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THE ASSOCIATION BETWEEN SLEEP DURATION AND DEMENTIA: A META-ANALYSIS

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A META-ANALYSIS

by

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PREFACE

I was inspired to pursue a Master's in Public Health when I realized the limitation of medicine. Through this degree I hope to become a medical epidemiologist who can help prevent diseases at the population level and treat diseases at the individual level. The topic of this research was inspired by my great grandmother who died from Alzheimer's disease and Dr. Zhang's lecture.

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Finally, I wish to thank my parents and brother who allowed me to complete my studies.

THE ASSOCATION BETWEEN SLEEP DURATION AND DEMENTIA:

A META-ANLYSIS

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In the United States, the current cases of Alzheimer's disease will double by 2050. Therefore, it is important to study risk factors associated with dementia such as sleep duration. This meta-analysis was conducted to understand the discrepancy in study results since some demonstrated a V shaped association between duration of sleep and dementia while others found no association. If there truly is an association then sleep duration could be targeted to decrease the burdens caused by dementia.

A meta-analysis of published studies was conducted to assess the association between sleep duration and the different forms of dementia. The articles were found using PubMed, Embase, Scopus, and EBSCO with the search terms ("Sleep Duration" OR "Change in Sleep Duration") AND (Alzheimer* OR Dementia) and reviewing bibliographies. Studies were included in the analysis if they met the following criteria 1) a longitudinal study 2) a cohort, case-control, or clinical trial 3) assessed the exposure and outcome of interest 4) diagnosed dementia using established diagnostic criteria 5) provided a risk estimate and 95% confidence interval (CI) 6) in English 7) a published paper. Analyses such as test of heterogeneity, sensitivity analysis, and tests of publication bias were done using STATA15.

The analysis included 11 cohort studies with a total of 48,360 participants. No significant

association was found between short or long sleep duration and any form of dementia. However, there was a significant association between increase in sleep and dementia but there were only two published papers that examined this association. This study suggests that there is likely no association between sleep duration and any form of dementia which differs from results of previous meta-analyses.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

BACKGROUND

Dementia is a general disease category used to describe degenerative brain diseases, such as Alzheimer's disease and vascular dementia, which affect the elderly population (Gatz, et al., 2010). While the risk of Alzheimer's disease is only 8-10% in those age 60-69 years old it triples to 33-38% at age 80 years for those who are carriers of the apolipoprotein E (*APOE) ε4*allele, the genetic variant that has been associated with an increased risk of Alzheimer's disease (Rasmussen, et al., 2018). Alzheimer's disease is characterized by a steady decline of memory and cognitive ability to the point that it interferes with daily activity, while the biological characteristics are the accumulation of extracellular beta-amyloid plaques and tau proteins in the brain. Vascular dementia differs from other forms of dementia because there must be evidence that the cognitive decline is due to vascular changes such as stroke (American Psychiatric Association, 2013). Those with vascular dementia are more likely to live with more activities of daily living limitations than those with Alzheimer's disease (Gure, et al., 2009). While there are several biomarkers and imaging techniques that can be used in the research setting to help diagnose dementia a definite confirmation can only be done after death by dissecting the brain (Scheltens, et al., 2016).

In the United States, it is estimated that there are around 5.7 million cases of dementia with 60-70% of cases being categorized as Alzheimer's disease dementia and 5-10% of cases being categorized as vascular dementia. Due to the increase in life expectancy, it is expected

that the number of people with dementia or Alzheimer's disease will double to around 13.8 million in 2050 (Hebert, et al., 2013).

Unfortunately, since there is no cure for dementia it is ultimately fatal. In 2014, Alzheimer's disease was the sixth leading cause of death in the United States with a mortality rate of 25.4 deaths per 100,000 people. (Taylor, et al., 2017). As a result, it is important to study and validate risk factors that could potentially be targeted to reduce the risk for dementia. There are several known modifiable risk factors for dementia such as being diabetic (Akomolafe, et al., 2006), obese (Whitmer, et al., 2007), having hypertension (Skoog, et al., 1996), a history of cardiovascular disease (Eriksson, et al., 2010), and low education (Gatz, et al., 2007). Recently, the role of sleep has been gaining attention as a potential risk factor for cognitive disorders.

Sleep has become a behavioral risk factor of interest because around one third of adults report having sleep issues such as experiencing symptoms of insomnia, abnormal sleep durations, and non-restorative sleep, making this a relatively common risk factor in the United States (Morin, et al., 2006). The elderly population is the most likely to complain about sleep disturbances, with the highest reported prevalence estimated at 70% (Jaussent, et al., 2011). It has become a risk factor of interest for dementia and Alzheimer's disease since around 45% of those with the disease have a type of sleeping disturbance and 25-44% have a type of sleeping disorder (Morin, et al., 2006). The development of sleeping disorders and changes in sleep patterns are part of the natural aging process just like cognitive decline. Thus, researchers have been trying to understand if they simply co-exist with one another or if one precedes the other. (Shi, et al., 2018).

The relationship between sleep duration and dementia has been gaining attention. This is because earlier studies have linked short and long duration of sleep to risk factors associated with dementia such as cardiovascular disease (Cappuccio, et al., 2011), diabetes mellitus (Gottlieb, et al., 2005), and obesity (Gangwish, et al., 2005). There are several studies that have demonstrated a V shaped association between duration of sleep and cognitive disorders such as dementia or Alzheimer's disease. This suggests that elderly individuals who have longer or shorter duration of sleep are more likely to develop a cognitive disorder than those who have average duration of sleep. (Chen, et al., 2015) However, there are some studies which only found an association for short duration of sleep (Potvin, et al., 2012), others only found an association for long duration of sleep (Benito-Leon, et al., 2009), and some even observed no association (Luojus, et al., 2017) between duration of sleep and cognition. The direction of effect is also not consistent with some studies finding that shorter duration of sleep was protective for dementia (Sindi, et al., 2009).

Review of Prior Studies

There are currently only three meta-analyses published, with the most recent of these published in 2018 and including articles through 2017 (Kim, et al., 2016: Liang & Ling-Bo & Hao, 2018: Wu & Sun & Tan, 2018). The methods of measuring duration of sleep in published studies is through self-report or questionnaires. Dementia and Alzheimer's disease were normally measured based on standardized criteria such as the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (Wu & Sun & Tan, 2018). The DSM-IV defines dementia of the Alzheimer's type as the gradual development of cognitive deficits that include both types of memory impairment (ability to learn new material or recall

previous knowledge) and one type of cognitive disturbance: language disturbance, impaired ability to perform motor activity, failure to recognize objects, and disturbance in executive functioning such as planning or organizing. These deficits must result in an extreme impairment in social or occupational functioning which is a significant decline from the previous level of functioning and does not occur exclusively during delirium. To be categorized as Alzheimer's disease dementia other disorders such as major depressive episode and schizophrenia must be accounted for to make sure they cannot explain the symptoms. Features that separate Alzheimer's disease from other dementias are that it cannot be due to other central nervous system conditions such as Parkinson's disease or cerebrovascular disease which can result in deficits in memory and cognition. It also cannot be due to substance-induced conditions or due to other systemic conditions that can cause dementia such as hypothyroidism and vitamin B deficiency (American Psychiatric Association, 2000). While the most recent version of the DSM (DSM-5) was published in 2013 it is not likely to have been be used by the longitudinal studies in this meta-analysis (American Psychiatric Association, 2013).

A new meta-analysis should be done because the previous meta-analyses focused on the relationship between duration of sleep and cognitive decline (Liang & Ling-Bo & Hao, 2018) or mild cognitive impairment (MCI) combined with dementia (Kim, et al., 2016: Wu & Sun & Tan, 2017). MCI is defined as the pre-clinical stage of dementia where an individual experiences slight impairment in one or more cognitive domains such as memory or language, but the person is still able to function independently. This differs from dementia where these cognitive domains must be impaired to the point that there is interference with

daily life. MCI can be diagnosed by an episodic memory test such as the word-list learning tests and by clinical judgment (Albert, et al., 2011). There has not been a meta-analysis which only includes studies that looked at dementia without MCI which may lead to different outcomes. This could occur because while people with MCI are more likely to develop dementia there are some individuals with MCI who return to normal cognition or remain mildly cognitively impaired (Kantarci, et al., 2009). These previous meta-analyses also did not examine the relationship between change in duration of sleep and risk for dementia which is a growing body of research. As a result, a more recent meta-analysis to improve our understanding of the association between Alzheimer's disease and sleep duration is needed.

Public Health Significance

If there truly is a causal association between abnormal sleep duration and cognitive decline, then sleep duration could be an important modifiable risk factor that could be targeted to improve the quality of life for the elderly (Youngstedt & Kripke, 2004). This could potentially be important information for public health programs because the percent of United State citizens who sleep 6 or less hours per day has increased from 28.6% in 2004 to 32.9% in 2017. This corresponds to around 9 million adults and could lead to an increase of dementia cases if the association with short sleep duration holds true (Sheehan, et al., 2018). As a result, it is important to study why differences in study results have arisen.

Hypothesis, Research Question, Specific Aims or Objectives

The specific purpose of this study will be to expand the current understanding of the association between sleep and dementia to see if some consistency can be found in the conflicting studies. This was done by 1) performing a literature search to include publications

beginning from inception to January 2019 to try to increase statistical power; 2) generating summary effect measures for studies that have homogeneous results; and 3) identifying factors that could explain variation in effect measures across studies.

METHODS

Study Design

This study was a meta-analysis that followed the guidelines set by Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (Moher, et al., 2009). The unit of analysis was each individual publication.

Literature Search

The articles were found by searching PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), Embase (https://www.embase.com/) , Scopus (https://www.scopus.com) , and EBSCO (https://origin.ebsco.com/). In all four databases articles were identified by matching the articles' title, keywords, and abstract to the following search terms: (change* in sleep duration" or "Sleep Duration") and (Alzheimer* or dementia). The literature search included studies published up to January 20th 2019. In Embase, the exposure and outcome variables were searched separately then combined. The search term "Sleep time" was added for the exposure because it was a keyword that was specific to Embase and not used in PubMed and Scopus. The results were then limited by using the result filter for publication types which limited the results to "Articles". The results were also refined in Scopus and EBSCO by limiting the document type to "Article". There were no restrictions when searching for papers using PubMed. The papers from previous meta-analyses that follow the eligibility criteria, stated below, were also included. Duplicates were removed by using the citation manger RefWorks.

Data Collection:

Two investigators independently selected the articles based on the following inclusion and exclusion criteria. Titles and abstracts were scanned to determine if they met the following eligibility criteria.

Inclusion Criteria

The articles included in the meta-analysis met the following inclusion criteria: 1) described a longitudinal study to allow the assessment of temporality 2) described the use of the following study designs: cohort, case-control, or clinical trial 3) assessed the relationship between the exposures sleep duration or change in sleep duration and the outcomes Alzheimer's disease or dementia 4) diagnosed Alzheimer's disease or dementia based on an established diagnostic criteria such as DSM-IV, medical records, or linkage to a national registry 5) provided enough data to calculate odds ratios (ORs), rate ratios (RRs), or hazard ratios (HRs) and the 95% confidence interval (CI) 6) the paper was written in English 7) the papers must be a published journal article and not a conference abstracts or excerpts.

Exclusion Criteria

1) Studies that included participants with Parkinson's disease at baseline and in the outcome measure. This was done because sleep disorders (Chaudhuri & Schapira, 2009) and dementia (Hely, 2008) are non-motor symptoms associated with Parkinson's disease. Another issue is that their level of cognition is different than the general population. 2) If the study subject was an animal model 3) Studies that had an outcome measure for MCI and dementia combined but not dementia independently 4) Studies that use napping duration as

the exposure of interest. This is because sleeping is fundamentally different from napping. 5) Articles based on a pilot study, when an article describing the full study is available.

Quality Assessment

Two investigators used the Newcastle-Ottawa quality assessment scale to independently perform the quality assessment. This assessment scale will be used since there are likely no clinical trials on this topic and because it was used by the previous three meta-analyses (Kim, et al., 2016: Liang & Ling-Bo & Hao, 2018: Wu & Sun & Tan, 2017).This assessment scale has a maximum score of 9 stars and assesses quality based on the selection of cases and controls which has a maximum score of 4 stars and comparability of cases and controls which contributes a maximum of 2 stars. For case-control studies the quality is also based on the ascertainment of the exposed and non-exposed as well as the non-response rate which all contribute a maximum of 3 stars. For cohort studies, the quality is based on the assessment of outcome, the time of follow up, and adequacy of follow up which contribute a maximum of 3 stars (Wells, et al., 2012). Disagreements on the score of each paper were settled by the investigators discussing their results to reach an agreement on the final score. There is currently no official threshold but a quality score of 0-3 stars will be considered low quality, 4-6 stars will be considered moderate quality, and 7-9 stars will be considered high quality (Liang & Ling-Bo & Hao, 2018).

Data Extraction:

Two investigators independently read the papers and extracted the variables of interest. The study characteristics: year of study, location of study (country), study design (case-control, retrospective cohort, prospective cohort or clinical trial), number of

participants, percent of male participants, percent of drop outs, the confounders that were adjusted for and how they were measured, how the study handled cases of dementia/Alzheimer's disease which developed in the first few years after baseline, the average age at baseline, the range of ages that was eligible for the study at baseline, duration of follow-up, and the number and percent of each ethnicity were extracted. The variables concerning the exposure: The cut-off for each category of sleep duration, the definition of sleep duration (e.g., 24 hours or night time sleep duration), the method that was used to measure duration of sleep, and number of participants in each sleep duration category were extracted. For the exposure variable "change in sleep duration": the categories for change in sleep duration, time between previous sleep duration and current sleep duration, and number of participants in each change in sleep duration category were extracted. The variables concerning the outcome: the type of dementia (all cause dementia, Alzheimer's disease, vascular dementia), the method that was used to determine Alzheimer's disease or dementia and the number of cases and controls were extracted. The category dementia was labeled all cause dementia if there were no other categories of dementia present in the results. This was done to make the studies comparable and to reduce the number of outcome categories. The risk estimate (OR, HR, or RR) that adjusted for the most variables and its corresponding 95% confidence interval was also extracted. This was done because it can be assumed that adjustment will result in the true risk estimate for the exposure and outcome, making the risk estimates from different populations comparable even if they are obtained through different study methods. If there were more than three categories of sleep duration, then the ORs of all categories were kept. Sleep duration categories above the reference group were considered

long duration of sleep and sleep duration categories below the reference category were considered short duration of sleep. If the association between duration of sleep and dementia at different times points was reported then the risk estimate for each time point as well as the description of the time point was extracted. For the variable "Method of sleep ascertainment" if the question is simply "how many hours do you sleep" then it will be assumed that it is a 24-hour period.

Data Analysis

All analyses were conducted using the software STATA version 15 (StataCorp, College Station, TX, USA). A p-value that was equal to or less than 0.05 indicated that the result was statistically significant. When analyzing the data, the effects of short duration of sleep and long sleep duration on the outcome were assessed separately. The analysis was also separated for the outcomes dementia, Alzheimer's disease, and vascular dementia. This was done to prevent a unit-of-analysis error since there were several studies that looked at more than one subtype of dementia. As a result, if the analysis was not separated by outcome then the participants in the control groups would be counted more than once in an analysis since the same control group was used for each disease in one study. To maintain consistency, if there were more than 3 categories of sleep duration, the risk estimate from the lowest duration of sleep was used for assessment of short duration of sleep while the risk estimate from the highest duration of sleep was used for long duration of sleep. In the main analyses, if sleep was ascertained at two different ages in the same cohort, then the risk estimates for sleep ascertainment at around age 65 will be used because most studies ascertained sleep

around that age. A forest plot was created to visually compare and present the summary measures from each study. The effect measures OR, RR, HR and their 95% confidence intervals were used to calculate the I^2 to evaluate the level of agreement between the studies (Higgins, et al., 2003).

The I^2 was calculated under the fixed effects model for short duration of sleep because there appeared to be homogeneity. It was used because all studies categorized sleep in the same manner. The random effects model was used to assess long sleep duration since there were clear differences in how the studies characterized sleep. For example, the risk estimate used from Westwood et al. defined long sleep duration as 9 hours compared to less than 9 hours. This differed from the definition of long duration of sleep from other studies which compared the highest sleep category with the average category. While Westwood et al. did have a risk estimate which defined long duration of sleep in a similar manner as other studies it could not be used because it included participants with MCI at baseline. The random effects model was also used to assess prolonged and reduced sleep duration because there were very few studies, so they are not expected to include the true association.

The I^2 statistic was used because it can be used for comparing studies with different types of designs, outcome data, and sizes. The I^2 values of 25%, 50%, and 75% were used to respectively represent low, moderate, and high heterogeneity. Values above 50% suggested statistical significance (Higgins, et al., 2003). Sensitivity analysis was performed to assess the contribution of each individual study to the magnitude of the overall summary estimates.

Publication Bias:

To assess publication, bias an Egger's regression test and a funnel plot were created. This was done because studies that suggests an association between the exposure and outcome may be more likely to be published then those that suggest no association which leads to publication bias. If no publication bias is present, then the plot should resemble a symmetrical inverted funnel because the plot indicates that precision increases as the study size increases. The Egger's regression was also performed to validate the results from the funnel plot since there is criticism that asymmetry could be due to factors besides publication bias (Egger, et al., 1997). For example, greater effects may be seen in smaller intervention studies because they are more likely to have greater compliance.

Meta-Regression and Subgroup Analysis

A meta-regression was performed using the following pre-set variables: study design, sample size (less than 1000, 1000-3000, more than 3000), the number of sleep duration categories (3 or 5), definition of sleep duration (24-hour period or nocturnal sleep), type of cognitive disorder (dementia or Alzheimer's disease), the number of cases (less than 500 or greater than 500), race/ethnicity (white or non-white), gender (male, female, or both), duration of follow up (less than 10 years, 10-19 years, or more than 20 years), age at baseline (younger than 65 or 65 and older), if they excluded people who developed a cognitive disorder after a certain number of years after baseline (yes or no), and the method of assessing sleep duration (self-report or questionnaire). The demographic variable age was chosen because the rate of dementia doubles every five years starting from age 65 (Evan, et al., 1989), ethnicity was selected because those who are non-Caucasian are more likely to

develop dementia then those who are Caucasian (Tang, et al., 1998), and gender because females are more likely to develop Alzheimer's disease compared to men (Seshadri, et al., 1997) while males are more likely to develop Lewy body dementia (Nelson et al., 2010). This was done to discover if any of these factors significantly affect the association between sleep duration and Alzheimer's disease or dementia. However, the meta-regression should not have been considered because there were less than ten studies in each meta-regression (Higgins & Green, 2011).

After the study characteristics were abstracted, it was not possible to conduct a meta-regression for study design since all the studies were cohort studies. There were several studies that did not describe the race/ethnicity of their cohort, so the studies were analyzed by the continent of the study cohort (Europe, Asia, or USA). The variables age of sleep ascertainment (early midlife or late-life) and MCI at baseline (yes or no) were included in further analysis. For age of sleep ascertainment, early mid-life was defined as obtaining data on sleep before age 60. If the study had both early mid-life and late-life risk estimates then the early mid-life was added to the analysis, so the analysis could reflect all findings. This variable was included because there were studies that assessed sleep duration after age 60 while others assessed sleep around age 40 to 50. This subgroup was also included because beta-amyloid accumulation, one of the hypothesized biological mechanisms for Alzheimer's disease, is believed to occur 20 years before the onset of dementia (Villemagne, et al., 2013).

Having mild cognitively impaired individuals at baseline was originally an exclusion criterion. This is because a study found that shorter duration of sleep was protective for those who were cognitively impaired while those that had normal cognition were at greater risk for

cognitive decline (Johar, et al., 2016). Unfortunately, only three (Hahn et al., 2014: Westwood, et al., 2017: Bokenberger, et al., 2017) out of the eleven studies explicitly stated that they stratified by baseline cognitive status to separate those who are cognitively intact and those who are mild cognitively impaired. As a result, instead of only including these three studies in the meta-analysis a subgroup analysis was conducted to determine if studies that included MCI at baseline were more likely to have significant results than studies that didn't include MCI at baseline. This was done by obtaining a summary effect estimate from studies that did not include MCI participants at baseline and a summary effect estimate from studies that had MCI participants at baseline.

Human Subjects, Animal Subjects, or Safety Considerations

There was no data obtained from human subjects since this study was a meta-analysis of published literature. The statistical analysis for this study was done using the effect measures calculated from group data that were extracted from each individual study.

RESULTS

Literature Search

The initial literature search identified 371 papers from PubMed, 624 papers from Embase, 20 from Scopus, 38 from EBSCO, and 28 citations from the previous three meta-analyses. (Kim, et al., 2016: Liang & Ling-Bo & Hao, 2018: Wu & Sun & Tan, 2017). After removing the 217 duplicates there were 573 articles left. After screening the titles and abstracts of the articles there were 48 articles left that were fully read to assess for eligibility. The 525 publications were excluded because they were not in English, used an animal model,

were not an article, were a review, or they clearly did not have the outcome or exposure of interest which made it irrelevant. Once this was completed, there were 11 studies left for quantitative synthesis after 36 articles were excluded for including the dementia/MCI outcome, being a cross-sectional study, or reporting dementia mortality without dementia incidence. The results of the literature search are presented in Figure 1. These eleven studies were considered high quality based on the Newcastle-Ottawa quality assessment scale.

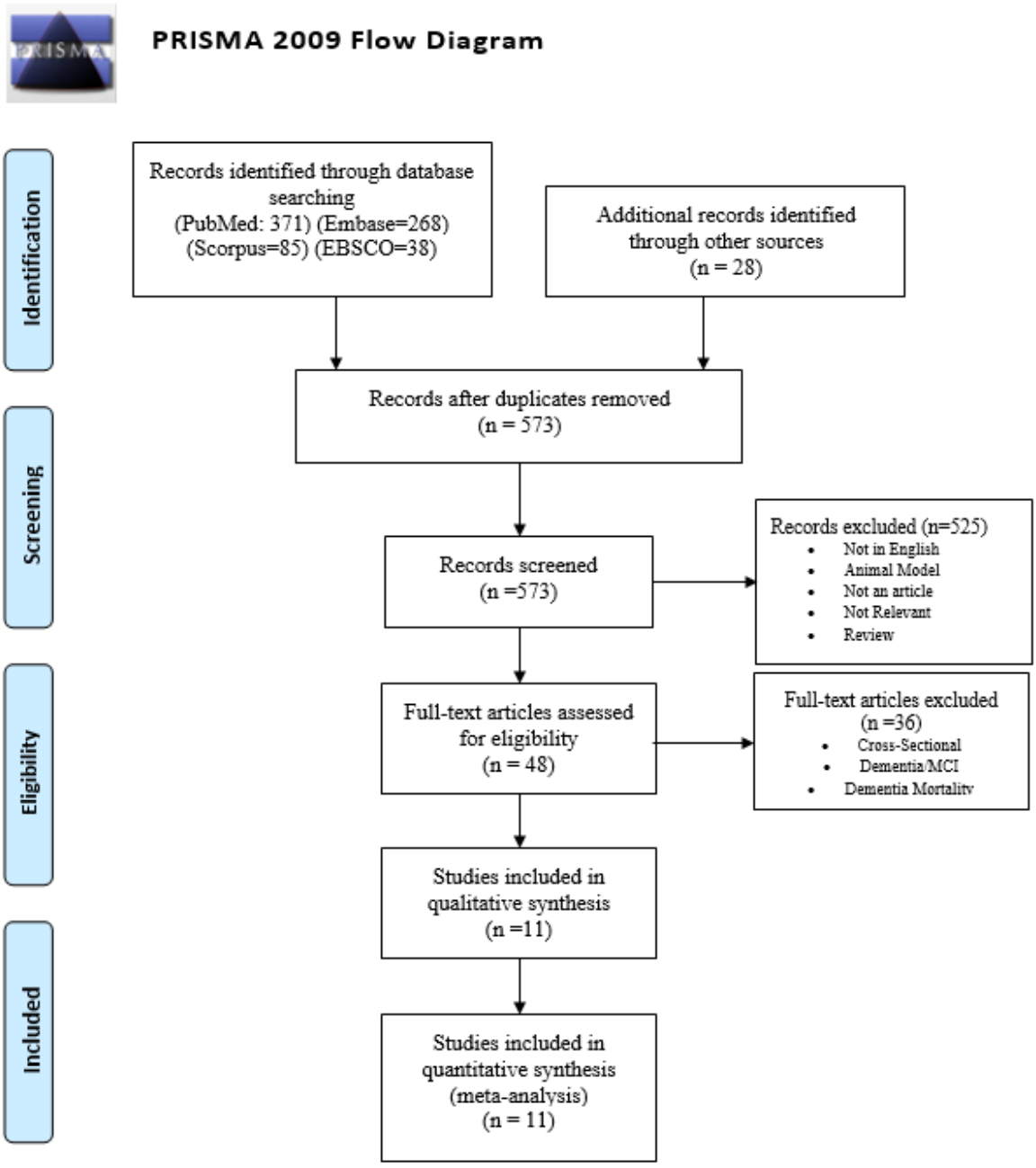


Figure 1. Results of the literature search. This flow diagram shows the process used to determine the final studies from all the studies that were found in the literature search.

Study Characteristics

All 11 studies consisted of cohort studies from 2009 to 2018 and were considered high quality by the independent investigators based on the Newcastle-Ottawa quality assessment scale (Appendix F). These studies had an average follow-up time of 14.9 years and a total of 48,360 participants. However, only 35,963 participants had data specific for sleep duration and 26,344 participants of these participants were included in the analysis portion of this meta-analysis. This drop-in participants from 48,360 to 26,344 occurred because the studies analyzed other sleep characteristics so there were some participants without information on sleep duration. The drop was also due to the use of only the highest and lowest sleep duration category in relation to the reference category. For the definition of sleep, there were four studies that defined sleep as night time sleep using a question such as "how many hours do you usually sleep at night" while seven studies defined sleep as the amount of sleep in a day by asking questions such as "how many hours on average do you sleep per day" (Appendix A). Three of the studies looked at change in sleep duration while 9 studies looked at sleep duration. Out of the studies that looked at sleep duration five had the outcome Alzheimer's disease, 6 had the outcome dementia, and one had the outcome vascular dementia. However, three of these studies categorized dementia as all-cause dementia. From the studies that assessed change in sleep duration all three assessed the outcome dementia while only 2 assessed Alzheimer's disease. There were 3 studies that defined sleep duration as sleep in a 24-hour period and 7 studies that defined sleep duration as time in bed. There were five studies which included assessment of sleep duration during

mid-life (35-64) and six studies which assessed sleep duration during late life (65+). The study characteristics can be found in **Error! Not a valid bookmark self-reference.**.

Table 1. Study Characteristics of the 11 Cohort Studies

					Exposure				Outcome			
Study	Location	Sample Size	Duration of Follow-up	Baseline Age	Type of Sleep	Definition of Sleep	Categories	Method of Ascertainment	Type of Cognitive Disorder	Number of Cases	Diagnostic Method	Adjusted Variables
Benito-Leon et al., 2009	Spain-NEDICE	2070	3	65+	Sleep Duration	24-Hr	≤5hr, 6hr, 7hr(ref), 8hr, ≥9hr	Self-Report: Interviewer asked for "Total hours of actual sleep in a 24-hr period)	All-cause Dementia/AD	Dementia: 140 AD: 99	MMSE/Neurological evaluation	1, 2,3,6, 15, 22, 23, 26,
Virta et al., 2013	Finland-Finnish Twin Cohort	1323	22	65+	Sleep Duration	24-Hr	<7hr,7-8hr(ref), >8hr	Self-Report: Reported how many hours they usually slept per day	AD	AD: 179	Record Linkage	1,2,3,6, 16, 23, 24, 31, 37
Hahn et al., 2014	Sweden-Kungshomen Project	214	9	75+	Change in Sleep Duration	24-Hr	≥2hr reduction of sleep, <2 hr reduction of sleep, no sleep reduction (ref)	Self-Report: CPRS scale	Dementia/AD	Dementia: 114 AD: 88	Neurological Evaluation/MMD-2	1,2,3,4,6,7,13,15,17,19,22,23, 24,26,29,30,33
Bokenberger et al., 2017	Sweden-SALT	6568	17	65+	Sleep Duration	Night Time Sleep	≤6hr, 6-9hr(ref), >9hr	Karolinska Sleep Questionnaire: TIB: Reported rise time-bed time	Dementia	Dementia: 1844	Record Linkage with national registers	1,2,3,4,8,15,17,18,22,23,24,26,32, 34
Luojus et al., 2017	Finland-KIHD	2386	21.9	42-62	Sleep Duration	Night Time Sleep	≤6.5hr, 7-8hr(ref), ≥8.5hr	Self-Report: How many hours do you usually sleep at night?	Dementia/AD	Dementia: 287 AD: 234	Recod Linkage with national registers	1,3,4,5,9,10,11,12,17,21,22,23,24, 25,26,30,38
Westwood et al., 2017	USA-Framingham Heart Study	2384	10	60+	Sleep Duration/ Change in Sleep Duration	24-Hr	**Sleep Duration**: <6hr, 6-9hr(ref), 9hr & ≤9hr(ref), >9hr **Change in Sleep Duration:** ≤9hr at former and baseline(ref), >9hr at former and baseline, change from >9hr to ≤9hr, change from <9hr to >9hr	Self Report: "How many hours do you typically sleep?"	Dementia/AD	Dementia: 182 AD: 144	DSM-IV	1,2,3,19,20,
Larsson et al., 2018	Finland-SIMPLER	2561	16	65+	Sleep Duration	24-Hr	≤6hr/night, 6.1-7 hr/night, 7.1-9hr/night(ref), >9 hr/night	Self Report: NA	AD	AD: 425	Record Linkage with national registers	1,2,3,6,14,15,22,23,24,35
Lu et al., 2018	Japan-Ohsaki Cohort Study	7422	7	65+	Change in Sleep Duration	24-Hr	≥2hr reduction in sleep , 1hr reduction in sleep, no reduction in sleep(ref), 1 hr increase in sleep, ≥2hr increase in sleep	Self-Report: "How many hours on average do you sleep per day?"	Dementia	Dementia: 688	Physician evalation using LTCI	1,2,3,4,6,7,13,15,17,22,23,24,27,2 9
Lutsey et al., 2018	USA-ARIC Study	505	15	54-73	Sleep Duration	Night Time Sleep	<7hr, 7hr≤x<8hr, 8hr≤x<9hr(ref), ≥9hr	SHHS Sleep Habits Questionnaire: How much sleep do you usually get at night (or in your main sleep period): on weekdays or workdays and on weekends or nonwork days?	Dementia	Dementia: 21	Neurological Evaluation/Neuropsychiatric inventory interview/MRI	1,2,3,5,6,15,17,19,21,22,24,32,36
Ohara et al., 2018	Japan-Hisayama Study	474	10	60+	Sleep Duration	24-Hr	<5hr, 5-6.9hr(ref) , 7-7.9hr, 8-9.9hr, ≥10hr	Self Report: Please describe the total duration of your sleep by adding your nighttime sleep and daytime napping in a 24hr period	Dementia/AD	Dementia: 101 AD: 70	Physician evaluation using DSM-III	1,2,3,4,7,14,15,17,22,23,24,
Sindi et al., 2018	Sweden-H70 Study	437	9	70	Sleep Duration	Night Time Sleep	2-6hr, 7-8(ref), 9-11hr	Self Report: On average, how many hours do you sleep per night?	Dementia	-	DSM-III &Tomography Scans	1,2,3,4,7,15,19,23,24,28,30

Table 1 Study Characteristics. This table displays the key characteristics of the studies that were used in the meta-regression as well as the subgroup analysis.

Adjusted variables: Age (1) Sex (2) Education (3) Heart disease (4) Blood pressure (5) Hypertension (6) Stroke (7) Chronic obstructive pulmonary disease (8) Total supernatant cholesterol (9) Low-density lipoprotein (10) High-density lipoprotein (11) hsCRP (12) Hyperlipidemia (13) Hypercholesterolemia (14) Diabetes (15) Obesity (16) Body mass index (17) Cancer history (18) APOE (19) Homocysteine (20) C-reactive protein (21) Smoking (22) Alcohol (23) Physical activity (24) Mental health (25) Depression (26) Psychological distress (27) Hopelessness (28) Pain (29) Living arrangement (30) Life satisfaction (31) Medication (32) Physical functional dependence (33) Night work status (34) Coffee consumption (35) Center (36) Follow-up time (37) Examination year (38)
AD: Alzheimer's Disease (ref): Reference group NA: Not available

Sleep Duration and Dementia

There were 9 studies that studied the association between sleep duration and a form of dementia. All 9 studies accessed the association between long sleep duration and a form of dementia while only 8 included the risk estimates for the association between short sleep duration and a form of dementia.

Short duration of sleep was defined as less than 5 hours of sleep in 2 studies, less than 6 hours in 2 studies, less than 6.5 hours for one study, and less than 7 hours for 2 studies. For short duration of sleep, all-cause dementia had a summary risk estimate of 1.18 (CI: 0.94-1.42) and an I^2 of 31.6% (p=0.199) (Figure 2). Alzheimer's disease had a summary risk estimate of 1.01 (CI: 0.92-1.09) and an I^2 of 10.0% (p=0.343) (Figure 2). There were only two studies of non-Alzheimer's dementia (1.08 CI: 0.30-1.86) and one study of vascular dementia (4.04 CI: -1.61-9.69) so a summary risk estimate could not be calculated for these two forms of dementia (Figure 2). The p-values of the meta-regression were all above the 0.05 significance level. The subgroup analysis found that all variables of interest contained 1 in their confidence interval, except for dementia studies with both genders in their cohort (1.43 CI: 1.03-1.83). The results of the meta-regression and subgroup analysis can be found in Appendix C. When determining publication bias in the studies that assessed the association between short sleep duration and incident dementia the Egger's regression had a p-value of 0.799 and the funnel plot was symmetrical (Appendix E). For studies that assessed the association between short sleep duration and Alzheimer's disease the Egger's regression had a p-value of 0.003 and an asymmetrical funnel plot (Appendix E).

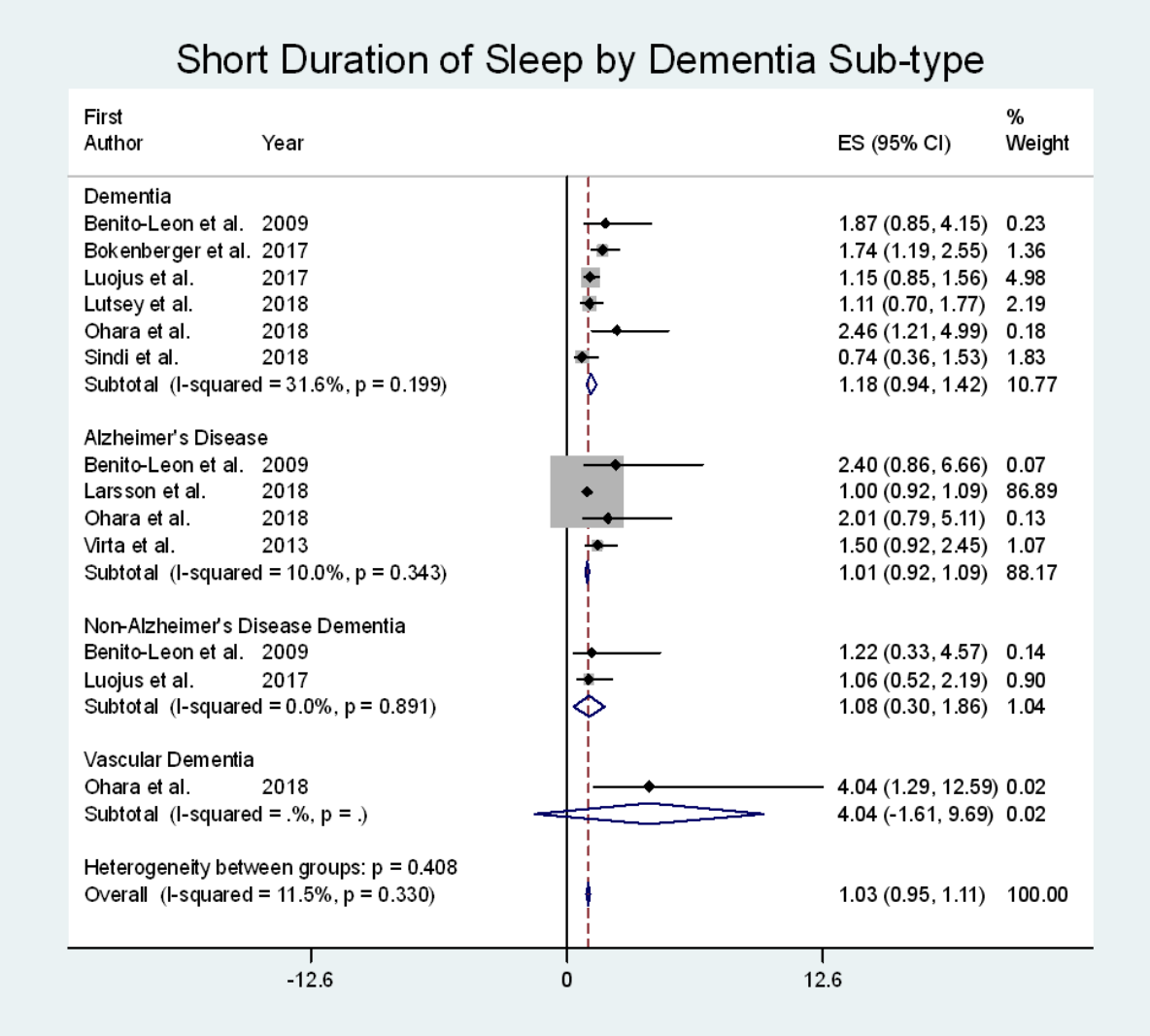


Figure 2 Forest plot for short duration of sleep and the different forms of dementia. Using the fixed effects model. The risk estimates for each individual study represent the shortest duration of sleep compared to the reference group.

Long duration of sleep was considered as more than 9 hours of sleep in 6 studies, more than 8 hours of sleep in one study, and 10 or more hours of sleep in one study.

Dementia had a summary risk estimate of 1.19 (CI: 0.90-1.48) and an I^2 of 37.1% (p=0.146) (Figure 3). Alzheimer's disease had a summary risk estimate of 1.32 (CI: 0.92-1.72) and an I^2 of 16.3% (p=0.065) (Figure 3. Forest plot for the association of long duration of sleep and the different forms of dementia. Figure 3). The summary effect measures for non-Alzheimer's disease dementia was 1.33 (CI: 0.36-2.30). There was only one study that assessed vascular dementia. The results of the meta-regression revealed that all variables of interest had p-values greater than 0.05 except for the variable time of follow-up (p=0.02) for dementia (Appendix D). The subgroup analysis found that most of the variables of interest contained one in their confidence interval. However, the confidence interval did not include one for studies that assessed dementia that had both genders in the cohort (1.22 CI: 1.04-1.39), duration of follow up that was less than 10 years (2.54 CI: 1.07-4.00), duration of follow up was between 10-19 years (1.21 CI: 1.03-1.38), ascertained sleep at early mid-life (1.27 CI: 1.02-1.53), and did not include mild cognitively impaired individuals at baseline (1.19 CI:1.01-1.38). For studies that assessed Alzheimer's disease, those that defined sleep as time in 24-hour sleep (1.79 CI: 1.11-2.47) and had less than 200 cases of Alzheimer's disease (1.75 CI: 1.16-2.35) had confidence intervals that did not include 1. The results of the meta-regression and subgroup analysis can be found in Appendix D. The studies that focused on long duration of sleep and dementia had an Egger's regression p-value of 0.201 and a symmetrical funnel plot (Appendix E). The studies that focused on long duration of sleep and Alzheimer's disease had a p-value of 0.022 and an asymmetrical funnel plot (Appendix E).

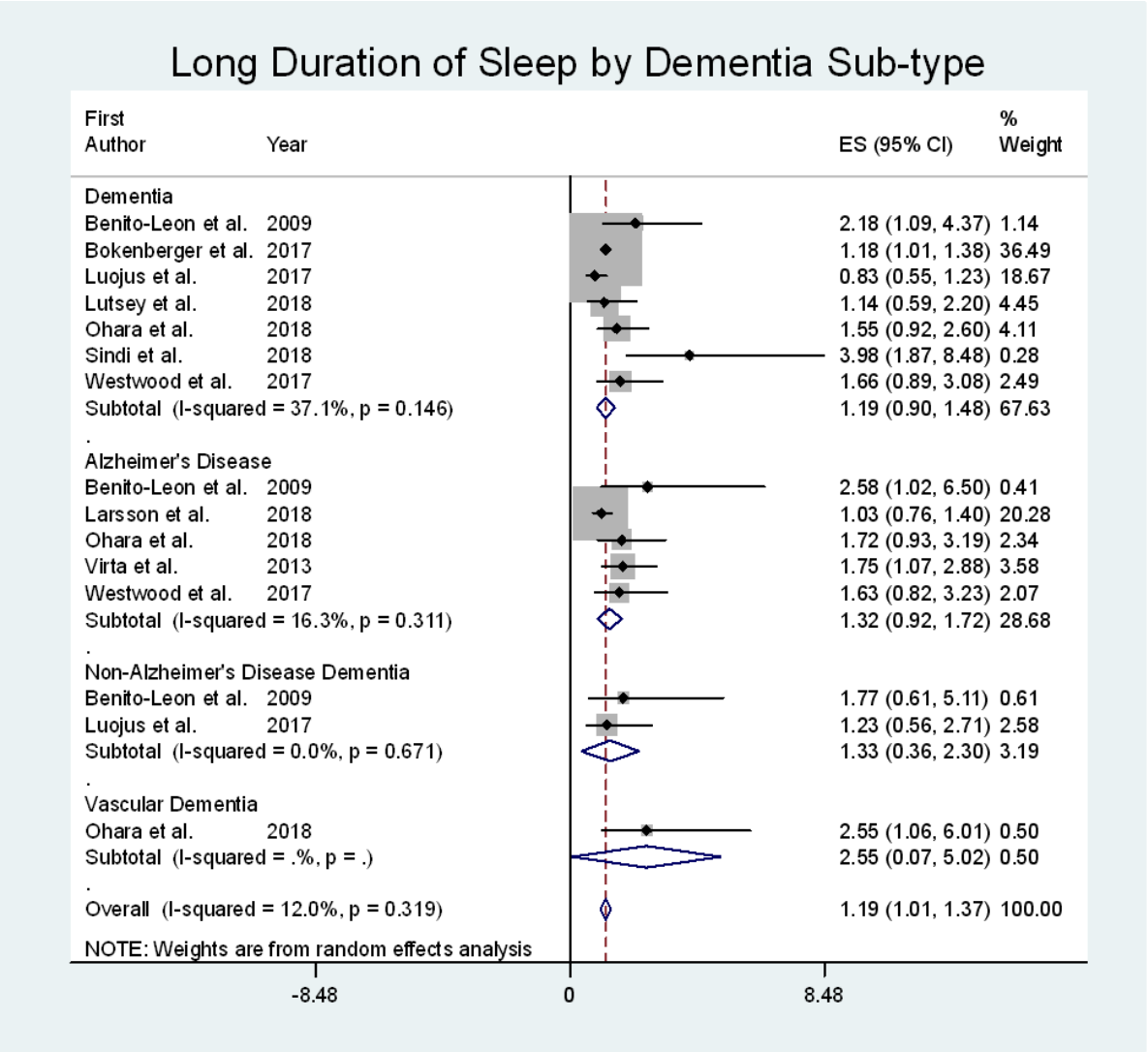


Figure 3. Forest plot for the association of long duration of sleep and the different forms of dementia. Using the random effects model.

Change in Sleep Duration

There were 3 studies that studied the association between change in sleep duration and a form of dementia.

Sleep reduction was defined as two or more hours of reduced sleep in two studies and a change of sleep duration from more than 9 hours to less than 9 hours in one study. The association between reduction of sleep duration and dementia had a summary risk estimate of 1.19 (CI: 0.79-1.68) and an I^2 of 21.9% (Figure 4). For Alzheimer's disease, the summary risk estimate was 1.65 (CI: 0.67-2.63) and I^2 was 0% (Figure 4). When assessing the publication bias of these three studies the Egger's regression p-value was 0.497 and the funnel plot was symmetrical. When assessing publication bias in studies that assessed the association between reduced sleep and dementia the funnel plot was symmetrical. There was only one study that assessed the association between reduced sleep and Alzheimer's disease (Appendix E). There was insufficient data for a meta-regression.

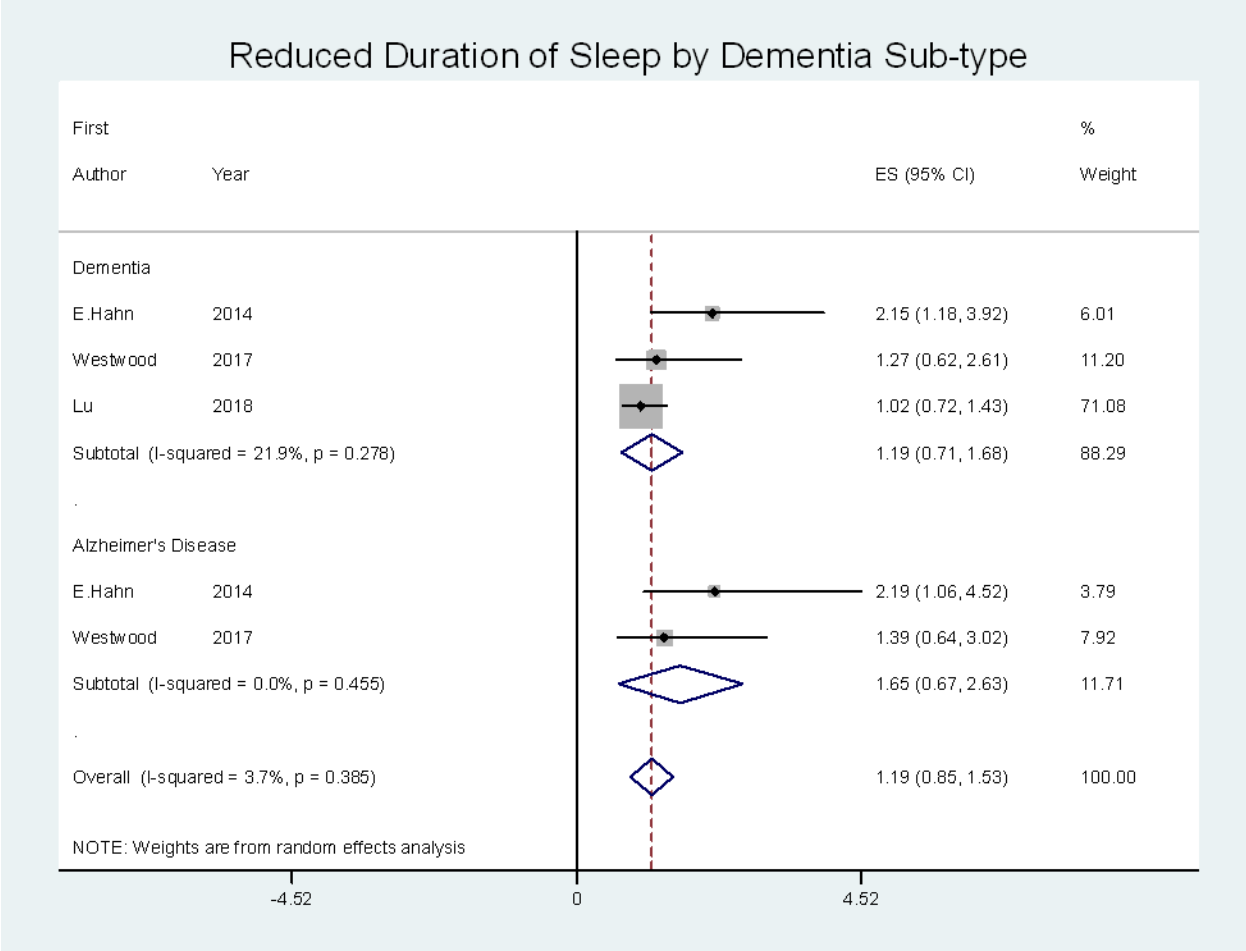


Figure 4. Forest plot for the association between sleep reduction and the different forms of dementia. Using the random effects model.

Increase in sleep duration was defined as an increase of sleep by 2 hours or more in two studies while one study defined increased sleep as a change of sleep duration from less than 9 hours of sleep to 9 or more hours of sleep (**Error! Not a valid bookmark self-reference.**). There were two studies that looked at the association between increase in sleep duration and incident dementia which resulted in a summary risk estimate of 2.11 (CI: 1.46-2.77) and an I^2 of 0% (Figure 5). For Alzheimer's disease, a summary risk estimate could not

be calculated because there was only one study that assessed this association. Publication bias could not be assessed for increase in sleep duration and Alzheimer's disease because there was only one study (Appendix E). The funnel plot for studies that assessed the association between increase in sleep and dementia was symmetrical (Appendix E). There was insufficient data for a meta-regression.

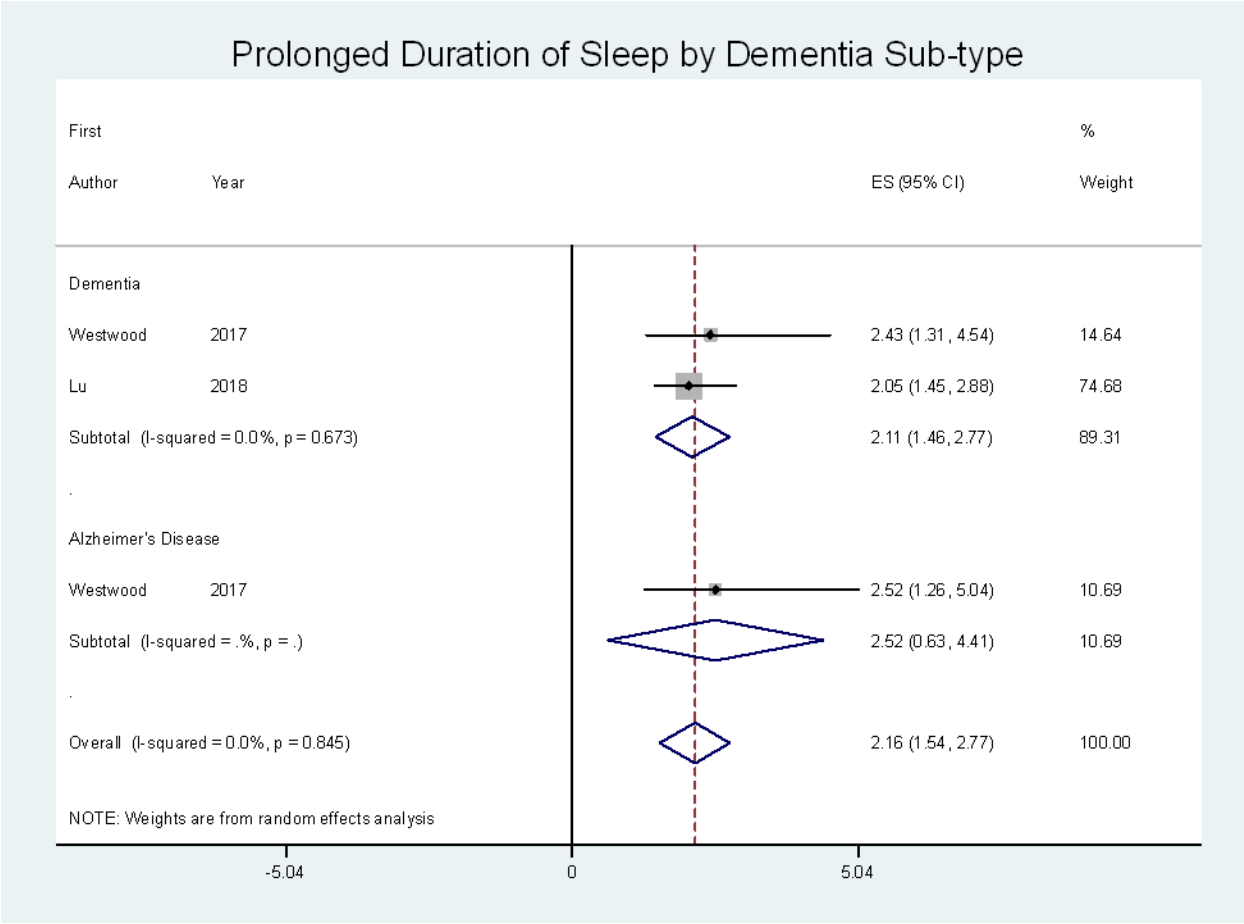


Figure 5. Forest plot for the association of increase of sleep duration and the different forms of dementia. Using the random effects model.

Sensitivity Analysis

For the association between short duration of sleep and dementia the removal of the study Sindi et al. gave a summary effect measure of 1.2741 (CI: 1.0091-1.5394). For the association between long duration of sleep and dementia the removal of the study Luojus et al. gave a summary effect measure of 1.2736 (CI: 1.0180-1.5291) while the removal of any of the other studies still gave a summary effect measure with a CI which contained one. For

the association between short duration of sleep and Alzheimer's disease the removal of any single study did not change the association and all confidence intervals still contained one. For the association between long duration of sleep and Alzheimer's disease the removal of the study Larsson et al. gave a summary effect measure of 1.7516 (CI: 1.1567-2.3464) while the removal of other studies did not shift the risk estimate's confidence interval to make it contain one. The results of the sensitivity analysis can be found in **Error! Reference source not found.** and **Error! Reference source not found.**.

Sensitivity Analysis: The summary effect measure after the removal of a single study								
	Dementia				Alzheimer's disease			
	Short duration		Long Duration		Short duration		Long Duration	
Study Removed	Estimate	CI	Estimate	CI	Estimate	CI	Estimate	CI
Bokenberger et. al	1.1029	0.8447-1.3611	1.3279	0.8215-1.8344	NA		NA	
Benito-Leon et. al	1.1682	0.9241-1.4122	1.1547	0.8691-1.4403	1.008	0.9232-1.0920	1.2928	0.8843-1.7013
Westwood et. al	NA		1.1642	0.8524-1.4760	NA		1.35	0.8441-1.8559
Luojus et. al	1.2117	0.8825-1.5409	1.2736*	1.0180-1.5291	NA		NA	
Lutsey et. al	1.2019	0.9314-1.4724	1.2241	0.8764-1.5718	NA		NA	
Larsson et. al	NA				1.6059	0.9061-2.3057	1.7516*	1.1567-2.3464
Sindi et al.	1.2741	1.0091-1.5394*	1.1453	0.9033-1.3873	NA		NA	
Ohara et. al	1.162	0.91861-1.4054	1.1585	0.8375-1.4796	1.0072	0.9228-1.0917	1.3021	0.8314-1.7729
Virta et. al	NA				1.0028	0.9179-1.0877	1.1721	0.8161-1.5281
Original	**1.18**	**0.94-1.42**	**1.19**	**0.90-1.48**	**1.01**	**0.92-1.09**	**1.32**	**0.92-1.72**

Table 2. Sensitivity Analysis: The summary effect measure after the removal of a single study. This sensitivity analysis showed the effect of removing a single study on the overall summary effect measure for sleep duration and incident dementia or Alzheimer's disease. Original represents the original summary effect measure and confidence interval for each association. ES represents effect measure while CI represents confidence interval. Red* indicates statistical significance.

DISCUSSION

Sleep Duration

The results from the meta-analysis indicate that there is no significant association between short or long sleep duration and any form of dementia. This differs from previous

meta-analyses that found a summary effect measure that suggested association between dementia and long duration of sleep (1.42 CI: 1.15-1.77) (Kim et al., 2016) and between Alzheimer's disease and both short (1.64 CI: 1.05-2.54) and long (2.19 CI: 1.08-4.46) sleep duration (Wu & Sun & Tan, 2018). In addition, the dose-response meta-analysis, performed in the two most recent meta-analyses, found that individuals reporting either long duration of sleep or short duration of sleep were more likely to develop dementia/MCI than those with normal sleep (Liang & Ling-Bo & Hao, 2018: Wu & Sun & Tan, 2018).

The difference in results for the association between Alzheimer's disease and sleep duration may be due to the inclusion of new studies that were not published by the time Wu et al. completed their literature search. This is supported by the sensitivity analysis which found that the association between long duration of sleep and Alzheimer's disease would become statistically significantly (1.7516 CI: 1.1567-2.3464) if Larrson, et al. was removed (**Error! Reference source not found.**). This study was not in the previous meta-analyses and contributed the greatest weight (28.63%) to the summary risk estimate for the association and made it statistically insignificant (Figure 3). This study had one of the longer follow-up times, 16 years, but what distinguishes it from other studies is that they accounted for the reverse causation effect by excluding cases of Alzheimer's disease five or ten years after baseline. This time period is longer than the other studies which excluded cases up to three years after the study was initiated. This study also had the largest sample size and highest number of Alzheimer's disease cases when compared to other studies that assessed sleep duration and Alzheimer's disease.

Another explanation is that studies that looked at the Alzheimer's disease outcome and defined sleep duration by a 24-hour period were more likely to see significant results. This was shown by subgroup analysis which found that studies that looked at the association between long duration of sleep and Alzheimer's disease and defined sleep duration in a 24-hour period had a summary risk estimate of 1.79 (CI: 1.11-2.47), while studies that used time in bed had a weaker risk estimate that was statistically non-significant (1.07 CI: 0.76-1.38) (Appendix D). This could occur because a study of total daily sleep time found that people who self-report long duration of sleep are more likely to complain of disrupted and poor sleep than those who sleep 7-8 hours daily (Grandner & Kripke, 2004). As a result, a sleep duration defined by a 24-hour hour period could capture sleep fragmentation or low-quality sleep which have been associated with increased risk of dementia (Lim, et al., 2013). However, the more plausible explanation is that Larsson et al. defined sleep as time in bed so when this study was separated from studies that defined sleep duration in a 24-hour period it results in a significant finding.

The removal of Sindi et al. resulted in a significant summary effect measure between short duration of sleep and dementia (1.2741 CI: 1.0091-1.5394). The likely explanation is that it was the only study to show a protective risk ratio (0.74 CI: 0.36-1.53) and it contributed the third most weight (1.83%) in the dementia subcategory (Figure 2). While this sample size was less than a quarter of the sample size of the other studies in the subgroup it did have a smaller variance, which could be attributed to a greater number of cases. However, this can only be assumed since the number of Alzheimer's disease and dementia cases was never stated.

The association between dementia and long duration of sleep became significant with the removal of Luojus et al. which resulted in a summary effect measure of 1.2736 (CI: 1.0180-1.5291) (**Error! Reference source not found.**). This was a study that was published after the Kim et al. study but the impact of this study was surprising because this study only carried 18.67% of the weight while Bokenberger et al. carried 36.49% of the weight. However, it was also the only study that found that long duration of sleep was protective for dementia (0.83 CI: 0.55-1.23) so its removal would likely shift the summary risk estimate to the right. (Figure 3). It was also the only study that had an all-male cohort which explains the results of subgroup analysis for gender (Appendix D). The study was also the only one that had a follow-up longer than 20 years. Thus, its separation resulted in the subgroup analysis finding that studies with less than 10 years of follow up (2.54 CI: 1.07-4.00) and follow up between 10 to 19 years (1.21 CI: 1.03-1.38) were statistically significant (Appendix D). As a result, it is likely the reason why the subgroup analysis and meta-regression suggested that follow-up time could explain the heterogeneity and insignificant association for long duration of sleep and dementia but not for other associations.

Change in Sleep Duration

This is the first meta-analysis to compile the results of studies that looked at the association between change in sleep duration and the different forms of dementia. While sleep reduction did not show any significant association with any form of dementia the association between increase in sleep and dementia was found to be statistically significant (2.11 CI: 1.46-2.77) (Figure 5). However, there were only two studies that assessed the association between prolonged sleep duration and dementia which means that there is likely

publication bias. However, the heterogeneity between the two studies was zero (Figure 5). While these two studies had similar study characteristics for length of follow up and method of sleep ascertainment they did have differences in how they categorized change in sleep and their definition of sleep. The study Westwood et al. defined increase in sleep duration as sleeping less than nine hours 13 years before baseline then more than 9 hours at baseline. The study Lu et al. defined sleep increase as a 1-hour increase in sleep or more than 2 hours of increase in sleep (**Error! Not a valid bookmark self-reference.**). However, for this analysis only the risk estimate from the 2 hours of increase in sleep category was used.

To the authors' knowledge, there is no well accepted hypothesis for why prolonged sleep duration could be associated with dementia incidence even though biological mechanisms have been proposed for reduced, short, and long duration of sleep. Reduced sleep and short duration of sleep are believed to prevent beta-amyloid clearing which causes beta-amyloid plaque build-up which is a defining characteristic of Alzheimer's disease (Spira, et al.,2013). Long duration of sleep has been associated with arterial stiffness (Niijima, et al., 2016) and blood pressure variability (Nagai, et al., 2017) which increases the risk of cardiovascular disease which is a known risk factor for dementia. However, one possible explanation is that prolonged sleep could be a marker for early neurodegeneration and not an actual cause of dementia (Westwood, et al., 2017). Another explanation is that the immunomodulators such as interleukin-6 and C-reactive protein which have been associated with dementia (Akiyama, et al., 2000), have also been shown to increase sleep duration and fragmentation during infections so the relationship may be bi-directional (Imeri & Opp, 2009).

Test of Heterogeneity

When assessing heterogeneity, The I^2 statistics suggested low heterogeneity for short sleep duration and dementia (31.6%) and Alzheimer's disease (10.0%) (Figure 2). It also suggested low heterogeneity for long sleep duration and the outcomes dementia (I^2 =37.1%) and Alzheimer's disease (16.3%) (Figure 3). The meta-regression for long duration of sleep and dementia suggest that the low heterogeneity could be explained by length of follow-up (p=0.002). When the subgroup analysis was conducted for this association, the I^2 statistics were reduced to 0% when separating the results by duration of follow up between 1-9 years, 10-19 years, and 20+ years. (Appendix D).

Publication Bias

Publication bias was expected in this meta-analysis because it included very few studies. However, the Egger's regression and funnel plot only indicated publication bias in the 5 studies that assessed the association between sleep duration and Alzheimer's disease and not the 7 studies that assessed the association between sleep duration and dementia (Appendix E). The reason why no publication bias was detected could be a result of the small number of studies which prevented the test from determining true asymmetry due to low power (Higgins & Green, 2011).

Subgroup Analysis

Due to the small number of studies the results from the subgroup analysis should be interpreted with caution. This is because when a variable was significant it was often only significant for one or two of the associations but not for others. The variables with the most consistency were gender and sleep duration categories. When subgrouping by gender, the

summary effect estimate was significant in studies which had a mixed gender cohort that assessed both long and short sleep duration and dementia. However, it is surprising that this result was seen in dementia and not Alzheimer's disease because females are more likely to develop Alzheimer's disease than males (Seshadri, et al., 1997), while males are more likely to develop dementia with Lewy bodies than females (Nelson, et al., 2010). There was no all-female cohort and only one male cohort, so this assumption cannot be verified. When subgrouping by duration of follow-up, the summary effect estimate was significant in studies that assessed long duration of sleep and dementia with 1-9 years of follow up (2.54 CI: 1.07-4.00) and 10-19 years of follow up (1.21 CI:1.03-1.38).

The results of the subgroup analysis for the inclusion of MCI at baseline were surprising because the summary effect measure for studies of the association of dementia and long sleep duration that did not have MCI at baseline was significant, while the studies that possibly had MCI at baseline didn't have a statistically significant summary effect measure (Appendix D). This was unexpected because mild cognitively impaired individuals are more likely to develop dementia. As a result, the subgroup analysis of studies that included MCI participants should have had significant results rather than the studies that did not include participants with MCI at baseline. However, this finding could be explained by the Bokenberger, et al., 2017 study which found an association between long duration of sleep and dementia because of their large number of participants and cases.

It is hypothesized that beta-amyloid accumulation can begin up to 20 years before the onset of Alzheimer's disease symptoms (Villemagne, et al., 2013). Since it is a suggested biological pathway that links sleep duration to dementia it is important for sleep duration to

be assessed before this accumulation is believed to begin. In the current research, only four of the eleven studies have the capability for this assessment because they have a measurement of sleep duration during mid-life (Larsson, et al., 2018: Luojus, et al., 2017: Virta, et al., 2013: Westwood, et al., 2017). The summary effect estimate of these studies suggests that there is no association between sleep duration and any form of dementia (Appendix C). As a result, these results suggest that beta-amyloid accumulation due to short sleep duration may not be a pathway between sleep and Alzheimer's disease since early mid-life sleep duration does not seem to increase disease risk. However, there were very few studies that studied sleep between ages 40-55 so more studies need to be done to determine if this is the case.

CONCLUSION

This meta-analysis suggests that there is no association between duration of sleep and any form of dementia which differs from the findings of previous meta-analyses. The analysis suggests that the difference could be a result of new studies that have longer follow up time and to differences in sleep definition. This meta-analysis did find that the association between prolonged sleep duration and dementia was statistically significant. However, this association needs to be verified by more research since only 2 studies have looked at this association.

The major limitation is that this study included very few studies. The funnel plots and Egger's regression suggested publication bias which means that the inclusion of new studies could possibility change the associations found in this study. The small number of studies also made the interpretation of subgroup analyses difficult because the small number of

studies increased the chance of seeing an association even when there was truly no association. It was difficult to discern if the significant result of the subgroup analysis was due to the actual variable or simply due to chance because of other variables that were included in the same paper. As a result, the conclusions from this study should be taken with caution. Another major issue is that most of these studies used self-reported data for sleep duration. While some studies attempted to use multiple questions to obtain data on sleep duration others simply asked, "how much sleep do you normally get" (Appendix A). Thus, it is likely that most studies suffer from reporting bias.

Another limitation of this study and the previous meta-analyses is the use of only the risk estimates from the longest and shortest sleep categories (Appendix A). This decreased the power of the findings because there were less participants in these categories and thus fewer cases. However, since these risk estimates were mostly hazard ratios there was no method available to combine categories, so this method was used at the recommendation of the Cochrane handbook (Higgins & Green, 2011).

The strength of this study is that it included more studies than the previous meta-analyses. This meta-analysis also only included studies that looked at the various forms of dementia without MCI. These studies had longer lengths of follow-up than the studies in the previous meta-analyses and they included non-Caucasian groups which was a limitation of previous meta-analyses. Even though the major limitation was the small number of studies it did allow the investigators to thoroughly read and understand all articles to try to find explanations for the differences in study results.

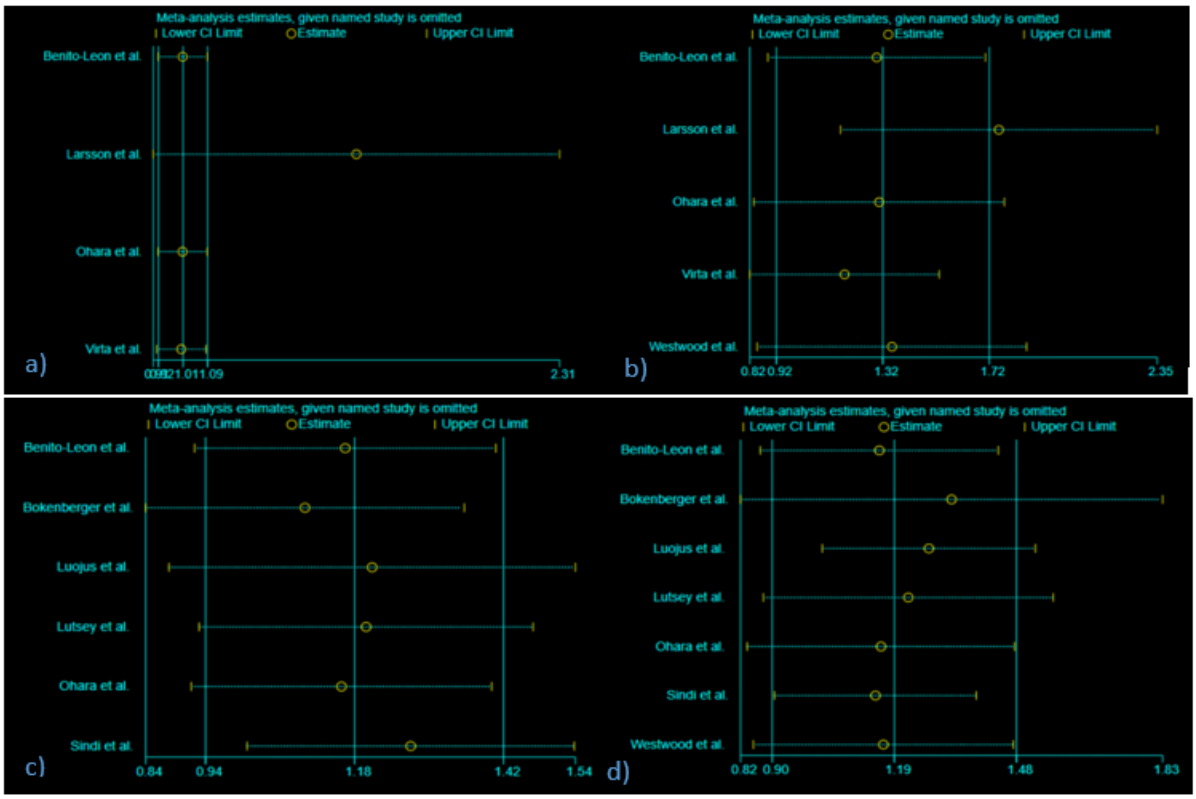
Recommendations for future studies would be to create a more accurate method for sleep duration ascertainment. While polysomnography would be the gold standard it would be difficult and costly for large cohorts an alternative might be fitness trackers that can record the duration of sleep. However, a more reasonable method would be to use multiple questions to obtain more accurate measures of sleep since many of these studies only used one question to determine sleep duration (Appendix A). Other recommendations include studying the effects of sleep duration at mid-life since the hypothesized beta-amyloid accumulation pathway is believed to start 20 years before the actual onset of Alzheimer's disease and for studies to stratify data on baseline cognitive status.

APPENDICES

Study	Question for Sleep Ascertainment	Sleep Category (N)	Dementia	Alzheimer's Disease	Non-Alzheimer's disease Dementia	Vascular Dementia
Benito-Leon et al., 2009	Self-Report: Interviewer asked for "Total hours of actual sleep in a 24-hr period)	<5hr (N=360) 6hr (N=437) 7hr (N=401) 8hr (N=789) ≥9 hr (N=1309)	**<5hr (1.87 CI: 0.85-4.15)** 6hr (1.13 CI: 0.48-2.69) 7hr (ref) 8hr (2.05 CI: 0.97-4.31) **≥9 hr (2.18 CI: 1.09-4.37)**	**<5hr (2.4 CI: 0.86-6.66)** 6hr (1.5 CI: 0.5-4.98) 7hr (ref) 8hr (3.17 CI: 1.22-8.28) **≥9 hr (2.58 CI: 1.02-6.5)**	**<5hr (1.22 CI: 0.33-4.57)** 6hr (0.69 CI: 0.15-3.08) 7hr (ref) 8hr (0.76 CI: 0.02-2.83) **≥9 hr (1.77 CI: 0.61-5.11)**	
Virta et al., 2013	Self-Report: Reported how many hours they usually slept per day	<7hr (N: 1774) 7-8hr (NA) >8hr (N=1809)		**<7hr (1.50 CI: 0.92-2.45)** 7-8hr (ref) **>8hr (1.75 CI: 1.07-2.88)**		
Halm et al., 2014	Self-Report: CPRS scale	NA	**≥2hr sleep reduction** (2.15 CI: 1.18-3.92) <2 hr sleep reduction (1.28 CI: 0.67-2.45) no sleep reduction (ref)			
Bokenberger et al., 2017	Karolinska Sleep Questionnaire: TIB: Reported rise time-bed time	≤6hr (PY: 3043) W/MCI 6-9(PY: 101864) W/MCI >9hr (PY: 33229) W/MCI	**≤6hr (1.74 CI: 1.19-2.55)** 6-9(ref) **>9hr (1.18 (CI: 1.01-1.38)**			
Luojus et al., 2017	Self-Report: How many hours do you usually sleep at night?	NA	**≤6.5hr** (1.15 CI:0.85-1.56) 7-8hr(ref) **≥8.5hr** (0.83 CI: 0.55-1.23)	**≤6.5hr (1.17 CI:0.84-1.64)** 7-8hr(ref) **≥8.5hr (0.73 CI:0.46-1.17)**	**≤6.5hr (1.06 CI:0.52-2.19)** 7-8hr(ref) **≥8.5hr (1.23 CI:0.56-2.71)**	
Westwood et al., 2017	Self Report: "How many hours do you typically sleep?"	Sleep Duration: <6hr (N=209) 6-9hr(N= 2,152) >9hr (N=961 <9hr (N=2,361) >9hr (N=96) Change in Sleep Duration: ≤9 at former&baseline(N=2180) >9 at former&baseline (N=16) change from >9 to ≤9 (N=68) change from <9 to >9 (N=75)	**Sleep Duration:** <6hr (0.90 CI: 0.58-1.38) W/MCI 6-9hr(ref) >9hr (2.01 CI: 1.24-3.26) W/MCI <9hr (ref) **>9hr (1.66 CI: 0.89-3.08)** **Change in Sleep Duration:** ≤9 at former&baseline(ref) >9 at former&baseline (1.42 CI:0.45-4.52) change from >9 to ≤9 (1.31 CI: 0.71-2.42) change from <9 to >9 (2.27 CI: 1.32-3.89)	**Sleep Duration:** <6hr (0.71 CI: 0.42-1.20) W/MCI 6-9hr(ref) >9hr (1.71 CI: 0.96-3.05) W/MCI <9hr (ref) **>9hr (1.63 CI: 0.82-3.23)** **Change in Sleep Duration:** ≤9 at former&baseline(ref) >9 at former&baseline (1.42 CI:0.45-4.52) change from >9 to ≤9 (1.31 CI: 0.71-2.42) change from <9 to >9 (2.27 CI: 1.32-3.89)		
Larsson et al., 2018	Self Report: NA	≤6hr/night (N=988 PY: 87,964) 6.1-7 hr/night (N: 1110 PY: 111,490) 7.1-9hr/night(N=1454 PY=149828) >9 hr/night (N=119 PY=7796)		**≤6hr/night** (1.00 CI: 0.92-1.09) **6.1-7 hr/night** (1.02 CI: 0.94-1.10) **7.1-9hr/night**(ref) >9 hr/night (1.56 CI: 1.30-1.88) >9 hr/night (5years) (1.22 CI: 0.97-1.52) **>9 hr/night (10years) (1.03 CI: 0.76-1.40)**		
Lu et al., 2018	Self-Report: "How many hours on average do you sleep per day?"	≥2hr reduction (N=624 PY: 3042) 1hr reduction (N=1468 PY: 7290) no reduction (N=2957 PY: 14533) 1 hr increase (N=1784 PY: 8741) ≥2hr increase (N=589 PY: 2733)	**≥2hr reduction** (1.02 CI: 0.72-1.43) 1hr reduction i (1.05 CI: 0.82-1.36) no reduction in sleep(ref) 1 hr increase (1.35 CI: 1.07-1.71) **≥2hr increase (2.05 CI: 1.45-2.88)**			
Lutsey et al., 2018	SHHS Sleep Habits Questionnaire: How much sleep do you usually get at night (or in your main sleep period): on weekdays or workdays and on weekends or nonwork days?	<7hr (N=257) 7hr≤x<8hr (N=435) 8hr≤x<9hr(N=330) ≥9hr (N=59)	**<7hr** (1.11 CI: 0.7-1.77) **7hr≤x<8hr** (1.00 CI: 0.66-1.53) **8hr≤x<9hr**(ref) **≥9hr** (1.14 CI: 0.59-2.20)			
Ohara et al., 2018	Self Report: Please describe the total duration of your sleep by adding your nighttime sleep and daytime napping in a 24hr period	<5hr (N=32) <5hr (N=32) LC 5-6.9hr(N=405) 7-7.9hr (N=446) 7-7.9hr (N=446) LC 8-9.9hr (N=522) 8-9.9hr (N=522) LC ≥10hr (N=92) ≥10hr (N=92) LC	<5hr (2.64 CI: 1.35-5.05) **<5hr (2.46 CI: 1.21-4.99) LC** 5-6.9hr(ref) 7-7.9hr (1.09 CI: 0.76-1.55) 7-7.9hr (1.02 CI: 0.71-1.47) LC 8-9.9hr (1.57 CI: 1.15-2.16) 8-9.9hr (1.31 CI: 0.94-1.83) LC ≥10hr (2.23 CI: 1.42-3.49) **≥10hr (1.55 CI: 0.92-2.60) LC**	<5hr (2.18 CI: 0.92-5.15) **<5hr (2.01 CI: 0.79-5.11) LC** 5-6.9hr(ref) 7-7.9hr (1.10 CI: 0.72-1.69) 7-7.9hr (1.03 CI: 0.66-1.60) LC 8-9.9hr (1.54 CI: 1.05-2.26) 8-9.9hr (1.23 CI: 0.82-1.85) LC ≥10hr (2.43 CI: 1.42-4.16) **≥10hr (1.72 CI: 0.93-3.19) LC**		**<5hr (4.04 CI: 1.29-12.59)** 5-6.9hr(ref) 7-7.9hr (1.20 CI: 0.57-2.50) 8-9.9hr (1.65 CI: 0.86-3.17) **≥10hr (2.55 CI: 1.06-6.01)**
Sindi et al., 2018	Self Report: On average, how many hours do you sleep per night?	NA	**2-6hr (0.74 CI: 0.36-1.53)** 7-8hr(ref) **9-11hr (3.98 CI: 1.87-8.48)**			

Appendix A. Characteristics and risk estimates of sleep categories. The question used to determine the sleep duration exposure, the number of participants per sleep category, and the risk estimates associated with each categories of sleep duration.

Bold: Represents the risk estimate that was used in the analyses, Red: Represents results of the specific study that were significant, Ref: Reference group, LC: Left censored by three years, W/MCI: With MCI participants, NA: Not available, PY: Person Years



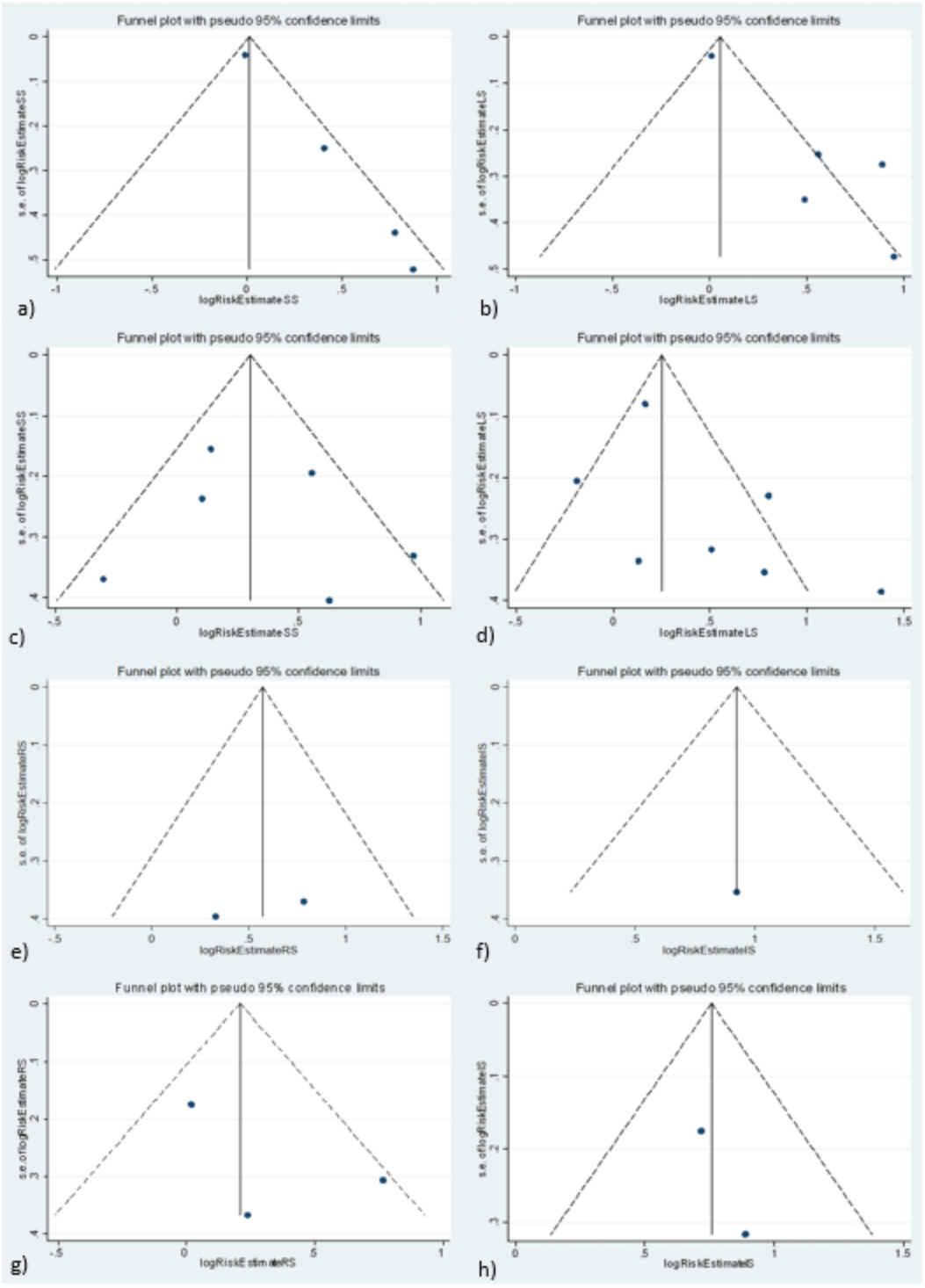
Appendix B. Sensitivity analysis: These graphs show visualization of the summary effect measure when the specific study is excluded a) The summary effect measure for short sleep duration and Alzheimer's disease b) The summary effect measure for long duration of sleep and Alzheimer's disease c) The summary effect measure for short duration of sleep and dementia d) the summary effect measures for long sleep duration and dementia.

	Sub-group Analysis and Meta-Regression for Short Sleep Duration									
	Dementia					*Alzheimer's Disease*				
	N	ES	I^2	P (Heterogeneity)	P (Meta-regression)	N	ES	I^2	P (Heterogeneity)	P (Meta-regression)
Subgroup										
Sleep Duration Category					0.261					0.602
3 categories	3	1.16 (0.88-1.43)	58.10%	0.092		1		NA	NA	
5 categories	2	2.13 (0.88-3.37)	0%	0.645		2	2.15 (0.42-3.86)	0	0.833	
Definition of Sleep Duration					0.15					0.126
24hr	4	2.13 (0.88-3.37)	0.00%	0.645		3	1.61 (0.91-2.31)	0	0.78	
Total Night Time Sleep	2	1.15 (0.90-1.39)	37.50%	0.187		1	0.99 (0.91-1.07)	NA	NA	
Continent of Study					0.42					0.531
Europe	4	1.18 (0.90-1.45)	45.20%	0.14		3	1.01 (0.92-1.09	20.20%	0.285	
Asia	1					1				
USA	1					0				
Gender					0.324					NA
Male	1					0				
Female						0				
Mixed	4	1.43 (1.03-1.83)*	16.40%	0.31		4	1.01(0.92-1.09)	10.00%	0.343	
Duration of Follow up					0.999					0.735
1-9 years	2	0.87 (0.31-1.42)	37.50%	0.206		1				
10-19 years	3	1.40 (0.99-1.81)	39.30%	0.192		2	1.01 (0.92-1.09)	38.30%	0.203	
20+ years	1					1				
Exclusion After follow-up					0.178					0.936
Yes	3	1.30 (0.99-1.61)	27.30%	0.253		2	0.99 (0.91-1.07)	0	0.341	
No	3	1.02 (0.63-1.40)	49.80%	0.137		1				
Age at Baseline					0.972					0.531
65+	3	1.21 (0.78-1.64)	63.20%	0.066		3	1.00 (0.92-1.08)	22.80%	0.274	
Younger than 65	3	1.18 (0.88-1.47)	20.80%	0.283		1				
Sleep Assessment					0.909					NA
Self-Report	2	1.10 (0.81-1.40)	31.10%	0.225		4	1.01 (0.92-1.09)	10%	0.343	
Questionnaire	4	1.35 (0.93-1.77)	50.90%	0.154		0				
Age of Sleep Ascertainment					0.591				0.988	
Early Mid-Life	1					1				
Late-Life	5	1.21 (0.88-1.54)	44.80%	0.124		3	1.00 (0.92-1.09)	0.00%	0.421	
MCI at Baseline					0.432					NA
Yes	5	1.10 (0.84-1.36)	8.20%	0.36		4	1.01 (0.92-1.09)	10%	0.343	
No	1					0				
Study Size					0.497					0.531
Less than 1000	3	1.00 (0.62-1.39)	37.80%	0.201		1				
1000-3000	2	1.18 (0.83-1.53)	0.00%	0.403		3	1.01 (0.92-1.09)	20.20%	0.285	
More than 3000	1									
Number of Cases					0.717					0.126
Less than 200	3	1.27 (0.78-1.76)	15.80%	0.305		3	1.61 (0.91-2.31)	0%	0.78	
200 or More	2	1.28 (0.96-1.59)	56.00%	0.132		1				

Appendix C. Subgroup analysis and meta-regression for short duration of sleep. Red* indicates statistical significance. ES represents the effect size for the association based on the subgroup. The I^2 represents the heterogeneity and P (Heterogeneity) is the p-value associated with the percent heterogeneity from the I^2 statistics for the specific sub-group. The P (Meta-regression) represents the p-value for the meta-regression of the specific variable.

	Sub-group Analysis and Meta-Regression for Long Sleep Duration									
	Dementia					*Alzheimer's Disease*				
	N	ES	I^2	P (Heterogeneity)	P (Meta-regression)	N	ES	I^2	P(Heterogeneity)	P (Meta-regression)
Subgroup										
Sleep Duration Category					0.697					0.819
3 categories	4	1.13 (0.74-1.52)	57.20%	0.072		2	1.85 (0.80-2.89)	0%	0.57	
5 categories	2	1.68 (0.93-2.43)	0	0.96		2	1.71 (0.98-2.43)	0%	0.876	
Definition of Sleep Duration					0.565					0.116
24hr	5	1.68 (0.93-2.43)	0.00%	0.503		3	1.79 (1.11-2.47)*	0%	0.843	
Total Night Time Sleep	2	1.12 (0.80-1.43)	43%	0.135		2	1.07 (0.76-1.38)	0%	0.346	
Continent of Study					0.952					0.698
Europe	4	1.14 (0.71-1.57)	60.90%	0.053		3	1.33 (0.69-1.96)	38.50%	0.197	
Asia	1					1				
USA	2	1.32 (0.67-1.97)	0	0.453		1				
Gender					0.147					NA
Male	1									
Female										
Mixed	5	1.22 (1.04-1.39)*	0.00%	0.601		5	1.32 (0.92-1.72)	16.30%	0.311	
Duration of Follow up					0.02*					0.814
1-9 years	2	2.54 (1.07-4.00)*	0%	0.339		1				
10-19 years	4	1.21 (1.03-1.38)*	0.00%	0.704		2	1.68 (0.85-2.50)	0.00%	0.915	
20+ years	1					2	1.26 (0.6-1.92)	53.70%	0.142	
Exclusion After follow-up					0.341					0.687
Yes	3	1.53 (0.65-2.41)	32.20%	0.228		3	1.22 (0.68-1.76)	18.70%	0.292	
No	4	1.13 (0.81-1.45)	48.30%	0.112		2	1.71 (0.96-2.43)	0%	0.876	
Age at Baseline					0.288					0.697
65+	3	1.77 (0.57-2.97)	51.6	0.127		3	1.33 (0.69-1.96)	38.50%	0.197	
Younger than 65	4	1.11 (0.71-1.51)	27.10%	0.249		2	1.68 (0.85-2.50)	0%	0.915	
Sleep Assessment					0.408					NA
Self-Report	5	1.47 (0.79-2.15)	55.60%	0.061		5	1.32 (0.92-1.72)	16.30%	0.311	
Questionnaire	2	1.18 (1.00-1.36)	0%	0.924		0				
Age of Sleep Ascertainment					0.092					0.747
Early Mid-Life	2	0.85 (0.54-1.16)	0	0.74		2	1.37 (0.64-2.09)	25.90%	0.245	
Late-Life	6	1.27 (1.02-1.53)*	7.80%	0.366		4	1.17 (0.82-1.53)	5.00%	0.368	
MCI at Baseline					0.749					0.875
Yes	5	1.29 (0.72-1.86)	48.80%	0.098		4	1.35 (0.94-1.96)	29.20%	0.237	
No	2	1.19 (1.01-1.38)*	0%	0.397		1				
Study Size					0.393					0.33
Less than 1000	3	1.47 (0.71-2.23)	57.00%	0.097		1				
1000-3000	3	1.29 (0.50-2.09)	53.00%	0.119		4	1.30 (0.83-1.77)	22.70%	0.274	
More than 3000	1									
Number of Cases					0.261					0.089
Less than 200	3	1.43 (0.88-1.98)	0.00%	0.501		4	1.75 (1.16-2.35)*	0%	0.942	
200 or More	3	1.08 (0.77-1.40)	51.50%	0.127		1				

Appendix D. Subgroup analysis and meta-regression for long duration of sleep. Red* indicates statistical significance. The I^2 represents the heterogeneity and P (Heterogeneity) is the p-value associated with the percent heterogeneity from the I^2 statistics for the specific subgroup. The P (Meta-regression) represents the p-value for the meta-regression of the specific variable.


Funnel plot with pseudo 95% confidence limits
s.e. of logRiskEstimateSS
logRiskEstimateSS
a)
Funnel plot with pseudo 95% confidence limits
s.e. of logRiskEstimateLS
logRiskEstimateLS
b)
Funnel plot with pseudo 95% confidence limits
s.e. of logRiskEstimateSS
logRiskEstimateSS
c)
Funnel plot with pseudo 95% confidence limits
s.e. of logRiskEstimateLS
logRiskEstimateLS
d)
Funnel plot with pseudo 95% confidence limits
s.e. of logRiskEstimateRS
logRiskEstimateRS
e)
Funnel plot with pseudo 95% confidence limits
s.e. of logRiskEstimateIS
logRiskEstimateIS
f)
Funnel plot with pseudo 95% confidence limits
s.e. of logRiskEstimateRS
logRiskEstimateRS
g)
Funnel plot with pseudo 95% confidence limits
s.e. of logRiskEstimateIS
logRiskEstimateIS
h)

Appendix E. The results of the funnel plots to determine publication bias. A)The funnel plot representing studies that assessed the assocation between Alzheimer's disease and short duration of sleep. B) The funnel plot representing studies that assessed the assocation between Alzheimer's disease and long duration of sleep. C) The funnel plot representing studies that assessed the assocation between dementia and short duration of sleep D) The funnel plot representing studies that assessed the assocation between dementia and long duration of sleep. E) The funnel plot representing studies that assessed the assocation between decreased sleep and Alzheimer's disease. F) The funnel plot representing studies that assessed the assocation between increase in sleep and Alzheimer's disease. G) The funnel plot representing studies that assessed the assocation between decreased sleep and dementia. H) The funnel plot representing studies that assessed the assocation between increase in sleep and dementia.

Study	Quality Score	Selection	Comparability	Outcome
Benito-Leon et al., 2009	9	****	**	***
Virta et al., 2013	8	***	**	***
Hahn, et al., 2014	8	***	**	***
Bokenberger et al., 2017	8	***	**	***
Luojus et al., 2017	8	***	**	***
Westwood et al., 2017	8	***	**	***
Larsson et al., 2018	8	***	**	***
Lu et al., 2018	8	***	**	***
Lutsey et al., 2018	9	****	**	***
Ohara, et al., 2018	8	****	*	***
Sindi et al., 2018	8	***	**	***

Appendix F. Quality scores of the eleven studies using the Ottawa Quality Assessment Scale. A quality score of 0-3 represents a low-quality score, 4-6 represents moderate quality, and 7-

9 represents high quality. The quality score is made up scores from how they selected their sample (0-4 stars), how the study was comparable to other studies based on variables they adjusted for (0-2 stars), and factors concerning the outcome (0-3 stars).

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