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ORIGINAL ARTICLE

Hospital-diagnosed sleep disorders and incident dementia: a nationwide observational cohort study

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Abstract

Background and purpose: Several smaller, community-based studies have suggested a link between sleep disorders and dementia with a focus on sleep as a modifiable risk factor for dementia. Studies on neurodegenerative diseases are prone to reverse causation, and few studies have examined the association with long follow-up time. Our aim was to explore the possible association between sleep disorders and late-onset dementia in an entire population.

Methods: In a nationwide cohort with 40-year follow-up, associations between hospital-based sleep disorder diagnoses and late-onset dementia were assessed. Incidence rate ratios (IRR) were calculated using Poisson regression.

Results: The cohort consisted of 1,491,276 people. Those with any sleep disorder had a 17% higher risk of dementia (IRR 1.17, 95% confidence interval [CI] 1.11–1.24) compared to people with no sleep disorder, adjusted for age, sex, calendar year, highest attained educational level at age 50, and somatic and psychiatric comorbidity. The risk of dementia was significantly increased 0–5 years after sleep disorder diagnosis (IRR 1.35, 95% CI 1.25–1.47), whilst the association after 5 years or more was non-significant (1.05, 95% CI 0.97–1.13).

Conclusions: Our findings show an increased short-term risk of dementia following a hospital-based sleep disorder diagnosis, whilst weaker evidence of a long-term risk was found. This could potentially point towards sleep disorders as an early symptom of dementia. Further research is needed to distinguish sleep disorders as an early symptom of dementia, a risk factor, or both.

KEYWORDS
dementia, epidemiology, risk factors, sleep apnea syndromes, sleep–wake disorders

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See commentary by L. Ferini-Strambi on page 3484.

INTRODUCTION

Dementia is a major public health challenge with an estimated 46.8 million people living with the disorder worldwide in 2015 [1]. Whilst dementia due to neurodegenerative diseases is typically diagnosed later in life, pathology begins to develop years and even decades earlier, probably beginning as a clinically silent disorder in midlife [2]. Therefore, significant research efforts have focused on identifying modifiable risk factors to be leveraged for dementia prevention.

Sleep is required for memory consolidation and normal brain functioning, and several mechanisms are proposed to underlie the link between poor sleep and cognitive impairment. Poor sleep might disrupt neurogenesis and promote neuroinflammation, especially in hippocampal areas, thus contributing to neurodegeneration [3]. Moreover, insufficient sleep facilitates accumulation of amyloid β, which is suspected to trigger conversion to Alzheimer's disease (AD) [4]. Short sleep duration has been associated with greater amyloid β burden and long sleep duration with worse performance across multiple cognitive domains [5].

Several smaller community-based studies suggest a link between sleep disorders and dementia. For instance, insomnia has been suggested to increase the risk of mild cognitive impairment (MCI) and AD [6] as well as all-cause dementia by 5% [7]. Sleep-disordered breathing has been linked to increased risk of MCI and AD [8, 9] and may cause earlier cognitive decline to MCI and AD by around 10 years compared to those without [10]. The association is widely considered to be bidirectional, with some sleep disturbances suspected both to increase risk of dementia and to be more prominent amongst people with dementia, suggesting a reciprocal relationship [11].

The diagnosis of dementia typically occurs years after onset of pathological changes in the brain, for AD patients an estimated 10–15 years from first identifiable amyloid plaque formation [11], making it difficult to determine directionality, especially in studies with short follow-up. Existing evidence regarding the association between sleep disorders and incident dementia is predominantly based on studies following smaller cohorts, conducted over an interval of <10 years, and often relies on retrospective surveys [12]. An improved understanding of the association between sleep disorders and dementia could facilitate further investigations of sleep disorders as a potential target for early prevention of dementia.

The aim of this study was to examine the association between sleep disorders diagnosed after age 50 in the secondary healthcare sector and subsequent late-onset dementia in an entire population.

METHODS

Data sources

Nationwide population data were linked with information on sleep disorders and dementia from the Danish National Patient Registry (DNPR), the Danish Psychiatric Central Research Register (DPCRR) and the Danish National Prescription Registry (DNPrR). DNPR and DPCRR contain information on primary and secondary discharge diagnoses given at somatic and psychiatric Danish hospitals since 1977 and 1969 respectively, with outpatient data added in 1995 [13, 14]. Since 1995, information on prescription medication has been recorded in the DNPrR using the Anatomical Therapeutic Chemical code [15].

Study design and population

A cohort design was applied in which all individuals born in 1928–1953 and living in Denmark on 1 January 1978 were included. These birth cohorts were selected to ensure data on exposure from age 50 years and risk time from age 65 years. As the focus was on late-onset dementia, persons with a dementia diagnosis before age 65 years were excluded. Patients were included from their 50th birthday between 1978 and 2018. Follow-up terminated on the date of dementia diagnosis, emigration, death or 31 December 2018, whichever came first.

Definition of sleep disorder

All primary or secondary discharge diagnoses recorded during hospital contacts in the DNPR or DPCRR were screened for sleep disorder diagnoses (Table S1). Individuals with a hospital-based sleep disorder diagnosis after the age of 50 were considered exposed from that date onward.

Definition of dementia diagnosis

Dementia onset was defined as the date of a first registered primary or secondary dementia diagnosis in the DNPR or DPCRR (Table S2) or the date of the first redeemed prescription for anti-dementia medication in DNPrR (Table S3), whichever came first.

Covariates

Analyses were adjusted for sex, age, calendar year, highest attained educational level at age 50 years, somatic comorbidity using the Charlson Comorbidity Index (CCI) (excluding dementia, Table S4) and psychiatric comorbidity, which may affect both sleep disorders and dementia (mood disorders [16, 17] and mental and behavioral disorders due to alcohol use [18, 19], Table S5). All variables except for sex and educational level were included as time-dependent variables.

Statistical analysis

Incidence rate ratios (IRRs) were calculated with survival analysis techniques using Poisson regression. IRRs for dementia diagnosis

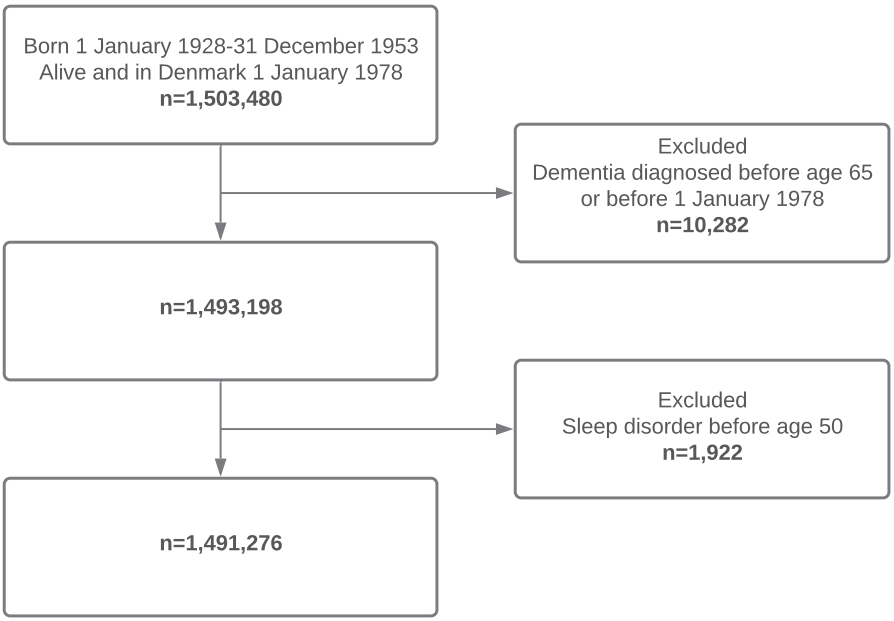

FIGURE 1 Flowchart of study population.

TABLE 1 Baseline characteristics

		Any sleep disorder	No sleep disorder
	Total	***n***	***n***
All	1,491,276	41,704	1,449,572
Women (%)	763,158 (51.2%)	12,877 (30.9%)	750,281 (51.8%)
Men (%)	728,118 (48.8%)	28,827 (69.1%)	699,291 (48.2%)
Dementia during study period	75,451	1235 (3.0%)	74,216 (5.1%)
Age at first dementia diagnosis, mean (range)	76.8 (65.0–90.9)	75.6 (65.0–90.3)	76.8 (65.0–90.9)
Age at first sleep disorder diagnosis, mean (range)		66.8 (50.0–90.6)	
Sleep disorder contact—age 50–64 years		17,588	
Sleep disorder contact—age ≥ 65 years		24,116	

were estimated for those with a sleep disorder diagnosis in comparison to no sleep disorder. Sleep disorders were treated as time-dependent variables. IRRs were also estimated in sub-group analyses by sex, type of sleep disorder and age. IRRs by category of sleep disorder were calculated for a first diagnosis of sleep apnea, narcolepsy and cataplexy, other specific sleep disorders or unspecified sleep disorders compared to those without a sleep disorder within that category. These subcategories were chosen due to either a large number of people with the sleep disorder and a suspected causal pathway to dementia (sleep apnea), a well-defined disease suspected to lead to hospital contacts and therefore more valid diagnosis (narcolepsy and cataplexy), or a large number of cases in the population (other specific disorders). There were too few patients with the remaining specific sleep disorders to warrant meaningful investigation, or the validity of the coding was deemed too low. Insomnia is an example of one such diagnostic code, with a markedly low number of cases in the cohort compared to general reports on prevalence, unfortunately hindering meaningful investigation of this sleep disorder. The remaining sleep disorders were pooled into two groups: other specific sleep disorders and unspecified sleep disorders. The age at sleep disorder diagnosis was categorized as midlife (50–64 years) and later life (≥65 years). IRRs were estimated for those with a sleep disorder diagnosis in midlife compared to those who did not have a sleep disorder in midlife, that is, those with a sleep disorder diagnosis in later life or no sleep disorder diagnosis ever. Similarly, IRRs were estimated for those with a sleep disorder diagnosis in later life compared to those with no sleep disorder diagnosis in later life. Furthermore, the association of dementia diagnosis within 5 years of first sleep disorder diagnosis and within more than 5 years was examined, compared to those without sleep disorders.

Three adjustment models were applied: model 1 adjusted for age, sex and calendar year; model 2 further adjusted for highest attained educational level at age 50 and CCI; model 3 further adjusted for psychiatric comorbidity. A 5% significance level was applied for all analyses. All statistical analyses were performed using SAS 9.4 software.

Lastly, post hoc analyses of those with other specific sleep disorders were conducted, removing one disorder at a time to identify the driver behind the risk. As removing parasomnias had a large effect, IRRs were calculated for parasomnias.

This research project was approved by the Danish Data Protection Agency, Statistics Denmark, and the Danish Health Data Authority. Danish law does not require ethics committee approval or informed patient consent.

RESULTS

There were 1,503,480 persons born between 1 January 1928 and 31 December 1953 and living in Denmark at inclusion. Of these, 10,282 persons were excluded due to dementia diagnosis before age 65 years or before 1 January 1978, and 1922 were excluded due to sleep disorder diagnosis before age 50 years; thus, the study population consisted of 1,491,276 persons (Figure 1). Of these, 41,704 persons had a sleep disorder diagnosis in the DNPR, and of those 1235 had a subsequent dementia diagnosis. Mean age at dementia diagnosis for the exposed group was 75.6 years, and 76.8 years for the non-exposed group (Table 1). IRRs were calculated for sleep apnea ($n = 28,327$), narcolepsy and cataplexy ($n = 412$), other specific sleep disorders ($n = 3869$) and unspecified sleep disorders ($n = 11,580$) (Figure 2).

Observing a total of 14,079,804 person-years, people diagnosed with any sleep disorder had a 1.17-fold (95% confidence interval [CI] 1.11–1.24) higher rate of dementia compared to those who had not been diagnosed with a sleep disorder when fully adjusted (Figure 2). Whilst there was not a statistically significantly increased IRR of dementia for women with any sleep disorder, the fully adjusted IRR of dementia for men with any sleep disorder was 1.25 (95% CI 1.17–1.34) compared to men with no sleep disorder. The IRR of dementia following any sleep disorder was 1.20 (95% CI 1.12–1.28) for those with a sleep disorder in later life compared to those with no sleep disorder diagnosis in later life (Figure 3). The IRR for dementia was 1.11 for those with a sleep disorder in midlife compared to those with no sleep disorder diagnosis in midlife; whilst this was statistically significant (95% CI 1.00–1.22), it was much less so than observed for later life sleep disorder diagnoses.

Figures 2 and 3 also show fully adjusted IRRs for dementia by type of sleep disorder, where possible stratified by sex and age. Persons with sleep apnea had a statistically significantly increased IRR, especially men and those with sleep apnea after age 65. The highest risk for dementia was for men with other specific sleep disorders, with a fully adjusted IRR of 2.00 (95% CI 1.71–2.32).

Table 2 shows results from the post hoc analyses. Excluding hypersomnias, insomnias, disorders of the sleep–wake schedule, sleep-related movement disorders and non-organic sleep disorders yielded similar but slightly increased IRRs as in the main analyses. Excluding parasomnias decreased the IRR to 1.40 (95% CI 1.21–1.62). Analyzing risk of dementia following a diagnosis of parasomnia an IRR of 5.87 (95% CI 4.70–7.34) was found.

When fully adjusted, those with any sleep disorder diagnosis had an IRR of 1.35 (95% CI 1.25–1.47) for dementia within 5 years, whilst there was no significant increase in the risk for a first dementia diagnosis >5 years after sleep disorder diagnosis (Table 3). Results from adjustment models 1 and 2 for all analyses are presented in Tables S6–S9.

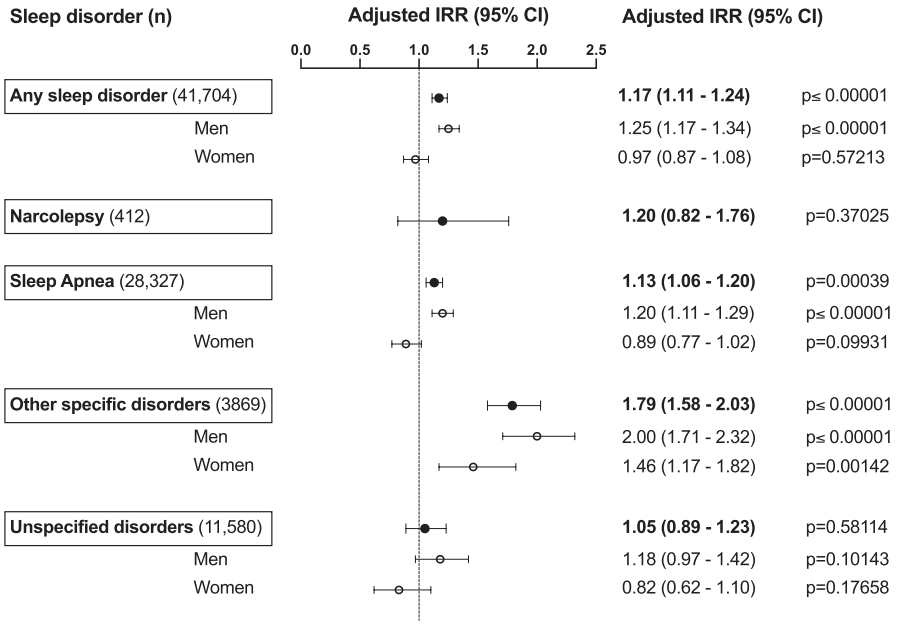

FIGURE 2 IRRs of dementia in individuals by sleep disorder category and sex. For the reference group (people with no diagnosis of the sleep disorder[s] analyzed), the IRR is equal to 1 (as indicated by the dotted vertical line). Error bars represent 95% confidence intervals (CIs). IRRs were estimated using Poisson regression. A two-sided type 1 error of 5% was considered statistically significant. Total person-years were 180,328 in people with sleep disorder and 13,899,476 in people with no sleep disorder. The IRRs presented are adjusted for age, sex, calendar year, highest attained educational level at age 50, somatic comorbidity (CCI) and psychiatric comorbidity (model 3). Adjustment models 1 and 2 are presented in Table S6. There were too few patients with narcolepsy and dementia to facilitate sub-analyses.

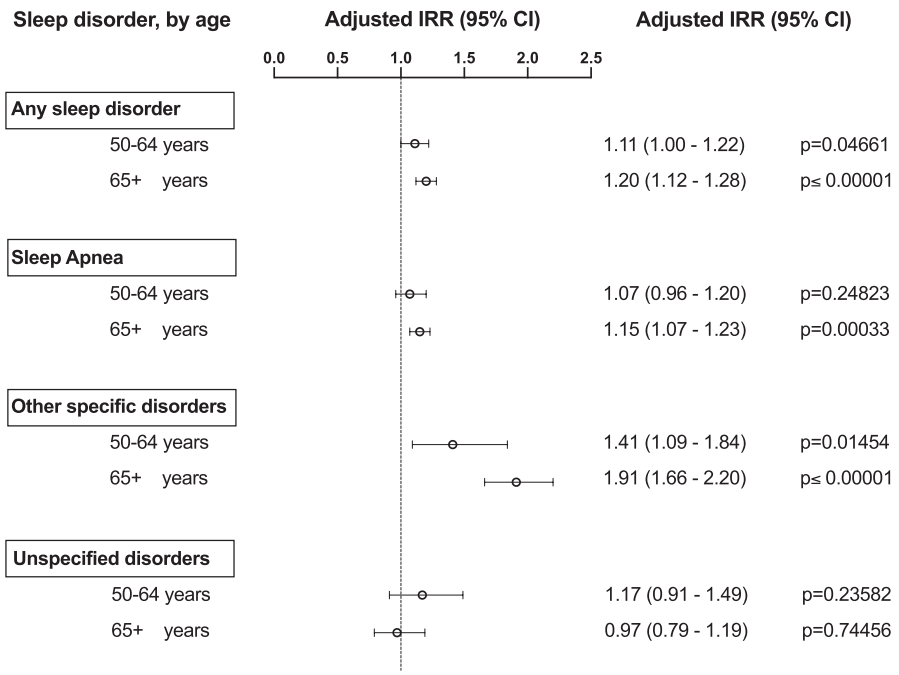

FIGURE 3 IRRs of dementia in individuals by sleep disorder category and age group. For the reference group (people with no diagnosis of the sleep disorder[s] analyzed in that age group), the IRR is equal to 1 (as indicated by the dotted vertical line). Error bars represent 95% confidence intervals (CIs). IRRs were estimated using Poisson regression. A two-sided type 1 error of 5% was considered statistically significant. Total person-years were 100,866 in people with sleep disorder age 50–64 and 13,978,938 in people with no sleep disorder age 50–64. Total person-years was 98,885 in people with sleep disorders age ≥65 and 13,980,920 in people with no sleep disorder age ≥65. The IRRs presented are adjusted for age, sex, calendar year, highest attained educational level at age 50, somatic comorbidity (CCI) and psychiatric comorbidity (model 3). Adjustment models 1 and 2 are presented in Table S7. There were too few patients with narcolepsy and dementia to facilitate sub-analyses.

DISCUSSION

Whilst previous studies have sought to investigate the link between sleep disorders and dementia, to our knowledge this is the first nationwide cohort study to investigate whether sleep disorders in midlife or later life might be a risk factor for dementia. Overall, there was a statistically significantly increased risk of dementia for those with hospital-based sleep disorder diagnoses compared to those without. For men the risk remained statistically significant in analyses for all sleep disorder types, whilst for women the risk was only significantly increased following a diagnosis of "other specific sleep disorders". The difference in risk by sex may in large part be because there are far more men than women in the exposed group. This is likely to be due to sleep apnea being the most prevalent sleep disorder in the cohort, accounting for over 60% of sleep disorder diagnoses, and is a disease more frequently diagnosed in men than women [20]. When examining individual sleep disorders our results support existing literature suggesting an association between sleep apnea and late-onset dementia [8, 10, 21] with a 13% overall risk increase after adjustment. Tsai et al. reported a significantly increased risk for AD following sleep apnea for patients aged ≥60 years (hazard ratio 4.42) [9]. The higher risk found in that study may in part be because the outcome is AD, whereas the present study investigated all-cause dementia. Several mechanistic pathways have been suggested between sleep apnea and AD, one of which is that apolipoprotein E ε4 seems to increase the risk of moderate-to-severe sleep apnea [22] whilst also being a well-known risk factor for AD [23]. However, sleep apnea has most often been linked to vascular dementia [21].

The highest risk in our study was found for "other specific sleep disorders" for men and in later life. This increase was largely driven by parasomnia; however, the increase was still significant when parasomnia was removed from the analysis (although as this was a post hoc analysis, caution is warranted when interpreting these results). Parasomnias include rapid eye movement sleep behavior disorder, which is recognized as a clinical manifestation of α-synucleinopathies including both Parkinson's disease, Parkinson's disease dementia and dementia with Lewy bodies [24, 25], with smaller studies having found an interval between the onset of rapid eye movement sleep behavior disorder and dementia up to 50 years [26]. Therefore, parasomnia is likely to be an early indicator of disease rather than a risk factor.

A 35% increased risk for dementia diagnosis was found in the first 5 years after a sleep disorder diagnosis; however, no significant increase in risk was seen after more than 5 years, suggesting short temporality between a hospital-based diagnosis of sleep disorder and dementia.

All but a few analyses performed reached statistical significance when only adjusted for age, sex and calendar year. A large decrease in risk estimates was seen when adjusted for highest attained

TABLE 2 Post hoc analysis: incidence rate ratios of dementia in individuals with other specific sleep disorders

	Dementia cases	Person-years at risk	Rate per 1000 person-years	Fully adjusted[a]	
				IRR (95% CI)	*p* value
Excluding insomnias					
Other specific sleep disorders	233	17,420	13.4	1.86 (1.64–2.12)	≤0.00001
No sleep disorder (ref)	75,218	14,062,384	5.3	1.00	
Excluding hypersomnias					
Other specific sleep disorders	205	12,782	16.0	1.97 (1.71–2.25)	≤0.00001
No sleep disorder (ref)	75,246	14,067,023	5.3	1.00	
Excluding disorders of the sleep–wake schedule					
Other specific sleep disorders	231	17,490	13.2	1.84 (1.62–2.09)	≤0.00001
No sleep disorder (ref)	75,220	14,062,314	5.3	1.00	
Excluding parasomnia					
Other specific sleep disorders	179	17,946	10.0	1.40 (1.21–1.62)	0.00002
No sleep disorder (ref)	75,272	14,061,859	5.4	1.00	
Excluding sleep-related movement disorders					
Other specific sleep disorders	209	15,522	13.5	1.87 (1.63–2.14)	≤0.00001
No sleep disorder (ref)	75,242	14,064,282	5.3	1.00	
Excluding non-organic sleep disorders					
Other specific sleep disorders	193	16,035	12.0	1.89 (1.64–2.18)	≤0.00001
No sleep disorder (ref)	75,258	14,063,770	5.4	1.00	
Parasomnia					
Parasomnia	77	1653	46.6	5.87 (4.70–7.34)	≤0.00001
No sleep disorder (ref)	75,374	14,078,152	5.4	1.00	

Note: IRRs are presented for the sleep disorder category other specific disorders excluding one diagnosis at a time from the exposure group. The reference group is individuals without the remaining other specific sleep disorders. Adjustment models 1 and 2 are presented in Table S8.

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; ref, reference group.

[a]Adjusted for age, sex, calendar year, highest attained educational level at age 50, somatic comorbidity (Charlson Comorbidity Index) and psychiatric comorbidity (model 3).

TABLE 3 Incidence rate ratios by time between any sleep disorder diagnosis and dementia diagnosis

	Dementia cases	Person-years at risk	Rate per 1000 person-years	Fully adjusted[a]	
				IRR (95% CI)	*p* value
Within 5 years	587	73,635	8.0	1.35 (1.25–1.47)	≤0.00001
After 5 years	648	106,694	6.1	1.05 (0.97–1.13)	0.24538
No sleep disorder (ref)	74,216	13,899,476	5.3	1.00	

Note: IRRs are presented for time between sleep disorder diagnosis and dementia diagnosis. The reference group is individuals without any sleep disorder. Adjustment models 1 and 2 are presented in Table S9.

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; ref, reference group.

[a]Adjusted for age, sex, calendar year, highest attained educational level at age 50, somatic comorbidity (Charlson Comorbidity Index) and psychiatric comorbidity (model 3).

education level at age 50 and somatic comorbidity, with the decrease driven largely by comorbidity. A slight decrease was seen when adjusted for psychiatric comorbidities. Notably, sleep disorders are themselves risk factors for and consequences of a range of medical and psychiatric comorbidities [27], and these comorbidities may therefore be on the causal pathway linking sleep disorders and

dementia. If these comorbidities contribute to or result from sleep disorders, this adjustment will lead to an underestimation of the true magnitude of the association between sleep disorders and dementia. This should be kept in mind when interpreting our findings.

This study presents a novel nationwide cohort study, enabling an in-depth examination of the role of sleep disorders as a potential target for early prevention of dementia. Data on hospital contacts were drawn from the DNPR, internationally considered to be the most comprehensive of its kind [13]. This allowed for detailed and reliable information on exposure, outcome and covariates for the entire cohort of 1.5 million people and facilitated a long follow-up time in later life. A previous study has shown a high validity of dementia diagnosis in the DNPR, concluding that it can be used as a data source for epidemiological research on dementia [28]. Due to low validity of diagnosis of specific dementia subtypes, analyses were not performed by subtype of dementia. Despite these strengths, our study has some limitations. Whilst diagnostic codes for dementia in the DNPR have been validated, no such validation has been performed on diagnostic codes for sleep disorders. Thus, it is not known whether patients with sleep disorders are routinely coded as such, which could potentially lead to an underestimation of the risk of dementia. Furthermore, sleep disorders are not as well specified in International Classification of Diseases 8 (ICD-8) as in ICD-10, meaning that data on exposure are more accurate from 1994 onwards (when ICD-10 was implemented in Denmark); however, as IRRs are adjusted by calendar year, this is similar for the entire cohort.

Some sleep disorders, such as sleep apnea and narcolepsy, are more likely to lead to hospitalization or outpatient contacts, compared to sleep disorders such as insomnia, which is rarely the main reason for a hospital contact. Out of our population of 1.5 million people only 615 had an insomnia diagnosis, and with an estimated prevalence of 6% [29] the association between insomnia and dementia is probably severely underestimated, precluding confident assessment of the association with the available data. Furthermore, many sleep disorders may only be treated in the primary care sector, for which the data are not available, arguably leading to a clinical subset of the population with more severe sleep disorders. Although national registers offer detailed data on all hospital contacts and diagnoses, it is unfortunately not possible to extract data on severity of sleep disorders. Whereas some studies suggest a causal link between sleep disorders and the pathophysiology of dementia, for example obstructive sleep apnea and neurocognitive impairment through oxidative stress [30], other studies suggest that the association between sleep disorders and cognitive decline is due to reduced sleep duration [31] or insufficient slow-wave sleep [32]. Given that sleep duration or architecture data were not available, it was not possible to study these aspects of sleep directly for those with or without sleep disorder diagnosis in the registries (i.e., those diagnosed in the primary care sector or those with undiagnosed sleep disorders). A recent study found short sleep duration (≤6 h) at age 50 and age 60 to be associated with increased risk of dementia, whilst sleep duration at age 70 was not associated with dementia after adjustment [31]. Whilst epidemiological approaches do not generally enable this kind of detailed knowledge on sleeping patterns of the cohort but instead rely on diagnostic codes, the strength of the present study lies in the magnitude of data available. A recent Danish register study used benign prostatic hyperplasia (BPH) as a proxy for poor sleep quality, assuming this leads to nocturia, and observed an increased risk for all-cause dementia of 21% compared to those without BPH. Another possible proxy measure would be to examine sleeping medication and risk of dementia, assuming this may be a proxy for insomnia. It would be uncertain, however, if what is measured is an effect due to the medication itself, poor sleep quality, or if those medicated have longer sleep duration or better sleep quality than those untreated, who would not be included in the case cohort.

A prominent short-term risk of dementia following sleep disorder diagnosis was found, as seen in the significant association in those with a first sleep disorder in later life and an increased risk for dementia only within the first 5 years after sleep disorder diagnosis. This raises the question as to whether a sleep disorder diagnosis is a risk factor for or an early symptom of dementia, or perhaps an accelerating factor in the development of dementia. Evidence of long-term risk is weaker in the present study, with association between a first sleep disorder diagnosis in midlife and dementia only marginally increased, and no association found between sleep disorders diagnosed >5 years before dementia diagnosis, further suggesting that our results may be an expression of reverse causation.

In conclusion, it was found that those diagnosed with a sleep disorder from age 50 and onwards have a 17% increased risk of late-onset dementia compared to those with no sleep disorder. The risk was higher for men, for those with a sleep disorder at ≥65 years and within the first 5 years after sleep disorder diagnosis. Of the specific disorders, sleep apnea presented the highest increase in risk, with an overall risk of 13% for dementia. Whilst our findings suggest sleep disorders may be an early symptom of dementia, further research is needed to understand the possible role of sleep as a risk factor for dementia. Some sleep disorders may accelerate cognitive decline after dementia diagnosis through the assumed bidirectional relationship. It is recommended that there should be a higher focus on sleep disorders as a red flag for possible early phase dementia disorders. Treating sleep disorders in midlife may decelerate cognitive decline.

AUTHOR CONTRIBUTIONS

Line Damsgaard: Conceptualization (equal); data curation (equal); formal analysis (equal); methodology (equal); writing – original draft (lead); writing – review and editing (equal). **Janet Janbek:** Conceptualization (equal); data curation (equal); formal analysis (equal); methodology (equal); writing – original draft (supporting); writing – review and editing (equal). **Thomas Munk Laursen:** Conceptualization (equal); data curation (equal); formal analysis (equal); methodology (equal); writing – review and editing (equal). **Annette Erlangsen:** Conceptualization (equal); methodology (equal); writing – review and editing (equal). **Adam Spira:** Conceptualization (equal); methodology (equal); writing – review and editing (equal). **Gunhild Waldemar:** Conceptualization (equal); methodology (equal);

project administration (lead); resources (lead); supervision (lead); writing – review and editing (equal).

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CONFLICT OF INTEREST

Dr Spira received honoraria for serving as a consultant to Merck and from Springer Nature Switzerland AG for guest editing a special issue of *Current Sleep Medicine Reports*. Professor Waldemar served as consultant/speaker for Roche, Biogen and Novo Nordisk (honorarium to department and without honorarium).

DATA AVAILABILITY STATEMENT

All of the data used in this study are derived from the Danish National and Public Health registries. These data are collected and stored by the relevant authorities and cannot be made public or accessed by unauthorized parties. Access to such data is given via standard rules and regulations of data access outlined by the Danish Data Protection Agency and Danish Health Data Authority.

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Additional supporting information can be found online in the Supporting Information section at the end of this article.

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