DEMENTIA – SUBJECTIVE SLEEP QUALITY

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Subjective sleep quality is not associated with incident dementia: The Rotterdam Study. Journal of Alzheimer's disease 2018

ABSTRACT

Poor sleep is related to higher dementia risk, but this association is more equivocal for subjective sleep quality specifically. This study investigates the link between subjective sleep quality and dementia risk in the general population. We studied the role of subjective sleep quality in the risk of dementia in the general population.

In the prospective population-based Rotterdam Study, 4,835 persons (mean age 72 years, 58% women) underwent a home interview (2002-2006) that included the validated Pittsburgh Sleep Quality Index (PSQI) to assess sleep quality. Participants were followed until 2015 for incident dementia, through in-person screening and continuous monitoring of medical records. We used Cox regression models to associate sleep quality with dementia risk, adjusting for age, sex, education, smoking, employment, coffee consumption, alcohol consumption, activities of daily living, cardiovascular risk factors, anxiety, depressive symptoms, cognition and snoring.

During 41,385 person-years (8.5 years mean), 420 participants developed dementia, of whom 320 Alzheimer's disease (AD). Poorer subjective sleep quality was not associated with the risk of all-cause dementia (hazard ratio [HR] per SD increase in PSQI score: 0.91, 95% CI 0.82-1.02) or AD (HR 0.92, 95% CI 0.81-1.05). Similarly, individual components of the PSQI were also not associated with dementia. Several sensitivity analyses, i.e. excluding last years of the follow-up time duration or restricting to those with best MMSE scores at baseline, did not reveal subgroups with increased risks.

In this study, we found no association of poor subjective sleep quality with higher risk of dementia.

INTRODUCTION

Sleep problems are highly frequent in the elderly and sleep deprivation is known to acutely affect cognitive performance. Emerging evidence suggests that chronic sleep problems might increase the risk of cognitive decline,[1] and possibly dementia.[2-4] These associations are supported biologically as undisturbed sleep has been implicated in the clearance of amyloid-β, a pathological hallmark of Alzheimer's disease (AD).[5,6] Other important mechanisms through which sleep may affect dementia risk is through regulating synaptic homeostasis,[7] affecting levels of neuro-inflammation in hippocampal areas,[8] or hypoxia-related increased activity in inflammatory or oxidative pathways occurring in sleep-disordered breathing.[1]

Two recent meta-analyses substantiated this link of poor sleep and higher AD[2] or dementia[4] risk in the general population, for both quantitative and qualitative aspects of sleep. However, authors suggest distinct roles for different sleep aspects in risk for different dementia types,[4] or even caution that short follow-up duration of studies, and use of heterogeneous, and thus incomparable, measures of sleep aspects hamper interpreting results.[2] Specifically for the general construct of subjective sleep quality, included studies used different measures, such as sleep disturbances or daytime problems, which only partly represent the construct. Also, sleep quality was measured with objective measures such as actigraphy, which, while important for accurate measurement of basic sleep parameters or insight in biological processes, might not fully capture the qualitative experience of sleep, which inherently involves a subjective component.[9-11]

Studies using validated instruments that take the qualitative experience of sleep into account, such as the Pittsburgh Sleep Quality Index (PSQI), are more equivocal about the relation of subjective sleep quality with dementia. They have shown a link with imaging[12,13] or CSF[14,15] markers of neurodegeneration, but results with cognitive decline have been inconclusive,[1,16-19] and risk of dementia was hardly investigated. The few studies that did, interestingly, failed to find an association.[20-22]

It is important to study the relation of subjective sleep quality to dementia risk, as subjective sleep quality seems to be an independent aspect of sleep[11] that has been ill-characterized in longitudinal studies in dementia risk so far. Also, in the context of identifying potentially modifiable risk factors for dementia, subjective measures are inexpensive and easily administered, and subjective sleep quality can be modified (e.g. through cognitive behavioral therapy, the recommended treatment approach for insomnia[23]). Studies investigating the relation of subjective sleep quality and dementia risk, with sufficient follow-up time to account for reverse causation, are needed. In this population-based cohort study we aim to investigate the association of subjective sleep quality, measured by the PSQI, and dementia risk over a 13-year follow-up period.

METHODS

Study setting

The Rotterdam Study (RS) is an ongoing prospective population-based cohort study, starting in 1990, of inhabitants of the Ommoord district in Rotterdam aged 55 years or over, details of which have been described previously.[24] The RS has been approved by the Medical Ethics Committee of the Erasmus MC and by the Ministry of Health, Welfare and Sport of the Netherlands, implementing the Population Studies Act: Rotterdam Study. All participants provided written consent to participate in the study and share information from their treating physicians.

In brief, inhabitants willing to participate underwent examination rounds, consisting of a home interview and two subsequent center visits, which were repeated every 4-5 years. In between, incident disease is assessed through continuous linkage of the study database and medical records of general practitioners (GPs) which, in the Netherlands, also holds summaries of medical records from all specialist and inpatient care. Also, regular checks of nursing home medical records were performed. In 2000, the cohort was extended with new invitees from the same district and inclusion age. The current study includes all persons participating in the fourth wave of the original cohort (RS-I-4; 2002-2004) and the second wave of the second cohort (RS-II-2; 2003-2006) when the PSQI was introduced. They were followed up from this baseline measurement until study ending at January 1st of 2014 (RS-I-4) or 2015 (RS-II-2).

Study population

Of 6052 individuals who were scheduled for a home interview, 145 did not complete the PSQI due to withdrawal of consent, calling in sick or logistic reasons. Another 140 participants were excluded from the current analyses because they missed more than one of the seven component scores of the PSQI. We excluded an additional 119 participants with prevalent dementia at baseline, and 74 persons for not having any follow-up available for dementia, which left 5574 participants. Lastly, we included only participants with a Mini Mental State Examination (MMSE) score >25 at baseline to a final sample of 4835 participants (82% of eligible).

Sleep quality

Sleep quality was measured with a Dutch version of the PSQI, which was filled out with the help of a research nurse. The PSQI assesses sleep quality and behavior in the past month using questions about bedtimes and multiple sleep problems.[25] It was designed to distinguish 'poor' sleepers from 'good' sleepers in a clinical setting, and also has good test-retest reliability and validity when tested in a non-clinical sample of older adults.[26] Answer scores are combined in seven component scores (range: 0 – 3): quality, latency,

duration, efficiency, disturbances, medication and daytime dysfunction. These are summed to provide a global sleep quality score (range: 0 – 21). Higher scores indicate poorer sleep, with scores >5.0 indicating 'poor' versus 'good' sleepers. We calculated weighted component scores for participants that had one component score missing (330 out of 4835 participants [7%]) by multiplying six-component sum scores by 7/6. Mainly the components latency (n=148) and efficiency (n=138) were missing.

Dementia screening and surveillance

Participants were screened for dementia at baseline and subsequent center visits with the Mini-Mental State Examination[27] and the Geriatric Mental Schedule organic level.[28] Those with a Mini-Mental State Examination score <26 or Geriatric Mental Schedule score >0 underwent further investigation and informant interview, including the Cambridge Examination for Mental Disorders of the Elderly[29]. All participants also underwent routine cognitive assessment. In addition, the entire cohort was continuously under surveillance for dementia through electronic linkage of the study database with medical records from general practitioners and the regional institute for outpatient mental health care. Available information on cognitive testing and clinical neuroimaging was used when required for diagnosis of dementia subtype. A consensus panel led by a consultant neurologist established the final diagnosis according to standard criteria for dementia (DSM-III-R), Alzheimer's disease (NINCDS–ADRDA) and vascular dementia (NINDS-AIREN).

Follow-up until end of the study was nearly complete (96.7% of potential person-time). Participants were censored starting at date of dementia diagnosis, death, loss to follow-up, or study ending, whichever occurred first.

Covariates

Analyses were adjusted for potential confounders measured at baseline; selection was based on relevant publications.[2,20-22,30-39] Smoking habits were assessed by interview and categorized as never, former or current smoking. Educational attainment was assessed by interview and categorized as primary, secondary/lower vocational, intermediate vocational and higher vocational/university. Having current paid employment was self-reported. Activities of Daily Living (ADL) were assessed by a Dutch version of the Stanford Health Assessment Questionnaire and measured in a 'disability index'.[40] Coffee consumption was categorized in 0-1, 2-3 or >3 cups/day. Habitual alcohol consumption was self-reported with a validated Dutch version of the Food Frequency Questionnaire,[41] harmonized over use of different types of preparations and expressed in gr/day intake. Body mass index (BMI) was calculated from measured weight and height (kg/m^2). Hypertension was defined as elevated systolic (≥160) or diastolic (≥100 mm Hg) blood pressure (averaged from two right-arm measurements, sitting up, using a random-zero sphygmanometer), or self-reported use of antihypertensive medication.

Diabetes mellitus was defined as a fasting serum glucose level ≥7.0 mmol/L and/or self-reported use of anti-diabetic medication. Self-reported history of coronary heart disease (CHD) and cerebrovascular disease were confirmed via medical records. Total and high-density lipoprotein-cholesterol and glucose levels in serum were processed through an automated enzymatic procedure (Boehringer Mannheim System). Depressive symptoms were assessed with the validated Dutch version of the Centre for Epidemiological Studies Depression Scale.[42] Cognitive status was assessed with the MMSE. Presence of one or more 12-month prevalent DSM-IV anxiety disorders was assessed by an adapted version of the Munich Composite International Diagnostic Interview. Loud snoring was reported by participants and/or bedpartners in categories of frequency per week. *APOE*-genotype was determined by either polymerase chain reaction on coded DNA samples in RS-I-4 or bi-allelic Taqman assays (rs7412 and rs429358) in RS-II-2, and classified by number of ε4-alleles.

Statistical analysis

We first explored the association of individual covariates with global PSQI score at baseline using age- and sex-adjusted linear regression. For our main analysis, we used Cox proportional hazard models to determine the association of global PSQI scores with incident dementia, with follow-up time as timescale. We constructed three incremental models. Model 1 was adjusted for age at baseline, sex, education, smoking, employment, coffee consumption, alcohol consumption and activities of daily living. Model 2 was additionally adjusted for cardiovascular risk factors. Model 3 further incorporated MMSE-score, CES-D score, prevalent anxiety disorders, and snoring.

We performed several additional analyses. First, we studied the seven components of the PSQI separately as well as dichotomized global PSQI score in 'poor' vs. 'good' sleep quality. Second, we studied potential effect-modification by age, sex and clinically relevant depressive symptoms by stratification and formally testing for multiplicative interaction in the fully adjusted model.[42] Third, to examine how the relation of sleep quality and dementia was modified by baseline cognitive status, beyond including only participants with an MMSE>25, we incrementally restricted our sample to participants with highest MMSE-scores, per point, as high as MMSE>28.Fourth, to aid comparison with other studies that use shorter follow-up times, we performed analyses after restricting follow-up duration by two incremental year intervals, i.e. end-date at 2, 4, 6, 8, and 10 years after baseline. Fifth, we studied AD separately. Finally, we additionally adjusted the main analysis for number of *APOE*-ε4 alleles.

Missing data on covariates (≤13%) before including only participants with an MMSE >25 were imputed using 5 multiple imputation based on all variables used in our analyses. We plotted Schoenfeld residuals of all variables against time, using the free and open 'R' software[43] (package: 'survival'): no violations of proportionality were identified.

Statistical testing was performed two-sided at $p<0.05$. Data were analysed using SPSS Statistics, version 21 (IBM Corp., Armonk, NY).

RESULTS

Baseline characteristics are summarized in Table 1. The median PSQI score was 3 and 30% of participants had poor sleep quality. At baseline, higher depressive symptoms, presence of anxiety disorders, female sex, higher age, less coffee consumption, worse scores on ADL, presence of hypertension or CHD, and less snoring were associated with

Table 1. Baseline characteristics of the study population.

Characteristic (unit)	N=4,835
Global PSQI score	3 (2-6)
Age in years	71.9 ± 7.4
Women	2791 (58%)
Medium or higher education	2264 (47%)
Never smoker	1483 (31%)
Currently employed	325 (7%)
Coffee consumption >3 cups/day	2489 (52%)
Alcohol consumption (gr/day)	7 (1-20)
Disability index	0.4 (0.1-0.7)
Body mass index (kg/m^2)	27.6 ± 4.0
Hypertension	1732 (36%)
Total cholesterol (mmol/l)	5.6 ± 1.0
HDL-cholesterol (mmol/l)	1.5 ± 0.4
Diabetes mellitus	716 (15%)
History of CHD	291 (6%)
History of TIA or stroke	284 (7%)
CES-D	4 (2-8)
MMSE-score	28 (27-29)
Anxiety disorder	357 (8%)
Snoring ≥ 1/week	2009 (31.6%)
≥1 *APOE-ε4* allele(s)	1211 (27%)
Missing	288 (6%)
Incident all-cause dementia	420 (9%)
Of which Alzheimer's disease	320 (76%)

Values include imputed missing values and indicate frequency (%), or median (interquartile range) for categorical variables, and mean ± standard deviation for continuous variables, unless specified otherwise. Abbreviations: PSQI=Pittsburgh Sleep Quality Index; IQR= interquartile range; HDL= high-density lipoprotein; CES-D=Center for Epidemiologic Studies – Depression Scale; MMSE=Mini Mental State Examination; CHD=Coronary heart disease.

worse sleep quality (Supplementary Table 1). During 13 years of follow-up (mean 8.5 years), we observed 420 incident dementia cases, of which 320 had AD (76%).

We found no association of subjective sleep quality with the risk of dementia (hazard ratio [HR] per SD increase 0.91, 95% CI 0.81-1.02, Table 2). Additional adjustment did not substantially alter effect sizes. We found no association between worse scores on the separate PSQI-components and dementia risk with results consistent across components (Table 3). After dichotomizing the global PSQI score, we found that poor sleep quality was not associated with a higher risk of dementia than good sleep quality (HR 0.93, 95% CI 0.74-1.16).

Table 2. Association of subjective sleep quality and dementia risk

Global PSQI score (per SD increase)	Hazard ratio (95% CI)
Model 1	0.96 (0.86 - 1.06)
Model 2	0.95 (0.86 - 1.06)
Model 3	0.91 (0.81 - 1.02)

Estimates obtained from models with cases/N: 420/4835. Model 1: adjusted for age, sex, education, smoking, employment, coffee consumption, alcohol consumption, activities of daily living. Model 2: Model 1 + cardiovascular risk factors. Model 3: Model 2 + MMSE-score, depressive symptoms, anxiety and snoring. Abbreviations: CI=Confidence Interval; PSQI=Pittsburgh Sleep Quality Index; SD=Standard Deviation.

Table 3. Association of PSQI component scores and dementia risk

PSQI-components	Cases/N	HR (95% CI)
Quality	420/4806	0.88 (0.76-1.02)
Latency	407/4660	1.00 (0.89-1.10)
Duration	420/4808	0.96 (0.88-1.06)
Efficiency	411/4669	0.93 (0.83-1.03)
Disturbances	417/4780	0.85 (0.70-1.03)
Medication	420/4808	0.93 (0.83-1.04)
Daytime dysfunction	418/4795	0.96 (0.80-1.14)

Hazard ratios adjusted for age, sex, education, smoking, employment, coffee consumption, alcohol consumption, activities of daily living, cardiovascular risk factors, MMSE-score, depressive symptoms, anxiety and snoring, calculated per point increase for every component score. Abbreviations: CI=Confidence Interval; HR=hazard ratio; PSQI=Pittsburgh Sleep Quality Index.

Incrementally restricting analyses to participants with higher MMSE-scores at baseline resulted in hazard ratio estimates that were even closer to the null-value (Figure 1). We observed no significant interaction of PSQI with age, sex and CES-D, although a difference between men and women was suggested in the stratified analysis (Supplementary Table 2). Results were similar when restricting the follow-up time to 2, 4, 6, 8 or 10 years (Figure 2). Finally, additionally adjusting for *APOE*-ε4 allele status (HR 0.91, 95% CI 0.79-1.30) or studying AD separately (0.92, 95% CI 0.81-1.05) did not change results from the main analysis.

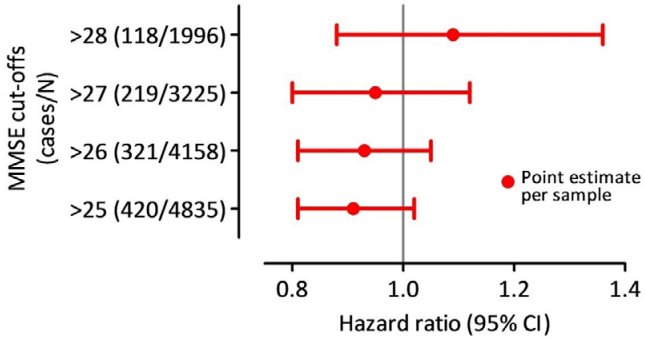

Figure 1. Association of subjective sleep quality and dementia risk, analyzed by incrementally restricting the sample to higher cognitive status.
Number of dementia cases per analyzed sample size is shown on the Y-axis. Hazard ratios adjusted for age, sex, education, smoking, employment, coffee consumption, alcohol consumption, activities of daily living, cardiovascular risk factors, MMSE-score, depressive symptoms, anxiety and snoring, calculated for samples incrementally restricted to higher MMSE scores. Abbreviations: CI=Confidence Interval; MMSE=Mini Mental State Examination.

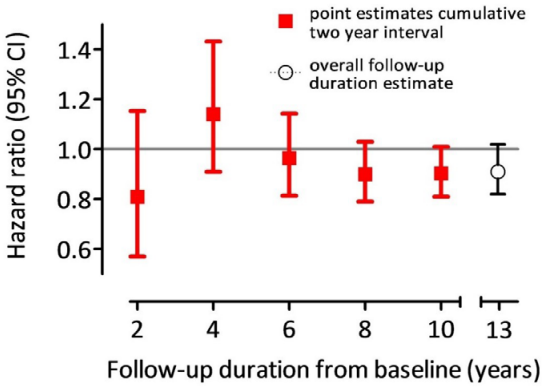

Figure 2. Association of subjective sleep quality and dementia risk, analyzed for cumulative 2-year follow-up intervals from baseline.
Hazard ratios adjusted for age, sex, education, smoking, employment, coffee consumption, alcohol consumption, activities of daily living, cardiovascular risk factors, MMSE-score, depressive symptoms, anxiety and snoring, calculated per standard deviation increase of global PSQI score. Estimates for each interval were obtained by censoring of all participants still at risk at year 2, 4, 6, 8 and 10 after baseline. Abbreviations: CI=Confidence Interval.

DISCUSSION

In this population-based cohort study with up to 13 years of follow-up, we did not find any association of subjective sleep quality, measured by PSQI, and the risk of all-cause dementia. All separate PSQI components were also not associated to incident dementia.

Some methodological considerations deserve mention. We lacked non-selectively repeated measures of the PSQI to assess the association of time-varying subjective sleep quality exposure on dementia risk, which could have accounted for intra-individual variability of subjective sleep quality over time. Yet, PSQI scores have been shown to remain relatively stable in elderly persons over 3 years.[44] Also, we could not assess the effect of time-varying covariates on our outcome. Next, baseline sleep quality in our study was relatively good compared to other population-based studies,[17,18,26] which might have precluded us finding an effect as the contrast between participants was small. Also, we could not assess to what extent associations of common sleep disorder (i.e. insomnia and sleep apnea), or excessive daytime sleepiness with our exposure and outcome might have influenced our results, although this cannot easily explain the lack of an association. Lastly, ethnic and socioeconomic differences in sleep (behavior) limit generalizability of findings to persons of European descent with middle or high income.

We did not find an association of the subjective experience of sleep with dementia risk. Such null associations have been reported before in similarly designed studies that, besides their main analysis, also specifically included sleep quality measures. A Finnish study with a median follow-up duration of 22.5 years found no association between a single sleep quality question ("Do you usually sleep well?") and AD.[20] A large registry-based study in Swedish twins[21] used a validated sleep quality index of four questions and reported a similar risk estimate (HR 0.93, 95% CI 0.85-1.01) to our study over a 17 year study period, just like the French Three City Study which studied the association of self-reported 'poor' sleep quality (rated 'poor', 'average' or 'good'; compared to answering 'good') with risk of dementia (OR 0.85, 95% CI 0.65-1.13) across 8 years.[22] Noteworthy in our study is that individual PSQI-components were also not associated to dementia risk, which range from very subjective experience (e.g. the 'quality' component) to components based on estimation of time. The components measure aspects of sleep quality that considerably overlap with sleep constructs that have been associated with dementia risk in previous prospective population-based studies, for instance self-reported sleep duration,[20,21,30-33] insomnia symptoms,[34,35] or self-reported sleep disturbances.[38,39]

There are several possible explanations for these discrepancies across studies, including ours. First, the predominantly positive associations in literature may indicate a role of sleep in dementia, but could equally well indicate publication bias. Indeed, in aforementioned meta-analysis of sleep and dementia, the funnel plot showed significant asymmetry, which is indicative of publication bias.[2] Another factor contributing to this predominance is the use of slightly differing sleep measures between studies that have been associated with dementia risk, caused by a lack of standardized measures of sleep feasible for use in large observational studies.[2,26] Use of validated or well-known sleep instruments might increase the reproducibility of reported findings.

Second, subjective reporting of sleep quality by persons that are at risk for dementia could introduce misclassification of sleep exposure that has to be taken into account in prospective studies. Intact cognition is a necessity for accurately recalling, reflecting on, and reporting past month's sleep, judging its 'quality'[9] using questionnaires.[45] As self-reported sleep is misclassified in the presence of cognitive impairment, even for measures as straightforward as sleep duration,[46] we only included participants with MMSE>25 to minimize misclassification bias of sleep quality. Noteworthy, persons with mild cognitive impairment with a low-normal MMSE score may still be included in our sample, for which we incrementally restricted the sample on higher MMSE scores. If not accounted for, such bias causes some aspects of sleep that deteriorate simultaneously with cognitive status before dementia diagnosis, or subjective sleep measures in general, to be falsely related to dementia. Importantly, such a restriction of the study population based on baseline cognition is not likely to have prevented us finding an increased dementia risk, as further incremental restrictions to higher MMSE-scores drove the hazard ratio estimate upwards: including participants with cognitive impairment might have further decreased the effect estimate towards an association of worse sleep quality and lower dementia risk, not higher dementia risk. This is supported by observations of better subjective sleep quality in early-stage AD-patients compared to controls, while actigraphic measures revealed their sleep to be worse than controls.[47]

Third, choice of follow-up duration influences the reported hazard ratios obtained from a Cox regression model, as it averages hazards over time into a single metric.[48] We accounted for this by analysing risks in shorter follow-up durations from baseline and found no association of poor sleep and higher dementia risk. We cannot exclude that poor sleep quality relates to increased dementia risk after 13 years, which might be biologically plausible considering that preclinical AD pathology is presumably present more than a decade[49] before diagnosis. However, this might be unlikely as absence of associations on the short term show that reverse causation, or the effect of preclinical neurodegenerative pathology on sleep quality, did not materially influence our results. Additionally, significant differences in strength of associations between studies with short and long follow-up duration were not found in a recent meta-analysis.[2]

Fourth, methodological concerns were identified in previous studies on subjective sleep measures and dementia risk[2]: the relative dearth of studies of sufficient quality, need for long-term follow-up to better study temporality and controlling for comorbid disorders. These concerns were well addressed by using data from the Rotterdam Study, which has sensitive case-finding which will in general increase the effect size of any association found between exposure and outcome, minimal loss to follow-up, adequate follow-up duration, and elaborate work-up to extensively control for confounding.

Currently, qualitative assessments of sleep are less preferred in dementia research in comparison to more quantitative or objective measures of sleep, as they may provide

more unbiased measures.[45] However, despite current efforts[10] to capture for instance sleep quality objectively, measures obtained with polysomnography, the gold standard sleep measurement, cannot sufficiently explain differences in perceived quality of sleep.[11] Therefore, a more quantitative assessment is not the same as a 'less biased qualitative assessment', as they seem to measure different constructs. Moreover, subjective assessments are important as perception of sleep will likely guide the diagnostic work-up in clinical practice. This underwrites the potential importance of studying sleep in dementia research with subjective assessments, also as great value is attributed to a person's appraisal of their own health status, such as in patient-reported outcomes, in medicine at large.[26]

This study indicates that the value of subjective sleep quality as a potentially modifiable risk factor, or marker, of dementia is limited. Compared to the recent meta-analyses, our study shows that the relation between sleep and dementia risk differs depending on the aspect of sleep studied. Also, it emphasizes that negative results should be published to not artificially inflate conclusions on the role of sleep in dementia risk.

Future studies may want to confirm that subjective sleep quality is not related to dementia risk, or investigate related topics, such as the association of subjective sleep quality with cognitive decline, or the role of sleep quality as a marker or risk factor for incident dementia or cognitive decline in vulnerable subgroups such as persons with subjective memory complaints, or *APOE-ε4* allele carriers.

Lastly, we reported determinants of sleep quality at baseline, most of which were related to sleep quality in the expected direction. Surprisingly, less coffee consumption and less snoring were related to worse sleep quality. An association of less coffee consumption and worse sleep quality may be explained by individuals cutting back on coffee after experiencing worse sleep quality[50] or may indicate a 'healthy coffee drinker'-effect.[51] The association with less snoring is not readily explained, and may be due to unreliability in self-reporting.

In conclusion, in this study we found that subjective sleep quality measured by the PSQI is not associated with risk of dementia, nor are the separate PSQI components.

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SUPPLEMENTARY TABLES

Supplementary Table 1. Cross-sectional ssociations of baseline characteristics with subjective sleep quality

Characteristic (unit or category)	Beta (95% CI)[a]	P-value
Age (per SD increase)	0.43 (0.33; 0.53)*	<0.001
Sex (women vs. men)	2.18 (1.98; 2.39)*	<0.001
Education (per higher level)	-0.05 (-0.17; 0.07)	0.430
Smoking status (ever vs. never)	0.02 (-0.14; 0.18)	0.819
Paid employment (present vs. absent)	-0.15 (-0.56; 0.27)	0.490
Coffee consumption (per category increase)	-0.21 (-0.38; -0.05)*	0.011
Alcohol consumption (per SD increase)	-0.10 (-0.20; 0.01)	0.070
Disability index (per SD increase)	0.68 (0.57; 0.79)*	<0.001
Body Mass Index (per SD increase)	-0.06 (-0.16; 0.04)	0.262
Hypertension (present vs. absent)	0.37 (0.16; 0.58)*	0.001
Total cholesterol (per SD increase)	-0.02 (-0.13; 0.08)	0.664
HDL-cholesterol (per SD increase)	0.04 (-0.06; 0.15)	0.438
Diabetes mellitus (present vs. absent)	0.02 (-0.26; 0.30)	0.895
History of coronary heart disease (present vs. absent)	0.67 (0.25; 1.09)*	0.002
History of TIA or stroke (present vs. absent)	0.26 (-0.17; 0.69)	0.235
CES-D (per SD increase)	1.46 (1.37; 1.55)*	<0.001
MMSE-score (per point increase)	-0.02 (-0.10; 0.06)	0.572
Anxiety disorder (present vs. absent)	1.74 (1.36; 2.12)*	<0.001
Snoring ≥ 1/week (present vs. absent)	-0.13 (-0.21; -0.04)*	0.003
APOE- ε4 alleles (per allele increase)	-0.17 (-0.38; 0.04)	0.111

Estimates from linear regression model adjusted for age and sex, if applicable, calculated per unit increase of the determinant, with global PSQI score as dependent variable, and marked for significance at P<0.05. Analysis for *APOE* in n=4,521.
Abbreviations: CI=Confidence Interval; PSQI=Pittsburgh Sleep Quality Index; IQR= interquartile range; HDL= high-density lipoprotein; CES-D=Center for Epidemiologic Studies – Depression Scale; MMSE=Mini Mental State Examination.

Supplementary Table 2. Association of subjective sleep quality and dementia risk, stratified by age, sex and depressive symptoms

Effect-modifier	Cases/N	HR (95% CI)	P-value interaction term
Age			0.780
≤ 71,0 years	97/2,550	0.95 (0.73-1.23)	
> 71,0 years	323/2,254	0.90 (0.80-1.02)	
Sex			0.342
Male	144/2,030	1.03 (0.82-1.30)	
Female	276/2,773	0.87 (0.76-0.98)	
Depressive symptoms			0.464
CES-D < 16	371/4,344	0.90 (0.79-1.02)	
CES-D ≥ 16	49/463	0.92 (0.70-1.23)	

Hazard ratios adjusted for age, sex, education, smoking, employment, coffee consumption, alcohol consumption, activities of daily living, cardiovascular risk factors, MMSE-score, depressive symptoms, anxiety and snoring (excluding stratified variable), calculated per standard deviation increase of global PSQI score. Age is split at the median of the sample.

Abbreviations: CI=Confidence Interval; HR=Hazard Ratio; CES-D=Center for Epidemiological Studies – Depression Scale.