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INCREASED INCIDENCE OF CORONARY ARTERY DISEASE IN SLEEP APNOEA: A LONG-TERM FOLLOW-UP

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Abstract

We have previously reported an increased incidence of cardiovascular disease in middle-aged men during a follow-up period of 7 years. In the current study, we addressed the incidence of coronary artery disease (CAD) in a larger sample (308 snorers; 245 men, 63 women; mean age 49.0±9.9 yrs in 1991) without any heart disease at baseline. Data was collected via the Swedish Hospital Discharge Register, National Cause of Death Registry, clinical charts and questionnaires. During 7 years, CAD was observed in 17 of 105 cases (16.2%) with OSA (overnight oxygen desaturations≥30) compared with in 11 of 203 (5.4 %) snorers without OSA (p=0.003). OSA diagnosis at baseline was associated with an increased relative risk (RR) of 4.6 (95% confidence interval [CI] 1.8-11.6) for development of CAD (p=0.001) in a multivariate model. In the OSA group, CAD was confirmed in 16 of 65 incompletely treated cases (24.6%) compared with in 1 of 26 (3.9%) efficiently treated subjects (p=0.022). Efficient treatment of OSA reduced this risk (RR 0.3, 95% CI 0.1-0.8; p=0.020). We conclude that middle-aged sleep apnoeics are at high risk of developing CAD if they are not treated efficiently, which should be considered in the cardiovascular prevention models.

Word count: 199.

Key words: Sleep apnoea, coronary artery disease, cardiovascular, intervention.

INTRODUCTION

Obstructive sleep apnoea (OSA) affects 9-24 % of the middle-aged population (1) and there is a growing awareness of this condition as a potential risk factor for cardiovascular diseases (CVD), including hypertension, coronary artery disease (CAD) and stroke (2-5). Epidemiological data suggest that OSA is over-represented in CAD (6-8), and 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 have 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 a rapidly increasing epidemiological support for an association between OSA and CAD, a causal relationship has yet not 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 hyperlipidemia. In this perspective OSA may provide an additive or synergistic risk factor for development of CAD.

In order to explore the possibility of a causal relationship between OSA and CVD, we have previously addressed the incidence of CVD during a follow-up period of seven years in middle-aged snoring men with or without OSA but free of hypertension and any other concomitant CVD, pulmonary disease, diabetes mellitus, psychiatric disorder, alcohol dependency or malignancy at baseline (13). A subanalysis of the incident CVD revealed even an increased CAD in a small sample. In the current study, we aimed to further explore the incidence of CAD in a larger sample of this sleep clinic cohort from 1991, including all middle-aged men and women without any concomitant heart disease at baseline.

METHODS

Study Population

The study population has been described in detail elsewhere (13). In brief, 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 during 1991. By review of baseline data of this cohort, 20 younger (age <30 yrs) and 17 elderly (age>69 yrs) 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 yr) 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 (*see* below). Ten patients with a concomitant heart disease (CAD and/or cardiac failure) at the baseline investigation were excluded. Finally, 308 middle-aged individuals without a concomitant heart disease at baseline were identified for the present study (Figure 1). The patients were enrolled independently of a history of associated excessive daytime sleepiness (EDS). A seven-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 (*see* below) was sent to the survivors. Moreover, objective data on therapy effectiveness of the OSA subjects during the follow-up period was obtained (*see* below). Consequently, 308 subjects (245 men, 63 women; mean age 49.0 ± 9.9 yrs at baseline) were analyzed 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, BP recordings and other measurements at baseline have been described in detail elsewhere (13). In brief, the subjects underwent an overnight sleep study in the sleep laboratory and investigations were initiated at approximately 11 P. M. and terminated at 6 A.M. allowing for 7 h of sleep. Lights out and lights on were recorded and the subjective sleep quality as well as subjective sleep duration was documented. Patients with self-reported sleep duration shorter than 5 h were reinvestigated. The average estimated sleep time was empirically chosen to be 6 h. The sleep study included a continuous recording of transcutaneous arterial oxygen saturation (SaO_2) 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 (SCSB [Bio-matt; Biorec Inc., Raisio, Finland]). Signals were amplified and recorded on a filter pen recorder (Kipp & Zonen, Delft, Holland). An apnea was scored when SaO_2 dropped by at least 4% from the immediately preceding baseline simultaneously with absence of nasal and oral airflow as well as presence of chest movements for more than 10 s. Scoring was made manually from each recording strip by trained technicians unrelated to the study itself. The total number of significant oxygen desaturations (OD) as well as the minimal SaO_2 reached during the overnight recording (SaO_2min) was determined. An overnight OD $\geq$ 30 was defined as obstructive sleep apnea. This value was based on previously established diagnostic criteria (14) of an apnea index $\geq$ 5 for the sleep apnea syndrome, which was accepted at the time of the baseline investigations. Additionally, Oxygen Desaturation 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 15 min supine rest in each

patient in 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 SDP ≥ 160 and/or DBP ≥ 95 mmHg were qualified for the diagnosis of hypertension based on the definition used at the time of the investigation (15). 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.

Swedish Hospital Discharge Register

The Swedish Hospital Discharge Register (SHDR) covers all public in-patient care since 1987. The number of cases not reported to the register was estimated to between one and two per cent according to 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, 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 thereafter. In order to identify cases without any cardiac diagnosis and to control for other concomitant diseases at baseline, data from the SHDR was obtained for a three-year extension period prior to the baseline investigation. The main outcome measure in the SHDR evaluation was the incidence of CAD (angina pectoris or myocardial infarction) requiring hospitalization. The SHDR does not include information about how the CAD diagnosis was confirmed in each patient. In the clinical practice, the diagnosis of angina pectoris is based on standard criteria, *i.e.* prolonged chest pain with typical changes of the electrocardiogram (ECG), therapeutic response to nitroglycerine administration,

and/or ECG changes at exercise testing and/or confirmation of the coronary artery stenosis by coronary angiography. The diagnosis of myocardial infarction requires standard criteria, ***i.e.*** prolonged chest pain, typically evolving ECG and increased levels of cardiac enzymes. Cases with more than one hospitalization 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

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

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 EDS and social aspects of loud snoring. Patients with EDS were offered either treatment with continuous positive airway pressure (CPAP) or surgery (uvulopalatopharyngoplasty [UPPP]) or oral appliance. Surgically treated cases were invited for renewed sleep study recordings for evaluation of effectiveness of the treatment and offered CPAP or oral appliance in case of remaining symptomatic OSA in spite of treatment. Therapeutic CPAP titration was performed according to the prevailing manual standardized procedure using a full night evaluation in a laboratory setting (*see* above) 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 in spite of treatment with UPPP or oral device or daily CPAP run-time less than 50% of estimated sleep time were regarded as incompletely treated cases. Efficiently treated patients were defined as the cases with OD below 30 at the renewed sleep study following 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 CAD diagnosis.

Statistics

The groups were compared by use of Student's t test for variables measured on a continuous scale, and where appropriate, by Fisher exact test (two tailed) or chi-squared test for categorical variables. The following variables were analyzed: Age, gender, BMI, current smoking at baseline, diabetes, hypertension, lung disease, usage of beta blocking agent, calcium channel antagonist, angiotensin converting enzyme inhibitor or angiotensin II antagonist, diuretics, SBP, DBP, OSA diagnosis at baseline, OD, ODI and SaO_2min. A multivariate Poisson model (18) was used to study the relationship between the variables above and the risk of CAD. The variables were chosen one after another due to the lowest p-value until no one of the other ones was significant. The hazard function was assumed to be exp ($\beta 0 + \beta 1 \cdot$ OSA diagnosis at baseline + $\beta 2 \cdot$ Time since baseline + $\beta 3 \cdot$ SBP + $\beta 4 \cdot$ Current age + $\beta 5 \cdot SaO_2$min). A beta coefficient reflected how the risk was changing depending

on the corresponding variable, and $\beta i = 0$ 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 done 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 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 heart disease was prevalent at baseline in 10 (3.1%) of the middle-aged sleep clinic cohort. Eight of these patients had experienced an acute myocardial infarction previously, and two had even cardiac failure. Three had OSA at baseline. In the final study population of the sleep clinic cohort without a concomitant heart disease at baseline, OSA was found in almost one third of the cohort (Figure 1). Compared with subjects without OSA at baseline, the OSA patients were dominantly male and hypertensive, had higher BMI while 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 had fewer desaturations at baseline. BMI, SBP, DBP, and proportion of male gender, hypertension, diabetes and smokers did not differ significantly between groups.

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

of six subjects treated with an oral device was considered as efficiently treated. Fourteen OSA subjects (five treated with CPAP, 9 with UPPP) with lacking 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 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 of 105 cases (16.2%) with OSA compared with in 11 of 203 (5.4 %) snorers without OSA (p=0.003; Table 1). The CAD diagnosis was associated with a fatal outcome in 9 out of the 28 cases; 8 in the OSA group and 1 in the non-OSA subjects (p<0.001). When analyzing the OSA group with regard to treatment effectiveness, CAD was confirmed in 16 of 65 incompletely treated cases (24.6%) compared with in 1 of 26 (3.9%) efficiently treated subjects (p=0.022; Table 2).

When analyzing the variables in multivariate we found that OSA diagnosis at baseline, SBP, current age, time since baseline and SaO_2min were the variables that had significant importance for CAD. No one of the other variables had significant importance beyond these (Table 3). Without any regard to 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 development of CAD (p=0.001). Figure 2 illustrates the probability of CAD for the sleep clinic cohort, calculated from the Poisson model, as an example where the age is 49 yr at baseline with a SBP of 133 mmHg and SaO_2min of 86% without any regard to treatment during the follow-up period. When analyzing the OSA group, efficient treatment of OSA was associated with a reduced risk for CAD (RR 0.3, 95% CI 0.1-0.8; p=0.020) after adjustment for significant confounding variables in this cohort (Table 4).

DISCUSSION

This study has demonstrated an increased incidence of CAD in middle-aged OSA patients during a follow-up period of seven years. Without regard to treatment, OSA was associated with an almost five-fold increase in risk for development of CAD independent of age, gender, hypertension, diabetes and current smoking. Efficient treatment of OSA significantly reduced this excess risk for CAD in OSA patients.

To our knowledge, this is the first long-term, clinic-based observational investigation of development of CAD in middle-aged OSA patients free of a concomitant heart disease at baseline. The present data strongly supports 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 for CAD prevalence after risk factor adjustment (6). At a five-year follow-up of this CAD group, Respiratory Disturbance Index, was an independent predictor of cardiovascular mortality (9). The prevalence of 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 severebly disabling nocturnal angina, and ischaemic episodes were reduced on CPAP-treatment (20).

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 epidemiological center providing reliable and complete data on diagnoses related to hospitalization episodes (16). The main weakness of this study is the lack of polysomnography for a fully accurate diagnosis of OSA. However, an overnight OD≥30 was defined as OSA based on previously established diagnostic

criteria (14), 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 SCSB combined with pulse-oximetry for an AI >5 verified by polysomnograpy has previously been shown to vary between 67 to 100 % (21). Although apnea events were counted, hypopneas could not be adequately detected at baseline in the present study, as 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. On the other hand, this may also be related to the selection criteria (free from outcome 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 previously discussed in an extensive article by Leung and Bradley (22), AHI may not accurately reflect the most relevant pathophysiologic aspect of OSA contributing to cardiovascular complications. 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 (22). In the present study, despite the low absolute number of the 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 we had missed OSA subjects with dominantly hypopneas with arousals but without significant desaturations at baseline, these subjects in this age group, were still free of a CAD 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.

One may argue that reduced lung function (FEV1), as a well-known independent predictor of mortality, should be discussed in this context. Thus, patients with impaired lung function might have had more oxygen desaturations in the study and this might have led to increased CAD and mortality. We did not have lung function values but could from the SHDR identify four cases with asthma bronchiale 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 patients as compared to OSA patients (Table 1), and the findings about lung function test, if provided, would unlikely to alter the main findings of this study. Moreover, findings in the OSA group regarding CAD incidence was adjusted for the asthma or COPD diagnosis at baseline (Table 4).

It may also be argued that a randomized study design of 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 baseline health status of the groups. However, when considering the serious haemodynamic changes associated with OSA (*see* below), it appears to be unethical to randomize OSA patients to non-treatment for any longer time period. Not only would randomization of OSA patients to non-treatment mean a potentially increased risk for cardiovascular morbidity, but it would also imply withholding of quality of life improvement due to reduced hypersomnolonce 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, prevalence of hypertension and diabetes at baseline. Incompletely treated OSA subjects were 2.6 yr older but this was statistically adjusted for in the multivariate analysis. In fact, the more severe OSA in terms of oxygen desaturations 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 the present results refer to gross clinical abnormalities but our patients may at baseline have had more subtile abnormalities including impaired glucose tolerance, 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 the surgically treated OSA subjects in the present 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 yr following surgery within the first 4 yr of the observation period and demonstrated 100% treatment effectiveness in the "effectively treated" group. Assuming that some of these subjects developed OSA later than 4 yr, the overall impact of effectiveness of UPPP during the whole observation period may be compared with the compliance defined by CPAP use of at least 50% of the sleep time. In fact, even if 40% of the OSA population treated with UPPP still had OSA at follow-up, this also implies that 60% were considered as success, and 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 CAD (Table 3, Fig 2). Nevertheless, some "efficient treatment" does exist and seems to reduce the risk of incidence of CAD in the OSA subjects (Table 4). In other words, the odds ration for CAD incidence will be even higher in the untreated group. However, the small number of the OSA subjects treated with CPAP in the present study and the relatively high proportion of the subjects not tolerating CPAP at long-term highlights the difficulties in the clinical setting for treatment selection in otherwise healthy subjects, especially if they do not have daytime sleepiness.

Mechanisms related with increased incidence of CAD in OSA patients have been discussed in detail elsewhere (24). During the cycle of the apneic 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.* hypoxemia, following sleep disordered breathing may trigger an attack of angina pectoris in patients with CAD who already have reduced coronary flow reserve (20, 25).

With the increasing recognition of OSA as an independent, additive or even synergistic risk factor for CAD, we are facing a need for early identification of high-risk individuals and a consensus on well-defined treatment strategies in such patients. Regarding the low ODI at baseline in our study population, even mild OSA seems to have a substantial effect on CAD risk and highly effective treatment should therefore be provided. In this concept, our study clearly suggests a causal relationship between OSA and CAD, and consequently supports including OSA among factors considered in the cardiovascular prevention models.

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

Figure 2. The probability of CAD, calculated from the Poisson model. This is an example where the age is 49 year at baseline with a SBP of 133 mmHg and SaO_2min of 86% without any regard to treatment during the follow-up period. The *bolded curve* gives the probability of CAD for OSA patients and the *dotted curve* gives the hazard function for the snorers without OSA.

TABLE 1. Baseline characteristics of the middle-aged sleep clinic cohort without a concomitant heart disease in 1991 as well as incidence of CAD at follow-up*

Variable	OSA (n=105)	non-OSA (n=203)	p Value
Age, years	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, n/6 h	94.1 ± 86.0	8.9 ± 8.3	<0.001
ODI, n/h	17.8 ± 15.1	1.6 ± 1.7	<0.001
SaO_2min, %	80.5 ± 7.8	88.6 ± 4.2	<0.001
Male gender, n (%)	91 (86.7)	154 (75.9)	0.026
Hypertension, n (%)	30 (28.6)	33 (16.3)	0.011
Diabetes mellitus, n (%)	2 (1.9)	2 (1.0)	NS
Smokers, n (%)	35 (34.0)	80 (41.5)	NS
Subjects with CAD incidence, n (%)	17 (16.2)	11 (5.4)	0.003
Cardiovascular death, n (%)	8 (7.6)	1 (0.5)	<0.001

*Continuous variables are expressed as mean ± SD, tatistics by unpaired Student's *t* test. Comparison of groups by chi-squared test. *Definition of abbreviations:* CAD = Coronary Artery Disease; OSA = Obstructive Sleep Apnea; BMI = Body-Mass-Index; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; NS = Non Significant; OD = Oxygen Desaturations $\geq$ 4%; ODI = Oxygen Desaturation Index; SaO_2min = Minimal Oxygen Saturation.

TABLE 2. Baseline and follow-up characteristics of the OSA patients in subgroups based on effectiveness of treatment*†

Variable	Incompletely treated (n=65)	Efficiently treated (n=26)	p Value
Age at baseline, years	53.2 ± 8.6	50.6 ± 8.7	NS
BMI 1991, kg/m^2	28.9 ± 4.5	27.9 ± 3.2	NS
BMI 1998, kg/m^2	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, n/6 h	76.8 ± 51.0	110.9 ± 124.5	NS
ODI 1991, (n/h)	14.9 ± 11.2	20.8 ± 19.8	NS
SaO_2min 1991, %	81.8 ± 6.3	78.4 ± 10.5	NS
Male gender, n (%)	57 (87.7)	21 (80.8)	NS
Hypertension 1991, n (%)	20 (30.8)	7 (26.9)	NS
Diabetes mellitus 1991, n (%)	1 (1.5)	0 (0.0)	NS
Smoker 1991, n (%)	19 (29.7)	9 (34.6)	NS
Responder to questionnaire, n (%)	51 (78.5)	25 (96.2)	0.040
Subjects with CAD incidence, n (%)	16 (24.6)	1 (3.9)	0.022

*Continuous variables are expressed as mean ± SD, statistics by unpaired Student's *t* test. Comparison of groups by chi-squared test. † Fourteen subjects receiving treatment without objective data on therapy effectiveness at follow-up excluded (see text). *Definition of abbreviations:* OSA = Obstructive Sleep Apnea; BMI = Body-Mass-Index; NS = Non Significant; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; OD = Oxygen Desaturations $\geq$ 4%; ODI = Oxygen Desaturation Index; SaO_2min = Minimal Oxygen Saturation; CAD = Coronary Artery Disase.

TABLE 3. A Poisson model significant predictors of incidence of CAD in a middle-aged sleep clinic cohort without regard to OSA treatment during the follow-up period

	β	RR (95 % CI)	p Value
Constant	-22.84		
Obstructive sleep apnea at baseline	1.53	4.60 (1.83-11.6)	0.001
Time since baseline (years)	0.19	1.21 (1.01-1.45)	0.043
Systolic blood pressure at baseline (mmHg)	0.04	1.03 (1.01-1.05)	<0.001
Current age	0.06	1.06 (1.02-1.11)	0.007
SaO_2min at baseline study (%)	0.11	1.11 (1.02-1.22)	0.019

Definition of abbreviations: CAD = Coronary Artery Disease; OSA = Obstructive sleep apnea; RR = Relative Risk; CI = Confidence interval; SaO_2min = Minimal Oxygen Saturation.

TABLE 4. A Poisson model significant predictors of incidence of CAD in the OSA patients during 7 years following the baseline sleep study in 1991

	β	RR (95 % CI)	p Value
Constant	-27.90		
Efficient treatment of OSA	-1.23	0.29 (0.10-0.82)	0.020
Time since baseline (years)	0.25	1.28 (1.01-1.64)	0.043
Current age	0.10	1.11 (1.03-1.18)	0.004
SaO_2min at baseline study (%)	0.22	1.24 (1.07-1.43)	0.004
Asthma bronchiale or COPD at baseline	5.03	153 (7.6- 3061)	0.001

Definition of abbreviations: CAD = Coronary Artery Disease; OSA = Obstructive sleep apnea; RR = Relative Risk; CI = Confidence interval; SaO_2min = Minimal Oxygen Saturation; COPD = Chronic Obstructive Pulmonary Disease.

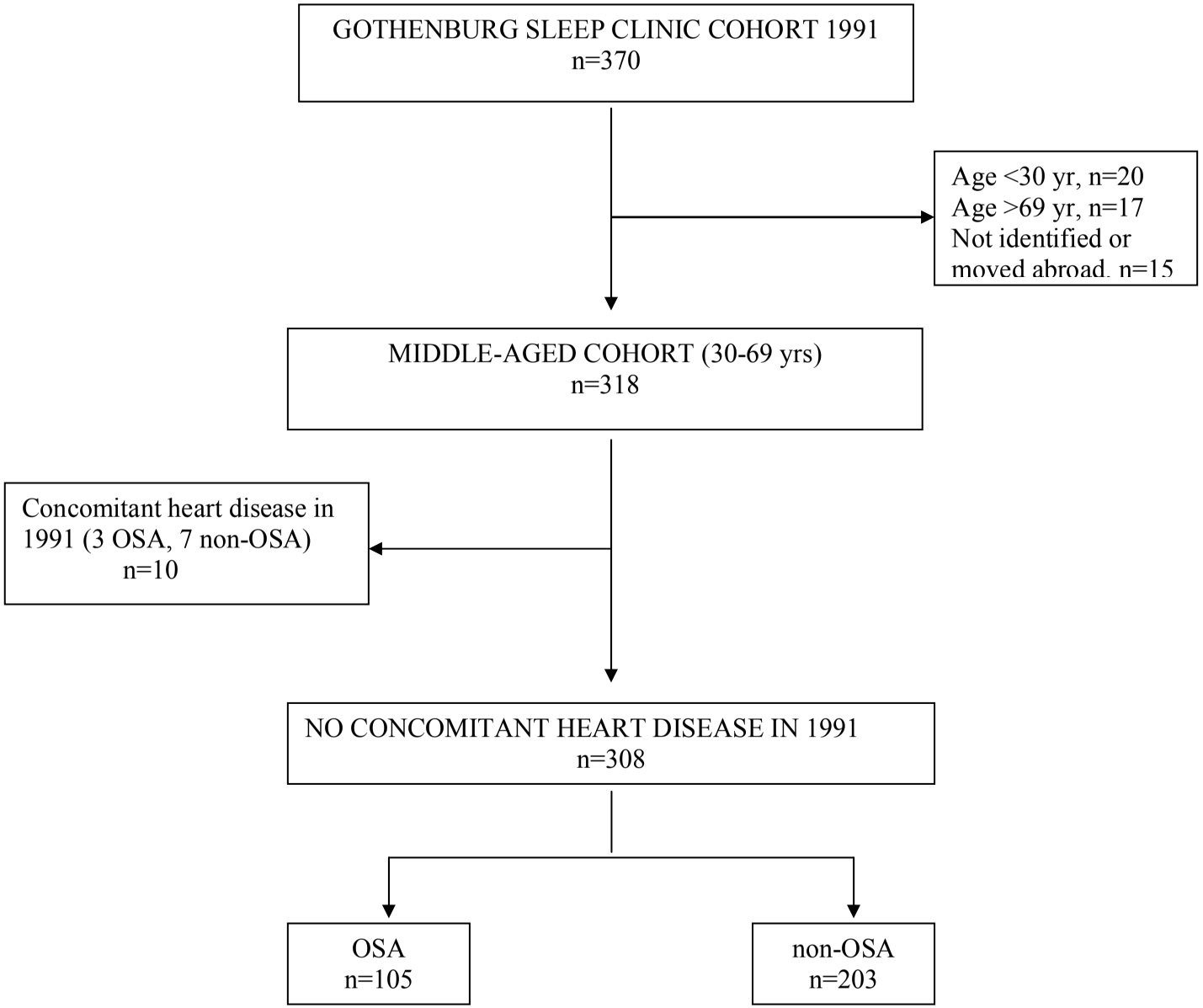
GOTHENBURG SLEEP CLINIC COHORT 1991
n=370
Age <30 yr, n=20
Age >69 yr, n=17
Not identified or
moved abroad, n=15
MIDDLE-AGED COHORT (30-69 yrs)
n=318
Concomitant heart disease in
1991 (3 OSA, 7 non-OSA)
n=10
NO CONCOMITANT HEART DISEASE IN 1991
n=308
OSA
n=105
non-OSA
n=203

Fig 1.

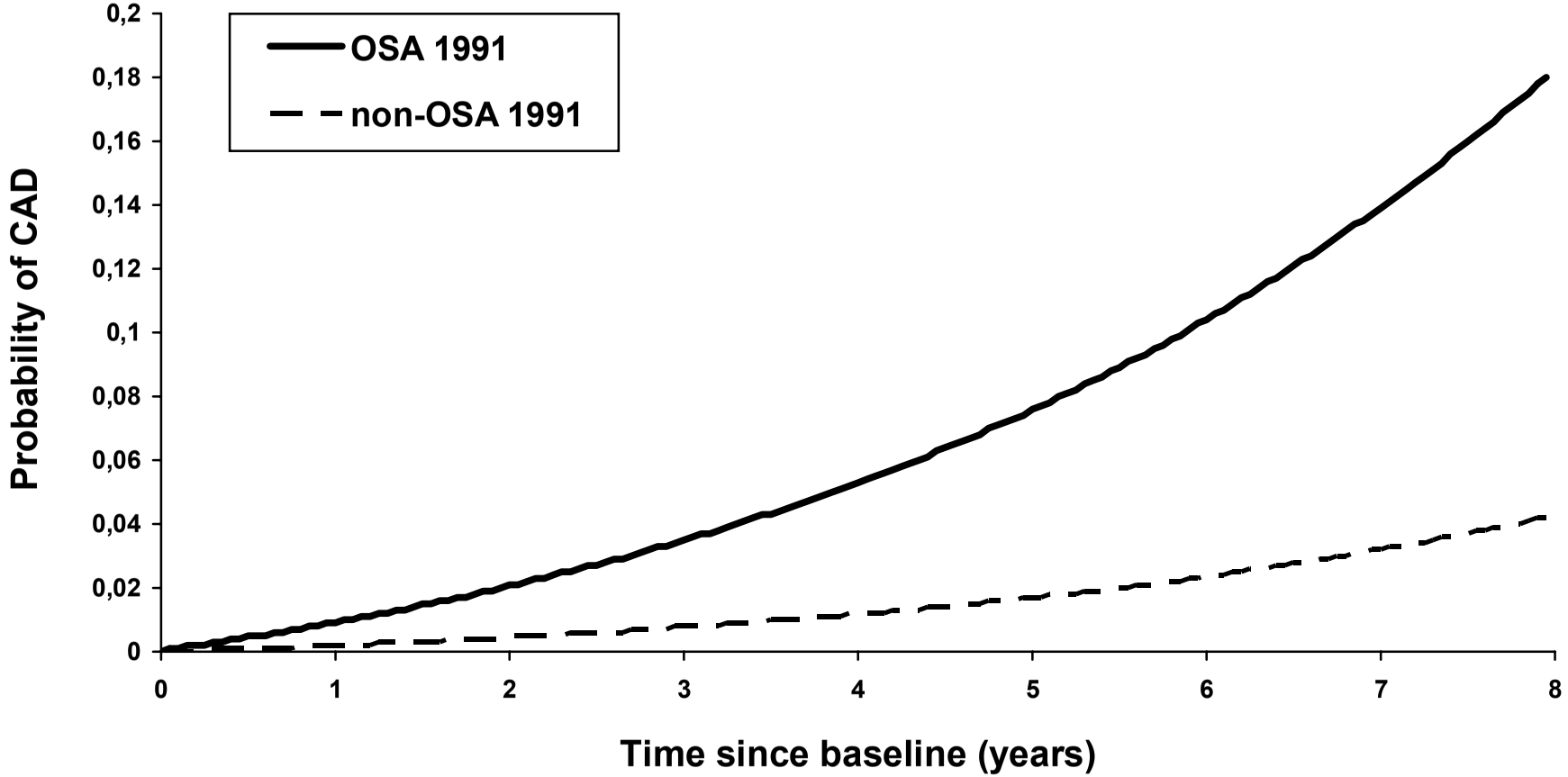
OSA 1991
non-OSA 1991
Probability of CAD
0,2
0,18
0,16
0,14
0,12
0,1
0,08
0,06
0,04
0,02
0
0
1
2
3
4
5
6
7
8
Time since baseline (years)

Fig 2.