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The effects of sleep duration on the risk of dementia incidence in short and long follow-up studies: A systematic review and meta-analysis

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ABSTRACT

Sleep duration's association with future dementia could be a cause or consequence, or both. We searched electronic databases on 14th April 2023 for primary peer-reviewed, longitudinal studies examining the relationship between sleep duration and dementia with any follow-up duration. We meta-analysed studies examining brief (≤6 h/night) and extended sleep duration (≥9 h/night) separately and divided the studies into those with follow-up periods of less or more than 10 years. The quality of evidence was assessed using the Newcastle-Ottawa scale. 31 studies fulfilled the inclusion criteria. For brief sleep duration, a meta-analysis of short follow-up studies (≤10 years) found a 46 % increased risk of future dementia (relative risk [RR] – 1·46; 95 % Confidence Intervals [CIs] 1·48–1·77; I^2 = 88·92 %, 6 studies). Studies with long follow-ups (>10 years) did not show a significantly increased risk (RR – 1·12; 0·95–1·29; I^2 = 65·91 %; 5 studies). For extended sleep duration, a meta-analysis of short and long follow-up studies reported an increased risk of dementia (respectively RR - 2·20; 1·11–3·3; I^2 = 94·17 %; 4 studies and RR – 1·74; 1·30–2·18; I^2 = 86·56 %; 4 studies). Our findings suggest that brief sleep duration might be a prodromal symptom but not a risk factor of dementia. Extended sleep duration may be a risk factor. However, our results had high heterogeneity limiting external validity and generalisability.

1. Introduction

Dementia is an umbrella term encompassing disorders characterised by a decline in cognition across multiple domains that affect daily function [1]. Abnormal sleep duration has been regarded as a possible risk factor for dementia onset. However, as people begin to experience brain changes for some years before developing dementia, it is unclear whether it is one of the prodromal symptoms [2–9].

Sleep plays a vital role in physiological functions associated with optimal health [10]. Current guidelines recommend between 7 and 8 h of sleep per night [11]. Although these parameters are flexible according to an individual's age, health and lifestyle, [12]. For example, elderly individuals typically follow a biphasic sleep pattern [13]. Inappropriate sleep durations have also been observed following shift work and 24/7 occupational requirements [14]. Sleep duration and efficiency become more fragmented with age [2,3] as melatonin production decreases [15]. Insufficient sleep is now a recognised public health concern in many countries given its high prevalence and association with poor health outcomes [16].

Some recent literature reports a U-shaped association between sleep duration and dementia risk, with both brief and extended sleep duration associated with increased dementia incidence [2,17–22]. Disturbed sleep can increase an individual's dementia risk profile in many ways, for example, by decreasing physical activity, or escalating social isolation, depressive symptoms [23], and physical health conditions such as diabetes and hypertension [24–26]. Specifically, depression and cardiovascular complications are mediated by increased inflammation which is strongly associated with inappropriate sleep duration [27].

Brief and extended sleep durations and prolonged sleep onset latency are associated with increased amyloid-β (Aβ) plaque [26,28]. Differing sleep duration is thought to exacerbate the effects of the apolipoprotein E (APOE) ε4 allele [8], a genetic risk factor of Alzheimer's disease (AD) [29]. A recent systematic review and narrative synthesis reported that brief and extended sleep duration are risk factors contributing to the aetiology of AD [30] and a meta-analysis reported that individuals with brief or extended sleep duration have a significantly higher risk of AD, cognitive impairment and preclinical AD compared to individuals without sleep problems [31]. Sleep onset latency has been reported to

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increase the risk of dementia, however, this association was not significant after adjusting for sociodemographic factors and health status [8]. Nevertheless, most research examining the relationship between sleep duration and dementia incidence is cross-sectional [30], with few longitudinal studies [2,8,30,32].

The lack of analysis according to follow-up duration makes it difficult to rule out reverse causation and establish whether brief or extended sleep duration is a risk factor or a prodromal symptom of dementia. Also, studies often lack dementia diagnostic information, use small sample sizes, and neglect important confounders [17]. To our knowledge, no systematic reviews examine the risk of sleep duration on dementia incidence dividing studies short- and long-term follow-up periods. We defined brief sleep duration as ≤6 h/night and extended as >9 h/night. Previous thresholds are varied, with all definitions being used in different studies [19,33]. However, most researchers agree that 7–8 h/night is normal [6,34,35] and therefore our definitions encompass atypically brief and extended sleep durations. So, we aimed to systematically review and meta-analyse the literature by dividing longitudinal studies of brief and extended duration of sleep and other sleep disturbances and dementia into short and long-term follow up (≤10 years or >10 years) to clarify whether brief or extended sleep duration are risk factors for or symptoms of dementia.

2. Methods

2.1. Search strategy and selection criteria

We searched four electronic databases MEDLINE, EMBASE, PsychINFO and AMED on the 14th of April 2023 without language restrictions. The search strategy contained terms relating to sleep or sleep duration as well as dementia and AD and was limited to human participants (see supplementary material). This study is registered on PROSPERO, registration number CRD42023411111.

2.1.1. Inclusion criteria

1. Primary peer-reviewed studies examining the effects of sleep duration on the risk of developing dementia in an adult (≥18 years of age) population
2. Quantitative measure of sleep duration measured through self-report, actigraphy (a wearable device measuring movement), or polysomnography (a wearable device measuring physiological activities and sleep stages)
3. Diagnosis of dementia using the International Classification of Diseases (ICD) [36] or Diagnostic and Statistical Manual of Mental Illness (DSM) [37] or any other valid clinical diagnosis tool

2.1.2. Exclusion criteria

1. Primary sleep disorders such as sleep apnoea
2. Abstracts, letters, reviews

After removing duplicate results all titles and abstracts were screened by one reviewer (CH). Two reviewers (CH and EH) screened full-text reviews and in the case of disagreements NM and GL discussed the results. CH and EH extracted data independently for 10 % of included studies to test the data extraction form recording participant demographics and measures of sleep duration and dementia diagnosis. All remaining data extraction was carried out by CH.

To assess the quality of studies CH and EH scored 10 % of the included studies using the Newcastle-Ottawa scale [38] and reached agreement before CH scored the rest.

2.2. Data analysis

STATA 17.0 was used to conduct all analyses. To synthesise the data, all hazard ratios (HRs) and odds ratios (ORs) were converted to relative risks (RRs) using standard formulas (see supplementary material) [39]. Meta-analyses using a random effects model by duration of follow-up (≤10 years and >10 years) and duration of sleep were conducted if there were at least two studies generating effect estimates and 95 % confidence intervals (CIs). The I^2 statistic was used to quantify the degree of variation in the results beyond those explained by chance and considerable heterogeneity was classified as over the 75 % boundary [40]. Heterogeneity exceeding this threshold meant that results would likely not be generalisable to the wider population. Further sensitivity analyses and meta-regressions were conducted to explore potential causes of heterogeneity. Meta-regressions were only conducted if there were >10 studies within a meta-analysis [41]. We assessed publication bias using the Begg's test.

There was no funding source for this study.

3. Results

The initial search identified 4963 unique studies of which 31 fulfilled the eligibility criteria. See Fig. 1. PRISMA diagram.

These papers included 1,087,534 individuals from the USA (11 studies [34,42–51]; Europe (16 studies [6,17,40,52–64]); and Asia (4 studies [33,65–67]). Seventeen studies had follow-up periods of 3 to <10 years. The remaining fourteen studies used long follow-up periods (10–25 years). Whilst there were sufficient studies measuring sleep onset latency (defined as >20 min to fall asleep) [68] to conduct a meta-analysis, the remaining measures (daytime sleepiness, sleep inadequacy) were not eligible for synthesis as there were too few studies.

Sleep duration was assessed using self-report measures by most studies within the review (28/31) whilst two studies used actigraphy measures and one study used overnight polysomnography. Dementia diagnoses were often established using a clinical exam or interview (21/31), however, eight studies referred to registries, mostly referencing ICD-10 or DSM-IV, and two studies used self-report questions for dementia diagnosis.

Risk of bias assessments (see supplementary material) demonstrated a moderate risk for most studies (20/31), with ten studies demonstrating a high risk of bias and only one study showing a low risk of bias. The most frequent issue was the use of self-report measures for ascertainment of exposure. However, there were several issues with the representativeness of cohorts (9/11) with the use of volunteers or no description of deviation from the cohort. All other studies were truly or somewhat representative of the community. All but three studies controlled for both age and sex meaning that 28 studies fulfilled the comparability criteria. Finally, in terms of outcome bias, the greatest risk of bias was that the follow-up was not long enough for the outcomes to occur which was required to be at least 10 years to reduce reverse causation [69].

3.1. Brief sleep duration

Short follow-up studies (N = 953,329; 6 studies) had a 46 % increased risk of dementia incidence (RR = 1·46; 95 % CIs 1·15–1·77). Studies with long follow-up durations (N = 537,524; 5 studies) did not show an increased risk of dementia incidence (RR = 1·12; 95 % CIs 0·95–1·29). The random effects meta-analysis of all brief sleep duration (≤6 h/night) was associated with a 25 % increased risk of dementia incidence in later life (RR = 1·25; 95 CIs 1·09–1·40). See the forest plot in Fig. 2.

Meta-regressions revealed that heterogeneity was not accounted for by follow-up duration (p = ·443), age (p = ·561), quality of study (p = ·494), publication year (p = ·414) or sample size (p = ·395). Leave-one-out meta-analyses demonstrated that results were not affected by excluding individual studies or studies based on their quality, outcome measure, and age. Heterogeneity reduced slightly when limiting analysis to European studies, however, heterogeneity is still considerable. See

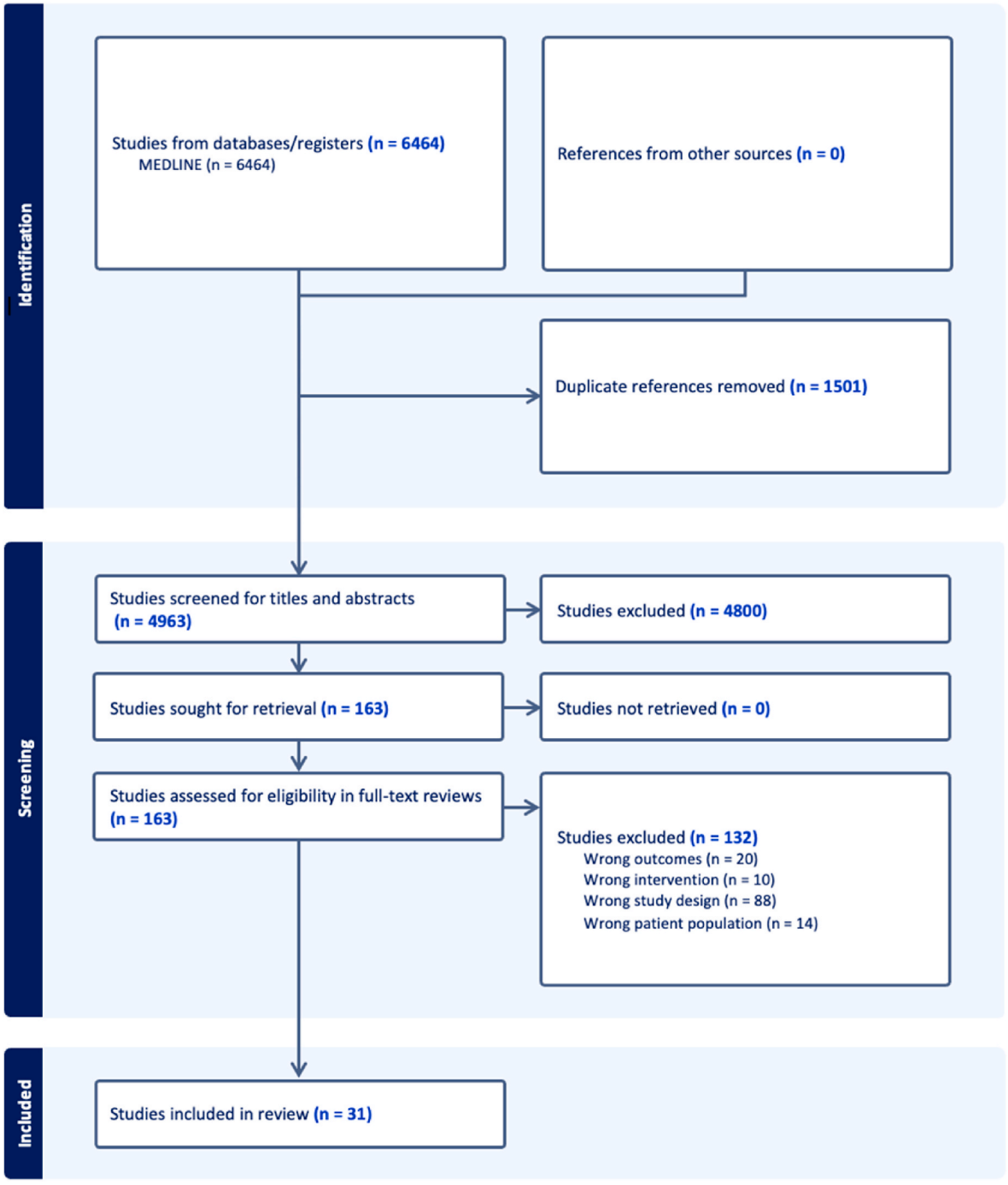

Fig. 1. Flow chart and summary statistics for included studies and reasons for exclusion.

Table 2 for sensitivity analysis.

A Begg's test revealed moderate publication bias (p = ·062). Also, analysis of the average age of participants in each study suggests that age did not correlate with the effect of sleep duration on dementia incidence. See Table 1.

3.2. Extended sleep duration

Studies with short follow-up periods (N = 10,001; 4 studies) demonstrated a 120 % increased risk of dementia incidence (RR – 2·20; 95 CIs 1·11–3·30). Moreover, long follow-up studies (N = 515,698; 4 studies) showed a 74 % increased risk of dementia incidence in later life (RR – 1·74; 95 CIs 1·30–2·18). The random effects meta-analysis of all extended sleep duration demonstrated a 93 % increased risk of dementia incidence (RR – 1·93; 95 CIs 1·49–2·37). See the forest plot in Fig. 3.

Meta-regressions revealed that heterogeneity was not accounted for by follow-up duration (p = ·607), age (p = ·345), quality of study (p = ·528), publication year (p = ·874) or sample size (p = ·340). Leave-one-out meta-analyses demonstrated that results were not affected by excluding individual studies or according to quality, age, outcome measures, or location. See Table 3 for sensitivity analysis results.

A Begg's test demonstrated low publication bias (p = ·174). Analysis of the average age of participants in each study suggests that age did not correlate with the effect of sleep duration on dementia incidence. See Table 1.

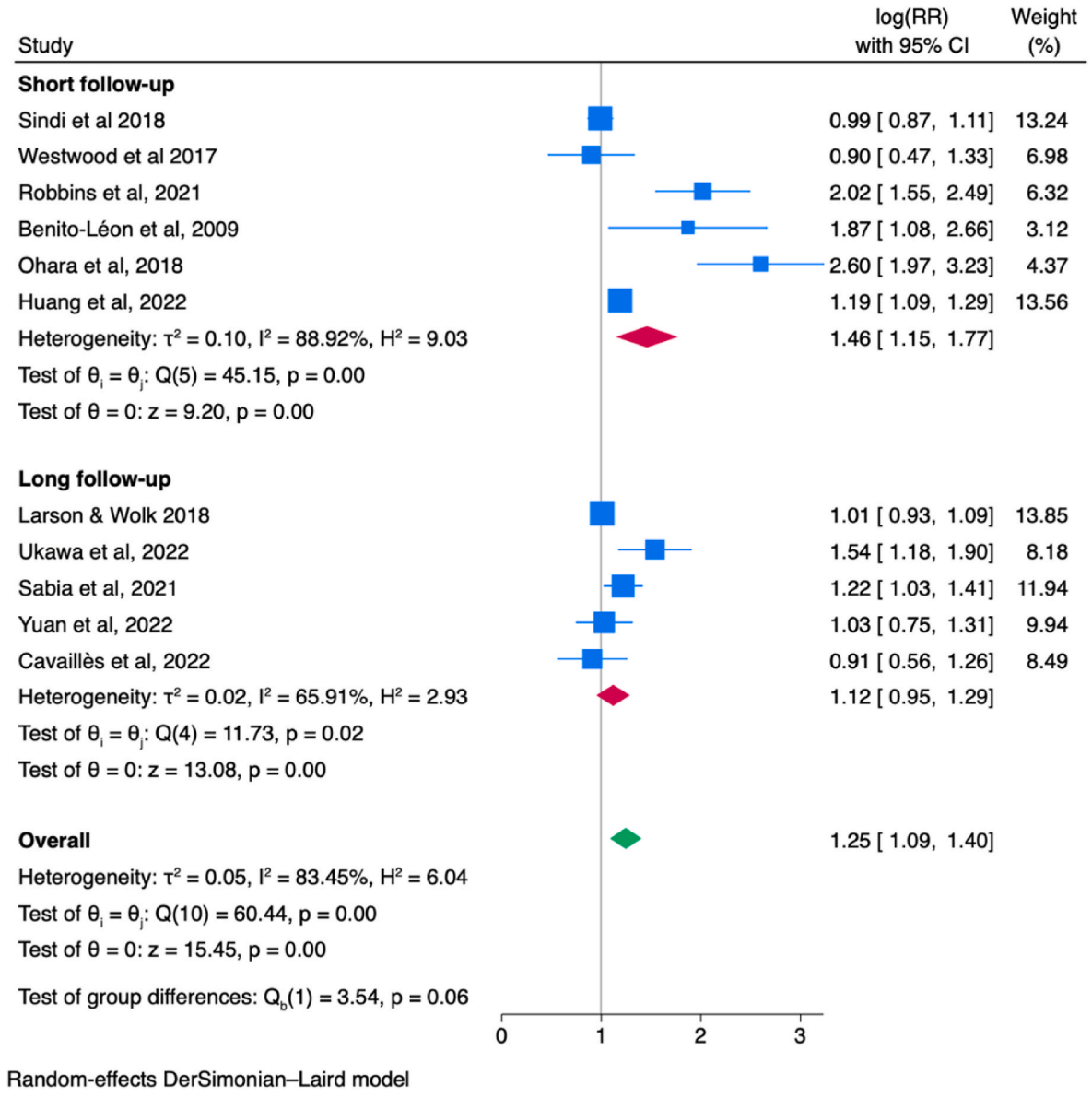

Fig. 2. Forest plot of brief sleep duration (≤6 h/night) association with dementia incidence according to follow-up duration (≤10 years/>10 years).

3.3. Sleep onset latency

Studies with short follow-up periods (N = 10,507; 3 studies) had a 45 % increased risk of dementia incidence (RR – 1·45; 95 % CI 1·33-1·57) associated with long sleep latency (measured using actigraphy, polysomnography and self-reports). As only one study used long follow-up periods, subgroup analysis was not performed. A random-effects meta-analysis of all sleep onset latency measures demonstrated that increased sleep latency was associated with a 38 % increased risk of dementia incidence (RR – 1·38; 95 % CI 1·19-1·58). See the forest plot in Fig. 4.

Sensitivity analyses using a leave-one-out meta-analysis produced summary estimates that corresponded with the original results and all 95 % CIs fit around the primary summary statistics. A Begg's test demonstrated that there was low publication bias (p = ·308).

4. Discussion

We found that brief sleep duration increased the risk of dementia in studies with short follow-up periods but not in studies with long follow-up periods. We also found that extended sleep duration increased the risk of dementia incidence across studies with both short and long follow-up periods. Nevertheless, the heterogeneous nature of our results and issues with the grade of evidence suggest that our findings have low external validity and certainty. In addition, most studies were not high quality.

The strengths of this review include the large sample size, the inclusion of studies from multiple continents that were not restricted by language, the longitudinal nature of the studies and the specific focus on sleep duration as opposed to sleep disorders, which have been the focus of past research. Notwithstanding these strengths, there are several limitations to this review. Firstly, the considerable unexplained heterogeneity reduced the reliability of our findings and limited the strength of the conclusions reached from the evidence. Problems concerning the risk of bias, publication bias and certainty of evidence also weakened our results' external validity and generalisability. All studies used validated measures of sleep, however, none used polysomnography. Some individual studies did not use clinical tools for a dementia diagnosis, opting for insurance records and hospital/death registers. Whilst uncertainty regarding the dementia stage and severity

Table 1
Participant and study characteristics for studies examining brief and extended sleep durations.

	Controlled for	Age, education, smoking, drinking	Age, sex, education, mobility, APOE-ε4, physical health, depression	Age, sex, education and APOE-ε4 status	Age, sex, education, BMI, health issues, lifestyle factors	Age, sex, education, APOE-ε4 status, smoking, BMI, physical activity	Age, sex, education, health issues, smoking, alcohol, exercise
Outcome	**Diagnosis method**	Consensus of two neurologists' clinical exam	Neurologist and independent board	Hospital inpatient records		Neurocognitive assessment/hospital records	Psychiatric assessment
	Diagnosis Tool	DSM-IV	DSM-IV	ICD codes	Swedish National Patient register	ICD code	ICD-10
Exposure	**Boundaries**	5 categories (≤5 h; 6 h; 7 h; 8 h; ≥9 h)	Brief - ≤6 h; Extended - ≥9 h	Brief – 0–6 h; moderate – 7hrs; extended ≥8 h)	Brief - ≤6 h; extended - > 9hrs	Brief - <7 h; Extended - ≥9 h	Brief - ≤5 h; extended - 10 h
	Identification	Self-report	Self-report	Self-report	Self-report	Self-report (SHHS Sleep Habits Questionnaire)	Self-report
Population	**Female (%)**	56.6	57.8	54	47	52.6	56
	Age at baseline (mean)	72.9	72.9	58	71.6	62.7	70.8
	Sample size	3286	1749	431,924	28,775	1667	1517
	Location	Spain	France	UK	Sweden	US	Japan
	Database	NEDICES	Three-City Study cohort	UK Biobank	SIMPLER	ARIC	Hisayama study
	Follow-up (years)	3.2	14	9	12.6	15	8.8
Study ID	**Author (year)**	Benito-Léon et al., (2009) [54]	Cavaillès et al. (2022) [52]	Huang et al. (2022)(55)	Larson et al. (2018)(57)	Lutsey et al., (2018)(45)	Ohara et al., (2018) (33)

Age, sex, marital status, education, ethnicity health status, depression	Age, sex, education, follow-up, study	Age, marital status, race, education, health conditions, body weight	Age, sex, marital status, employment, alcohol, smoking, exercise, depressive tendencies	Age, sex, APOE-ε4 status	Age, sex, marital status, education and chronic conditions
National registers	Death/hospital registers, psychiatric assessment	Proxy physician report and psychiatric assessments		Research assistant and neuropsychologist assessments	Memory-related activities or proxy report of physician diagnosis
ICD-10	DSM-IV	Ad8 Screening Questionnaire	Japanese LTCI scheme	Trail Making test from Weschler Memory scales	AD8 Screening Questionnaire
Brief - ≤6 h; extended - ≥ 8 h	Brief – 2–6 h; Extended – 9–11 h)	Very brief - ≤ 5 h; brief – 6–7 h; normal – 7–8; extended - ≥9 h	Brief - < 6hrs; extended - ≥8 h	Brief - <6 h; extended - >9 h	Brief - <6 h; extended >9 h
Self-report	Self-report	Self-report	Self-report	Self-report	Self-report
66	68	60		57	49
50.6	70	76.9	64/65	72	62
10,308	1446	2812	1954	2457	483,507
UK	Sweden and Finland	US	Japan	US	UK
Whitehall II study	CAIDE study; KP; H70 study	NHATS UDS	NISSIN project	Framingham Heart Study	UK Biobank
25	3–9	5	15.6	10	11.3
Sabia et al. (2021)(10)	Sindi et al. (2018) (17)	Robbins et al. (2021)(43)	Ukawa et al. (2022)(66)	Westwood et al., (2017) (42)	Yuan et al. (2021)(40)

NEDICES, Neurological Disorders in Central Spain; CSS, Clinical Sleep Severity; SIMLPER, Swedish Infrastructure for Medical Population-based Life-course Environmental Research; NHATS, National Health and Ageing Trends Study; AD8, Eight-item Informant Interview to Differentiate Ageing and Dementia; SHHS Sleep Heart Health Study; ARIC, Atherosclerosis risk in communities study; CAIDE, Cardiovascular Risk Factors, Ageing and Dementia; KP, Kungsholmen project; NISSIN project, New Integrated Suburban Seniority Investigation; LTCI scheme, Long-term care insurance.

Table 2
Leave-one-out analyses of the random effects meta-analysis of brief sleep duration and dementia incidence, excluding studies based on demographic criteria.

Variable	Inclusion criteria	No. of studies	Effect estimate (95 % CIs)	Heterogeneity (%)
Study quality	Low	3	1·28 (0·98-1·58)	90·09
	Moderate	8	1·27 (1·03-1·50)	82·06
	High	0	–	–
Age	≤55	1	1·22 (1·03-1·41)	–
	>55 - ≤65	2	1·32 (0·99-1·65)	69·85
	>65 - ≤75	7	1·14 (0·94-1·34)	79·65
	>75	1	2·02 (1·55-2·49)	–
Outcome measure	Self-report	4	1·35 (0·97-1·73)	87·64
	DSM/ICD	7	1·22 (1·01-1·44)	82·43
Location	Europe	7	1·09 (0·98-1·19)	63·39
	N. America	2	1·46 (0·36-2·55)	91·58
	Asia	2	2·04 (1·00–3·07)	87·73

Effect estimates and heterogeneity scores were produced by limiting the analysis to certain studies according to each parameter listed.

of all individuals at the start of their observations was considered during risk of bias assessments, we cannot determine how much this altered our findings.

Finally, the observational nature of cohort studies means there may have been unmeasured confounding variables. For example, our conclusions for extended sleep duration might reflect the relationship between sleep duration and other risk factors for dementia such as lack of exercise, physical illness, or depression, and not be a direct link between abnormal sleep duration and future dementia incidence.

Our findings support previous studies that have reported an association between sleep duration and dementia incidence [19,70,71], however, our study is the first to examine this relationship relative to follow-up length. This means that our findings provide greater insight into whether sleep duration is a risk factor or a prodromal symptom of dementia. Our study also acknowledged calls for research to focus on studies with long follow-up periods to establish the possible long-term influence of sleep duration on dementia incidence.

Moreover, our findings have addressed the issue of reverse causation by examining the association between sleep duration and risk of

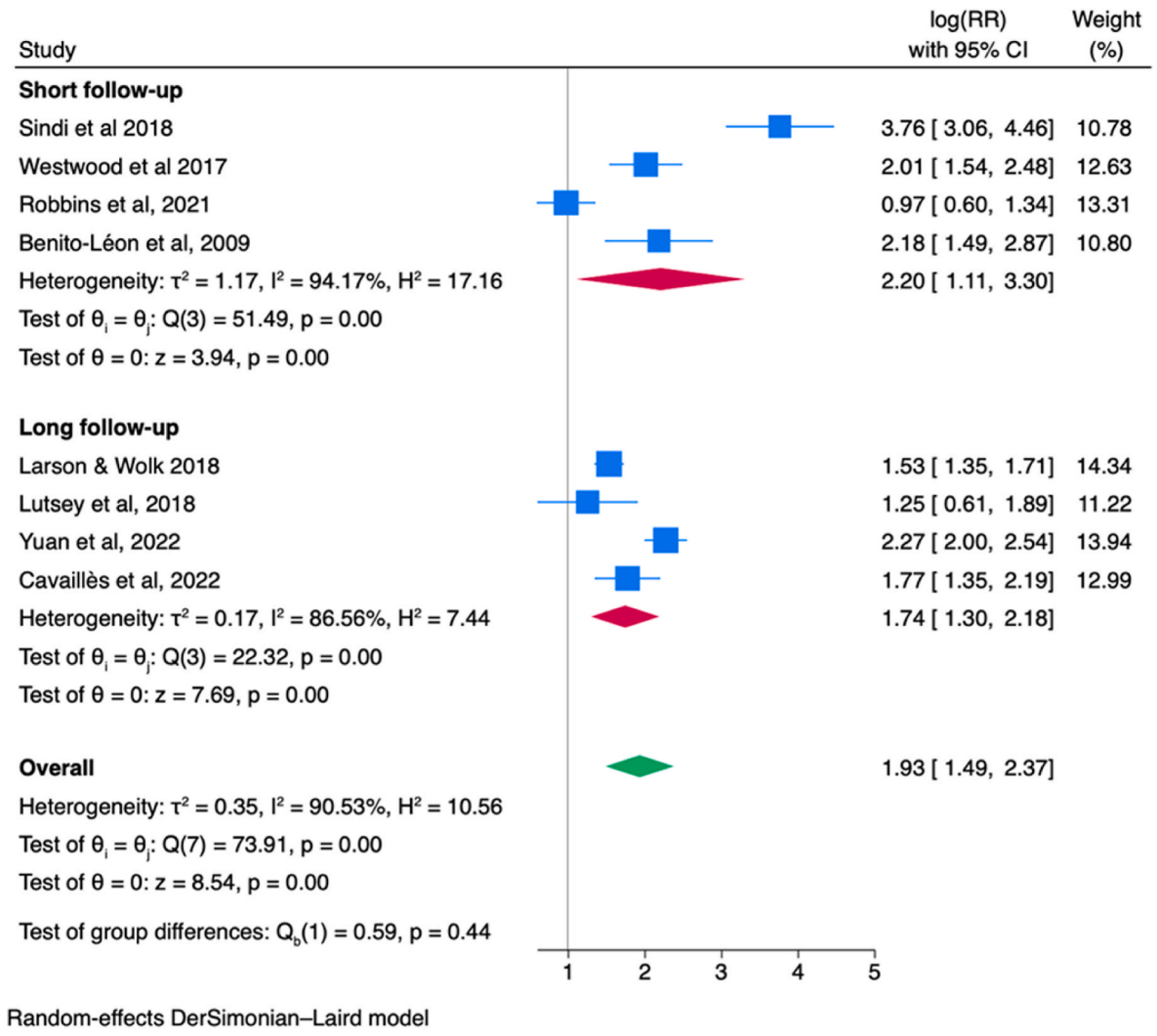

Fig. 3. A forest plot demonstrating the effects of extended sleep duration (≥9 h/night) on d dementia incidence according to follow-up duration (≤10 years/ >10 years).

Table 3
Leave-one-out analyses of the random effects meta-analysis of extended sleep duration and dementia incidence, excluding studies based on demographic criteria.

Variable	Inclusion criteria	No. of studies	Effect estimate (95 % CIs)	Heterogeneity (%)
Study quality	Low	2	2·35 (−0·39-5·08)	97·92
	Moderate	6	1·84 (1·50-2·18)	79·87
	High	0	–	–
Age	≤55	0	–	–
	>55 - ≤65	1	1·25 (0·61-1·89)	–
	>65 - ≤75	6	2·20 (1·71-2·70)	90·30
	>75	1	0·97 (0·60-1·34)	–
Outcome measure	Self-report	4	1·53 (0·98-2·08)	91·75
	DSM/ICD	4	2·40 (1·62-3·17)	87·51
Location .	Europe	5	2·24 (1·66-2·82)	92·19
	N. America	3	1·41 (0·73-2·09)	83.03
	Asia	0	–	–

Effect estimates and heterogeneity scores were produced by limiting the analysis to certain studies according to each parameter listed.

dementia incidence relative to follow-up. The direction of our results implies that our findings are not entirely due to reverse causation and suggest that extended sleep duration is a risk factor for dementia incidence and not a prodromal symptom. This direction of effect and our substantial sample size allow us to provide greater consistency and clarity to an evidence base that has been thus far undermined with uncertainty.

Finally, our review demonstrated the low quality of the current longitudinal cohort studies. Most importantly, studies consistently utilise self-report measures for sleep duration. Moreover, all studies with follow-up periods of ≤10 years failed to provide adequate time for dementia incidence to occur according to previous thresholds [69] and were allocated a higher risk of bias. Despite the value of our findings, our study found considerable heterogeneity that could not be explained by further statistical analysis, introducing issues with external validity and low certainty of evidence.

Clinicians should remain aware of the possible but unclear and unproven role of sleep duration on the risk of incident dementia. We have yet to determine the relative contribution of comorbid conditions and how they mediate the association between sleep duration and dementia incidence. It is important to re-emphasise the concerns surrounding our external validity and be cautious when making recommendations to the broader population.

Future research should use clear cut-offs for sleep duration, utilise objective sleep duration measures and establish stricter criteria for dementia diagnoses. Future research would also benefit from stratified analyses to control for potential confounders.

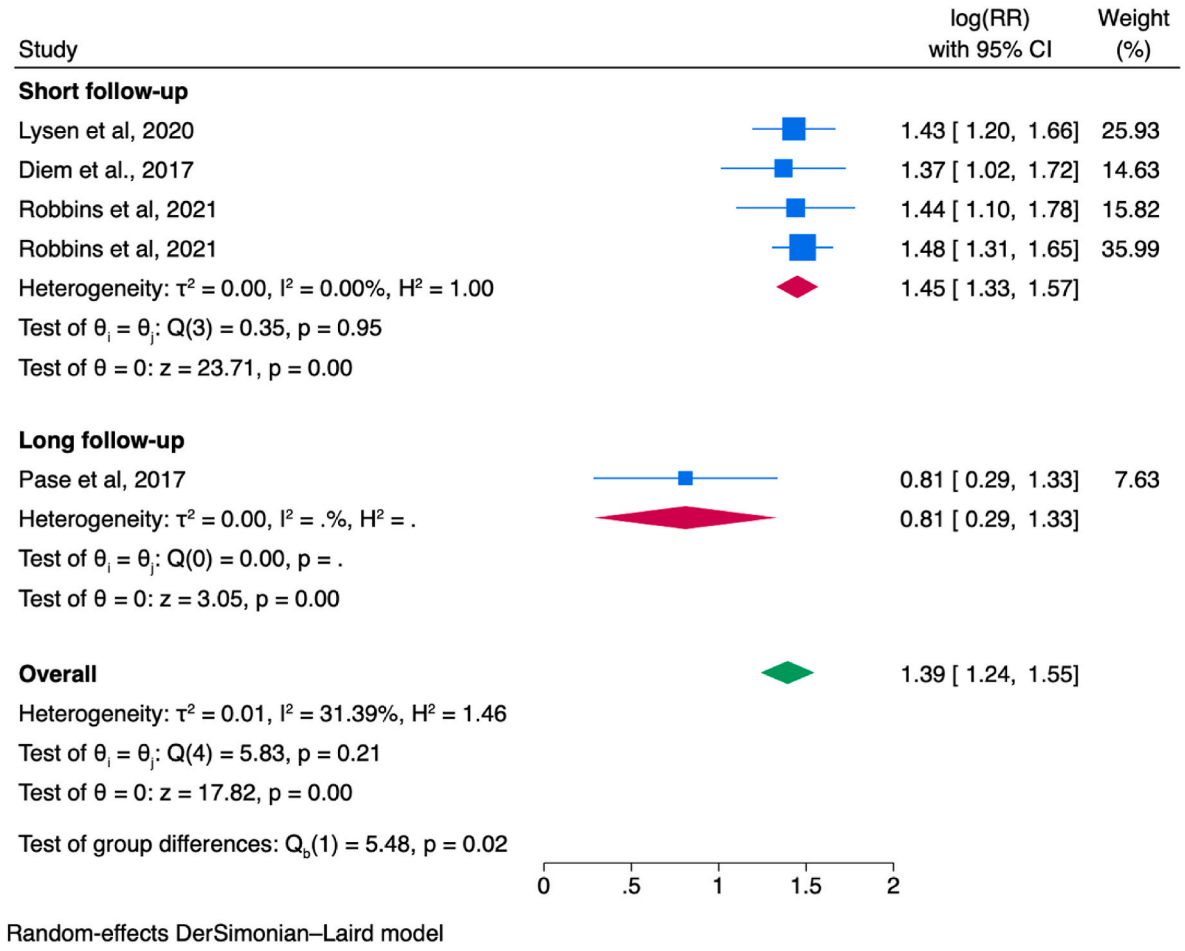

Fig. 4. A forest plot of sleep onset latency (>20 min) association with dementia incidence according to follow-up duration (≤10 years/>10 years).

5. Conclusion

We found evidence to suggest that brief sleep duration is a prodromal symptom of dementia, whilst long sleep duration may be a risk factor for dementia. However, several limitations weakened the generalisability of our results. So, future research is required to explore the heterogeneity and assess the effect of sleep duration on dementia using more objective and standardised techniques. Assessing heterogeneity has informed the external validity of the evidence base and further evidence may advise more efficient preventative strategies to minimise dementia incidence in our population. At present, we cannot conclude that brief sleep duration is a risk for incident dementia.

CRediT authorship contribution statement

Connie Howard: Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Naaheed Mukadam:** Supervision, Methodology, Conceptualization. **Esther K. Hui:** Investigation, Data curation. **Gill Livingston:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization.

Data sharing

All deidentified data collected for this study will be made available on request along with the study protocol.

Funding

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2024.10.022.

Abbreviations

Aβ Amyloid-β
AD – Alzheimer's Disease

CIs – confidence intervals
DSM – Diagnostic and Statistical Manual of Mental Disorders
HRs – hazard ratio
ICD – International Classification of Diseases
ORs – odds ratio
RRs – risk ratio

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