BMJ Neurology Open

Obstructive sleep apnoea and risk of dementia: a Danish population-based cohort study

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To cite: Gribsholt SB, Horváth-Puhó E, Elser H, *et al*. Obstructive sleep apnoea and risk of dementia: a Danish population-based cohort study. *BMJ Neurology Open* 2025;**7**:e001174. doi:10.1136/bmjno-2025-001174

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjno-2025-001174).

Received 05 May 2025
Accepted 17 July 2025

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ABSTRACT

Background Obstructive sleep apnoea (OSA) is associated with adverse health outcomes. However, the association with dementia remains uncertain. Thus, we examined the association of OSA with all-cause dementia and Alzheimer's disease.

Methods We conducted a Danish nationwide population-based cohort study using health registries. Patients with OSA were identified from 1995 to 2017. Furthermore, a propensity score-matched comparison cohort was defined. Propensity scores were computed based on age, sex, comorbidities and education. With follow-up until 2018, we computed incidence rates (IRs) and HRs for all-cause dementia and Alzheimer's disease. Subgroup analyses were conducted by sex, age, overweight/obesity, hypertension and continuous positive airway pressure (CPAP) treatment.

Results We identified 62 928 patients with OSA and 62 928 in the propensity score-matched comparison cohort (76% male, median age 52 years). The IR for all-cause dementia was 1.27 (95% CI 1.17 to 1.37) per 1000 person-years in patients with OSA and 1.15 (95% CI 1.05 to 1.25) in the propensity score-matched comparison cohort, yielding an HR of 1.10 (95% CI 0.98 to 1.24). The HR for Alzheimer's disease was 1.16 (95% CI 0.94 to 1.43). Among individuals with overweight/obesity, the HR for all-cause dementia was 0.71 (95% CI 0.51 to 0.99), while it was 1.17 (95% CI 1.03 to 1.33) in those without. CPAP treatment attenuated associations.

Conclusion Our findings support a modest association between OSA and dementia, including Alzheimer's disease, motivating early clinical detection of OSA as a potentially modifiable risk factor for subsequent dementia. The finding that the dementia hazard was not increased in the setting of overweight or obesity requires further study and points to the need for research on mechanisms underlying the association between OSA and dementia.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ While obstructive sleep apnoea (OSA) is associated with adverse health outcomes, the association between OSA and dementia remains less clear.

WHAT THIS STUDY ADDS

⇒ In this cohort study, we found evidence of a modest association of OSA with both all-cause dementia and Alzheimer's disease. Among individuals with a diagnosis of overweight or obesity, we found an inverse association between OSA and all-cause dementia.

⇒ We found no evidence of heterogeneity within subgroups defined by sex and age, but an attenuation of the association between OSA and dementia with continuous positive airway pressure treatment.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings indicated that early clinical detection of OSA may be a potentially modifiable risk factor for subsequent dementia. The finding that the association with dementia was not increased in the setting of overweight or obesity requires further study.

BACKGROUND

Obstructive sleep apnoea (OSA) is a disorder characterised by collapse of the upper airway during sleep, leading to brief periods of reduced or obstructed airflow.[1] These episodes are associated with recurrent arousal from sleep and reduced blood oxygenation.[1] OSA is a common disorder estimated to affect almost 1 billion people worldwide, with increasing incidence by age.[1] Furthermore, the condition occurs more frequently among people who are overweight or obese and among men.[1 2] Previous research associated OSA with an increased risk of a wide range of adverse health outcomes, including hypertension, atrial fibrillation, heart failure, type 2 diabetes mellitus, stroke and death.[3 4]

Neurocognitive sequelae of OSA include excessive daytime sleepiness and impaired cognition.[2] Chronic fragmented sleep, low-grade systemic inflammation and oxidative stress from OSA may increase the risk of Alzheimer's disease by disrupting glymphatic circulation, reducing the egress of toxic metabolites and accelerating the accumulation of neuropathological proteins in the brain, including amyloid-ß plaques and intraneuronal neurofibrillary tangles.[5 6]

While some studies have demonstrated a positive association between OSA and dementia,[7–11] others have found no evidence of an association between sleep apnoea and cognitive impairment, including dementia.[12–14] Previous studies were limited by relatively small sample sizes, high attrition rates, variable control of confounding and variations in follow-up time.[7–9 12 14] Moreover, only a few studies have considered potential effect modification by overweight/obesity.[7 14] Overweight/obesity is an important risk factor for OSA and may further increase dementia risk, potentially mediated by low-grade systemic inflammation and oxidative stress.[15 16] Large population-based studies with complete and long-term follow-up, granular data on potential confounders and inclusion of data on overweight/obesity are thus needed.

This nationwide population-based cohort study examined the association of OSA with all-cause dementia, Alzheimer's disease and vascular dementia. Furthermore, we conducted subgroup analyses defined by overweight/obesity, hypertension, sex, age and continuous or bilevel positive airway pressure (collectively referred to as CPAP treatment).

METHODS

Design, setting and data sources

We conducted this nationwide population-based study in Denmark using routine prospectively collected healthcare data, with follow-up from 1 January 1995 to 31 December 2018. The Danish National Health Service provides tax-supported universal healthcare.[17] Medical and administrative registries can link individual patients using their civil registration number, a unique identifier encoding sex and date of birth that has been assigned to all Danish residents upon birth or immigration since 1968.[17] Daily vital status data are available from the Danish Civil Registration System (CRS).[17] The Danish National Patient Registry (DNPR) records all Danish hospital contacts using diagnostic codes from the International Classification of Diseases, 8th revision through 1994 and 10th revision thereafter.[18] Dementia diagnoses made during inpatient hospital admissions became available beginning in 1977, and those made during hospital-based outpatient clinic contacts became available beginning in 1995. Data on selected treatments for dementia also began to be collected in 1995.[18] The Danish Central Psychiatric Research Registry (DCPRR) contains information on all contacts with psychiatric hospitals and clinics in Denmark since 1970.[19] The Integrated Database for Labour Market Research (IDLMR) contains information on labour force participation and the highest level of education achieved for the Danish general population since 1980.[20]

In Denmark, diagnoses of both OSA and dementia are primarily made and recorded within specialist settings. OSA is typically diagnosed following referral from a general practitioner to a hospital-based sleep clinic, where diagnostic procedures are conducted. Diagnostic confirmation relies on overnight polysomnography or home sleep studies. As such, most clinically confirmed OSA cases are captured in the DNPR. Similarly, dementia diagnoses generally occur following referrals from primary care to specialist geriatric or neurology clinics and involve standardised assessments. These diagnoses are recorded in the DNPR.

Obstructive sleep apnoea

We used the DNPR to identify adults (aged 18–70 years) with a first-time inpatient or outpatient hospital diagnosis of OSA 1995–2017,[18] including both primary (covering the main cause of the hospital contact) and secondary diagnoses (other contributing diagnoses or causes for the hospital contact) (online supplemental table 1). Coding of diagnosis codes for OSA in the DNPR has previously been validated with a positive predictive value of 82%.[21] The diagnosis codes have been validated, using the Apnoea-Hypopnoea Index from the patients' medical charts.[21]

Comparison cohorts

We defined two comparison cohorts: a general population comparison cohort and a propensity score-matched (PSM) comparison cohort. A PSM comparison cohort offered a balanced comparison by accounting for confounding variables. However, it may also reduce the generalisability of the findings by limiting the analysis to a subset of the population with similar characteristics. In contrast, comparing the OSA cohort to the general population cohort provided insights into the overall burden of OSA on dementia risk in a more diverse and representative sample. The general population comparison cohort included individuals from the general population with no prior diagnosis of OSA matched 10:1 to cases based on sex, birth year and calendar year of OSA diagnosis. Matching was performed with replacement (table 1).[22] We then defined a PSM comparison cohort sampled from the general population comparison cohort. Propensity scores were estimated using generalised boosted models based on patient age, sex, calendar year, medical comorbidities (diabetes mellitus, chronic kidney disease, hypertension, hypercholesterolaemia, traumatic brain injury, smoking-related disorders, depression, disorders related to alcohol use and overweight/obesity), educational level, income and employment status.[23] Follow-up extended for 1 year after the OSA diagnosis date and the corresponding matching date for comparison cohort members (ie, the index date) until the occurrence of a dementia diagnosis, emigration, death or study end on 31 December 2018. Follow-up began 1 year following OSA diagnosis in order to minimise risk of diagnostic and surveillance bias, as patients with cognitive complaints may be more likely to undergo evaluation for OSA, which is viewed as a potentially modifiable underlying cause of their complaints. Individuals with less than 1 year of follow-up time or with a baseline diagnosis of dementia, mild cognitive impairment or an amnestic syndrome on or before the index

Table 1 Baseline characteristics of patients with a first-time diagnosis of OSA, members of the general population comparison cohort and members of the propensity score-matched comparison cohort, Denmark, 1995–2018

	Obstructive sleep apnoea cohort*		General population comparison cohort		Propensity score-matched comparison cohort	
	N	%	N	%	N	%
Total	62 928	100	628 444	100	62 928	100
Male	47 825	76	477 647	76	47 904	76.1
Median age (IQR)	52 (43–60)		52 (43–60)		52 (43–60)	
Age group						
18–49	27 470	43.7	274 426	43.7	26 747	42.5
50–59	20 572	32.7	205 259	32.7	20 761	33
60–70	14 886	23.7	148 759	23.7	15 420	24.5
Calendar period						
1995–2003	11 539	18.3	115 283	18.3	11 255	17.9
2004–2010	19 342	30.7	193 182	30.7	19 268	30.6
2011–2017	32 047	50.9	319 979	50.9	32 405	51.5
Comorbidities						
Overweight/obesity	9107	14.5	13 822	2.2	9145	14.5
Cardiovascular disease	6281	10	29 545	4.7	4990	7.9
Type 2 diabetes	4857	7.7	17 578	2.8	5048	8
Chronic kidney disease	1115	1.8	4179	0.7	1044	1.7
Hypertension	9739	15.5	38 373	6.1	10 134	16.1
Hyperlipidaemia	4347	6.9	18 075	2.9	4580	7.3
Traumatic brain injury	1862	3	14 371	2.3	1846	2.9
Smoking-related diseases	6374	10.1	25 941	4.1	6162	9.8
Depression	3300	5.2	13 900	2.2	3349	5.3
Substance abuse	3833	6.1	32 006	5.1	3775	6
Type of diagnosis code						
Primary	47 099	87.5			.	.
Secondary	6722	12.5			.	.
Income						
Low (first quartile)	15 994	25.4	152 415	24.3	15 928	25.3
Intermediate (second quartile)	18 241	29	162 952	25.9	18 255	29
High (third quartile)	15 373	24.4	153 509	24.4	15 446	24.5
Very high (fourth quartile)	13 320	21.2	158 240	25.2	13 299	21.1
Missing			1328	0.2		
Employment						
Employed	42 264	67.2	455 523	72.5	42 457	67.5
Unemployed	5458	8.7	46 122	7.3	5232	8.3
Retired early	10 911	17.3	83 842	13.3	10 866	17.3
State pension recipient	4217	6.7	40 911	6.5	4308	6.8
Missing	78	0.1	2046	0.3	65	0.1
Education						
Low	18 574	29.5	161 312	25.7	18 102	28.8
Low-medium	29 450	46.8	284 535	45.3	28 585	45.4
High	13 365	21.2	165 254	26.3	14 586	23.2
Missing	1539	2.4	17 343	2.8	1655	2.6

Continued

Table 1 Continued

	Obstructive sleep apnoea cohort*		General population comparison cohort		Propensity score-matched comparison cohort	
	N	%	N	%	N	%
Continuous positive airway pressure treatment	31 002	49.3	.	.	.	.

*International Classification of Diseases 10th revision diagnostic codes used to identify the OSA cohort included specific codes for obstructive sleep apnoea (n=14 148; G47.32) and other sleep apnoeas (n=48 780; E66.2, G47.3, G47.30, G47.34, G47.35, G47.36 and G47.39).
OSA, obstructive sleep apnoea.

date were excluded from the regression analyses (online supplemental table 1).

Dementia

The primary outcome was a diagnosis of incident all-cause dementia. The secondary outcome was Alzheimer's disease and vascular dementia. All-cause dementia, Alzheimer's disease and vascular dementia were defined on the basis of inpatient and outpatient diagnostic codes[24] from the DNPR and the DCPRR.[19] The positive predictive value of the coding of all-cause dementia in the DNPR and DCPRR is 86%, and that of Alzheimer's disease is 81%.[25] Positive predictive values for coding of vascular dementia and other dementia subtypes are lower, and the diagnostic sensitivity of registry diagnoses of dementia or Alzheimer's disease is unknown.[25]

Covariates

From the CRS, the DNPR and the IDLMR, we obtained information on the following covariates: sex, age group (18–49, 50–59 and 60–70 years), calendar period (1995–2003, 2004–2010 and 2011–2017), income quartile, employment (employed, unemployed, on early retirement or state pensioner) and quartiles of educational level (low, medium, high and very high).[26] We also obtained information from the DNPR on baseline hospital diagnoses of overweight/obesity, type 2 diabetes mellitus, smoking-related diseases, chronic kidney disease, hypertension, hyperlipidaemia, traumatic brain injury, depression and disorders related to alcohol use (online supplemental table 1).[4 15 16 27 28]

We included codes for CPAP beginning in 2001 (when reporting became mandatory).[3] To ensure adherence, we required two successive CPAP-related codes within 1 year; we used the second date to define initiation of CPAP treatment.

Statistical analyses

We computed incidence rates (IRs) per 1000 person-years and used Cox proportional hazards regression to compute HRs with 95% CIs to examine the association of sleep apnoea with dementia, Alzheimer's disease and vascular dementia. The proportional hazards assumption was met, according to visual inspection of log-log plots. To assess the exchangeability of the OSA and PSM cohorts, we assessed the balance of covariates after propensity score computation by calculating the standardised mean difference for all covariates used to estimate the propensity scores (online supplemental figure 1).[29 30]

In subgroup analyses, we stratified by sex, calendar year, age, presence of overweight/obesity, hypertension and overweight/obesity with and without CPAP and repeated the analyses after re-estimating the propensity scores in each stratum and using stratum-specific PSM cohorts. We further performed an analysis within strata defined by CPAP treatment from 2001 onwards.

We conducted a sensitivity analysis in which follow-up began 2 years after OSA diagnosis. All statistical analyses were carried out using SAS V.9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

In the OSA cohort (n=62 928), the general population comparison cohort (n=628 444) and the PSM comparison cohort (n=62 928), 76% of participants were male, and the median age was 52 years (table 1). Median follow-up time was 7.2 years (IQR 4.1–12 years) in the OSA cohort, 7.1 years (IQR 4–11.9 years) in the PSM comparison cohort, and 7.2 years (IQR 4.1–12 years) in the general population comparison cohort.

Prevalence of comorbidities was higher in the OSA cohort than in the general population comparison cohort but similar to the prevalence in the PSM comparison cohort. Common hospital-diagnosed comorbidities included hypertension (15.5% in the OSA cohort, 6.1% in the general population cohort and 16.1% in the PSM comparison cohort), overweight/obesity (14.5% in the SA cohort, 2.2% in the general population cohort and 14.5% in the PSM comparison cohort) and smoking-related diseases (10.1% in the OSA cohort, 4.1% in the general population cohort and 9.8% in the PSM comparison cohort) (table 1). The prevalence of a very high educational level was 21.2% in the OSA cohort, 26.3% in the general population comparison cohort and 23.2% in the PSM comparison cohort.

In the OSA cohort, the IR for all-cause dementia was 1.27 (95% CI 1.17 to 1.37) per 1000 person-years, and in the general population comparison cohort, it was

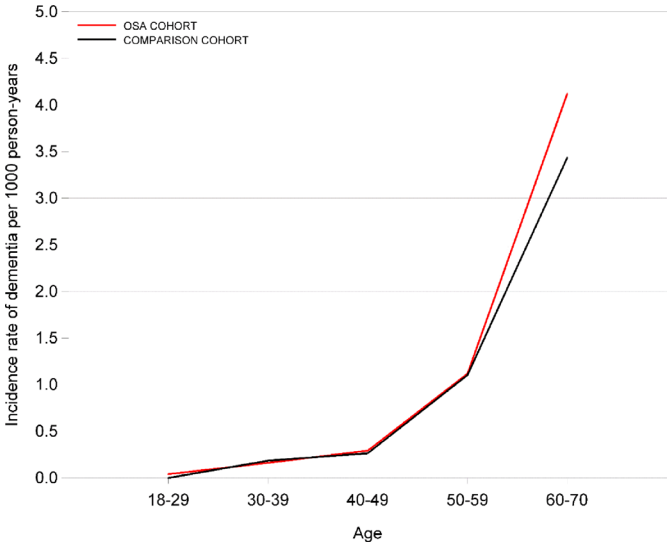

Figure 1 Crude incidence rates of dementia, stratified by 10-year age intervals, in the OSA and the propensity score-matched comparison cohorts. OSA, obstructive sleep apnoea.

1.15 (95% CI 1.05 to 1.25) per 1000 person-years. Crude IRs of dementia stratified by 10-year age intervals in the OSA and the PSM comparison cohorts are presented in figure 1. Compared with the general population cohort, OSA was associated with all-cause dementia (HR 1.29, 95% CI 1.18 to 1.40) and with Alzheimer's disease (HR 1.14, 95% CI 0.97 to 1.32), and for vascular dementia, the HR was 1.17 (95% CI 0.84 to 1.62) (table 2A). Compared with the PSM cohort, the HR for all-cause dementia was 1.10 (95% CI 0.98 to 1.24), and the HR for Alzheimer's disease was 1.16 (95% CI 0.94 to 1.43), although the CIs were wide and included the inferential null value of 1 (table 3). For vascular dementia, the HR was 1.14 (95% CI 0.84 to 1.54) (table 3).

In subgroup analyses involving comparisons with the PMS cohort, results were similar according to sex (table 4). We observed a similar magnitude of association in subgroup analysis by age, although the results were less imprecise among younger adults. The adjusted HRs were 1.25 (95% CI 0.81 to 1.94) for those aged 18–49 years, 1.22 (95% CI: 0.98 to 1.51) for those aged 50–59 years and 1.23 (95% CI 1.05 to 1.44) for those aged ≥60 years. Among individuals diagnosed with overweight/obesity, the HR for the association between OSA and dementia was 0.71 (95% CI 0.51 to 0.99). Among those without overweight/obesity, the corresponding HR was 1.17 (95% CI 1.03 to 1.33), both compared with the PSM cohort. Among individuals diagnosed with hypertension, the HR for the association between OSA and dementia was 1.14 (95% CI 0.88 to 1.48), and the HR was 1.15 (95% CI 1.01 to 1.32) for those without hypertension. CPAP treatment only weakly influenced associations in PMS cohort comparisons (CPAP: HR 1.03, 95% CI 0.83 to 1.27; no CPAP: HR 1.17, 95% CI 1.01 to 1.35) (table 4). The sensitivity analysis, in which follow-up was started 2 years after the index date, showed the robustness of our main results (online supplemental tables 2A,B).

DISCUSSION

In this population-based cohort study, OSA was associated with a 10% increase in the hazard of all-cause dementia diagnoses and a 16% increase in the hazard of Alzheimer's disease when compared with the PSM comparison cohort. We found similar results when compared with the general population comparison cohort. Among individuals with a comorbid diagnosis of overweight or obesity, we found an inverse association between OSA and all-cause dementia. We found no evidence of heterogeneity within subgroups defined by sex and age, but an attenuation of the association with CPAP treatment.

Prior research provides a strong pathophysiological basis for the association between OSA and dementia. Intermittent hypoxia in patients with OSA may perturb

Table 2 Incidence rates and HRs for dementia among patients with obstructive sleep apnoea compared with members of the general population comparison cohort

Follow-up	Obstructive sleep apnoea cohort Incidence rate/1000 person-years (95% CI)	General population comparison cohort Incidence rate/1000 person-years (95% CI)	Unadjusted HR* (95% CI)
Dementia			
1 to <10 years	1.00 (0.89 to 1.10)	0.74 (0.72 to 0.77)	**1.36 (1.21 to 1.51)**
1–24 years	1.28 (1.17 to 1.38)	1.02 (0.99 to 1.05)	**1.29 (1.18 to 1.40)**
Alzheimer's disease			
1 to <10 years	0.29 (0.23 to 0.34)	0.24 (0.23 to 0.26)	1.18 (0.96 to 1.45)
1–24 years	0.41 (0.35 to 0.47)	0.38 (0.36 to 0.39)	1.14 (0.97 to 1.32)
Vascular dementia			
1 to <10 years	0.15 (0.11 to 0.19)	0.10 (0.09 to 0.11)	1.24 (0.97 to 1.59)
1–24 years	0.20 (0.16 to 0.24)	0.13 (0.12 to 0.14)	1.17 (0.84 to 1.62)

*Adjusted by design for age, sex and calendar year.

Table 3 Incidence rates and HRs for dementia among patients with obstructive sleep apnoea compared with members of the propensity score-matched comparison cohort

	Obstructive sleep apnoea cohort		Propensity score-matched comparison cohort		
Follow-up	Outcome, N	Incidence rate/1000 person-years (95% CI)	Outcome, N	Incidence rate/1000 person-years (95% CI)	HR (95% CI)*
Dementia					
1 to <10 years	358	1.00 (0.89 to 1.10)	320	0.90 (0.80 to 1.00)	1.11 (0.95 to 1.29)
1–24 years	584	1.27 (1.17 to 1.37)	523	1.15 (1.05– to 1.25)	1.10 (0.98 to 1.24)
Alzheimer's disease					
1 to <10 years	104	0.29 (0.23 to 0.35)	80	0.23 (0.18 to 0.27)	1.28 (0.96 to 1.72)
1–24 years	189	0.41 (0.35 to 0.47)	161	0.35 (0.30 to 0.41)	1.16 (0.94 to 1.43)
Vascular dementia					
1 to <10 years	54	0.15 (0.11 to 0.19)	53	0.15 (0.11 to 0.19)	0.97 (0.66 to 1.42)
1–24 years	79	0.17 (0.14 to 0.21)	91	0.20 (0.16–0.24)	1.14 (0.84 to 1.54)

*Adjusted by propensity score-matching design; the propensity score was calculated based on diabetes mellitus, chronic kidney disease, hypertension, hypercholesterolaemia, traumatic brain injury, smoking-related disorders, depression, disorders related to alcohol use and overweight/obesity.

cellular functioning and result in increased oxidative stress and metabolic dysfunction, which in turn may promote neurodegenerative processes, such as Alzheimer's disease[5 6] and cardiovascular and cerebrovascular diseases, including stroke, heart failure and coronary artery disease.[4 5] Metabolic disturbances, diabetes and endothelial dysfunction are also linked to OSA. In persons with overweight/obesity, adipose tissue-derived proinflammatory mediators cause systemic low-grade inflammation, oxidative stress and endothelial dysfunction, increasing the risk of diabetes, hypertension and cardiovascular disease. These factors may theoretically increase dementia risk.[15 16] However, our results suggest that OSA is a risk factor only in people who are not classified as overweight/obese.

Our finding that an OSA diagnosis was associated with modestly increased rates of diagnosed dementia aligns with some,[7–11] but not all, prior studies.[12–14] The two largest prior studies found that OSA was associated with a 12%–27% increased risk of dementia,[10 11] consistent with our findings of a 15% increased risk associated with OSA compared with the general population cohort and a 27% increased risk associated with OSA compared with the PSM comparison cohort. Past research suggests that patients with OSA are more likely to have biomarkers of Alzheimer's neurodegeneration in the cerebrospinal fluid than those without OSA.[5 6] However, relatively few epidemiological studies have examined associations between OSA and Alzheimer's disease and, with two exceptions,[10 11] are limited by small sample size,[7–9 12 14] short follow-up and varying control of confounding.[7–9 12 14] Furthermore, many prior studies were conducted between two and three decades ago, limiting generalisation to contemporary populations.

In our subgroup analysis, there was a robust association between OSA and dementia in patients aged ≥60 years, a finding that aligns with existing literature.[31 32] Although OSA is not recognised as a modifiable risk factor for dementia,[33] findings from our analysis suggest that OSA is a modest risk factor for dementia among older adults, potentially due to the cumulative effects of chronic hypoxia and sleep fragmentation associated with OSA over time. Associations between OSA and dementia were most precise among patients aged ≥60 years, but the magnitude of the associations was similar among younger adults. This precision reflects a higher prevalence in the older age group. Other studies have reported that the cognitive decline associated with OSA may progress over time.[31 34] Our findings suggest that there may be increased risk among younger patients as well, underscoring the importance of prompt clinical evaluation regardless of age.

We found an inverse association between OSA and dementia among patients diagnosed with overweight/obesity, which is in contrast to previous findings of a stronger association between OSA and cognitive impairment in the presence of obesity than in patients without obesity.[31] However, one other study found greater cognitive decline in older adults with OSA alone compared with older adults with both OSA and obesity.[34] One possible explanation for this unanticipated finding is reverse causality, whereby mild cognitive impairment results in weight loss in the years before diagnosis of dementia, leading to increased risk of dementia diagnoses among persons with OSA but without current overweight/obesity.[16] Another plausible mechanism involves the duration of follow-up in our study, with shorter median follow-up time among patients with both OSA and overweight/obesity (5.1 years) versus OSA alone (7.5 years) (data not shown). A shorter follow-up could result in fewer diagnoses of dementia, which may explain our findings. Finally, mechanisms of OSA probably differ in people who are underweight or normal weight compared with people who are overweight or obesity. OSA in people

Table 4 Incidence rates and HRs for dementia among patients with obstructive sleep apnoea compared with members of the propensity score-matched comparison cohort, stratified by sex, calendar year, age, overweight/obesity status, hypertension and CPAP treatment

	Obstructive sleep apnoea cohort	Propensity score- matched comparison cohort	
	Incidence rate/1000 person-years (95% CI)	Incidence rate /1000 person-years (95% CI)	HR* (95% CI)
Sex			
Male	1.33 (1.21 to 1.45)	1.20 (1.08 to 1.31)	1.11 (0.97 to 1.26)
Female	1.06 (0.86 to 1.27)	1.00 (0.80 to 1.20)	1.06 (0.81 to 1.40)
Calendar year			
1995–2003	1.78 (1.58 to 1.98)	1.50 (1.32 to 1.68)	1.19 (1.00 to 1.40)
2004–2010	1.10 (0.95 to 1.26)	1.13 (0.98 to 1.29)	0.97 (0.80 to 1.18)
2011–2017	0.68 (0.53 to 0.84)	0.58 (0.43 to 0.72)	1.18 (0.84 to 1.65)
Age group			
18–49	0.21 (0.15 to 0.27)	0.17 (0.11 to 0.22)	1.25 (0.81 to 1.94)
50–59	1.14 (0.97 to 1.30)	0.94 (0.78 to 1.09)	1.22 (0.98 to 1.51)
≥60	4.01 (3.59 to 4.43)	3.28 (2.90 to 3.66)	**1.23 (1.05 to 1.44)**
Overweight/obesity			
No	1.26 (1.15 to 1.37)	1.08 (0.98 to 1.18)	**1.17 (1.03 to 1.33)**
Yes	1.21 (0.91 to 1.52)	1.66 (1.30 to 2.03)	**0.71 (0.51 to 0.99)**
Hypertension			
No	0.99 (0.90 to 1.09)	1.15 (1.04 to 1.25)	**1.15 (1.01 to 1.32)**
Yes	1.97 (1.59 to 2.34)	2.25 (1.85 to 2.65)	1.14 (0.88 to 1.48)
CPAP treatment			
No	1.42 (1.28 to 1.55)	1.20 (1.08 to 1.33)	**1.17 (1.01 to 1.35)**
Yes	1.01 (0.85 to 1.16)	1.07 (0.91 to 1.22)	1.03 (0.83 to 1.27)
Overweight/obesity and CPAP treatment			
No	1.64 (1.15 to 2.13)	1.57 (1.07 to 2.07)	0.98 (0.63 to 1.52)
Yes	0.78 (0.42 to 1.14)	1.37 (0.90 to 1.83)	0.60 (0.34 to 1.06)
No overweight/obesity and CPAP treatment			
No	1.40 (1.26 to 1.54)	1.09 (0.96 to 1.22)	**1.27 (1.09 to 1.48)**
Yes	1.06 (0.89 to 1.23)	1.05 (0.88 to 1.22)	1.04 (0.83 to 1.30)

Follow-up time was 1–24 years.
*Adjusted by propensity score-matching design; the propensity score was calculated based on age, sex, calendar year, diabetes mellitus, chronic kidney disease, hypertension, hypercholesterolaemia, traumatic brain injury, smoking, depression and disorders related to alcohol use.
CPAP, continuous positive airway pressure.

without obesity may partly result from centrally mediated mechanisms linked to early neurodegenerative changes,[35] suggesting that reverse causation could explain the association in this subgroup.

We also examined the potential effect of the measure modification by CPAP treatment. Previous research suggests improved cognitive function in patients with OSA who received CPAP treatment.[6] However, findings have been inconsistent.[36] Our study indicated that the OSA–dementia association was attenuated by CPAP treatment, suggesting a potential protective effect, but we do not know whether the effect pertains to all patients with OSA or only to patients who are of normal weight or underweight, where the hazard of dementia is greater. It is possible that the diagnosis and treatment of OSA is delayed, thus any potential cognitive benefits of CPAP are only realised to a small extent.[37] It is also important to recognise that patient adherence to CPAP therapy may be variable. While we examined CPAP treatment, we could not account for adherence, which is a limitation. Given the high rates of non-adherence in other populations, our findings may underestimate the potential benefit of effective CPAP use. Future studies should include objective adherence data. Given the potential for CPAP to

mitigate cognitive decline, future research is needed that examines the timing of CPAP initiation and adherence as potential modifiers of the association between OSA and dementia. Investigating these factors could provide valuable insights into whether early and sustained CPAP treatment can serve as an effective intervention for reducing dementia risk and what subgroups are most likely to benefit.

Our subgroup analysis revealed similar associations between OSA and dementia among individuals without hypertension compared with those with hypertension. These findings suggest that hypertension may not markedly modify the relation between OSA and dementia in our cohort, but further investigation with detailed blood pressure data may help clarify potential interaction effects. However, we did not have information on antihypertensive medication use. Nevertheless, certain medications may have differential effects on cognitive outcomes.

Limitations

OSA, overweight/obesity and dementia may all be both underdiagnosed and incompletely recorded. Despite the high positive predictive value of the OSA diagnosis coding (82%),[38] OSA may be underreported, since diagnostic coding does not capture patients with very mild, subclinical disease and those who do not seek treatment for OSA.[37] In our previous validation of the overweight/obesity diagnosis code, we found a low sensitivity of coding but a high positive predictive value associated with the code.[39] Finally, a diagnosis of dementia may be delayed for several years due to both its insidious onset and the lack of disease recognition. Phung *et al* reported high validity of all-cause dementia and Alzheimer's disease diagnosis coding in Denmark, but lower validity for other dementia subtypes, including vascular dementia.[25] All these factors may have led to an underestimation of the true magnitude of the association. Furthermore, we were unable to stratify by OSA severity. The strength of the association between OSA and dementia may vary across different levels of OSA severity; thus, a potential dose-response relation was not examined. Future research should incorporate objective severity measures, such as the Apnoea-Hypopnoea Index, to assess differential risk. Patients with mild to moderate OSA or those who cannot tolerate CPAP may have been prescribed, for example, a mandibular advancement splint. However, these treatments are not systematically recorded in the Danish administrative health data.

Factors such as smoking, alcohol use, physical activity and other lifestyle factors may also influence late-life dementia risk.[28 40] We lacked information about these variables, possibly leading to residual confounding. However, we did use smoking-related disorders and alcohol-related disorders as proxies for smoking and alcohol intake. We also cannot exclude the risk of surveillance bias in the exposed cohorts.

Our findings support a modest association between OSA and dementia, including Alzheimer's disease, motivating early detection of OSA as a potentially modifiable risk factor for dementia onset. However, the finding that dementia hazard was not increased in the setting of overweight or obesity requires further examination and points to the need for future research focused on the mechanisms underlying the association between OSA and dementia. Last, trials evaluating the effect of OSA treatment (eg, CPAP and other targeted therapies) on cognitive outcomes would help clarify causality and identify subgroups where targeted intervention might best be applied.

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Funding The study was funded by Centre for Population Medicine, Aarhus University and Aarhus University Hospital, Denmark. This work was also supported by a grant from Lundbeckfonden (grant no. R433-2023-1140). SBG was funded by the Independent Research Fund, Denmark (490-63-2618), by the Novo Nordisk Foundation (NNF18OC0052917) and by the Central Denmark Region. VH was funded by the National Institutes of Health P30 AG066515.

Competing interests NS was affiliated with the Department of Clinical Epidemiology, Aarhus University and Aarhus University Hospital during the initiation and conduct of this study but is now employed by Novo Nordisk A/S. SBG has received honoraria and support for attending conferences from Novo Nordisk A/S. VH has received honoraria as a member of the External Advisory Committee of the Kansas University Alzheimer's Disease Centre and has received honoraria from the Institute for Clinical and Economic Review, the American Academy of Neurology and the Oregon Health Sciences University. VH has received travel reimbursements from the University of Southern California, the Alzheimer's Disease Cooperative Study, Aarhus University and the Menopause Society. The other authors declare they have no potential conflicts of interest.

Patient consent for publication Not applicable.

Ethics approval No human participants were included. As we developed plans for study design and implementation, patients were not involved in determining the research question or the outcome measures. No patients were asked to advise on the interpretation or presentation of results. According to Danish law, registry-based research requires registration by the Danish Data Protection Board, but not ethical approval or informed consent. The study was registered with the Danish Data Protection Agency by Aarhus University (Record number: 2016-051-000001, 605). This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Data are available as presented in the paper. According to Danish legislation, our own approvals to use the Danish data sources for the current study do not allow us to distribute or make patient data directly available to other parties. Interested researchers may apply for data access through the Research Service at the Danish Health Data Authority.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been

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