Subjective cognitive decline and self-reported sleep problems: The SCIENCe project

Lieza G. Exalto1,2 | Heleen M.A. Hendriksen2 | Frederik Barkhof3,4 | Karlijn A. van den Bosch2 | Jarith L. Ebenau2 | Mardou van Leeuwenstijn-Koopman2 | Niels D. Prins2,5 | Charlotte E. Teunissen6 | Leonie N.C. Visser2,7 | Philip Scheltens2 | Wiesje M. van der Flier2,8

1 Department of Neurology, UMCU Brain Centre, University Medical Center Utrecht, Utrecht, the Netherlands
2 Alzheimer’s Center Amsterdam, Department of Neurology, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, the Netherlands
3 Department of Radiology and Nuclear Medicine, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, the Netherlands
4 UCL Institutes of Neurology and Healthcare Engineering, University College London, London, UK
5 Brain Research Center, Amsterdam, the Netherlands
6 Neurochemistry Laboratory, Department of Clinical Chemistry, Amsterdam Neuroscience, Amsterdam University Medical Centers, Vrije Universiteit, Amsterdam, the Netherlands
7 Division of Clinical Geriatrics, Center for Alzheimer’s Research, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden
8 Department of Epidemiology and Biostatistics, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, the Netherlands

Abstract

We aim to investigate the frequency and type of sleep problems in memory clinic patients with subjective cognitive decline (SCD) and their association with cognition, mental health, brain magnetic resonance imaging (MRI), and cerebrospinal fluid (CSF) biomarkers. Three hundred eight subjects (65 ± 8 years, 44% female) were selected from the Subjective Cognitive Impairment Cohort (SCIENCe) project. All subjects answered two sleep questionnaires, Berlin Questionnaire (sleep apnea) and Pittsburgh Sleep Quality Index (sleep quality) and underwent a standardized memory clinic work-up. One hundred ninety-eight (64%) subjects reported sleep problems, based on 107 (35%) positive screenings on sleep apnea and 162 (53%) on poor sleep quality. Subjects with sleep problems reported more severe depressive symptoms, more anxiety, and more severe SCD. Cognitive tests, MRI, and CSF biomarkers did not differ between groups. Our results suggest that improvement of sleep quality and behaviors are potential leads for treatment in many subjects with SCD to relieve the experienced cognitive complaints.

KEYWORDS
Alzheimer's disease, Berlin questionnaire, Pittsburgh Sleep Quality Index, sleep, subjective cognitive decline
1 | INTRODUCTION

Sleep problems are frequent in adults, especially in the elderly. In the Netherlands, >20% of people aged ≥50 years report to have had sleep problems in the previous 2 weeks.¹ A growing body of evidence suggests that sleep problems are associated with cognitive impairment and progression to Alzheimer’s disease (AD) dementia.² ³ Sleep disturbances are common in patients with AD dementia; among two-thirds of AD dementia patients report sleep problems, and it is associated with poorer daily functioning.⁴ Sleep disturbances have even been suggested as an early symptom of AD.⁴ A meta-analysis estimated that sleep problems (including poor sleep quantity, poor sleep quality, circadian rhythm abnormality, insomnia, and sleep apnea) are associated with a 1.65-fold higher risk of cognitive decline and dementia, compared to individuals without sleep problems.⁵ The different sleep complaints that comprised sleep problems had pooled relative risk estimates ranging between 1.38 and 2.36. For instance, poor sleep quality has been associated with a 1.62 higher risk and obstructive Sleep Apnea Syndrome with a 2.37 times higher risk of cognitive decline and dementia.⁵ Preventive measures to improve sleep have therefore been suggested as putative targets for the prevention of dementia.

Persons that seek help because of self-experienced cognitive decline, in the absence of objective cognitive deficits, are labeled as having subjective cognitive decline (SCD).⁶ Causes of SCD include mood disorders, personality traits, or systemic illnesses.⁷ In addition, SCD may herald the onset of neurodegenerative diseases such as AD.⁶ ⁸ Sleep problems have also been associated with SCD. In a population-based cohort, higher scores on a sleep complaints questionnaire were related to severity of cognitive complaints.⁹ Recently, Ettore et al.¹⁰ showed that in 68 participants of the INSIGHT-pre-AD cohort, subjects with SCD and positive AD biomarkers showed more sleep disturbances such as a longer sleep latency, more frequent awakenings, and worse sleep efficiency compared to subjects with SCD who had negative AD biomarkers. However, in a memory clinic study, persons with SCD who reported sleep problems (not further specified) were less likely to experience cognitive decline during follow-up compared to those without sleep problems.¹¹ Unfortunately, the type of sleep problems (e.g. poor sleep quality, sleep apnea etc.) was not specified, while this could provide clinical leads in persons with SCD presenting at a memory clinic.

We aimed to assess the frequency and type of sleep problems in a large sample of memory clinic patients with SCD and investigated if the presence of self-reported sleep problems was associated with cognitive performance, self-reported cognitive decline, depressive symptoms, anxiety, and/or biomarkers for AD.

2 | METHODS

2.1 | Subjects

We included 308 subjects from the ongoing Subjective Cognitive Impairment Cohort (SCIENCe) at Alzheimer Center Amsterdam.¹² In short, subjects received a standardized diagnostic assessment including an interview on cognitive complaints and medical history, medication use (verified through current pharmacy listings), and educational level.¹³ Physical examination included blood pressure measurement, height (centimeters), and weight (kilograms). Body mass index (BMI) was calculated as kg/m². They all underwent a neuropsychological evaluation, and brain magnetic resonance imaging (MRI). The label SCD was given by consensus in a multidisciplinary meeting when clinical and cognitive testing were normal and criteria for mild cognitive impairment (MCI), dementia, or any psychiatric or neurological disorder were not met. After inclusion in the SCIENCe project, subjects are invited for annual follow-up visits consisting of clinical evaluation, extensive neuropsychological assessment, and questionnaires. Sleep questionnaires were introduced ≥3 years after the start of the SCIENCe project. For the current study, we included subjects if they had completed both sleep questionnaires at baseline. The research is in accordance with ethical consent by VU University and the Declaration of Helsinki. Written informed consent was available for all patients.

2.2 | Identification of sleep problems

We used two questionnaires to assess different aspects of sleep. A Dutch translation of the Berlin questionnaire was used to identify patients likely to have sleep apnea.¹⁴ This questionnaire contains three categories related to the risk of having sleep apnea: snoring (range 0–6, positive ≥2), daytime sleepiness (range 0–3, positive ≥2), and the history of high blood pressure or BMI > 30 (positive when at least one of

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the existing literature on sleep problems in patients with subjective cognitive decline (SCD). A few previous studies have associated sleep problems with SCD. Additionally, in the current SCD guidelines, sleep disorders are mentioned as a potentially reversible cause of SCD. However, the type of sleep problems in memory clinic patients with SCD and their association with cognition, mental health, brain magnetic resonance imaging (MRI), and cerebrospinal fluid (CSF) biomarkers has not been described.

2. Interpretation: Our findings show robust relationships among sleep and anxiety, depressive symptoms, and self-reported cognitive decline, among memory clinic patients with SCD. Sleep problems were not associated with MRI markers and CSF AD biomarkers in these patients.

3. Future directions: Overall, our findings imply that improvement of sleep quality and hygiene are potential leads for treatment in SCD.
the two is present). Subjects are at high risk of sleep apnea if ≥2 categories are positive.  

A Dutch translation of the Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality in the past month. The questionnaire consists of 19 questions that are combined to form seven component scores, each of which has a range of 0 to 3 points. The seven component scores are: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The seven component scores together form one global score, with a range of 0 to 21 points, “0” indicating no difficulty and “21” indicating severe difficulties in all areas. A global score ≥5 indicates a high risk of reduced sleep quality. The proportion of missing tests ranged from 2.3% for TMT were log transformed, because the data were right-skewed, and subsequently inverted, such that a lower score implies worse performance. The false discovery rate (FDR) procedure was applied to correct for multiple testing, meaning p < 0.05FDR was considered statistically significant. For exploratory comparative analyses, we stratified our sample into four sleep groups: 1) positive on both sleep questionnaires (BQ−PSQI+), 2) positive on sleep apnea only (BQ−PSQI−), 3) positive on reduced sleep quality only (BQ−PSQI+), and 4) negative on both sleep questionnaires (BQ−PSQI−) (Supplementary material, table 4–6). Comparison between groups were calculated with \( \chi^2 \), Kruskal-Wallis or analysis of variance. All analyses were done using SPSS version 26.

2.3 | Self-reported cognitive decline and mental health assessment

We used the self-report section of the Dutch translation of the Cognitive Change Index (CCI self; range 20–100) to assess subjective cognitive functioning compared to 5 years ago. We used the Hospital Anxiety and Depression Scale-Anxiety subscale (HADS-A; range 0–21) and Center for Epidemiological Studies Depression Scale (CES-D, range 0–60) to evaluate (subclinical) anxiety and depressive symptoms. Higher scores reflect more severe complaints/symptoms.

2.4 | Neuropsychological assessment

All subjects received a standardized neuropsychological assessment. We used the Mini-Mental State Examination (MMSE) for global cognition. To assess memory, we used the total immediate and delayed recall of the Dutch version of the Rey Auditory Verbal Learning Test (RAVLT). For language, we used category fluency (animals). To assess attention, we used the Trail-Making Test A (TMT-A). To assess executive functioning, we used the TMT-B. Raw test scores for TMT were log transformed, because the data were right-skewed, and subsequently inverted, such that a lower score implies worse performance. The proportion of missing tests ranged from 2.3% for the RAVLT (immediate) and category fluency (animals) to 0.3% for the MMSE.

2.5 | MRI

Two hundred eighty-three (92%) subjects underwent an MRI scan of the brain. The protocol included 3D T1-weighted images, 3D T2-weighted images, and 3D T2-weighted fluid attenuated inversion-recovery (FLAIR) images. Visual rating of medial temporal lobe atrophy (MTA) was performed on coronal T1-weighted images averaging 0.25 cm between the two is present). Subjects are at high risk of sleep apnea if ≥2 categories are positive. A Dutch translation of the Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality in the past month. The questionnaire consists of 19 questions that are combined to form seven component scores, each of which has a range of 0 to 3 points. The seven component scores are: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The seven component scores together form one global score, with a range of 0 to 21 points, “0” indicating no difficulty and “21” indicating severe difficulties in all areas. A global score ≥5 indicates a high risk of reduced sleep quality. We used the self-report section of the Dutch translation of the Cognitive Change Index (CCI self; range 20–100) to assess subjective cognitive functioning compared to 5 years ago. We used the Hospital Anxiety and Depression Scale-Anxiety subscale (HADS-A; range 0–21) and Center for Epidemiological Studies Depression Scale (CES-D, range 0–60) to evaluate (subclinical) anxiety and depressive symptoms. Higher scores reflect more severe complaints/symptoms.

2.6 | Cerebrospinal fluid

Cerebrospinal fluid (CSF) was obtained from 206 (67%) subjects by lumbar puncture between the L3/L4, L4/L5, or L5/S1 intervertebral space by a 25-gauge needle and syringe and collected in polypropylene tubes. The three biomarkers, 42 amino acid form of amyloid beta (Aβ)1–42, total tau (t-tau), and tau phosphorylated threonine 181 (p-tau) were measured using sandwich enzyme-linked immunosorbent assays (Innotest β-amyloid1–42,n = 579; Innotest hTAU-Ag, and Innotest PhosphoTAU-181p). CSF Aβ levels were adjusted for the drift in CSF biomarker analyses that occurred over the years. For 43 subjects, we used Elecsys for analyses of Aβ. These values were transformed to the Innotest-equivalent values by the following formula: Elecsys Aβ (pg/mL) = −365 + 1.87 × Innotest Aβ (pg/mL).

2.7 | Statistics

We compared demographic and clinical variables according to the presence of any sleep problem. For continuous variables, we used independent samples t-tests or Mann-Whitney U tests. Categorical variables were compared using \( \chi^2 \) test. To assess potential influence of the delay between the sleep questionnaire and CSF and MRI markers, a sensitivity analysis was performed in the subset of subjects with ≤1 year interval between the sleep questionnaire and biomarkers. The false discovery rate (FDR) procedure was applied to correct for multiple testing, meaning \( p < 0.05FDR \) was considered statistically significant. For exploratory comparative analyses, we stratified our sample into four sleep groups: 1) positive on both sleep questionnaires (BQ−PSQI+), 2) positive on sleep apnea only (BQ−PSQI−), 3) positive on reduced sleep quality only (BQ−PSQI+), and 4) negative on both sleep questionnaires (BQ−PSQI−) (Supplementary material, table 4–6). Comparison between groups were calculated with \( \chi^2 \), Kruskal-Wallis or analysis of variance. All analyses were done using SPSS version 26.

3 | RESULTS

3.1 | Demographics and clinical features

Baseline characteristics are shown in Table 1. Subjects were (mean ± standard deviation) 65 ± 9 years old and 136 (44%) were female. The MMSE was on average 29 ± 1, and 101 (35%) subjects were apolipoprotein (APOE) ε4 carriers. One hundred ninety-eight (64%) participants...
### Table 1  
Sociodemographic and sleep questionnaire information

| Demographic/clinical data          | Total n = 308 | Any sleep problem n = 198 | No sleep problem n = 110 | P value |
|-----------------------------------|--------------|---------------------------|--------------------------|--------|
| Female, n (%)                     | 136 (44%)    | 93 (47%)                  | 43 (39%)                 | .190   |
| Age                               | 64.5 ± 8.3   | 63.8 ± 8.1                | 65.7 ± 8.5               | .064   |
| Education, median (IQR)           | 6 (5–7)      | 6 (5–7)                   | 6 (5–7)                  | .866   |
| BMI (n = 304)                     | 25.8 ± 3.9   | 25.9 ± 4.0                | 25.7 ± 3.8               | .830   |
| Waist circumference (cm, n = 301) | 94.7 ± 11.6  | 94.4 ± 11.2               | 95.1 ± 12.3              | .623   |
| Orthostatic hypotension (n = 303), n (%) | 45 (15%) | 33 (17%)                  | 12 (11%)                 | .181   |
| Systolic blood pressure (n = 303) | 146 ± 19.3   | 145.8 ± 19.2              | 144.9 ± 19.5             | .693   |
| Diastolic blood pressure (n = 303)| 85.8 ± 9.9   | 86.3 ± 9.6                | 84.8 ± 10.3              | .218   |
| APOE ε4 carriers (n = 285)        | 101 (35%)    | 72 (40%)                  | 29 (28%)                 | .055   |

#### Sleep questionnaires

| BQ high-risk (≥2 categories abnormal) | 107 (35%) | 107 (54%) | 0 | <.001 |
|---------------------------------------|-----------|-----------|---|-------|
| Category 1: snoring                   | 162 (53%) | 112 (57%) | 50 (45%) | .074  |
| Category 2: daytime sleepiness        | 62 (20%)  | 62 (31%)  | 0 | <.001 |
| Category 3: High blood pressure/BMI > 30 | 135 (44%) | 122 (62%) | 13 (12%) | <.001 |
| PSQI poor sleeper (≥5, 0–21)         | 164 (53%) | 164 (83%) | 0 | <.001 |

#### Notes:
Data are presented as mean ± SD or median (IQR) and comparison between any and no sleep problem were calculated with χ², Mann-Whitney U or independent samples t-test. Education is rated using the Dutch Verhage system, ranging from 1–7.13

*Defined as one or two ε4 alleles.

#### Abbreviations:
- APOE: apolipoprotein E
- BMI: body mass index
- BQ: Berlin questionnaire
- IQR: interquartile range
- PSQI: Pittsburgh Sleep Quality Index
- SD: standard deviation

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reported sleep problems, by scoring positive on the Berlin questionnaire and/or the PSQI (Figure 1).

### 3.2 Sleep problems versus no sleep problems

#### 3.2.1 Demographics and clinical features

Subjects with sleep problems did not differ significantly in age (63.8 ± 8.1) nor sex (39% female) from subjects without sleep problems (65.7 ± 8.5, P = .064; 47% female, P = .19), see Table 1. The percentage of APOE ε4 carriers (40% vs. 28%, P = .055) tended to be slightly higher in the group with sleep problems.

#### 3.2.2 Sleep details

The Berlin questionnaire identified 107 (35%) subjects at high risk of having sleep apnea. Among Berlin questionnaire categories, 57% of the any sleep problem group met the criteria for snoring versus 45% of the no sleep problem group. Roughly one third (31%) of the sleep problem group reported daytime sleepiness versus 0% of the no sleep problem group. The third Berlin questionnaire category, self-reported high blood pressure or BMI > 30, was present in 62% of the any sleep problem group versus 12% of the no sleep problem group (P < .001).

According to the PSQI, 164 (53%) subjects met the criteria of having reduced sleep quality (global score ≥5). There were differences in total sleep time and sleep efficiency between the any sleep problem (6.7 hours ± 1.2, 83 ± 14%) and no sleep problem group (7.7 hours ± 0.8, 93 ± 7%; all P < .001). There was no difference in time spent in bed between these groups.

#### 3.2.3 Cognitive performance and mental health

The results of the self-reported cognitive decline, mental health assessment, and neuropsychological tests are reported in Table 2. Subjects with sleep problems reported more depressive symptoms (CES-D median [interquartile range (IQR)]: 10 [5–16] vs. 4 [2–7]) and anxiety [HADS-A] 5 [2–10] vs. 2 [0.25–4]) than those without sleep problems. They also experienced more SCD on the CCI (43 [31–56] vs. 35 [25–47]). Objective cognitive performance did not differ according to the presence of sleep problems. Neither performance on the MMSE, nor any of the cognitive domains including memory, language,
### TABLE 2  Cognitive test performance and anxiety, depression, and complaining measures in subjects with any versus no sleep problem

| Cognitive tests                  | Total n = 308 | Any sleep problem n = 198 | No sleep problem n = 110 | P value |
|----------------------------------|---------------|---------------------------|--------------------------|---------|
| **Global cognition**             |               |                           |                          |         |
| MMSE (n = 307)                   | 28.9 ± 1.1    | 28.9 ± 1.1                | 28.9 ± 1.2               | .465    |
| **Attention**                    |               |                           |                          |         |
| TMT A (seconds) (n = 303)        | 35.2 ± 13.4   | 35.3 ± 11.7               | 34.8 ± 16.1              | .341    |
| **Memory**                       |               |                           |                          |         |
| RAVLT immediate recall (n = 301) | 47.7 ± 9.9    | 48.2 ± 10.1               | 46.7 ± 9.4               | .218    |
| RAVLT delayed recall (n = 302)   | 9.8 ± 2.9     | 9.9 ± 3.1                 | 9.6 ± 2.7                | .344    |
| **Language**                     |               |                           |                          |         |
| Category fluency animals (n = 301)| 24.4 ± 5.7   | 24.6 ± 6.1                | 24.0 ± 4.9               | .405    |
| **Executive functioning**        |               |                           |                          |         |
| TMT B (seconds) (n = 303)        | 85.9 ± 46.6   | 85.4 ± 39.9               | 86.9 ± 58.0              | .628    |

| Questionnaires                   |               |                           |                          |         |
|----------------------------------|---------------|---------------------------|--------------------------|---------|
| HADS-A (n = 304), median (IQR)   | 3 (1–6)       | 4 (2–7)                   | 2 (0.25–4)               | <.001   |
| CES-D (n = 304), median (IQR)    | 8 (3–14)      | 10 (5–16)                 | 5 (2–10)                 | <.001   |
| CCI (n = 273), median (IQR)      | 39 (28–52.5)  | 43 (31–56)                | 35 (25–47)               | .001    |

Notes: Data are presented as mean ± SD or median (IQR) and comparison between any and no sleep problem were calculated with Mann-Whitney U or independent samples t-test. Higher scores on TMT A and B indicate worse performance.

Abbreviations: CCI, Cognitive Change Index; CES-D, Center for Epidemiologic Studies Depression scale; HADS, Hospital Anxiety and Depression Scale; IQR, interquartile range; MMSE, Mini-Mental State Examination; RAVLT, Rey Auditory Verbal Learning Test; SD, standard deviation; TMT A, Trail Making Test part A; TMT B, Trail Making Test part B.

### FIGURE 1  Reported sleep problems. Risk of sleep apnea (Berlin questionnaire ≥2 categories positive), poor sleep quality (Pittsburgh Sleep Quality Index score ≥5). Subjects were classified as having a sleep problem when the score on at least one sleep questionnaire was above the cut-off.

Attention, and executive functioning differed between groups with and without sleep problems. Explorative analyses showed that subjects scoring positive on both sleep questionnaires reported more depressive symptoms, anxiety and experienced more subjective cognitive decline on the CCI than those reporting only one sleep problem or no sleep problem. In addition, subjects positive on sleep apnea only, performed lower on MMSE and verbal fluency compared to the other sleep problem groups (Supplements table 5).

### 3.2.4 MRI measures and AD CSF biomarkers

MRI and CSF biomarkers are shown in Table 3. There were no significant differences in the MRI markers of atrophy and WMH between subjects with and without sleep problems. The CSF biomarkers Aβ [42], t-tau, or p-tau did not differ between sleep groups. When we stratified sleep problems into four sleep groups, we found no differences in MRI markers and CSF biomarkers (Supplements table 6).

Finally, we performed sensitivity analyses in the subset of subjects with ≤1 year interval between the sleep questionnaire and MRI and CSF biomarkers (n = 40). Although these analyses were underpowered due to the small sample size, directions of the effects were similar.

### 4 DISCUSSION

Our results showed that in a cohort of subjects with SCD about two-thirds reported a sleep problem. The presence of sleep problems was associated with aspects of mental health, including more severe depressive symptoms, anxiety, and self-reported cognitive decline.
The presence of sleep problems was associated with neither objective cognitive performance, nor with MRI or CSF biomarkers of AD pathology.

Sleep problems were common (64%) in our cohort, about 53% reported poor sleep quality and 35% categorized as high risk of sleep apnea. These percentages are slightly higher compared to the general population, while the reported time in bed, total sleep time, and sleep efficiency in our total cohort are comparable to the general population. Previous studies in the general population showed poor sleep quality and 35% categorized as high risk of sleep apnea. These percentages are slightly higher compared to the general population, while the reported time in bed, total sleep time, and sleep efficiency in our total cohort are comparable to the general population.

About 30% of the elderly is categorized as at high risk of sleep apnea (based on Berlin questionnaire). In a representative sample of the Dutch population, about 30% of persons in the age category 55 to 70 years reports general sleep disturbances. By contrast, our frequency of sleep problems was in line with an earlier memory clinic population study—among patients with MCI or dementia, 60% reported sleep problems based on PSQI and/or Berlin questionnaire. Moreover, in a Swedish memory clinic study, among subjects with SCD, 58% reported the presence of a sleep problem (not further specified). Our study complements these findings, by showing that in memory clinic patients with SCD 64% reported sleep problems based on PSQI and/or Berlin questionnaire.

Sleep problems have consistently been shown to be associated with depressive symptoms, anxiety, and self-reported cognitive decline. Moreover, poor sleep quality (measured by PSQI) and sleep apnea (measured by Berlin questionnaire) have both been associated with depressive symptoms and anxiety in the elderly. In our cross-sectional study, causality is difficult to infer. Former studies have found a bidirectional relationship between sleep disturbances, anxiety, and depression, suggesting that each contributes to the development and are a consequence of one another. A systematic review was not able to draw definitive conclusions regarding bidirectionality due to the small number and heterogeneity of cohort samples used across studies. Nonetheless, our results suggest that sleep problems might be an underrecognized cause of SCD, which—importantly—could be amenable to treatment.

In the current cross-sectional study, we did not find a relationship between self-reported sleep quality and cognitive test performance nor AD biomarkers in subjects with SCD. Previous longitudinal population based studies show that several measures of sleep problems are associated with cognitive decline in the subsequent years, although these associations disappeared after adjustment for depressive symptoms. In another large Dutch prospective population-based cohort, self-reported sleep quality was not associated with dementia risk during a mean follow-up time of 8.5 years. These findings suggest that other mechanisms than AD pathology, such as depressive mood, influence the subjective experience of cognitive decline in patients with sleep problems. However, these studies did not report on MRI and CSF biomarkers. A review by Wennberg et al. describes that sleep disturbances are associated with Aβ dynamics and deposition. Community-based cohort studies showed that sleep disturbances are associated with greater cerebral Aβ deposition, as measured by [11C]-Pittsburgh compound B-positron emission tomography (PiB-PET) and CSF Aβ levels. These former studies are all population based, and findings may be different in individuals that visit a memory clinic with SCD.

In the current SCD guidelines, sleep disorders are mentioned as potentially reversible cause of SCD. Recommendations on how to examine or quantify sleep problems in a memory clinic setting are lacking. We have used standardized questionnaires, but in clinical
practice completing two questionnaires might not be realistic. Regarding the categories of the Berlin questionnaire, all components were scored higher in the sleep problem group, except for snoring. This suggests that inquiring after snoring alone would not assist in identifying the presence of sleep problems. This is in line with the body of literature showing only about 40% of subjects that report snoring have objective measures of sleep apnea.\(^\text{44}\) Completing the other two categories, daytime sleepiness and the presence of high blood pressure or BMI > 30, will likely add to the discriminative ability to identify high risk of sleep apnea. Regarding the PSQI, we found that subjects with sleep problems have a comparable time in bed to subjects with no sleep problems, however on average they sleep 1 hour shorter, resulting in a lower sleep efficiency of 83 ± 14% (vs. 93 ± 7%). To sum up, based on our findings, total sleep time, daytime sleepiness, and snoring in the presence of high blood pressure or BMI > 30 would be clinically relevant sleep markers to examine during the consultation.

Our results have important clinical implications, as they provide evidence for the notion that sleep deserves attention as a potential and treatable cause of self-experienced cognitive complaints in a memory clinic. A considerable proportion of patients presenting at a memory clinic has SCD.\(^\text{20,45}\) We showed that two-thirds of them have sleep problems. In our cross-sectional study, we cannot demonstrate causality between the self-reported sleep problems and the experienced cognitive complaints. However it is worthwhile to prospectively investigate whether people benefit from a sleep intervention. Several studies have presented successful strategies to improve sleep quality and behaviors, also in the elderly.\(^\text{46–52}\) For example, exercise programs in generally healthy elderly can improve sleep quality.\(^\text{47}\) Cognitive behavioral therapy has been shown to improve both sleep quality and self-reported cognitive impairment.\(^\text{50,51}\) Furthermore, sleep apnea treatment by continuous positive airway pressure (CPAP) has been shown to improve cognition in patients with MCI.\(^\text{52}\) SCD patients might thus benefit from treatment focusing on improving sleep as it could relieve the experienced cognitive complaints.

A limitation of the current study is the use of subjective measures of sleep. Previous studies have shown that subjective measures of sleep do not necessarily match with objective measures of sleep, especially in subjects with cognitive impairment.\(^\text{38}\) Furthermore, previous literature suggests that females report more subjective sleep complaints compared to males,\(^\text{27,32,49}\) whereas an objective (actigraphy) measure indicates the opposite.\(^\text{27}\) These previous results are population based and might not be applicable to a memory clinic context with patients with SCD. In our cohort there was no difference in the percentage of females and males reporting sleep problems. Another limitation is the later introduction of the sleep questionnaires in the SCIENCE protocol, causing different time intervals between the measurement of the biomarkers and sleep function. We expect this has not influenced the results, because sensitivity analyses in the subset of subjects with ≤1 year interval showed comparable results, although with limited power. A strength of the current study is the unique and detailed memory clinic work-up of subjects with SCD, including a brain MRI, neuropsychological testing, and CSF analyses. Furthermore, two complementary sleep questionnaires, the PSQI and the Berlin questionnaire, were used to measure sleep quality and to identify patients who are likely to have sleep apnea.

5 | CONCLUSION

In our memory clinic cohort with subjects with SCD, we did not find a relationship between sleep problems and MRI or CSF markers of AD pathology, nor with objective cognitive performance. We did, however, find robust relationships between sleep and anxiety, depressive symptoms, and self-reported cognitive decline. These findings highlight the relevance of sleep problems as a putative contributing factor to the experience of cognitive complaints. This implies that improvement of sleep quality and hygiene are potential leads for treatment in SCD.

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CONFLICT OF INTEREST

LE has been invited speaker at Center for Innovation Medical Technology of the NAS of Ukraine. NDP is consultant to Boehringer Ingelheim, Arborio, and Amylyx. He is co-PI of a study with Fuji Film Toyama Chemical. NDP received a speaker fee from Biogen. NDP served on the DSMB of Abbvie’s M15-566 trial. NDP is CEO and co-owner of Brain Research Center, the Netherlands. CET was involved in Alz Res therapy Medidact Neurology and received travel support from Roche. LV received a small fee for the development of an online course on shared decision-making, by EACH, the international organization for communication in health care (paid to her). PS has received consultancy fees (paid to the institution) from AC Immune, Alkermes, Alnylam, Biogen, Care4Dx, Brainstorm Cell, Cortexyme, Denali, EIP ImmunoBrain Checkpoint, GemVax, Genentech, Green Valley, Novartis, Novo Nordisk, PeopleBio, Renew LLC, Roche. He is PI of studies with AC Immune, CogRx, FUJI-film/Tayoma, IONIS, UCB, and Vivoryon.

PhS is a part-time employee of Life Sciences Partners Amsterdam. PhS serves on the board of Brain Research Center and New Amsterdam Pharma. PhS served on the DSMB of Genentech SAF. WF is consultant to Oxford Health Policy Forum CIC, Roche, and Biogen MA Inc. and has been an invited speaker at Boehringer Ingelheim, Biogen MA Inc, Danone, Eisai, WebMD Neurology (Medscape). All funding is paid to her institution. WF holds the Pasman chair. WF has performed contract research for Biogen MA Inc and Boehringer Ingelheim. All funding is paid to her institution. The other authors (HMAH, KAB, JLE, MLK) have nothing to disclose.

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**SUPPORTING INFORMATION**

Additional supporting information may be found in the online version of the article at the publisher’s website.

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