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Cardiovascular risk in patients with sleep apnea with or without continuous positive airway pressure therapy: follow-up of 4.5 million Danish adults

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Abstract

Background. The prognostic significance of age and continuous positive airway pressure (CPAP) therapy on cardiovascular disease in patients with sleep apnoea has not been assessed previously.

Methods. Using nationwide databases, the entire Danish population was followed from 2000 until 2011. First-time sleep apnoea diagnoses and use of CPAP therapy were determined. Incidence rate ratios (IRRs) of ischaemic stroke and myocardial infarction (MI) were analysed using Poisson regression models.

Results. Among 4.5 million individuals included in the study, 33,274 developed sleep apnoea (mean age 53 years, 79% men) of whom 44% received persistent CPAP therapy. Median time to initiation of CPAP therapy was 88 days (interquartile range 34–346). Patients with sleep apnoea had more comorbidities compared to the general population. Crude rates of MI and ischaemic stroke were increased for sleep apnoea patients (5.4 and 3.6 events per 1000 person-years compared to 4.0 and 3.0

in the general population, respectively). Relative to the general population, risk of MI [IRR 1.71, 95% confidence interval (CI) 1.57–1.86] and ischaemic stroke (IRR 1.50, 95% CI 1.35–1.66) was significantly increased in patients with sleep apnoea, in particular in patients younger than 50 years (IRR 2.12, 95% CI 1.64–2.74 and IRR 2.34, 95% CI 1.77–3.10, respectively). Subsequent CPAP therapy was not associated with altered prognosis.

Conclusions. Sleep apnoea is associated with increased risk of ischaemic stroke and MI, particularly in patients younger than 50 years of age. CPAP therapy was not associated with a reduced rate of stroke or MI.

Introduction

In recent years, sleep apnoea has received increased attention from the medical community as the condition has been associated with thrombosis, metabolic disturbances and cognitive dysfunction [1, 2]. European and American cardiology societies recommend systematic investigation of sleep apnoea in high-risk subjects such as those with hypertension and atrial fibrillation [3, 4]. Most studies investigating cardiovascular outcomes in sleep apnoea patients have been small with limited follow-up and conducted at single centres [5–8]. Understanding the epidemiology of sleep apnoea is crucial to determine whether this condition is a cardiovascular disease risk factor, and the Danish nationwide databases offer the potential of unique insight into the risk profile of unselected sleep apnoea patients with long-term follow-up. Furthermore, initiation of continuous positive airway

pressure (CPAP) therapy has been shown to improve some pathophysiological parameters such as blood pressure, left ventricular systolic function, inflammation and glucose homeostasis but the effect on cardiovascular outcome in a real-world setting remains unclear [5, 9–12].

We examined the relationship among 4.5 million Danish adults between sleep apnoea, with and without CPAP therapy, and the risk of both ischaemic stroke and myocardial infarction (MI). In addition, a validation sample was investigated to ensure the accuracy of the diagnosis of sleep apnoea.

Methods

Databases and study population

Nationwide databases with an encrypted personal identifier for all Danish residents enabled cross-linkage of the following databases. The Danish National Patient Registry records all hospital contacts according to the International Classification of Diseases (ICD) codes [eighth revision before 1994 and 10th revision (ICD-10) thereafter] and treatments according to the Nordic Medico-Statistical Committee Data from privately run ambulatory clinics were available between 2002 and 2008. The National Prescription Registry holds data on all claimed prescriptions with information on the date and amount dispensed according to the Anatomical Therapeutic Chemical classification system, use of which is recommended by the World Health Organization. Vital status, gender and date of birth are available from the Civil Personal Registry.

At study baseline (1 January 2000), all subjects without a previous diagnosis of sleep apnoea were characterized by comorbidities and medication. The following prior comorbidities were defined according to ICD codes: ischaemic stroke, MI, peripheral arterial disease, atrial fibrillation, chronic renal failure and chronic obstructive pulmonary disease. Medication at baseline was defined as dispensed prescriptions 180 days prior to inclusion for antihypertensive drugs, statins, antiplatelet agents, warfarin and loop diuretics.

Hypertension was defined as combination treatment with at least two antihypertensive drugs, as previously validated [13]. Diabetes mellitus was defined as the use of glucose-lowering medication and heart failure as prior diagnosis plus the use of loop diuretics, as previously validated [14]. Patient characteristics were recorded at study start for the entire population, and at the date of diagnosis and the date of subsequent CPAP therapy where appropriate (Table 1).

Definition of sleep apnoea and CPAP therapy

: We identified all patients with a first-time primary or secondary diagnosis of sleep apnoea (ICD-10 code G473) between 1 January 2000 and 31 December 2011. Patients aged 18 years or older were eligible for inclusion, and at the date of inclusion patients changed status to sleep apnoea group from the general population. To define subsequent CPAP therapy, we used codes involving CPAP therapy, CPAP device availability, adjustment of CPAP device and control of CPAP device (codes BGFC32, ZZ3911, ZZ3912, ZZ3913, ZZ3914, ZZ3915 and ZZ3916).

To ensure adherence to therapy, two successive CPAP-related codes were required and the second date was used to define the initiation of CPAP therapy.

Outcomes

Ischaemic stroke was defined as non-fatal hospitalization or death due to ischaemic stroke, and MI was defined as non-fatal hospitalization or coronary death. Diagnoses of ischaemic stroke (positive predictive value: 97%) and MI (specificity: 93%) in the registries have been validated [15, 16].

Validation sample

To validate the diagnostic coding of sleep apnoea in The National Patient Registry, we examined patients from our hospital (including a dedicated sleep apnoea ambulatory clinic and a ear, nose and throat clinic).Preliminary assessment of charts with a sleep apnoea code at a hospital without dedicated sleep apnoea function, we experienced that most patients were referred or already had been seen at hospital clinics with a dedicated work-up for sleep apnoea. Among a total of 749 patients aged 18 years or older with sleep apnoea as a primary or secondary diagnosis during the period 2007–2010, we randomly selected 153. For each selected patient, a definite diagnosis of sleep apnoea was determined from chart documentation based preferably on polysomnography or cardio-respiratory monitoring and satisfying the definition of obstructive sleep apnoea according to the diagnostic criteria of the International Classification of Sleep Disorders, second edition [17]. When this information was unavailable, the presence of sleep apnoea was confirmed if patients were treated with CPAP. If available, the apnoea–hypopnoea index (AHI) and body

mass index prior to initiation of CPAP therapy were recorded. When neither an AHI nor information on the use of CPAP therapy were available, patients were registered as not having sleep apnoea. Comorbidities was also recorded. Treatment in relation to the contact with sleep apnoea (prior to and within 1 year from contact) was recorded for CPAP therapy. All charts were read independently (by ML, SLK, GHG and CBC) and disagreement was resolved by consensus.

Statistical analysis

A first-time diagnosis of sleep apnoea and initiation of CPAP therapy were considered time dependent, and subjects contributed to at-risk time in the general population until the date of a first-time diagnosis of sleep apnoea (sleep apnoea group). Incidence rates were presented as events per 1000 person-years at risk. Multivariable Poisson regression models were fitted to estimate the incidence rate ratio (IRR) between the general population (as the reference) and the sleep apnoea group. Sleep apnoea status and CPAP therapy were incorporated in the models as time-dependent variables. In addition to follow-up period, timescales of age and calendar year were included in the models. Three models were defined: (i) adjusted for age, gender and year of inclusion; (ii) fully adjusted including for the presence of ischaemic stroke, MI, peripheral arterial disease, liver disease, chronic kidney disease, atrial fibrillation, heart failure, chronic obstructive pulmonary disease, diabetes mellitus, hypertension and statin use at baseline, and this model was used to estimate the treatment effect of CPAP therapy; and (iii) fully adjusted with all covariates incorporated as time-dependent variables (e.g. if a patient developed diabetes during follow-up, this information was included in the model). Effect

modification of age was present on the risk of ischaemic stroke and MI, hence three age groups were defined (18–49 years, 50–64 years and >65 years). There was no effect modification for gender. Model assumptions [linearity of continuous variables, lack of interactions (except age) and goodness of fit] were found to be valid.

Ethics

Statistics Denmark provides scientists with secure access to the abovementioned databases with anonymized personal data; this allows linkage between databases and ensures that individuals cannot be identified. The study was approved by the Danish Data Protection Agency (Ref. 2007-58-015 / int.ref. 00916 GEH-2010-001). Retrospective registry studies do not require ethical approval in Denmark. The validation sample was obtained from the patient database of a local hospital (using ICD-10 codes).

Results

Among 4.5 million subjects followed for up to 11 years, the prevalence of sleep apnoea was 0.7% (33,274 patients with a first-time diagnosis). The average age of the sleep apnoea patients was 53 years and 79% were men (Table 1). Overall, 43.5% (14,468) of patients with sleep apnoea received CPAP therapy. The median time to initiation of CPAP therapy was 88 days [interquartile range (IQR) 34–346]. At the time of sleep apnoea diagnosis and of initiating CPAP therapy, patients were characterized by a more severe disease burden compared to the general population. Fig. 1 shows an increasing incidence of first-time sleep apnoea diagnosis according

to inclusion year, as well as an increasing proportion of patients receiving CPAP therapy.

Risk of ischaemic stroke and MI

The crude incidence rates and IRRs of ischaemic stroke and MI according to the presence of sleep apnoea are shown in Table 2. Estimates are presented stratified in age groups because of effect modification. Whereas the crude rates of ischaemic stroke and MI were lowest in the youngest age group, the IRRs of these conditions were highest for sleep apnoea patients below 50 years of age compared to individuals of the same age from the general population. In addition, regardless of age group, no significant beneficial effect of CPAP therapy was found for patients with sleep apnoea.

Validation sample

Among 153 patients registered with sleep apnoea, 125 (positive predictive value: 82%) fulfilled the criteria for a diagnosis of sleep apnoea. AHI was available for 140 (92%) individuals and mean AHI was 26.0. A total of 96 (63%) patients were treated with CPAP therapy, and one of whom received surgical treatment. The mean age of this validation group was 50.6 (SD 12.6) years and 71% were men. Table 3 shows the characteristics of the total validation sample, and subgroups of patients correctly diagnosed with sleep apnoea and selected for CPAP therapy. Among patients with confirmed sleep apnoea who were treated with CPAP, 48%, 89% and 86% had mild, moderate and severe disease, respectively. In addition, 31 (32%) patients with

confirmed sleep apnoea who initiated CPAP therapy subsequently discontinued this treatment.

Sensitivity analysis

Altering the definition of CPAP therapy to the requirement of only one CPAP-related therapy code increased the number of CPAP-treated patients to 19,820 (60% of patients with sleep apnoea). Median time to first CPAP therapy code was 79 days (IQR 8–342). However, this definition of CPAP therapy did not change our findings (data not shown).

Discussion

Among 4.5 million individuals followed for up to 11 years, we found that a diagnosis of sleep apnoea was associated with an increased risk of cardiovascular disease. In particular, the risk was substantially raised among patients below 50 years of age. To our knowledge, no studies have been conducted to investigate a countrywide cohort of patients with sleep apnoea with respect to age at the time of diagnosis and with a long follow-up period. Our findings support the hypothesis that the relation between sleep apnoea and cardiovascular disease risk is particular important in younger patients. In the elderly, increasing co-existence of additional established cardiovascular disease risk factors might reduce the relative contributory role of sleep apnoea to the development of cardiovascular disease. Additionally, sleep apnoea has been associated with a range of established risk factors of cardiovascular disease, including hypertension, atrial fibrillation and metabolic

disturbances, and taking into account accumulated risk factors in our analyses lowered the cardiovascular disease risk for patients with sleep apnoea compared to the general population. This suggests that some risk factors may have a role in the causal pathway between sleep apnoea and cardiovascular events; however this possibility needs further investigation. In a recent study, the burden of morbidity 3 years prior to a diagnosis of sleep apnoea was assessed, and it was found that diabetes, hypertension, atrial fibrillation and chronic obstructive pulmonary disease in particular were associated with sleep apnoea [18]. However, age-specific risk stratification was not reported, and our results suggest that, the presence of sleep apnoea should be considered a 'high-risk' cardiovascular condition in patients younger thatn 50 years. Although no significant beneficial effect of CPAP therapy was found across age groups, further investigation of a potential cardiovascular protective effect of CPAP therapy in the youngest group is warranted. In an observational study of men with sleep apnoea or who snored, Marin *et al*. found an association between sleep apnoea severity and cardiovascular disease risk, especially among those who were not treated with CPAP [19]. However, the study was limited to a single sleep apnoea clinic, included small numbers of patients (***n*** = 1651) and a combined cardiovascular outcome was used. A potential reduction in stroke and MI risk with CPAP therapy is supported by the findings of Martinez-Garcia ***et al***. [20]. These authors found that in 939 patients >65 years of age with moderate/severe sleep apnoea, CPAP reduced cardiovascular disease mortality to a level that was comparable to that of patients with untreated mild sleep apnoea. Confounding-by-indication should be considered when interpreting our data (and also the results from other observational studies). In the absence of information about the degree of severity of sleep apnoea, CPAP therapy could be a marker of

moderate or severe disease; this is supported by the findings from the validation sample (i.e. 89% and 86% of patients with moderate and severe compared to only 48% with mild sleep apnoea, respectively, were treated with CPAP). Assuming that the group of sleep apnoea patients treated with CPAP comprise those with a more severe disorder, the actual beneficial effect of CPAP could be more pronounced than indicated by our data. It is hoped that results from ongoing randomized trials will provide evidence of a true causal treatment effect (ClinicalTrials.gov Identifier: NCT01335087, NCT00519597 and NCT00738179). However, these trials include 'high-risk' patients with cardiovascular disease, and therefore the clinical effect of CPAP therapy among unselected patients remains unclear. The findings in the present study may provide ideas for further investigation among patients younger than 50 years in whom interventions might provide greater benefit.

Our study population and validation sample were comparable with regard to age, gender, comorbidities and the proportion treated with CPAP. Because of a high positive predictive value (82%), the nationwide Danish registries are useful for future investigation of patients with sleep apnoea.

Strengths and limitations

The major strength of this study was the inclusion of a large and unselected nationwide cohort of sleep apnoea patients independent of gender, age, ethnicity, participation in health insurance programmes and socioeconomic status. The main limitations are the observational design and the fact that data were collected from

administrative registries. A potential bias in the registration of sleep apnoea and selection of patients for CPAP therapy could be present. In addition, although the coding of sleep apnoea is reliable with a high positive predictive value, we did not know the reasons for (or for not) initiating CPAP therapy. However, the proportion of sleep apnoea patients treated with CPAP was comparable in the validation sample (63%) and in the main analysis (60%). The implications of discontinuing CPAP treatment are unknown. Finally, detailed information was lacking on clinical variables such as the degree of severity of sleep apnoea, type of CPAP device, body mass index and patient and physician preferences for initiation of and compliance with CPAP therapy.

Conclusion

Sleep apnoea is associated with increased risks of ischaemic stroke and MI, in particularly in patients younger than 50 years of age. In unselected sleep apnoea patients in a real-life setting, CPAP therapy was not associated with a reduced rate of cardiovascular events. Further studies of the association between sleep apnoea and cardiovascular disease risk as well as of the clinical impact of CPAP are warranted.

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Table 1 Characteristics of the study population

Characteristics	Total population	Patients with sleep apnoea	Patients with sleep apnoea and receiving CPAP therapy
n	4,514,327	33,274	14,468
No. of patient-years	50,132,576	149,592	43,197
Male, *n* (%)	2,250,022 (49.8)	26,363 (79.2)	11,705 (80.9)
Mean age (SD) in men, years	46.0 (17.4)	52.5 (11.8)	54.4 (11.2)
Mean age (SD) in women, years	48.4 (18.9)	54.2 (12.0)	56.5 (11.0)
Comorbidity, *n* (%)			
Ischaemic stroke	85,060 (1.9)	1319 (4.0)	647 (4.5)
Myocardial infarction	77,607 (1.7)	1335 (4.0)	649 (4.5)
Liver disease	29,437 (0.7)	360 (1.1)	149 (1.0)
Renal failure	17,500 (0.4)	442 (1.3)	203 (1.4)
Heart failure	45,811 (1.0)	1090 (3.3)	513 (3.6)
Atrial fibrillation	41,891 (0.9)	1327 (4.0)	701 (4.9)
Hypertension	286,486 (6.4)	8715 (26.2)	4646 (32.1)
COPD	51,211 (1.1)	1082 (3.3)	516 (3.6)
Diabetes mellitus	100,205 (2.2)	3333 (10.0)	1880 (13.0)
Medication, *n* (%)			
Antiplatelet agents	289,975 (6.4)	7175 (21.6)	3812 (26.4)
Warfarin	55,623 (1.2)	1763 (5.3)	943 (6.5)
Statins	74,718 (1.7)	7736 (23.3)	4448 (30.7)
Loop diuretics	231,522 (5.1)	4790 (14.4)	2431 (16.8)

CPAP, continuous positive airway pressure; COPD, chronic obstructive pulmonary disease.

Table 2 Cardiovascular disease risk

	General population		Patients with sleep apnoea				Effect of CPAP therapy:
	Crude rate[a] (no. of events)	IRR	Crude rate (no. of events)	IRR[b] (95% CI)	IRR[c] (95% CI)	IRR[d] (95% CI)	estimate[e] (95% CI)
Risk of myocardial infarction							
18–49 years	0.4 (10,183)	Reference	1.7 (79)	2.12 (1.64–2.74)	1.82 (1.41–2.35)	1.41 (1.09–1.83)	1.00 (0.60–1.67)
50–64 years	2.7 (36,232)	Reference	5.3 (356)	1.61 (1.42–1.82)	1.34 (1.18–1.51)	1.12 (0.99–1.27)	1.04 (0.83–1.30)
>65 years	13.6 (150,206)	Reference	11.7 (354)	1.42 (1.25–1.60)	1.24 (1.09–1.40)	1.06 (0.94–1.21)	0.96 (0.76–1.20)
Overall	4.0 (196,621)	Reference	5.4 (789)	1.71 (1.57–1.86)	1.48 (1.36–1.61)	1.28 (1.18–1.39)	0.99 (0.85–1.15)
Risk of ischaemic stroke							
18–49 years	0.3 (8,482)	Reference	1.3 (61)	2.71 (2.05–3.59)	2.34 (1.77–3.10)	1.80 (1.36–2.39)	0.77 (0.41–1.44)
50–64 years	2.2 (30,064)	Reference	3.1 (212)	1.29 (1.10–1.52)	1.11 (0.94–1.30)	0.96 (0.82–1.13)	0.97 (0.72–1.31)
>65 years	10.2 (111,748)	Reference	8.6 (257)	1.22 (1.05–1.42)	1.10 (0.95–1.28)	1.02 (0.88–1.18)	1.07 (0.82–1.39)
Overall	3.0 (150,294)	Reference	3.6 (530)	1.50 (1.35–1.66)	1.35 (1.22–1.49)	1.23 (1.11–1.36)	0.99 (0.82–1.19)

[a]Crude rate denotes incidence rate per 1000 person-years.

IRRs with reference to the general population: [b]model adjusted for age, gender and year; [c]fully adjusted model (ischaemic stroke, myocardial infarction, peripheral arterial disease, liver disease, chronic kidney disease, atrial fibrillation, heart failure, chronic obstructive pulmonary disease, diabetes mellitus, hypertension and statin use; and [d]fully adjusted model (as above) with time-dependent variables.

[e]Estimated effect of <1 denotes a protective effect of CPAP therapy; based on the estimates of the fully adjusted model.

CPAP, continuous positive airway pressure; IRR, incidence rate ratio; CI, confidence interval.

Table 3 Data from the validation cohort

	Total sample	Confirmed sleep apnoea	CPAP therapy
Total charts	153 (100)	125 (100)	96 (100)
Confirmed sleep apnoea[a]	125 (82)	-	N/A
CPAP therapy	96 (63)	96 (77)	-
Male gender	119 (78)	98 (78)	74 (77)
Mean age (SD), years	50.6 (12.6)	51.6 (12.3)	52.7 (11.3)
Mean (SD) AHI[b]	26.0 (20.7)	30.0 (19.7)	33.4 (19.2)
<5 (no SA)	22 (14)	N/A	N/A
5–15 (mild SA)	33 (22)	33 (26)	16 (17)
16–3) (moderate SA)	37 (24)	37 (30)	33 (34)
>30 (severe SA)	48 (31)	49 (39)	42 (44)
Mean (SD) BMI[c], kg/m^2	31.3 (6.7)	31.9 (6.8)	33.1 (8.0)
Reporting day time symptoms	118 (77)	103 (82)	84 (88)
History of:			
Atrial fibrillation	5 (3)	5 (4)	4 (4)
Ischaemic heart disease	14 (9)	14 (11)	12 (13)
Stroke	8 (5)	6 (5)	5 (5)
Diabetes mellitus	15 (10)	15 (12)	13 (14)
Hypertension	49 (32)	46 (37)	38 (40)
Heart failure	5 (3)	5 (4)	5 (5)
COPD	4 (3)	4 (3)	4 (4)
Alcohol abuse	19 (12)	17 (14)	14 (15)
Hypercholesterolaemia	28 (18)	26 (21)	20 (21)
Smoking	47 (31)	37 (30)	33 (34)

Unless otherwise stated, all data represent *n* (%).
[a]Positive predictive value; defined as AHI >5 (*n* = 119) and use of CPAP therapy (*n* = 6). [b]Not including patients lacking information on AHI (*n* = 13); [c]not including patients lacking information on BMI (*n* = 55).
AHI, apnoea–hypopnoea index; BMI, body mass index; CPAP, continous positive airway pressure; COPD, chronic obstructive pulmonary disease; SA, sleep apnoea; N/A, not available.

Fig. 1 Number of patients with sleep apnoea and treated with continuous positive airway pressure (CPAP) therapy, according to year of inclusion