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Cognitive decline in short and long sleepers: A prospective population-based study (NEDICES)

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Abstract

Background—It is not clear whether cognitive decline progresses more quickly in long sleepers than in short sleepers or than in participants with usual sleep duration. We assessed cognitive decline as a function of self-reported sleep duration in a prospective population-based cohort (NEDICES).

Methods—Participants were evaluated at baseline and 3 years later. Baseline demographic variables were recorded and participants indicated their daily sleep usual duration as the sum of nighttime sleep and daytime napping. The average daily total usual sleep duration was grouped

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Dr. Benito-León reports no disclosures.
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into three categories: ≤5 hours (short sleepers), 6 to 8 hours (reference category), and ≥9 hours (long sleepers). At baseline and at follow-up, a 37-item version of the Mini-Mental State Examination (37-MMSE) was administered.

Results—The final sample, 2,715 participants (72.9±6.1 years), comprised 298 (11%) short sleepers, 1,086 (40%) long sleepers, and 1,331 (49%) in the reference group (6 to 8 hours). During the three year follow-up period, the 37-MMSE declined by 0.5±4.0 points in short sleepers, 0.6±4.3 points in long sleepers, and 0.2±3.8 points in the reference group (p=0.08). The difference between short sleepers and the reference group was not significant (p=0.142); however, the difference between long sleepers and the reference group was significant (p=0.040). In analyses adjusted for baseline age and other potential confounders, this difference remained robust.

Conclusions—In this study, cognitive test scores among long sleepers declined more rapidly than observed in a reference group. Additional studies are needed to confirm these results.

Keywords

Cognitive function; elderly; epidemiology; sleep duration; population-based study

INTRODUCTION

Dementia and cognitive disorders are among the major public health challenges of aging societies today. It is not surprising therefore, that scientific and clinical research in the area of cognitive disorders has shifted during the last decade to focus on the possible predictors of these disorders in an effort to prevent the consequences of dementia. Thus, there is clearly a need to understand the possible predictors of cognitive disorders and to develop effective prevention strategies. Understanding the link between these disorders and sleep may represent one important part of that effort. Since sleep duration is potentially modifiable, the relation between sleep duration and cognitive decline might well have practical implications for the primary prevention of these disorders.

Sleep problems are common conditions in modern society, especially in elderly people.(Myers & Badia, 1995) Chronic insomnia or prolonged daytime sleepiness has been associated with poorer cognitive function in the elderly.(Bastien et al., 2003; Cricco, Simonsick, & Foley, 2001; Ohayon & Vecchierini, 2002) In addition, subjects with daytime sleepiness or prolonged sleep duration are at increased risk for incident dementia.(Benito-León, Bermejo-Pareja, Vega, & Louis, 2009; Foley et al., 2001) However, the few prospective population-based studies that have assessed whether sleep duration predicted cognitive decline have yielded conflicting results.(Ferrie et al., 2011; Keage et al., 2012; Potvin et al., 2012; Tworoger, Lee, Schernhammer, & Grodstein, 2006) Unmeasured confounders, including medications that potentially affect cognitive function (e.g., anxiolytics, stimulants, antipsychotics, antidepressants, antihistamines, or antiepileptics drugs) may have influenced the results of community or population-based surveys outcomes. It is not clear whether cognitive decline progresses in long sleepers more rapidly than in short sleepers or than in participants with usual sleep duration. We hypothesized that the cognitive deficits in long sleepers would worsen more than in short sleepers and in elderly participants reporting usual sleep duration (6-8 hours) (i.e., controls). To address this question, we utilized data from the Neurological Disorders in Central Spain (NEDICES) study, in which participants were prospectively evaluated at two times points separated by three years. We aimed to adjust for confounders such as medications with central nervous system effects.

MATERIAL AND METHODS

Study population

Data for these analyses were derived from the NEDICES study, a longitudinal, population-based survey of the prevalence, incidence, and determinants of major age-associated conditions of the elderly, including Parkinson's disease (PD), essential tremor, stroke, and dementia.(Benito-León, Bermejo-Pareja, Louis, & Neurological Disorders in Central Spain Study, 2005; Benito-León et al., 2004; Benito-León, Bermejo-Pareja, Morales, Vega, & Molina, 2003a; Benito-León et al., 2003b; Bermejo-Pareja et al., 2008a; Bermejo-Pareja, Benito-León, Vega, Medrano, & Román, 2008b; Bermejo-Pareja et al., 2009; Diaz-Guzman et al., 2008; Martínez-Salio, Benito-León, Diaz-Guzman, & Bermejo-Pareja, 2010; Morales et al., 2004; Vega et al., 2010) Detailed accounts of the study population and sampling methods have been published.(Bermejo-Pareja et al., 2008a; Morales et al., 2004; Vega et al., 2010) The survey area consisted of three communities: Margaritas (approximately 14,800 inhabitants), a working-class neighborhood in Getafe (Greater Madrid); Lista (approximately 150,000 inhabitants), a professional-class neighborhood in Salamanca (Central Madrid), and Arévalo (approximately 9,000 inhabitants), the agricultural zone of Arévalo County (125 km northwest of Madrid). Up-to-date lists of residents were generated from population registers. In each community, survey eligibility was restricted to residents aged 65 years or older who were present there on December 31, 1993, or during 6 or more months of 1993. Eligible persons who had moved away from the survey area were not traced. In Margaritas and Arévalo, every eligible subject was to be screened. However, in Lista, proportionate stratified random sampling was used to select subjects for screening because of the large number of elderly residents. All procedures were approved by the ethical standards committees on human experimentation at the University Hospitals “12 de Octubre” (Madrid) and “La Princesa” (Madrid). Written (signed) informed consent was obtained from all enrollees.

Study evaluation

Briefly, at the time of their baseline assessment (1994–1995), 5,278 elderly subjects were interviewed using a 500-item screening questionnaire that assessed demographic factors and medical conditions. The face-to-face interview included data collection on demographics, current medications (including drugs that affect the central nervous system), and medical conditions. Subjects were asked to bring all medications taken in the past one week to the clinic where the interviewer viewed and recorded the name and the dose of each one. We assessed depressive symptoms by self-report, using a single screening question (‘Do you suffer from depression?’). This same approach has similarly been utilized in previous population studies of depression.(Benito-León, Louis, Bermejo-Pareja, & Neurological Disorders in Central Spain Study, 2009; Benito-León et al., 2010a; Louis, Benito-León, Bermejo-Pareja, & Neurological Disorders in Central Spain Study, 2007b) We also assessed the use of antidepressant medications, a marker that may be less prone to biases than a simple screening question.(Louis, Benito-León, & Bermejo-Pareja, 2007a) Participants indicated their total daily usual sleep duration as the sum of nighttime sleep and daytime napping.

A short form of the questionnaire was mailed to subjects who refused, or were unavailable for face-to-face or telephone screening. This form assessed demographic characteristics, several neurological disorders (essential tremor, stroke, dementia, and parkinsonism), current medications, and the name of their family doctor. During the second (i.e., follow-up) evaluation (1997–1998), the same methods were used.

As described,(Bermejo-Pareja et al., 2008a; Morales et al., 2004; Vega et al., 2010) a 37-item Mini-Mental State Examination (37-MMSE) was administered in both baseline assessment (1994–1995) and follow-up evaluation (1997–1998).(Benito-León, Louis, & Bermejo-Pareja, 2006a; b; Benito-León et al., 2011; Benito-León, Louis, Vega, & Bermejo-Pareja, 2010b; Benito-León, Mitchell, Vega, & Bermejo-Pareja, 2010c; Bermejo-Pareja et al., 2008b; Bermejo-Pareja et al., 2009; Prieto, Contador,Tapias-Merino, Mitchell, & Bermejo-Pareja, 2012) This was a Spanish adaptation of the standard MMSE. (Benito-León et al., 2006a; b; Benito-León et al., 2011; Benito-León et al., 2010b; Benito-León et al., 2010c; Bermejo-Pareja et al., 2008b; Bermejo-Pareja et al., 2009; Prieto et al., 2012) It included all of the standard MMSE items as well as three additional items: (1) an attention task, i.e., “say 1, 3, 5, 7, 9 backwards”, (2) a visual order, i.e., a man raising his arms, and (3) a simple construction task, i.e., copying two overlapping circles. (Benito-León et al., 2006a; b; Benito-León et al., 2011; Benito-León et al., 2010b; Benito-León et al., 2010c; Bermejo-Pareja et al., 2008b; Bermejo-Pareja et al., 2009; Prieto et al., 2012)

Ten percent of our sample was illiterate, although only a small proportion was completely illiterate and many could read or write a simple phrase. If the participant was completely illiterate, then the one 37-MMSE reading item and the one 37-MMSE writing item were assigned the value 0. Diagnosis of dementia (Bermejo-Pareja et al., 2008b; Bermejo-Pareja et al., 2009) fulfilled the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (American Psychiatric Association. & American Psychiatric Association. Task Force on DSM-IV., 1994) and required evidence of cognitive impairment (based on a neuropsychological test battery and a clinical mental status examination) as well as impairment in social or occupational function.

Final selection of participants

Of the 5,278 participants evaluated at baseline, we excluded 1,462 participants who were evaluated at baseline because they declined a follow-up assessment or had incomplete follow-up assessments, had died or were unreachable (Figure 1). We further excluded 1,025 participants with incomplete 37-MMSE examinations, 29 without available data on daily sleep duration, and 47 with prevalent dementia, which left 2,715 remaining participants who were included in our analyses (Figure 1). The final sample of 2,715 was similar to the base sample of 5,278 participants in terms of gender (1,545 [56.9%] vs. 3,040 [57.6%] women, chi-square = 0.35, $p = 0.55$). However, they were more educated (298 [11.0%] vs. 711 [13.6%] were illiterate, chi-square = 11.15, $p = 0.011$) and, on average, 1.4 years younger (72.9 ± 6.1 vs. 74.3 ± 7.0 years, $t = 9.23$, $p < 0.001$).

Statistical analyses

Analyses were performed in SPSS (version 20.0). All tests were two sided, and significance was accepted at the 5% level ($\alpha = 0.05$). Using a one-sample Kolmogorov–Smirnov test, we determined that age and sleep duration were not normally distributed. Therefore, although mean and median values were reported, differences were compared using nonparametric tests (Mann-Whitney and Kruskal–Wallis tests). The X2 test was used to analyze categorical variables. The change in 37-MMSE score = baseline score – follow-up score. The 37-MMSE scores (baseline, follow-up, and change in 37-MMSE) were not normally distributed, even after transformations were attempted. Therefore, scores were compared using the same non-parametric approach (Mann-Whitney and Kruskal–Wallis tests). Linear regression analyses were not possible because the change in 37-MMSE was not normally distributed. Therefore, to initially assess the effects of possible confounders (age, depressive symptoms and medications with central nervous system effects), stratified analyses were performed. The aim of these analyses was to determine whether the magnitude of the case–control difference persisted after stratification. Due to the loss of power in these stratified

analyses, p values were not reported; rather, the aim of these analyses was to determine whether the magnitude of the case-control difference persisted after stratification.

In additional analyses, we divided change in 37-MMSE into two groups. Those who declined 4 or more points were considered as the "decline group" vs. those who declined by 3 or fewer points between the two evaluations ("no decline group"). This was based on previous reports of MMSE change in healthy elderly subjects.(Aevarsson & Skoog, 2000) In a longitudinal population-based Swedish study, a decrease of 4 or more points in MMSE during a 3-years follow-up had a sensitivity of 83% and a specificity of 80% for a diagnosis of dementia.(Aevarsson et al., 2000) Therefore, we decided to use this 4 point change score as a clinically relevant threshold.(Aevarsson et al., 2000) Logistic regression analyses were performed, thereby allowing us to assess, for a second time, potential confounders. In these models, the dependent variable was "Decline"/"No Decline" and the independent variable was sleep duration category. Participants were divided in short sleepers (≤ 5 hours daily) and long sleepers (≥ 9 hours daily), according to the categories used in previous studies.(Potvin et al., 2012; Tworoger et al., 2006) Short and long sleep duration categories were compared with the reference category (6 to 8 hours daily).

RESULTS

The final sample, 2,715 participants (mean ± standard deviation age = 72.9 ± 6.1 years), comprised 298 (11%) short sleepers (≤ 5 hours daily), 1,086 (40%) long sleepers (≥ 9 hours daily), and 1,331 (49%) who reported 6 to 8 hours of daily sleep (reference category) (Figure 1). The mean follow-up was 3.4 ± 0.5 years.

Baseline characteristics of the participants in the three sleep duration categories are shown (Table 1). At baseline, short sleepers were more frequently women, older and less educated. In addition, they were more likely to have diabetes mellitus, chronic obstructive pulmonary disease, and depressive symptoms/or antidepressant use; a higher proportion was taking medications with central nervous system effects (Table 1).

At baseline, the mean 37-MMSE in short sleepers was 28.3 ± 5.4 (median = 28.5) vs. 29.7 ± 5.0 (median = 30) in long sleepers vs. 30.1 ± 4.8 (median = 31) in the reference category (Kruskal-Wallis, $p < 0.001$), with a significant difference in short sleepers and the reference group (Mann-Whitney test, $p < 0.001$); but no difference between the long sleepers and the reference group (Mann-Whitney test, $p = 0.113$). During the three year follow-up period, the 37-MMSE declined by 0.5 ± 4.0 points (median = 0 point) in short sleepers vs. 0.6 ± 4.3 points in long sleepers (median = 0 points) vs. 0.2 ± 3.8 points in the reference group (median = 0 points) (Kruskal-Wallis, $p = 0.08$) (Table 2). The difference between short sleepers and the reference group was not significant (Mann-Whitney test, $p = 0.142$), similarly that between short and long sleepers was not significant (Mann-Whitney test, $p = 0.908$); however, the difference between long sleepers and the reference group was significant (Mann-Whitney test, $p = 0.040$).

In the reference group, we examined whether baseline 37-MMSE scores were associated with potential confounding variables. The 37-MMSE was correlated with age ($rS = -0.277$, $p<0.001$), educational category ($rS = 0.387$, $p<0.001$), geographical area (mean ± SD [median] = 28.8 ± 4.9 [29] in Las Margaritas vs. 32.3 ± 4.0 [33] in Lista and 29.1 ± 4.8 [29] in Arévalo, Kruskal-Wallis test, $p <0.001$), subjective depressive symptoms or antidepressant use (29.1 ± 4.9 [29] in those who responded "yes" vs. 30.4 ± 4.8 [31] in those who responded "no", Mann-Whitney test, $p <0.001$) and gender (mean ± SD [median] = 31.8 ± 4.2 [33] in men vs. 28.8 ± 4.9 [29] in women, Mann-Whitney test, $p <0.001$). However, baseline 37-MMSE was not correlated with medications that could affect

cognition (mean ± SD [median] = 29.8 ± 5.1 [30] in those taking a medication vs. 30.1 ± 4.8 [31] in those who do not take a medication, Mann-Whitney test, p = 0.437).

In stratified analyses, in nearly all strata, except for medications with central nervous system effects and Las Margaritas geographical area for short sleepers, the decline in 37-MMSE score in both short and long sleepers was higher than the decline in score in the reference group (Table 2), indicating that these variables were not likely to be a source of confounding.

In 14 (0.5%) participants, the 37-MMSE changed by greater than 15 points; when these outliers were excluded, the results were similar (data not shown).

We also assessed the cognitive decline per unit time (i.e., the rate of cognitive decline). The rate of cognitive decline was 0.0 ± 1.2 (median = 0.0) points/year for the reference group, 0.2 ± 1.2 (median = 0.0) points/year for short sleepers, and 0.2 ± 1.3 (median = 0.0) points/year for long duration sleepers (Kruskal-Wallis test, p = 0.07). The difference between short sleepers and controls was not significant (Mann-Whitney test, p = 0.106); however, there was a statistically significant difference between long sleepers and the reference group (Mann-Whitney test, p = 0.043) (figure 2). On the other hand, the difference between short and long sleepers was not significant (Mann-Whitney test, p = 0.762).

In a logistic regression model, long sleepers were 1.3 times more likely than the reference group to have a “decline” in 37-MMSE (OR= 1.3, 95% CI= 1.0-1.6, p = 0.020). However, the odds of “decline” in 37-MMSE was similar in short sleepers vs. controls (OR = 1.2, 95% CI= 0.9-1.7, p = 0.178). To further assess the potential confounding effect of age, gender, geographical area, educational level, diabetes mellitus, chronic obstructive pulmonary disease, depressive symptoms or antidepressant use, and medications with central nervous system effects, we adjusted for these in a logistic regression model, and long sleepers were 1.3 times more likely to decline than the reference group (OR = 1.3, 95%, CI= 1.1-1.6 p = 0.012) yet the odds of “decline” in 37-MMSE was similar in short sleepers than controls (OR = 1.1, 95%, CI= 0.8-1.5, p = 0.630). In another analyses, we included rather than excluded all participants with prevalent dementia. In these analyses, long sleepers cases were 1.3 times more likely to decline than the reference group (adjusted OR = 1.3, 95%, CI= 1.0-1.6, p = 0.025). Likewise, the odds of “decline” in 37-MMSE was similar in short sleepers vs. controls (adjusted OR = 1.1, 95%, CI= 0.7-1.5, p = 0.735).

DISCUSSION

In the current prospective study of non-demented community-dwelling elders, we further demonstrated that baseline cognitive test scores were lower in longer sleepers than the reference group; moreover, during the three year follow-up period, these scores declined at a rate in long sleepers than the reference group. Long sleepers on average experienced a 0.6 point reduction in the 37-MMSE over 3 years. Although this reduction was significantly greater than that seen in controls, in absolute terms, it was a modest change.

There has been several studies addressing cognitive function according to sleep duration; however, the majority of them have been performed using a cross-sectional design, (Auyeung et al., 2013; Faubel et al., 2009; Kronholm et al., 2009; Saint Martin, Sforza, Barthelemy, Thomas-Anterion, & Roche, 2012; Xu et al., 2011) making it impossible to determine the causal relationship between sleep duration and the risk of cognitive decline, or have been performed using clinical series, potentially biasing the results due to case ascertainment.(Miyata et al., 2013; Vetter, Juda, & Roenneberg, 2012). We could only identify four previous prospective community or population-based studies that analyzed the risk of cognitive decline according to sleep duration.(Ferrie et al., 2011; Keage et al., 2012;

Potvin et al., 2012; Tworoger et al., 2006). In one study in older women using a 2-year follow-up, no association was found between sleep variables (subjective sleep duration, subjective sleep difficulties, and snoring) and the decline in cognitive function measured by the Telephone Interview for Cognitive Status.(Tworoger et al., 2006) In the Whitehall II study, 1459 women and 3972 men aged 45-69 at baseline were assessed at two times (baseline and between 2002-2004, average follow-up 5.4 years) using a complete neuropsychological battery.(Ferrie et al., 2011) In analyses adjusted for age, gender, and education, and corrected for multiple testing, adverse changes in sleep between baseline and follow-up (decrease from 6, 7, or 8 hours, increase from 7 or 8 hours) were associated with lower scores on most cognitive function tests.(Ferrie et al., 2011) In a sample of 2,012 elderly cognitively unimpaired participants from the MRC Cognitive Function and Ageing Study, it was found that daytime napping at baseline was associated with a lower risk of cognitive decline at two and 10 years, and that obtaining ≤6.5 hours of night-time sleep and excessive daytime sleepiness at baseline were associated with an increased risk at 10 years. (Keage et al., 2012) Finally, in a sample of 1,664 cognitively intact individuals age 65 to 96 years, cognitive functioning was assessed at baseline and 12 months later using the MMSE. (Potvin et al., 2012) Incident general cognitive impairment was defined according to a follow-up MMSE score below the 15(th) percentile according to normative data and of at least 2 points below baseline.(Potvin et al., 2012) In women, long sleep duration (≥ 9 hours) was associated with amnestic incident cognitive impairment. In men, short sleep duration (≤ 5 hours) was associated with amnestic cognitive impairment.(Potvin et al., 2012)

Although the current findings suggest that longer sleeping may predict a significant cognitive decline, the mechanisms underlying this association remain unknown. One possibility is that an unrecognized confounder (e.g., sleep apnea) could lead to both cognitive decline and an increased need for sleep.[29] Second, long sleep duration may be an early symptom of cognitive decline. Third, excessive sleep per se could directly lead to an increased risk of cognitive decline. Currently, however, we know of no plausible physiologic explanation for such a cause-and-effect relationship.

This study had several limitations. First, the 37-MMSE is a relatively abbreviated screening tool for dementia. The use of more detailed neuropsychological test batteries would enable future investigators to study these changes in greater detail. Nevertheless, even with this relatively simple, abbreviated tool, we were able to establish clear case-control differences. Second, the 37-MMSE was administered at two time points; use of additional time points would allow one to assess the extent to which the case-control difference continued beyond the three-year time window. Third, there were some baseline differences with potential confounding effects between the cases and the controls. However, we controlled this source of confounding with stratified analysis and logistic regression. Finally, although we performed analyses in which we adjusted for depressive symptoms, our evaluation of depression was limited and we may have under-ascertained depression, resulting in residual confounding. Nevertheless, a validation study showed a high level of agreement between the data generated from the screening question we used and a more detailed in-person psychiatric assessment, suggesting that such residual confounding is likely to have been low. (Louis et al., 2007a)

This study also had several strengths. First, short and long sleepers were compared to a large sample size of several thousand participants who reported sleeping between 6 and 8 hours. Second, the assessments were conducted prospectively in a standardized manner. Finally, we were able to adjust for the potential confounding effects of a number of important factors.

Using a prospective, population-based design, we demonstrated that cognitive test scores in long sleepers declined more rapidly compared to those who reported sleeping 7 to 8 hours per day. This study provides further evidence that cognitive deficits in sleep disturbances are not static.

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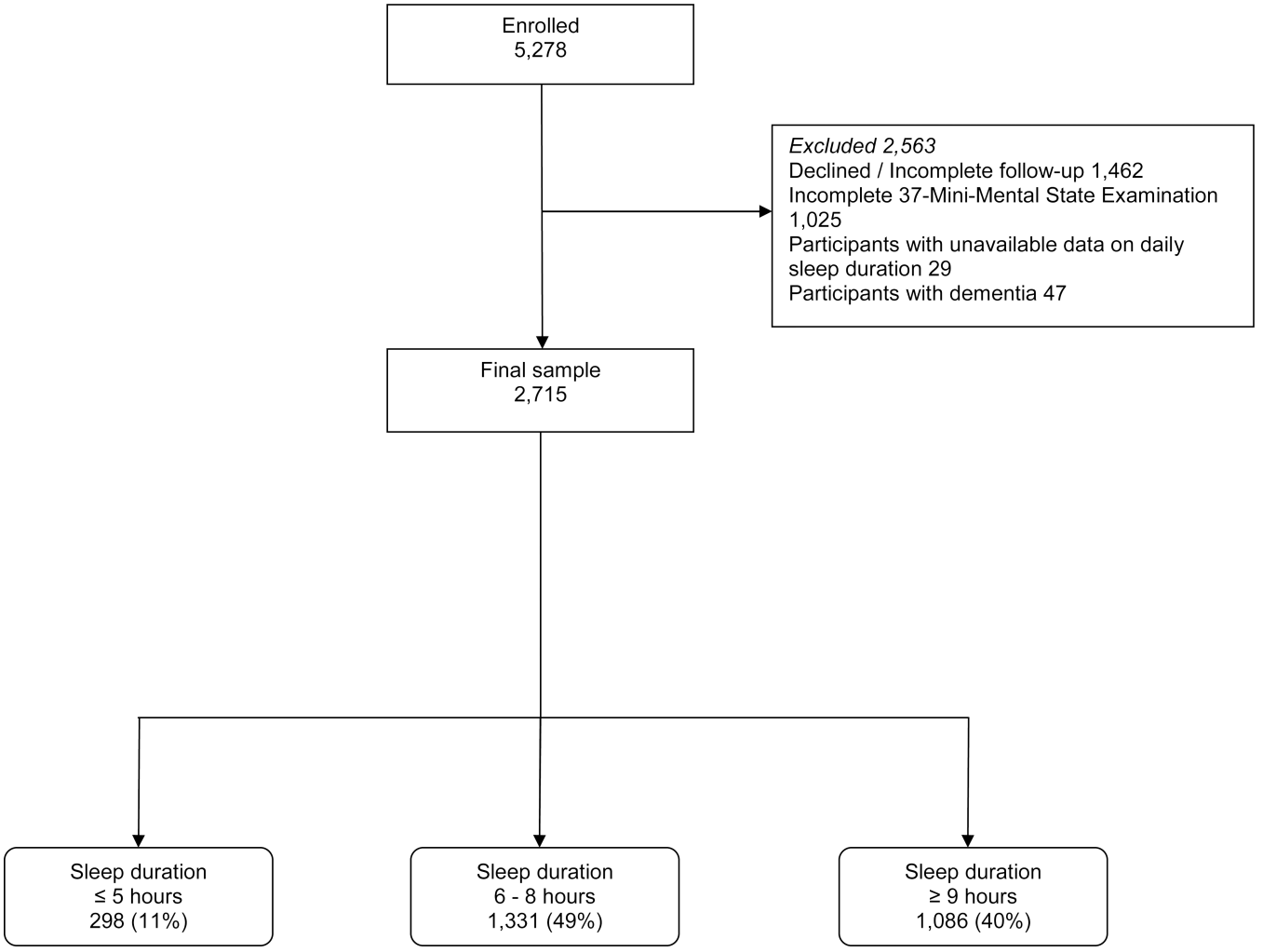

Figure 1.
Flow-Chart of the Study

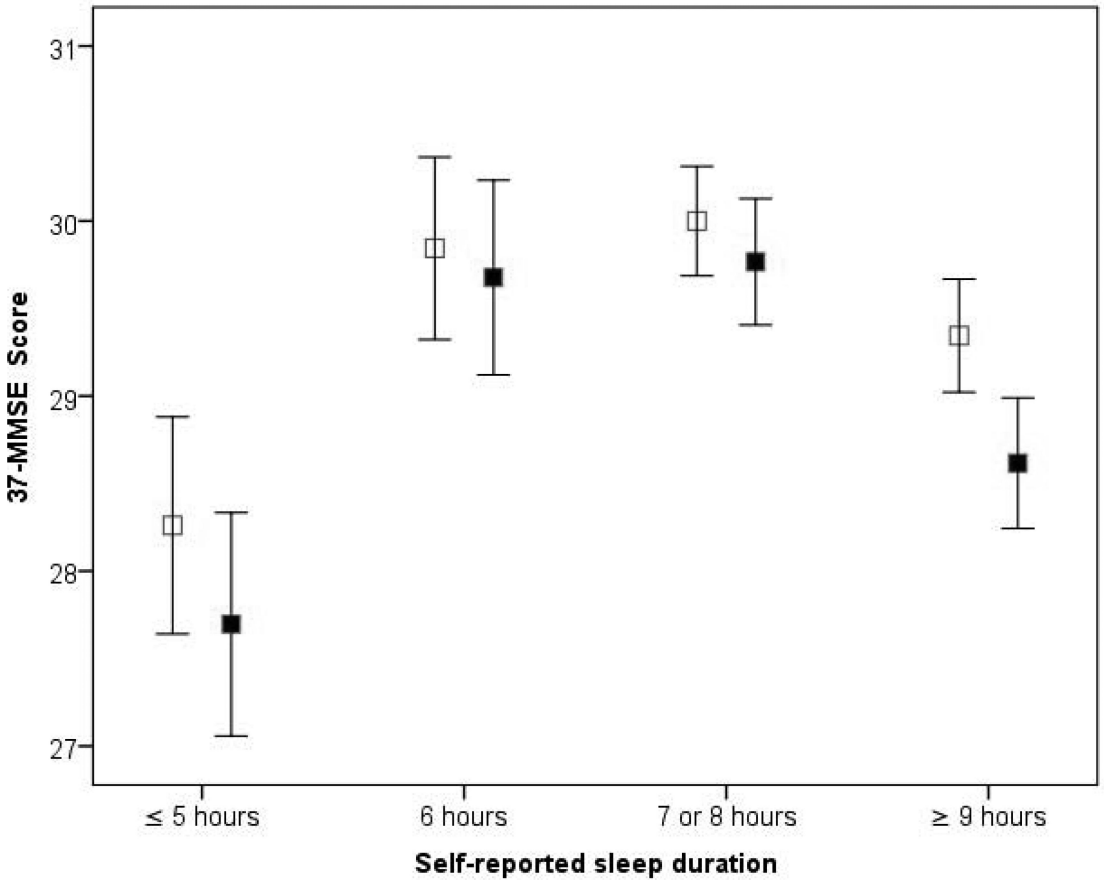

Figure 2. MMSE decline from baseline to follow up at the NEDICES Cohort

Mean baseline 37-MMSE scores are shown by open squares. Follow-up 37-MMSE scores are shown by closed squares. Mean ± 1 standard deviation are shown. Baseline scores were lower in shor and long sleepers than the reference group (those who reported to sleep 7 to 8 hours); moreover, during the three year follow-up period, these scores declined to a greater extent in long sleepers cases than in the reference group.

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Table 1

Baseline characteristics of the study participants, according to habitual sleep duration.

	Sleep duration (hours per day)			
	≤5 (n = 298)	**6 to 8 (n = 1,331)**	**≥9 (n = 1,086)**	***p* value**
Age in years	74.2 ± 6.3 (73)	72.6 ± 5.9 (71)	73.0 ± 6.1 (72)	< 0.001[a]
Gender (women)	205 (68.8%)	774 (58.2%)	566 (52.1%)	< 0.001[b]
Educational level				
Illiterate	41 (13.8%)	129 (9.7%)	128 (11.8%)	0.014[b]
Can read and write	123 (41.3%)	532 (40.0%)	469 (43.2%)	
Primary studies	104 (34.9%)	455 (34.2%)	351 (32.3%)	
Secondary and higher studies	30 (10.1%)	215 (16.2%)	138 (12.7%)	
Geographical area				
Lista	52 (17.4%)	435 (32.7%)	369 (34.0%)	< 0.001[b]
Arévalo	123 (41.3%)	504 (37.9%)	468 (43.1%)	
Margaritas	123 (41.3%)	392 (29.5%)	249 (22.9%)	
Hypertension	156 (52.3%)	677 (50.9%)	545 (50.3%)	0.815[b]
Diabetes mellitus	62 (20.8%)	187 (14.2%)	187 (17.3%)	0.008[b]
Chronic obstructive pulmonary disease	58 (19.7%)	168 (12.7%)	162 (15.0%)	0.006[b]
Depressive symptoms or antidepressant use	113 (38.3%)	323 (24.5%)	236 (21.8%)	< 0.001[b]
On medication with central nervous system effects	72 (24.2%)	202 (15.2%)	156 (14.4%)	< 0.001[b]

Mean ± SD (median) and frequency (%) are reported.

[a] Kruskal Wallis test was used for continuous variables

[b] chi-square test for categorical variables.

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Table 2

Mean decline in 37-MMSE score during follow-up (points).

	Sleep duration (hours per day)		
	≤5	**6 to 8**	**≥9**
All participants	0.5 [0.0] ± 4.0	0.2 [0.0] ± 3.8	0.6 [0.0] ± 4.3
Age Strata			
Tertile 1 (≤ 69)	0.6 [0.0] ± 3.5 (67.1 ± 1.4)	−0.1 [0.0] ± 3.5 (67.1 ± 1.3)	0.5 [0.0] ± 4.3 (67.1 ± 1.4)
Tertile 2 (70-74)	0.4 [0.0] ± 3.7 (71.9 ± 1.4)	0.0 [0.0] ± 3.7 (71.8 ± 1.4)	0.5 [0.0] ± 3.8 (72.0 ± 1.3)
Tertile 3 (≥ 75)	0.6 [0.0] ± 4.6 (80.2 ± 4.0)	0.6 [0.0] ± 4.2 (79.9 ± 4.0)	0.9 [1.0] ± 4.7 (80.3 ± 4.3)
Depressive symptoms or antidepressant use strata			
Yes	0.3 [0.0] ± 4.5	0.2 [0.0] ± 3.6	0.8 [0.0] ± 4.4
No	0.6 [0.0] ± 3.7	0.2 [0.0] ± 3.9	0.6 [0.0] ± 4.3
Medications with central nervous system effects strata			
Yes	0.2 [0.0] ± 4.1	0.6 [0.0] ± 3.6	1.0 [0.5] ± 4.1
No	0.7 [0.0] ± 4.0	0.1 [0.0] ± 3.8	0.5 [0.0] ± 4.3
Geographical área			
Las Margaritas	0.2 [0.0] ± 3.9	0.3 [0.0] ± 3.7	0.7 [0.0] ± 4.5
Lista	0.1 [0.0] ± 4.4	0.1 [0.0] ± 3.9	0.3 [0.0] ± 4.3
Arévalo	1.1 [1.0] ± 4.0	0.1 [0.0] ± 3.8	0.8 [1.0] ± 4.2

Mean [Median] ± standard deviation and frequency (%) are reported. Negative value indicates that the baseline 37-MMSE score was lower than the 37-MMSE score at follow-up (i.e., improvement in score). All positive values indicate a decline in score (i.e., baseline 37-MMSE ± follow-up 37-MMSE). In each age stratum, the numbers in parentheses indicate the mean ± standard deviation age of participants in that stratum; these values demonstrate that cases and controls had similar ages within the three age strata.