middle-aged sleep clinic cohort[#]

| | β | RR (95% CI) | p-value |
|---|---|---|---|
| **Constant** | -22.84 | | |
| **OSA at baseline** | 1.53 | 4.60 (1.83–11.6) | 0.001 |
| **Time since baseline yrs** | 0.19 | 1.21 (1.01–1.45) | 0.043 |
| **SBP at baseline mmHg** | 0.04 | 1.03 (1.01–1.05) | <0.001 |
| **Current age yrs** | 0.06 | 1.06 (1.02–1.11) | 0.007 |
| **$S_{a,O_2,min}$ at baseline %** | 0.11 | 1.11 (1.02–1.22) | 0.019 |

RR: relative risk; CI: confidence interval; OSA: obstructive sleep apnoea; SBP: systolic blood pressure; $S_{a,O_2,min}$: minimal arterial oxygen saturation. [#]: without regard to OSA treatment during the follow-up period.

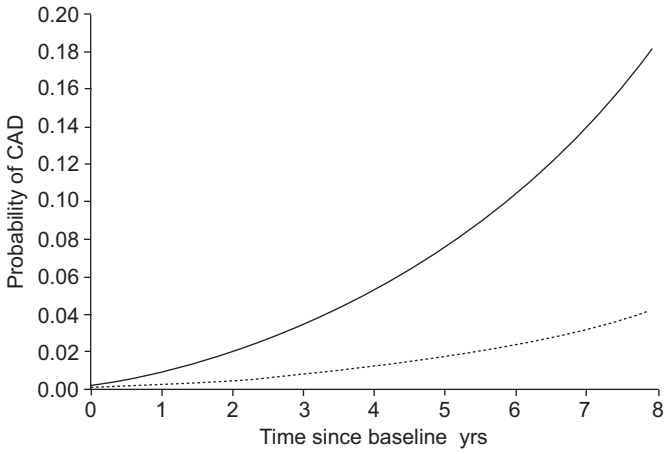


**FIGURE 2.** Probability of coronary artery disease (CAD; ——: obstructive sleep apnoea (OSA) patients 1991; ------: non-OSA patients 1991), calculated from the Poisson model. In this example, age at baseline is 49 yrs, with a systolic blood pressure of 133 mmHg and minimal arterial oxygen saturation of 86%, and treatment during the follow-up period is disregarded. 1 mmHg=0.133 kPa.

p=0.020) after adjustment for significant confounding variables in this cohort (table 4).

## DISCUSSION

The present study has demonstrated an increased incidence of CAD in middle-aged OSA patients during a follow-up period of 7 yrs. Disregarding treatment, OSA was associated with an almost five-fold increase in risk of development of CAD independent of age, sex, hypertension, diabetes and current smoking. Efficient treatment of OSA significantly reduced this excess risk of CAD in OSA patients.

To the present authors' knowledge, this is the first long-term clinic-based observational investigation into the development of CAD in middle-aged OSA patients free of concomitant heart disease at baseline. The present 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 three-fold increased risk of CAD after risk factor adjustment [6]. At a 5-yr follow-up of this CAD group, respiratory disturbance index was an independent predictor of cardiovascular mortality [9]. Electrocardiographically verified myocardial ischaemia during sleep was common in OSA patients without a history of CAD, and ischaemic episodes were reversed on CPAP treatment [19]. Moreover, OSA was found in the patients with severely disabling nocturnal angina, and ischaemic episodes were reduced on CPAP treatment [20].

**TABLE 4** Poisson model significant predictors of incidence of coronary artery disease in the obstructive sleep apnoea (OSA) patients[#]

| | β | RR (95% CI) | p-value |
|---|---|---|---|
| **Constant** | -27.90 | | |
| **Efficient OSA treatment** | -1.23 | 0.29 (0.10–0.82) | 0.020 |
| **Time since baseline yrs** | 0.25 | 1.28 (1.01–1.64) | 0.043 |
| **Current age yrs** | 0.10 | 1.11 (1.03–1.18) | 0.004 |
| **$S_{a,O_2,min}$ at baseline %** | 0.22 | 1.24 (1.07–1.43) | 0.004 |
| **Bronchial asthma/COPD at baseline** | 5.03 | 153 (7.6–3061) | 0.001 |

RR: relative risk; CI: confidence interval; $S_{a,O_2,min}$: minimal arterial oxygen saturation; COPD: chronic obstructive pulmonary disease. [#]: during 7 yrs following the baseline sleep study in 1991.

It should be also be kept in mind that the strength of the present study lies in the construction of an inception cohort of known OSA status and free of outcome measures at baseline, as well as the use of the SHDR from a well-organised public epidemiological centre providing reliable and complete data on diagnoses related to hospitalisation episodes [16]. The main weakness of the study is the lack of polysomnographic data for a fully accurate diagnosis of OSA. However, an overnight (6 h) OD of $\geqslant$30 events was defined as OSA based on previously established diagnostic criteria [14], which were accepted at the time of the baseline investigations in 1991. Although the diagnosis was mainly based on the oximetric results, it was supported by data from oronasal thermistors, as well as respiratory and body movements. The specificity and sensitivity of the static-charge-sensitive bed combined with pulse oximetry for an apnoea index of $\geqslant$5 events·h$^{-1}$ verified by polysomnograpy has previously been shown to range 67–100% [21].

Although apnoea events were counted, hypopnoeas could not be adequately detected at baseline in the present study, since the equipment used could not detect respiratory events without desaturation that were causing arousals. This diagnostic procedure might explain the relatively low proportion of OSA (33%) in this sleep clinic cohort from 1991. Conversely, it may also be related to the selection criteria (free from outcome at baseline). Moreover, many otherwise healthy subjects were referred to the sleep laboratory from the Dept of Otorhinolaryngology for screening before surgical treatment of habitual snoring was considered. This may also explain the relatively high proportion of sleep apnoeics who underwent surgery. However, as OSA subjects with mainly hypopnoeas and/or without desaturations may have been missed, the present results apply to desaturating OSA subjects. Conversely, as previously discussed in an extensive article by LEUNG and BRADLEY [22], apnoea/hypopnoea index may not accurately reflect the most relevant pathophysiological aspects of OSA contributing to cardiovascular complications. Some combinations, such as frequency and duration of apnoeas, as well as frequency and degree of desaturations, were suggested to provide a better overall index of the cardiovascular burden of OSA [22]. In the present study, despite the low absolute number of cases with CAD incidence in the non-OSA group, it is noteworthy that the development of CAD was proportionally more prevalent in the subgroup with borderline OSA. In other words, assuming that OSA subjects with predominantly hypopnoeas with arousals but without significant desaturations at baseline had been missed, these subjects in this age group were still free of CAD after a follow-up period of 7 yrs. These findings might, therefore, have some implications in consideration of intermediate- or long-term randomised trials of the subgroup of OSA subjects with regard to cardiovascular morbidity.

It may be argued that reduced lung function (forced expiratory volume in one second), as a well-known independent predictor of mortality, should be discussed in this context. Thus, patients with impaired lung function might have experienced more oxygen desaturations during the study and this might have led to increased CAD and mortality. Lung function data were not available, but, from the SHDR, it was possible to identify four patients with bronchial asthma or chronic obstructive pulmonary disease (COPD) at baseline (two in the OSA and two in the non-OSA group). However, the group of smokers was larger in the non-OSA compared to the OSA group (table 1), and lung function findings, if provided, would be unlikely to alter the main findings of the present study. Moreover, findings in the OSA group regarding CAD incidence were adjusted for asthma or COPD diagnosis at baseline (table 4).

It may also be argued that a randomised study design for the OSA subjects would provide a better understanding of a possible causal relationship between OSA and CAD, and that observed differences at follow-up in the present study might reflect a difference in the baseline health status of the groups. However, when considering the serious haemodynamic changes associated with OSA (see below), it appears to be unethical to randomise OSA patients to nontreatment for any longer time period. Not only would randomisation of OSA patients to nontreatment mean a potentially increased risk of cardiovascular morbidity, but it would also imply withholding of quality-of-life improvement due to reduced hypersomnolence in these patients. After careful selection of otherwise healthy subjects in the present sleep-clinic cohort, baseline health status was comparable in the OSA subgroups in terms of BMI, current smoking, blood pressure measurements, and prevalence of hypertension and diabetes at baseline. Incompletely treated OSA subjects were 2.6 yrs older, but this was adjusted for in the multivariate analysis. Indeed, the more severe OSA in terms of oxygen desaturations was found in the efficiently treated group, leading to potential underestimation of the therapy effect.

It should also be borne in mind that the present results refer to gross clinical abnormalities, and that the patients might have shown more subtle abnormalities at baseline, including impaired glucose tolerance and elevated fasting cholesterol and/or triglyceride levels [23]. Consequently, it is likely that the CAD process might have begun, but not yet manifested as clinically diagnosable CAD, in many of the patients with severe OSA. Although those with apparent CAD were eliminated from the baseline sample, it is likely that occult CAD was present.

Regarding the relatively high proportion of surgically treated OSA subjects in the present cohort, it may be argued that, even if the initial results of UPPP were positive, the subjects might have developed OSA after a few years. However, the first follow-up recordings were carried out 1–2 yrs following surgery within the first 4 yrs of the observation period and demonstrated 100% treatment effectiveness in the effectively treated group. Assuming that some of these subjects developed OSA after >4 yrs, the overall impact of effectiveness of UPPP during the whole observation period may be compared with the compliance defined by CPAP use of $\geqslant$50% of sleep time. Indeed, even if 40% of the OSA population treated with UPPP still had OSA at follow-up, it implies that 60% were considered successfully treated, and that the relative reduction in obstructive events might have contributed to a favourable impact on prognosis, especially in the younger patients in this middle-aged cohort. Assuming that all OSA subjects (even those efficiently treated) were not efficiently treated, OSA seems to be an independent risk factor for CAD (table 3; fig. 2). Nevertheless, some efficient treatment exists and seems to reduce the risk of incidence of CAD in OSA subjects (table 4). In other words, the odds ratio for CAD incidence would be even higher in the untreated group. However, the small number of OSA subjects treated with CPAP in the present study, and the relatively high proportion of subjects not tolerating long-term CPAP, highlights the difficulties in the clinical setting for treatment selection in otherwise healthy subjects, especially if they do not exhibit daytime sleepiness.

Mechanisms related to the increased incidence of CAD in OSA patients have been discussed in detail elsewhere [24]. During the cycle of an apnoeic event, there is increased work of breathing, considerable negative intrathoracic pressure, recurrent hypoxia/reoxygenation and fluctuating autonomic activity [22]. Increased oxygen demand and reduced oxygen supply, *i.e.* hypoxaemia, following sleep-disordered breathing may trigger an attack of angina pectoris in patients with CAD who already exhibit reduced coronary flow reserve [20, 25].

With the increasing recognition of obstructive sleep apnoea as an independent, additive or even synergistic risk factor for coronary artery disease, there is a need for early identification of high-risk individuals and a consensus regarding well-defined treatment strategies in such patients. Regarding the low oxygen desaturation index at baseline in the present study population, even mild obstructive sleep apnoea seems to have a substantial effect on coronary artery disease risk and highly effective treatment should therefore be provided. In this context, the present study clearly suggests a causal relationship between obstructive sleep apnoea and coronary artery disease, and consequently supports the inclusion of obstructive sleep apnoea among factors considered in cardiovascular disease prevention models.

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