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SLEEP BREATHING PHYSIOLOGY AND DISORDERS • REVIEW

Association between sleep apnoea and risk of cognitive impairment and Alzheimer's disease: a meta-analysis of cohort-based studies

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Abstract

Purpose To provide updated evidence on the association of obstructive sleep apnoea (OSA)/sleep-disordered breathing (SDB) with risk of all-cause cognitive impairment/dementia and Alzheimer's disease (AD).

Methods A systematic literature search was done in PubMed, EMBASE and Scopus databases for cohort studies (retrospective or prospective) that documented the association of SDB/OSA with the risk of cognitive impairment or all-cause dementia or AD. Only studies that were published in the year 2000 and onwards were included. The random-effects model was used for all the analyses and effect sizes were reported as hazards ratio (HR) with 95% confidence intervals.

Results Of 15 studies were included in the meta-analysis, SDB/OSA was diagnosed with at-home polysomnography in six studies, while five studies relied on self-report or questionnaires. In the remaining studies, International Classification of Diseases (ICD) codes determined the diagnosis of SDB. The overall pooled analysis showed that patients with SDB/OSA had higher risk of cognitive impairment and/or all-cause dementia (HR 1.52, 95% CI: 1.32, 1.74), when compared to patients without SDB/OSA. However, when studies with diagnosis of SDB based on polysomnography were pooled together, the strength of association for all-cause cognitive impairment was weaker (HR 1.32, 95% CI: 1.00, 1.74).

Conclusion Findings suggest a possible association of SDB/OSA with risk of all-cause cognitive impairment and/or dementia. However, careful interpretation is warranted as the majority of the studies did not rely on objective assessment based on polysomnography.

Keywords Sleep-disordered breathing · Obstructive sleep apnoea · Cognitive decline · Cognitive impairment · Dementia · Alzheimer's disease · Meta-analysis

Introduction

Current evidence indicates that around 2 to 4% of the middle-aged population may be affected by obstructive sleep apnoea/hypopnea (OSA) syndrome [1]. OSA is more prevalent in men and in individuals who are older than 65 years [1]. There is a recent interest in this potentially treatable condition because of its potential association with disorders such as hypertension, diabetes and cardiovascular diseases [2, 3]. A meta-analysis of 17 prospective cohort studies found a link between OSA and a higher risk of cardiovascular diseases (2.48 times higher) and stroke (2 times higher) [2]. Although recent studies suggest the association of OSA with cognitive decline in the elderly, the evidence is still inconclusive. There have been systematic reviews and meta-analyses conducted on the association of sleep disturbances, including OSA or sleep-disordered breathing (SDB), with cognitive decline or dementia but there has been no consistent methodology [4–7]. Some reviews included cross-sectional studies, which may be potentially biased, whereas others used a combination of all study designs (cross-sectional, case-control, data from randomized controlled trials and cohort-based studies) [4–7].

A study by Emamian et al. included prospective cohort studies ($n = 5$) and showed that patients with Alzheimer's disease (AD) have 5 times higher risk of having OSA than cognitively normal subjects of the same age [5]. Another review by Leng et al. included both prospective and cross-sectional studies and documented, through pooled analysis of prospective studies, that patients with sleep-disordered

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breathing (SDB) have higher risk of cognitive impairment that those without SDB [4]. Findings from pooled analysis of cross-sectional studies indicated that patients with SDB had lower executive function but there was no effect of SDB on cognition [4]. Furthermore, there are reviews that have proposed an association between OSA/SDB and cognitive decline/dementia based on studies using blood and cerebrospinal biomarkers and brain pathology-based diagnosis. Cui et al. in their meta-analysis indicated abnormal biomarkers of AD in cerebrospinal fluid (CSF) and on brain positron emission tomography (PET) scans in patients with OSA [8]. Their overall analysis showed significantly reduced levels of amyloid-β 42 (Aβ42) and increased total tau (t-tau) levels in cerebro-spinal fluid (CSF), as well as amyloid burden on PET scans in OSA patients, compared to normal subjects [8].

Studies have also differed in their method of diagnosis of OSA/SDB as well as the tools used for cognitive assessments. In view of this significant and substantial heterogeneity between different studies, this review and meta-analysis aimed to provide updated and reliable evidence on the association between SDB/OSA with a cognitive decline and/or a risk of AD. We purposefully decided to include only cohort-based studies and studies that used validated psychometric tools, instead of blood or cerebrospinal fluid or brain tissue related parameters, to assess cognitive decline or dementia or AD.

Methods

Selection of studies

The protocol of the current study was registered at PROSPERO (CRD42023393558). PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed [9]. Table 1 summarizes the search strategy used to systematically search for studies in three databases, i.e. PubMed, EMBASE and Scopus. English language studies published until the 15th of January 2023 were eligible for inclusion.

Studies that documented the association of SDB/OSA with risk of cognitive impairment or all-cause dementia or AD were eligible for inclusion. Specifically, we wanted to include only studies that reported on a clinical diagnosis of cognitive decline or dementia or AD. Therefore, all studies that reported blood or cerebrospinal fluid or brain tissue-related parameters were not considered. We were only interested in studies that had a cohort design. Studies with matched case-control and cross-sectional designs were excluded. We also excluded studies that used data collected as part of a randomized controlled trial. To provide contemporary evidence, we included only those studies that were published in the year 2000 and onwards.

The total number of studies in each of the three databases were identified and duplicates were removed. The title and abstract of the remaining unique studies were reviewed by two study authors independently and further exclusions were made. Following this, the full texts were reviewed by the two authors independently and decisions were made for the final inclusion in the meta-analysis. Any discrepancies were resolved with the help of a senior author.

Data extraction and analysis

Data extraction was done using pre-tested electronic sheet. The extracted data included study identifiers (name of the author, study setting and year of publication), study design, ways in which data on exposure and outcome(s) of interest were collected, characteristics of the study subjects, sample size and key findings. All analyses were conducted using STATA 16 software (TX, USA). We reported pooled effect sizes as hazards ratio (HR) along with 95% confidence intervals. It is important to mention that not all studies reported their effect sizes as hazards ratio and in such instances, we converted the reported effect sizes (either as odds ratio or relative risk) into HR based on the methods reported previously [10, 11]. As an a priori decision, we used random effects model for all analyses. This was done because the included studies differed in the characteristics of the subjects; study setting and design; definitions of SDB/OSA adopted; tools used for exposure and outcomes assessment and duration of follow-up. These differences would have led to substantial heterogeneity in the reported findings.

The Newcastle-Ottawa Scale was used for assessment of the risk of bias [12]. We used Egger's test along with visual inspection of funnel plot to assess for publication bias [13]. A p-value of less than 0.05 was considered to denote statistical significance. Post hoc subgroup analysis was conducted based on the study design (prospective and retrospective cohort), sex (male and female) and age of the subjects (< 60 years and ≥ 60 years) and assessment method for SDB/OSA (polysomnography and self-reported/ICD coding based).

Results

Our search strategy resulted in retrieval of a total of 3726 studies. Duplicates ($n = 1386$) were removed. Additional studies ($n = 2205$) were excluded after the title and abstract review. A total of 135 studies were excluded after the full-text review, as summarized in Fig. 1. A total of 15 studies were considered for this meta-analysis [14–28].

Table 1 Characteristics of the studies included in the meta-analysis

Author (year of publication)	Study design and country	Sample size	Exposure and outcome assessment	Study subjects	Key outcomes (adjusted effect sizes reported)
Tsai et al. (2020) (14)	Retrospective cohort Taiwan	19,890	OSA: largely based on overnight polysomnographic data; subjects included only if ICD-9-CM was coded either in an inpatient setting or in three or more outpatient visits. AD: diagnosis established as per ICD-9-CM code 331.0; diagnosis of AD either in an inpatient setting or in three or more ambulatory care visits	70% subjects in the age range of 40–59 years; around 65% males; higher proportion of subjects with OSA had coronary artery disease, hypertension, diabetes, stroke, depression, anxiety. Mean follow-up of 5.5 years	Risk of AD: HR 2.17 (95% CI: 1.34, 3.51) *Subgroup analysis* < 60 years: HR 1.74 (95% CI: 0.45, 6.72) ≥ 60 years: HR 3.00 (95% CI: 1.86, 4.82) Female: HR 1.75 (95% CI: 0.89, 3.43) Male: HR 4.42 (95% CI: 2.36, 8.28)
Lee et al. (2019) (15)	Retrospective cohort Republic of Korea	4362	Sleep-disordered breathing (SDB): diagnosis based on ICD-10: G47.3; or documentation for surgical intervention, CPAP or bilevel positive airway pressure treatment. AD based on International Classification of Diseases (ICD) codes in the medical records (ICD-10: G30)	Around 77% men; age 40–49 years (50%) and 50–59 years (34%); those with SDB had higher incidence of hypertension, diabetes and cardiovascular disease. Follow-up for 14 years	Risk of AD: HR 1.58 (95% CI: 1.01, 2.45)
Blackwell et al. (2015) (16)	Prospective cohort USA	2636	Sleep-disordered breathing (SDB): in-home polysomnography. Cognitive decline: modified mini mental state examination (3MS) and Trails B test	All subjects were males; mean age of around 76 years; higher BMI in those with SDB; higher proportion with hypertension, diabetes and coronary heart disease in those with SDB. Mean follow-up period- 3.4 years	Risk of cognitive decline: HR 0.99 (95% CI: 0.80, 1.23)
Chang et al. (2013) (17)	Prospective cohort Taiwan	8484	Sleep apnoea based on two or more diagnoses of sleep apnoea in outpatient visits or ≥1 inpatient service. Dementia: based on assigned ICD-9 code by neurologists, psychiatrists, or general practitioners; should have had at least 2 ambulatory visits or one inpatient service	All subjects with aged ≥ 40 years; subjects in the age range of 40–59 years (71%); males (60%); those with sleep apnoea had higher incidence of hypertension, diabetes, hyperlipidaemia and stroke. Mean follow-up of 5.0 years	Risk of dementia: HR 1.70 (95% CI: 1.26, 2.31) *Subgroup analysis* < 60 years: HR 3.97 (95% CI: 2.13, 7.38) ≥ 60 years: HR 2.04 (95% CI: 1.42, 2.94) Female: HR 2.38 (95% CI: 1.51, 3.74) Male: HR 1.26 (95% CI: 0.83, 1.92)
Lutsey et al. (2016) (18)	Prospective cohort USA	966	OSA: in-home polysomnography Cognitive impairment: battery of cognitive tests that measure memory and executive functions	Mean age of 61 yrs; males (48%); those with OSA had higher incidence of smoking, hypertension, diabetes, previous heart failure and coronary artery disease. Mean follow-up of 14.9 years	Risk of cognitive impairment: HR 0.99 (95% CI: 0.63, 1.55)

Table 1 (continued)

Author (year of publication)	Study design and country	Sample size	Exposure and outcome assessment	Study subjects	Key outcomes (adjusted effect sizes reported)
Martin et al. (2015) (19)	Prospective cohort France	559	SDB: At home unattended ambulatory nocturnal respiratory recording; defined as apnoea-hypopnea index (AHI) of > 15 events per hour. Cognitive impairment based on battery of neuropsychological tests	Mean age of 67 yrs; females (60%); those with SBD had higher body mass index (BMI), Mean follow-up of 7.8 years	Risk of cognitive impairment: HR 1.28 (95% CI: 0.62, 2.65)
Yaffe et al. (2011) (20)	Prospective cohort USA	298	SDB: At home unattended ambulatory nocturnal respiratory recording; defined as apnoea-hypopnea index (AHI) of ≥ 15 events/hour. Cognitive impairment- assessed using a battery of tests (MMSE, Trails B, CVLT, digit span, verbal fluency test)	All the subjects were females with a mean age of 82 years; those with and without SDB did not differ in baseline characteristics (hypertension, diabetes, smoking, history of stroke, BMI, age, presence of depressive symptoms) Mean follow-up of 4.7 years	Risk of cognitive impairment: HR 1.85 (95% CI: 1.11, 3.08)
Yaffe et al. (2015) (21)	Retrospective cohort USA	179,736	Data on both sleep apnoea and cognitive decline/dementia were based on International Classification of Diseases (ICD)-9 Revised codes	All subjects were males and aged ≥ 55 years; those with sleep apnoea were younger, had higher proportion with hypertension, diabetes, obesity, previous cardiovascular disease and depression compared to those with sleep apnoea Mean follow-up of 8 years	Risk of cognitive impairment: HR 1.27 (95% CI: 1.20, 1.34) Risk of Alzheimer's disease: HR 1.20 (95% CI: 1.01, 1.42)
Sharafkhaneh et al. (2005) (22)	Retrospective cohort USA	4,060,504	Data on both obstructive sleep apnoea and dementia were based on International Classification of Diseases (ICD)-9-CM codes	Mean age of subjects was around 58 yrs; almost all subjects were males (> 90%); those with sleep apnoea had higher prevalence of hypertension, obesity, diabetes mellitus, cardiovascular disease	Risk of dementia: HR 1.50 (95% CI: 1.34, 1.67)
Lutsey et al. (2018) (23)	Prospective cohort USA	1083	SDB: in-home polysomnography; apnoea-hypopnea index (AHI) of ≥ 30 events/hour Cognition-comprehensive neurological examination and hospital diagnostic codes	Mean age of around 62 years; 54% females; more proportion of females and those with smoking in those with SDB Follow-up of around 15 years	Risk of dementia/cognitive impairment: HR 1.30 (95% CI: 0.87, 1.93) Risk of AD: HR 1.37 (95% CI: 0.82, 2.30)
Osorio et al. (2015) (24)	Retrospective cohort USA	MCI (445) AD (1165)	Sleep apnoea: self-reported Cognitive impairment: based on hospital diagnostic codes (? Not clearly mentioned) and review of medical history description by trained physicians	Subjects aged more than 70 years; ~ 50% females; those with sleep apnoea had higher BMI, higher prevalence of hypertension, diabetes mellitus, cardiovascular disease	Risk of cognitive impairment: HR 8.40 (95% CI: 3.10, 22.7) Risk of AD: HR 1.52 (95% CI: 0.95, 2.43)

Table 1 (continued)

Author (year of publication)	Study design and country	Sample size	Exposure and outcome assessment	Study subjects	Key outcomes (adjusted effect sizes reported)
Ding et al. (2016) (25)	Prospective follow-up USA	7547	OSA: self-reported sleep apnoea Dementia: using Memory Impairment Screen (MIS); AD8 Dementia Screening Interview, self-reported, use of memory-enhancing medications and cognitive assessments	All subjects were males, aged ≥ 60 years; comparatively higher males with sleep apnoea were of Black race, smoked, had hypertension and diabetes. Mean follow-up of 5.7 years	Risk of dementia: HR 1.44 (95% CI: 0.96, 2.17)
Choe et al. (2022) (26)	Retrospective cohort Republic of Korea	1058	OSA: self-reported Cognitive assessments using a battery of tests (MMSE, NINCDS/ADRDA, CDR, Wechsler logical memory II subscale)	Mean age of 73 years, males (56%), mean BMI of 27.0 kg/m^2. Mean follow-up of 4.2 years	Risk of cognitive impairment: HR 2.17 (95% CI: 1.29, 3.67)
Agudelo et al. (2022) (27)	Retrospective cohort USA	1391	SDB: questionnaire based/self-reported. Cognitive impairment: established clinical tests (MMSE, CDR)	Mean age of 74 years; females (45%); those with SDB had higher BMI, higher proportion of hypertension, previous stroke, cardiovascular disease and smokers	Risk of cognitive impairment: HR 1.40 (95% CI: 0.89, 2.21)
Bubu et al. (2019) (28)	Retrospective cohort Multicentric	1639	SDB: self-reported during clinical interview Cognitive impairment/AD: using MMSE, CDR, established clinical assessment for AD	Subjects aged > 70 years; females (50%); those with SDB had higher BMI, higher proportion of hypertension and diabetes	Risk of cognitive impairment: HR 2.49 (95% CI: 1.62, 3.82) Risk of AD: HR 1.22 (95% CI: 0.69, 2.16) *In subgroup of females* Risk of cognitive impairment: HR 2.31 (95% CI: 1.06, 5.03)

OSA, obstructive sleep apnoea; *AD*, Alzheimer disease; *CPAP*, continuous positive airway pressure; *NINCDS/ADRDA*, National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association; *NIA-funded ADCs*, The National Institute on Aging funded Alzheimer's Disease Research Centres; *MMSE*, mini-mental state Examination; DSM-IV, The Diagnostic and Statistical Manual of Mental Disorders fifth edition criteria; *CVLT*, California Verbal Learning Test; *SSRIs*, selective serotonin reuptake inhibitors; *IADL*, instrumental activities of daily living; *CDR*, clinical dementia rating; *MCI*, mild cognitive impairment

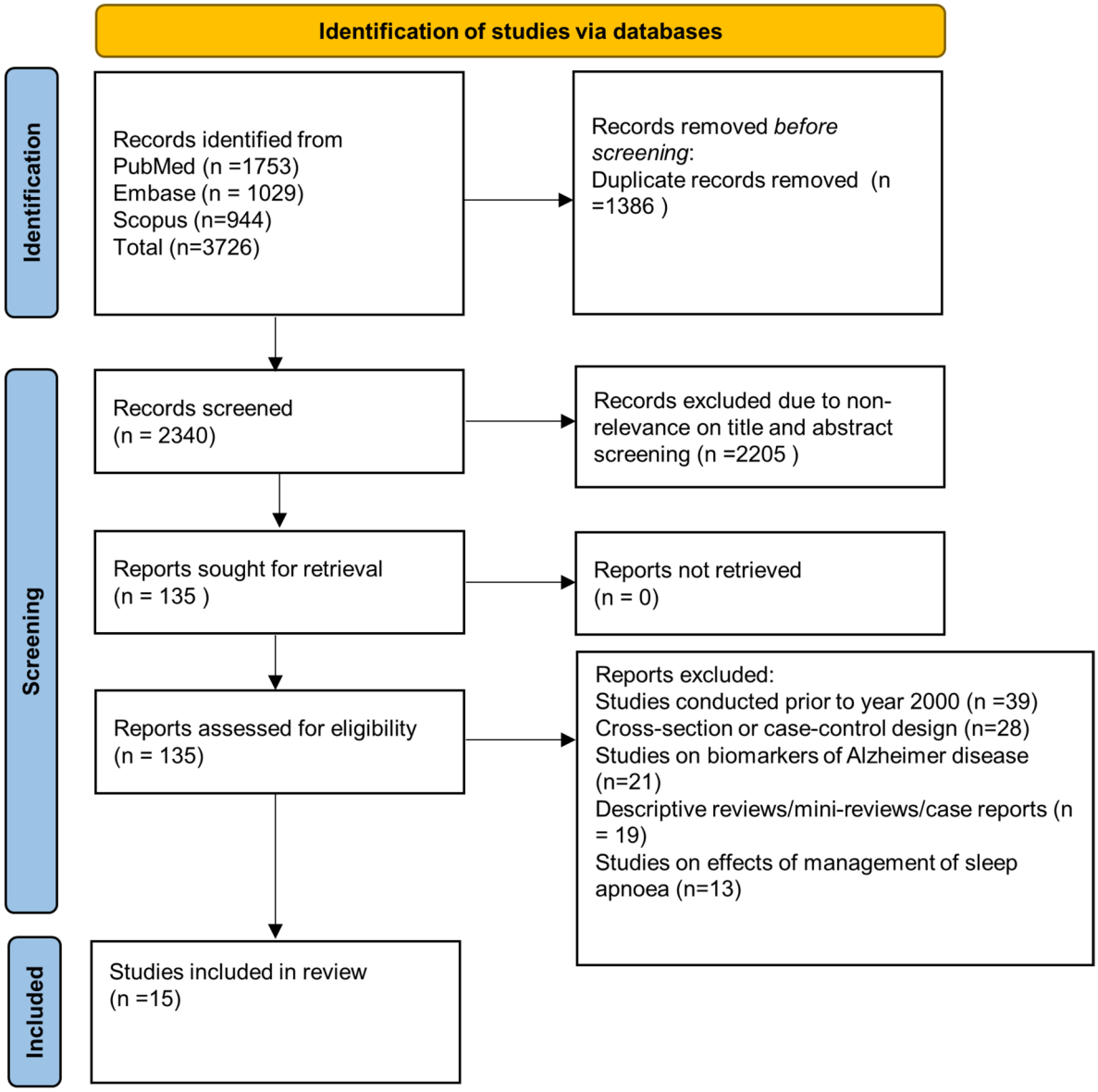

Fig. 1 Selection process of studies included in the review

Characteristics of the included studies

Table 1 presents the specific details of the included studies. Out of included studies ($n = 15$), seven were prospective cohort and remaining ($n = 8$) were retrospective cohort studies. The majority of the studies were done in the USA ($n = 9$). Two each were conducted in Taiwan and the Republic of Korea. Out of the remaining two studies, one was conducted in France and the other one was multicentric. In most of the studies, there were significant differences in baseline characteristics between patients with sleep-disordered breathing (SDB) and those without SDB. Subjects with SBD had higher mean body mass index and increased prevalence of comorbidities such as coronary artery disease, hypertension, diabetes, previous history of stroke, depression and anxiety. The mean follow-up period ranged from 3.4 to 15 years in all included studies. There were significant variations in the tools used for neuropsychological/cognitive assessments, specific aspects that were assessed (e.g., logical memory, global cognition, dementia, language, executive functions), and in the way, cognitive impairment was defined (Table 2). At-home polysomnography was used for establishing the diagnosis of SBD/sleep apnoea in six studies. Apnoea was self-reported or assessed using questionnaire in five studies. In the remaining studies, diagnosis of SDB was based on the International Classification of Diseases (ICD) codes (Table 2). The quality assessment has been presented in supplementary tables 2 and 3. All studies were of good quality.

Table 2 Subgroup analysis for cognitive impairment and/or all cause dementia

	Effect size; HR (95% CI)
Sex of the subject	
Male	1.38 (1.15, 1.66) ($N = 6$; $I^2 = 82.3\%$)*
Female	2.08 (1.57, 2.76) ($N = 4$; $I^2 = 0.0\%$)*
Study design	
Prospective cohort	1.31 (1.06, 1.61) ($N = 7$; $I^2 = 51.1\%$)*
Retrospective cohort	1.74 (1.42, 2.12) ($N = 8$; $I^2 = 80.8\%$)*
Age	
< 60 years	3.30 (1.68, 6.48) ($N = 2$; I^2=15.3%)*
≥ 60 years	2.40 (1.65, 3.48) ($N = 2$; $I^2 = 37.2\%$)*
Diagnosing SDB	
Using polysomnography	1.32 (1.00, 1.74) ($N = 6$; $I^2 = 60.1\%$)
Self-reported/ICD coding based	1.65 (1.39, 1.96) ($N = 9$; $I^2 = 77.1\%$)*

*Statistically significant at $P < 0.05$; *SDB*, sleep-disordered breathing

Findings from pooled analysis

The pooled findings indicate that patients with sleep-disordered breathing (SDB) had higher risk of all-cause cognitive impairment and/or all-cause dementia (HR 1.52, 95% CI: 1.32, 1.74; $N = 15$, $I^2 = 71.9\%$), when compared to patients without SDB (Figure 2). No publication bias was detected on Egger's test ($P = 0.37$) or on the visual inspection of the funnel plot (Supplementary figure 1). SDB patients had higher risk of AD (HR 1.39, 95% CI: 1.17, 1.66; $N = 6$, $I^2 = 21.4\%$), compared to those without SDB (Figure 3). There was no publication bias ($P = 0.83$) (Supplementary figure 2).

The risk of all-cause cognitive impairment and/or all-cause dementia was higher in both males (HR 1.38, 95% CI: 1.15, 1.66; $N = 6$, $I^2 = 82.3\%$) and females (HR 2.08, 95% CI: 1.57, 2.76; $N = 4$, $I^2 = 0.0\%$) with SDB, compared to males and females without SDB (Table 2). Pooling of findings from both prospective cohort (HR 1.31, 95% CI: 1.06, 1.61; $N = 7$, $I^2 = 51.1\%$) and retrospective cohort studies (HR 1.74, 95% CI: 1.42, 2.12; $N = 8$, $I^2 = 80.8\%$) showed a higher risk of SDB with all-cause cognitive

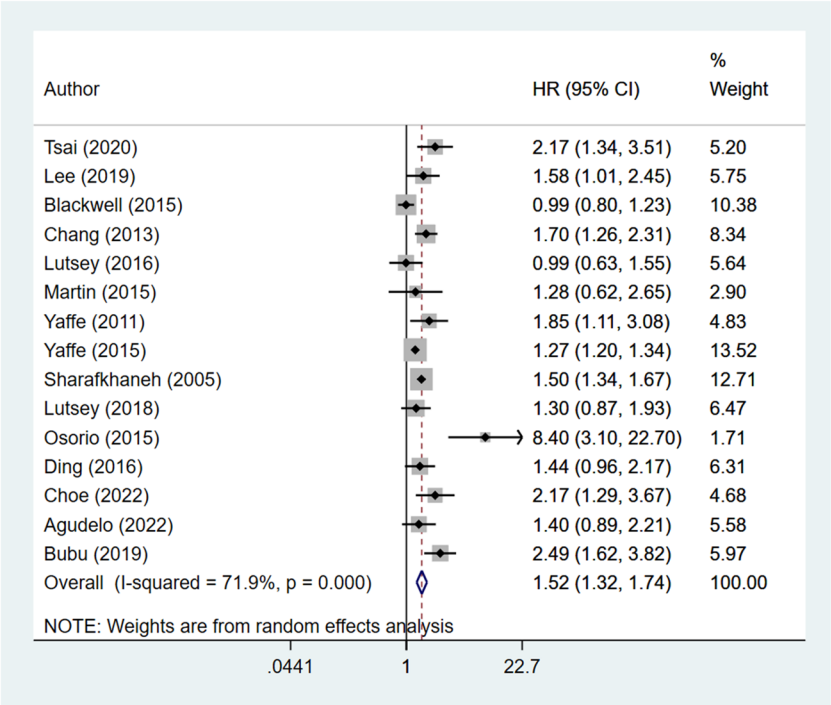

Fig. 2 Risk of cognitive impairment and/or all-cause dementia in those with sleep-disordered breathing (SDB), compared to those without SDB

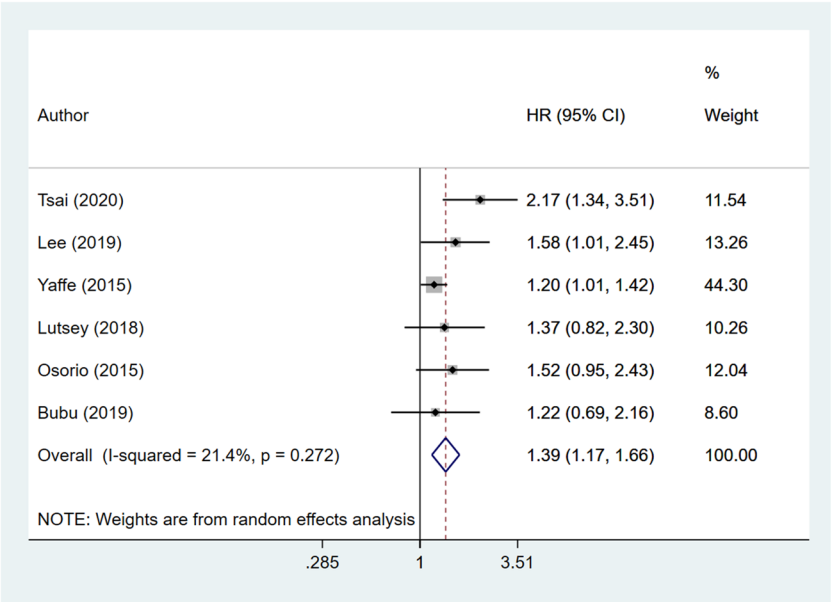

Fig. 3 Risk of Alzheimer's disease in those with sleep-disordered breathing (SDB), compared to those without SDB

impairment and/or all-cause dementia (Table 2). A higher risk of all-cause cognitive impairment with SDB was observed among patients younger than 60 years (HR 3.30, 95% CI: 1.68, 6.48; $N = 2$, $I^2 = 15.3\%$) and for those ≥ 60 years (HR 2.40, 95% CI: 1.65, 3.48; $N = 2$, $I^2 = 37.2\%$) (Table 2). When studies with diagnosis of SDB based on polysomnography were pooled together, the strength of association between SDB and all-cause cognitive impairment was weaker (HR 1.32, 95% CI: 1.00, 1.74; $N = 6$, $I^2 = 60.1\%$) compared to studies with diagnosis of SDB based on patient reports or ICD based codes (HR 1.65, 95% CI: 1.39, 1.96; $N = 2$, $I^2 = 37.2\%$) (Table 2).

Discussion

Meta-analysis found that presence of SDB/OSA was significantly associated with the risk of all-cause cognitive impairment and/or all-cause dementia and AD. The risk of cognitive impairment and/or all-cause dementia was higher in both men and women with SDB/OSA, compared to men and women without SDB/OSA. Studies with polysomnography-based diagnosis of SDB/OSA had a weaker strength of association with cognitive impairment compared to studies with diagnosis of SDB based on patient reports or ICD based codes. The findings are similar to those of previous reviews. Leng et al., through pooled analysis of prospective studies, observed that patients with SDB had 26% higher chance of developing cognitive impairment compared to patients without SDB [4]. Emamian et al. included prospective cohort studies ($n = 5$) with a sample size of 236 subjects and that found that patients with AD were 5 times more at risk of having OSA than cognitively normal subjects of the same age [5].

Our current limited understanding on the factors linking SDB/OSA with cognitive decline and/or dementia suggests a multi-factorial causation [29]. The current view is that the immediate effects of SDB/OSA such as hypoxemia and sleep fragmentation may cause neuronal injury and thereby affect memory, attention and executive functions [29–32]. Hypoxemia is also proposed to accelerate cognitive ageing [30, 32]. Brain hypoperfusion, commonly seen in SDB/OSA, has also been linked to the underlying pathological process leading to dementia/AD [33] through mechanism that involves hypoperfusion-induced chronic hypoxemia that accelerates the progression of cerebral small vessel disease [34, 35]. This, in turn, leads to lesions in white matter, lacunar infarcts, loss of grey matter and white matter fibre abnormalities [32–37]. Additional concern is the development of intermittent hypoxaemia and altered sleep architecture (such as sleep fragmentation and adverse impact on REM sleep) that lead to metabolic derangements, oxidative stress, inflammation and blood-brain barrier dysfunction [32]. These processes together lead to reduced neurogenesis, decreased plasticity, development of microinfarcts, changes in grey and white matter and cerebral neuronal networks [32, 38, 39]. Studies have also shown increased accumulation of amyloid plaques and hyperphosphorylated tau protein in brain of patients with SDA/OSA [40, 41].

Studies have shown that obstructive sleep apnoea could be associated with higher scores on depression and anxiety scales when compared to individuals without this condition [42–44]. It is crucial to recognize that these mood changes can have significant repercussions on cognitive performance.

These mood disturbances may result in difficulties with concentration, memory and decision-making, all of which are essential components of cognitive functioning. Moreover, individuals experiencing depression and anxiety often report reduced motivation and energy levels, further contributing to cognitive impairment. Therefore, consideration of the possible presence of affective disorders, such as depression and anxiety, among OSA patients and their potentially adverse impact cognitive performance is important.

SDB/OSA is a potentially treatable condition. Therefore, its timely management can potentially lead to a reduced risk of cognitive decline. Sonia et al. conducted a randomized controlled trial to examine whether the treatment with continuous positive airway pressure (CPAP) leads to better cognitive function in AD patients with OSA [45]. The study found an improvement in the neuropsychological scores in intervention group that received therapeutic CPAP, compared to those that received placebo CPAP. However, the study was small and involved only 52 mild to moderate AD/OSA patients. Similarly, Troussiere et al. evaluated annual mini-mental state examination (MMSE) score decline in patients with mild to moderate AD (n = 23), based on whether the subjects received CPAP therapy or not [46]. The study found significantly lower decline in the group of patients that received CPAP therapy. Kushida et al. conducted a two arm, double-blinded randomized controlled (RCT) with the aim to understand the cognitive effects of CPAP therapy in patients with documented OSA [47]. The authors found a small and transient improvement in some measures of executive function with the use of CPAP, especially in cases of severe OSA. A meta-analysis of RCTs (n = 14) by Wang et al. demonstrated partial improvement of cognitive impairment in patients with severe OSA after the CPAP treatment [48]. In a large retrospective study that utilized Medicare claims, data of around 50,0000 beneficiaries that were aged older than 65 years found CPAP treatment to be associated with lower risk of incident AD [49]. However, there are studies that have also shown no beneficial effect of CPAP on cognitive scores [50, 51]. Furthermore, while CPAP is the most widely used management for SDB/OSA and evidence is overall supportive of its role in reducing the risk of cognitive impairment, there is still a need to identify and test other treatment modalities and their effect on cognitive performance in patients with SDB/OSA.

There are certain limitations of the current review. First, in some of the studies, either ICD-based codes for SDB/OSA were employed, or self-reported and questionnaire-based assessments of apnoea were utilized. The absence of a direct, objective assessment method in these instances may have introduced bias into the analysis. For the same reason, we were also unable to conduct stratified analysis based on the severity of SDB. Second, we acknowledge that deriving hazard ratios (HR) from either odds ratios or relative risks using statistical methods may entail some degree of imprecision. Nevertheless, our primary objective was to maximize the utilization of available data and extract the most insights possible. Third, our findings were only focused on the risk of cognitive impairment/decline (as categorical/dichotomous outcome) and we were unable to analyse continuous cognitive scores. The main reason was that the included studies considered different cognitive outcomes and used different tools for assessment, thereby posing challenge to derive meaningful estimates. Even for the risk of cognitive impairment/decline, the studies used different cutoffs that corresponded to a wide range of interpretation, i.e. from mild to severe cognitive impairment. Therefore, we presented our findings as risk of all-cause cognitive impairment/decline. Fourth, in most of the included studies, there were baseline differences in the characteristics of subjects with and without SDB/OSA. We think that the associations observed in our analysis may be influenced by these differences, to some extent. Fifth, there were some studies in our review that had retrospective cohort designs and therefore may not have collected data to allow for adjustment for important confounders.

Conclusion

The findings of the current meta-analysis indicate a possible association of SDB/OSA with risk of all-cause cognitive impairment and/or dementia. However, it is important to note that the majority of the studies in our review did not rely on objective assessment of SDB/OSA based on polysomnography. Therefore, careful interpretation regarding the strength and significance of the observed association is advised. Furthermore, there is a possibility that unmeasured confounders may influence or mediate this association. Consequently, future studies should identify and consider adjustments for important confounders such as hypertension, diabetes, obesity, low physical activity, history of traumatic brain injury or respiratory diseases, smoking, alcohol use and depression.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11325-023-02934-w.

Author contributions Q.T. and J.L. designed the project; Q.T., J.S., X.L., J.L., H.Z., J.D. and J.L. were involved in data collection and data analysis; Q.T. and J.L. prepare the manuscript; J.L. edit the manuscript; all authors read and approved the final manuscript.

Data Availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Code availability None.

Declarations

Consent to participate None.

Consent to publish None.

Ethics approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent None.

Conflict of interest The authors declare no competing interests.

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