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Sleep duration, cognitive decline, and dementia risk in older women

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Abstract

Background—Consistent evidence linking habitual sleep duration with risks of mild cognitive impairment (MCI) and dementia is lacking.

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Methods—We conducted a prospective study on 7444 community-dwelling women (aged 65–80) with self-reported sleep duration, within the Women's Health Initiative Memory Study in 1995–2008. Incident MCI/dementia cases were ascertained by validated protocols. Cox models were used to adjust for multiple sociodemographic and lifestyle factors, depression, cardiovascular disease (CVD), and other clinical characteristics.

Results—We found a statistically significant (p=0.03) V-shaped association, with a higher MCI/dementia risk in women with either short (≤6 hours/night) or long (≥8 hours/night) sleep duration (vs.7 hours/night). The multicovariate-adjusted hazard for MCI/dementia was increased by 36% in short sleepers irrespective of CVD, and by 35% in long sleepers without CVD. A similar V-shaped association was found with cognitive decline.

Conclusion—In older women, habitual sleep duration predicts the future risk for cognitive impairments including dementia, independent of vascular risk factors.

Keywords

sleep duration; elderly; cognition; cognitive decline; mild cognitive impairment; dementia; longitudinal analysis; cohort studies

1. INTRODUCTION

Since the first experimental sleep deprivation study on humans reported in 1896 [1], considerable evidence has shown that sleep loss impairs cognitive performance [2]. However, the focus of previous clinical studies has been on *short-term* sleep deprivation. As insufficient sleep was increasingly recognized an important public health problem (e.g., 32% reporting ≤ 6 hours of sleep on weekdays among people aged > 60 years in a US national survey [3]), a growing attention has been directed to studying the *long-term* neurocognitive effects of sleep deprivation. Cross-sectional analyses of population studies on older people worldwide (e.g., in the US [4], UK [5], Finland [6], France [7], and China [8]) have revealed an inverse U-shaped or V-shaped association between cognitive function and self-reported sleep duration. Only a small number of longitudinal studies have begun to examine whether habitual short or long sleep duration increases the risk for cognitive declines [9–12] or dementia [13–15] in the elderly, but the results were mixed. Interpretation of previous findings was uncertain due to short follow-up time or lack of rigorous control of potential confounders. To examine associations of cognitive decline and mild cognitive impairment (MCI)/dementia with habitual sleep duration, we conducted a longitudinal analysis based in the Women's Health Initiative Memory Study (WHIMS), 1995–2008.

2. METHODS

2.1 Study Population

The WHIMS [16] was an ancillary study to the Women's Health Initiative trials of hormone therapy (WHI-HT), two large, randomized, double-blind, placebo-controlled, clinical trials of conjugated equine estrogen treatment alone (E-alone) for women with prior hysterectomy or in combination with medroxyprogesterone acetate (E+P) for women without prior hysterectomy [17]. The WHIMS was designed to test the hypothesis that HT reduces the incidence of all-cause dementia in women aged 65 and older. Community-dwelling women

were recruited during 1995–1998 from WHI-HT participants who were aged 65 to 80 years at enrollment, free of dementia defined by WHIMS protocols. After discovering an unfavorable risk-to-benefit ratio of its non-cognitive endpoints, the E+P trial was discontinued in July, 2002. The E-alone trial also ended earlier than planned in February, 2004, because of a greater risk of stroke and a lack of benefit for coronary heart disease. These decisions also ended the WHIMS trial, but annual follow-up was continued for cognitive assessment. The WHIMS study design, eligibility criteria, and recruitment procedures have been described elsewhere [16]. The current analyses are based on 7444 participants who had complete data on sleep duration at WHIMS baseline.

2.2 Study Variable

The measures of sleep disturbance in WHI cohort were developed by sleep research consultants to the WHI Behavioral Advisory Committee [18]. As part of the baseline examination, each WHI participant was asked to report *"hours of sleep on a typical night during the past 4 weeks"* (≤5, 6, 7, 8, 9, ≥10). Levine *et al*. assessed the psychometric properties of these sleep measures [19], and showed that self-reported sleep duration did not cluster with other sub-constructs of sleep disturbance, such as insomnia and sleepiness. Very good test-retest reliability was found for self-reported sleep duration (Spearman R=0.97 for same-day administration and 0.89 for 8–14 days).

2.3 Neurocognitive Outcome Variables

Our analyses included two endpoints: defined significant decline in global cognitive function, as assessed by the Modified Mini-Mental State (3MS) Examination [20]; and the incidence of mild cognitive impairment (MCI) or probable dementia, as determined by the validated 4-phase WHIMS protocols [16, 21]. In phase 1, trained, masked and certified technicians administered the 3MS test at baseline and annually. Women who screened positively for cognitive impairment, according to education-adjusted 3MS cut-points, proceeded to more extensive neuropsychological testing (phase 2), including a modified Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery [22]. Participants subsequently received a detailed clinical neurological and neuropsychiatric evaluation by physicians (i.e., neurologists, geriatricians, or geriatric psychiatrists) with experience in diagnosing dementia (phase 3). Each suspected case of dementia then underwent cranial CAT scan and a series of laboratory tests to rule out possible reversible causes of cognitive decline and dementia (phase 4). Cognitive decline during the follow-up, regardless of subsequent clinical classification, was defined as loss of 3MS score by 8 units (~2 standard errors) from baseline, corresponding to a clinically significant decline [15, 23]. Following the accepted criteria [24] at WHIMS baseline, MCI was defined as poor performance (≤10^{th} percentile in CERAD norms) on at least one CERAD test, evidence of functional impairment (but not severe enough to interfere with activities of daily living), and absence of psychiatric or other medical disorders (including probable dementia) that could explain the cognitive impairment. All clinical/testing data were then transmitted to central adjudication committee for final confirmation of dementia, based on *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* [25].

2.4 Measurement of Covariates

Participants completed structured questionnaires to provide baseline information on: demographics (age, race-ethnicity), socioeconomic status (SES, including education in years, family income, employment status), lifestyle factors (smoking, alcohol consumption, physical activity), and relevant clinical characteristics (use of menopausal HT, prior depression, CVD and related risk factors). Women were grouped according to body mass index (BMI, in kg/m^2) categories (< 25.0 vs. 25.0–29.9 vs. ≥30.0). Hypertension was defined as antihypertensive medication or elevated blood pressure (systolic≥140 or diastolic≥90 mmHg). Treated diabetes mellitus (DM) was defined as a physician diagnosis plus oral medications or insulin therapy. History of CVD included previous coronary heart disease (myocardial infarction, coronary angioplasty, or coronary artery bypass graft), stroke, or transient ischemic attack. Good reliability and validity of both the self-reported medical histories and the physical measures have been documented [26–27]. The Burnam screening algorithm [28] was used to characterize the presence of prior depressive disorders, which increased the MCI/dementia risk [29] in WHIMS. Additional covariates included: the depressive symptoms (assessed by the Center for Epidemiological Studies Depression Scale [28]; insomnia symptoms (assessed by the well-validated WHI Insomnia Rating Scale [19, 30]); and self-rated frequency of snoring (*"Did you snore"*) and sleepiness ("*falling asleep during quiet activities like reading, watching TV, or riding in a car*"), based on a 5-point scale.

2.5 Statistical Analyses

We compared the distributions of sleep duration across different population characteristics, using chi-square tests. Follow-up time for each woman was calculated from WHI randomization (baseline) to the 3MS examination date triggering the ultimate classification of defined cognitive impairment, or the last date of completing annual cognitive assessment, whichever came first. Data on cognitive decline and incidence of MCI/dementia were analyzed separately. Because our exploratory analyses revealed a similar pattern of association between sleep duration and clinical endpoint separately for MCI and dementia, the MCI/dementia incidence was treated as a composite outcome variable, as also used in pooled analyses of WMIMS trials [21, 24]. Cox models were used to estimate hazard ratios (HRs) for each outcome associated with habitual sleep duration, adjusting for potential confounders. The assumed proportional hazard was supported by the proportionality test. Analytically, we used older women with self-reported sleep of 7 hours/night as the referent, because a growing number of sleep-health epidemiologic studies have found the lowest mortality and morbidity in people with seven hours of nightly sleep [31–32]. To obtain more precise estimates of incidence rate and the resulting HRs, small numbers of cases were pooled across the categories of more extreme sleep duration. We also stratified the effect estimates by prior histories of CVD and associated risk factors (DM, hypertension, and obesity) to assess whether these clinical attributes modified the putative neurocognitive effects of habitual sleep duration, using the tests of interaction. Several sensitivity analyses were carried out to evaluate whether the results were sensitive to use of sedatives/hypnotics/antidepressants or adjusting for concurrent depressive symptoms. Statistical analyses were performed using the SAS System for Windows, Version 9.3 (SAS Institute, Cary, NC).

3. RESULTS

Distribution of Sleep Duration and Population Characteristics

Table 1 presents the population distribution of sleep duration in relation to selected baseline socio-demographics and lifestyle factors. In this cohort of 7444 older women (aged 70.1±3.8 years), 38.3% reported nightly sleep durations of 6 hours or less and 25.6% reported 8 hours or more. The proportion of short-duration sleepers (≤6 hours/night) was higher in minority women (50–57%) than that in white (36%). Older women with < high school education, family income ≤ $19,999, or alcohol use <1 drink/week were more likely to report sleep duration ≤6 hours/night, when compared to their counterparts. The percentage of extreme shorter sleep (≤5 hours/night) or longer sleep (≥9 hours/night) was higher in women with low physical activities (< 2 episodes/week), prior depression, or treated DM. We noted that the efficient randomization of HT assignment resulted in nearly identical distribution of sleep duration comparing older women in either E+P or E-alone with those in the control groups, making it unlikely to confound any putative associations with sleep duration.

Frequencies of Cognitive Declines and MCI/Dementia

There were 802 subjects with significant cognitive decline (i.e., 3MS decreased ≥ 8 units from baseline) and 549 new cases of MCI/dementia (368 MCI and 265 dementia including 84 progressed from MCI) during an average of 7.3–7.7 years of follow-up (Table 2). The frequencies of cognitive decline (p=0.0003) and MCI/dementia (p=0.0003) differed by habitual sleep duration, with greater cognitive decline and higher incidence of MCI/dementia noted in women reporting average sleep duration of ≤5, 6, 8 or ≥9 hours/night, as compared to women reporting sleep of 7 hours/night. Because of the relatively small numbers of events accrued in women with extreme sleep durations (e.g., 23 cases of MCI/dementia in women with sleep duration ≥9 hours/night and 65 in women with sleep duration ≤5 hours/night), we reclassified the sleep duration into three subcategories (≤6, 7, ≥8 hours/night) in the subsequent multicovariate-adjusted Cox models.

Adjusted Main Associations

Using a sleep time of 7 hours/night as the referent (Table 3), we found 35% and 22% increases in HRs for cognitive declines among women reporting sleep duration ≤ 6 and ≥8 hours/night, after adjustment for age and race/ethnicity (p<0.01). Additional adjustment for SES, lifestyles, depression, previous HT use, and conventional CVD risk factors resulted in only small changes to the estimated HR in women reporting sleep duration ≤6 hours/night, but the observed HR among women with ≥8 hours of sleep/night was attenuated. In the model accounting for multiple potential confounders (Model-V covariates in Table 3), the adjusted risk of cognitive decline significantly differed by self-reported habitual sleep pattern (p<0.01), with the HR=1.36 (95%CI: 1.14, 1.62) in short sleepers and the HR=1.18 (95%CI: 0.96, 1.45) among long sleepers. We also found 36% and 23% increases in HRs for MCI/dementia among women reporting sleep duration ≤ 6 and ≥8 hours/night (vs. 7 hours/night), after adjustment for age and race/ethnicity (p<0.01). These HR estimates were not substantially altered with further adjusting for SES, lifestyle factors, depression, and CVD-related clinical characteristics. In the model accounting for all these potential confounders (Model-V), habitual sleep duration was associated with subsequent risk for MCI/dementia

(p=0.03), with the corresponding HR=1.36 (95%CI: 1.09, 1.71) in short sleepers and 1.27 (95%CI: 0.98, 1.64) among long sleepers.

Sensitivity Analyses

In sensitivity analyses, we found similar patterns of associations between habitual sleep duration and cognitive impairments. Effect estimates changed very little in further analyses after controlling for the influence of sedatives/hypnotics/antidepressants use or adjusting for concurrent depressive symptoms (CES-D, excluding sleep item). Comparing women reporting ≤6 and ≥8 hours of sleep/night to women with 7 hours of sleep/night in multicovariate-adjusted analyses (Model-V), the HRs (95%CIs) became 1.36 (1.13, 1.62) and 1.18 (0.96, 1.45) for significant cognitive decline (p<0.01) and 1.36 (1.08, 1.71) and 1.27 (0.98, 1.65) for MCI/dementia (p=0.03), after including the use of sedatives/hypnotics. Adjusting for the use of antidepressants resulted in the corresponding HRs of 1.36 (1.13, 1.62) and 1.17 (0.96, 1.44) for significant cognitive decline (p<0.01) and HRs of 1.36 (1.08, 1.70) and 1.25 (0.96, 1.62) for MCI/dementia (p=0.03). After we substituted the history of depression with “depressive symptoms,” the multivariable-adjusted HRs (95% CIs) were 1.35 (1.13, 1.61) and 1.13 (0.92, 1.38) for significant cognitive decline (p<0.01) and 1.35 (1.07, 1.70) and 1.22 (0.94, 1.60) for MCI/dementia (p=0.04), comparing women reporting ≤6 and ≥8 hours of sleep/night to women with 7 hours of sleep/night. The V-shaped associations remained robust in the additional analyses adjusting for insomnia symptoms or frequencies of snoring and sleepiness.

Effect Measure Modification by CVD/Risk Factors

There was little evidence that the adverse effects of short sleep were substantially modified by CVD/risk factors (e.g., hypertension, DM, or obesity), because the effects sizes were comparable in women with vs. without these clinical attributes (Tables 4 and 5). For instance, the HR for MCI/dementia associated with short sleep was 1.35 (1.06–1.72) in non-diabetic women and 1.39 (1.02–1.88) in those with DM. The estimates of putative adverse effects of long sleep were statistically significant without prior CVD (HR=1.32 [1.06–1.65] for cognitive decline; 1.35 [1.01–1.80] for MCI/dementia) or in non-obese women (HR=1.34 [1.05–1.72] for cognitive decline).

4. DISCUSSION

During an average of more than 7-year follow-up in this group of community-dwelling, cognitively intact and generally healthy older women, both short-duration (≤6 hours/night) and long-duration (≥8 hours/night) sleepers had greater cognitive decline, and an increased risk for cognitive impairments including dementia, compared to those with self-reported sleep of 7 hours/night. These observed adverse neurocognitive effects remained after adjustment for demographics and socioeconomic status, and the associations could not be fully explained by lifestyle factors or several clinical risk factors for dementia. To our knowledge, this is the largest prospective study with the longest follow-up to demonstrate the consistent V-shaped associations linking habitual sleep duration to both cognitive decline and subsequent risk for MCI/dementia.

Our study aimed to address the data inconsistencies and methodological limitations of previous studies on the longitudinal associations between habitual sleep duration and increased risk of cognitive impairment (including dementia) and cognitive decline (Table 6). Although an adverse effect of sleep loss on MCI/dementia was suggested by the three published cohort studies [13–15], none of the reported associations with short sleep duration were statistically significant. Increased dementia risk associated with long sleep was noted in one report [13], which, however, did not differentiate night-time sleep from daytime napping, incorrectly assuming two different behavioral constructs with common antecedents and similar threats to cognitive health in the elderly [33]. Interpretation of results from these studies also suffered from the lack of rigorous control of potential confounders, such as physical activities, depressive symptoms, and CVD/risk factors. In our analyses, the V-shaped association between habitual sleep duration and MCI/dementia remained statistically significant ($p=0.03$) even after we accounted for sociodemographic features, lifestyle factors, depressive symptoms, and CVD-related clinical characteristics. Our study findings on cognitive decline in 3MS add to the growing evidence linking habitual sleep duration with cognitive aging in the elderly. The Nurses' Health Study investigators did not find a statistically significant longitudinal association between self-reported sleep duration and cognitive decline [9, 12], but a V-shaped association was suggested in two other cohorts [10–11], which, however, only partially accounted for some relevant clinical characteristics and did not address the potential confounding by lifestyle factors (e.g., smoking, alcohol consumption, physical activities). In our analyses, the V-shaped association between habitual sleep duration and significant cognitive decline remained ($p=0.01$) even after we accounted for sociodemographic features, lifestyle factors, depression, and CVD-related clinical characteristics.

The demonstrated consistent increase in MCI/dementia risk among short sleepers raises the questions of possible clinical mediators and underlying mechanisms. As large epidemiologic studies have linked short sleep duration with increased risks for CVD [31, 34] and metabolic disorders [35] that play a pivotal role in cognitive decline and dementia, one may consider cardiometabolic health indicators as plausible mediators linking sleep loss with pathological brain aging. However, we found that increased risk for MCI/dementia associated with sleep ≤6 hours/night remained statistically significant (HR=1.36 [1.09–1.71]) after adjusting for CVD and conventional risk factors, and such adverse effects were also present in older women without hypertension (HR=1.39 [1.02–1.88]) or DM (HR=1.35 [1.06–1.72]). One neuroimaging study on community-dwelling older adults (n=70; aged: 76.4±8.0 years) found self-reported short sleep correlated with Aβ deposition even after adjusting for CVD and BMI [36], and one night of total sleep deprivation might perturb Aβ metabolism in healthy brains [37]. Emerging data from animal models with sleep deprivation point to likely complex mechanism that may involve activation of neuroendocrine stress axis [38], neuroinflammation [39] and oxidative stress [40] in hippocampus, interruption of hippocampal neurogenesis [41], and augmentation of aging-related protein misfolding with resulting proapoptosis [42]. Together these data suggest the possibility of direct effects of long-term sleep loss on pathological brain aging and the neuropathological pathways may go beyond cerebrovascular damages.

Several important questions on mechanistic mediators may arise if our study findings are replicated to demonstrate that long sleep duration is an independent neurobehavioral risk factor for cognitive impairment. For instance, what exactly predisposes long sleepers to be more likely to develop MCI/dementia, than those usually with 7 hours of sleep? Does long sleep duration reflect a proinflammatory state [43], especially in women [44], making the affected individuals more susceptible to microglia activation [45] involved in the pathogenesis of Alzheimer's disease? Are habitual long sleepers more likely to reset their circadian rhythms for rest-activity patterns (e.g., decreased circadian activity rhythms with less stimulating social activities) that predispose them to the neurodegenerative processes [46]? Is it possible that the longer than average duration of recumbent position increases the period with high intracranial pressure which may alter the cerebrospinal/interstitial fluid dynamic and compromise the β-amyloid clearance during sleep [47]?

The reported detrimental health effects associated with habitual sleep patterns have been criticized for either not accounting for potential confounding by co-existing depression [48] or simply representing the adverse effects of other common sleep disorders such as chronic insomnia or sleep apnea [49]. Although WHIMS participants with prior depression were more likely to have short sleep duration (Table 1) than those without depression, we did not find strong confounding by depression; adjusting for prior depression (Model-IV and V in Table 3), use of antidepressants, or concurrent depressive symptoms did not alter the observed associations. We noted that short sleepers in WHIMS did complain of more insomnia symptoms and report more frequent snoring and sleepiness (*data not shown*). Long sleepers in WHIMS, although also reporting frequent snoring and sleepiness, did not have more insomnia symptoms (*data not shown*). Considering these differences, we thus conducted additional analyses adjusting for insomnia symptoms and frequencies of snoring and sleepiness along with the covariates already included in the full model (Model V in Table 3). The V-shaped associations remained robust in these additional analyses, suggesting that the adverse neurocognitive effects of habitual short and long sleep durations are possibly independent of other sub-constructs of sleep disturbance in older women.

We recognize several limitations in our study. First, our classification of habitual sleep duration relied on self-reports. However, it has been shown that objective sleep measures have a much larger nightly variability of sleep duration than their corresponding yearly variability [50], indicating that usual sleep behavior changes little in one year, despite large short-term fluctuations. Good reproducibility of exposure classification of self-reported habitual sleep duration has been documented in large cohort studies [9, 51]. Second, although the multi-ethnic WHIMS cohort was recruited from communities, certain population characteristics may limit the generalizability of our findings. Because WHIMS participants had relatively high educational attainment, we might have underestimated the long-term neurocognitive effects associated with unhealthful sleep patterns in subpopulations of low SES that are presumably more sensitive to the detrimental health effects of sleep disturbance. Also, because WHIMS participants were all postmenopausal women aged 65 years or older, future investigations in middle-aged women and in men are needed to clarify the importance of different sleep duration during vulnerable periods and possible sex-specificity. Third, we were unable to provide reliable effect of more extreme

sleep durations (e.g., ≥ 9 hours/night), due to low statistical power in such pair-wise comparisons based on a small number of events and possible attrition of older women with extreme sleep patterns. Fourth, we did not conduct analyses on dementia subtypes, also concerning the lack of statistical power. Extended WHIMS follow-up may offer an opportunity to examine the risk of Alzheimer's disease associated with habitual sleep duration. Finally, although many potential confounders and relevant clinical characteristic were included in our analyses, we cannot rule out the possibility of unmeasured confounding or alternative explanations. For instance, extreme sleep patterns may be indicative of the presence of psychosocial attributes or environmental stressors which could lead to adverse neurocognitive outcomes by alternative pathways other than through the mediation of conventional CVD risk factors or associated lifestyle modification. Extreme sleep patterns may share common neurobiological changes [52] underlying subclinical dementia or simply reflect prodromal manifestation of subsequent cognitive impairment.

In summary, this prospective study of cognitively intact and generally healthy older women shows a consistent pattern of V-shaped associations linking habitual sleep duration to significant decline of global cognitive function and subsequent risk for developing cognitive impairment including dementia. These results do not only substantiate the important role of sleep duration in determining cognitive decline, but also support the hypothesized adverse effect of chronic sleep loss on pathological brain aging.

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Research in Context

1. Systematic review

A standard literature search (e.g., PubMed, PsycINFO) was conducted to identify original papers (focused on clinical endpoints or repeated cognitive assessment), official reports (e.g., IOM), and review articles. We found neither consistent nor convincing data on sleep duration and dementia risk. Several methodological limitations of previous research were uncovered. Whether vascular risk factors interacting with sleep duration and cognitive impairment was unclear.

2. Interpretation

We demonstrated consistent V-shaped associations linking sleep duration with cognitive decline and subsequent risk for MCI/dementia in older women. Increased risks (~30% elevation) in short sleepers (≤6 hours/night) remained after rigorous control for potential confounding, even present in those with low CVD risk. Our study results support the hypothesized adverse effect of chronic sleep loss on pathological brain aging and suggest the underlying mechanisms may go beyond cerebrovascular damages.

3. Future directions

Multidisciplinary researches are needed to better understand mechanistic mediators, substantiate the causal link, and develop behavioral intervention for optimal sleep and healthy brain aging.

Table 1

Distributions* of Sleep Duration by Sociodemographics, Lifestyle Factors, and Clinical Characteristics in the Women's Health Initiative Memory Study Cohort, 1995–2008

		Hours of sleep per night					
	N†	≤5	6	7	8	≥9	p-value‡
All subjects	7444	696 (9.4%)	2150 (28.9%)	2688 (36.1%)	1611 (21.6%)	299 (4.0%)	
Age group at screening							0.0764
63–69	3419	313 (9.2%)	924 (27%)	1270 (37.1%)	773 (22.6%)	139 (4.1%)	
70–74	2667	243 (9.1%)	811 (30.4%)	947 (35.5%)	561 (21%)	105 (3.9%)	
≥75	1358	140 (10.3%)	415 (30.6%)	471 (34.7%)	277 (20.4%)	55 (4.1%)	
Ethnicity							<.0001
Black or African-American	528	105 (19.9%)	196 (37.1%)	134 (25.4%)	72 (13.6%)	21 (4%)	
Hispanic White	178	26 (14.6%)	63 (35.4%)	53 (29.8%)	29 (16.3%)	7 (3.9%)	
White (not of Hispanic origin)	6466	520 (8%)	1797 (27.8%)	2416 (37.4%)	1471 (22.7%)	262 (4.1%)	
Other or Missing	272	45 (16.5%)	94 (34.6%)	85 (31.3%)	39 (14.3%)	9 (3.3%)	
Education							<0.0001
<High school	569	92 (16.2%)	169 (29.7%)	168 (29.5%)	113 (19.9%)	27 (4.7%)	
High school/GED	1640	158 (9.6%)	488 (29.8%)	597 (36.4%)	343 (20.9%)	54 (3.3%)	
School after high school	2989	290 (9.7%)	878 (29.4%)	1052 (35.2%)	638 (21.3%)	131 (4.4%)	
	2989	290 (9.7%)	878 (29.4%)	1052 (35.2%)	638 (21.3%)	131 (4.4%)	
College degree or higher	2224	155 (7%)	606 (27.2%)	863 (38.8%)	515 (23.2%)	85 (3.8%)	
Family income							<0.0001
≤$ 19,999	1828	240 (13.1%)	555 (30.4%)	603 (33%)	356 (19.5%)	74 (4%)	
$20,000 to $34,999	2204	187 (8.5%)	615 (27.9%)	827 (37.5%)	484 (22%)	91 (4.1%)	
$35,000 to $49,999	1434	115 (8%)	408 (28.5%)	556 (38.8%)	295 (20.6%)	60 (4.2%)	
$50,000 to $74,999	979	80 (8.2%)	277 (28.3%)	343 (35%)	241 (24.6%)	38 (3.9%)	
≥$75,000	741	57 (7.7%)	206 (27.8%)	275 (37.1%)	178 (24%)	25 (3.4%)	
Missing	258	17 (6.6%)	89 (34.5%)	84 (32.6%)	57 (22.1%)	11 (4.3%)	

		Hours of sleep per night					
	N[†]	≤5	6	7	8	≥9	p-value[‡]
Employment status							0.0007
Currently employed	1319	117 (8.9%)	425 (32.2%)	499 (37.8%)	243 (18.4%)	35 (2.7%)	
Not working	813	72 (8.9%)	246 (30.3%)	273 (33.6%)	190 (23.4%)	32 (3.9%)	
Retired	5287	504 (9.5%)	1470 (27.8%)	1908 (36.1%)	1174 (22.2%)	231 (4.4%)	
Smoking							0.896
Never smoked	3899	361 (9.3%)	1130 (29%)	1415 (36.3%)	846 (21.7%)	147 (3.8%)	
Past smoker	2917	267 (9.2%)	830 (28.5%)	1062 (36.4%)	635 (21.8%)	123 (4.2%)	
Current smoker	524	54 (10.3%)	159 (30.3%)	177 (33.8%)	110 (21%)	24 (4.6%)	
Alcohol consumption							<0.0001
Non drinker	975	94 (9.6%)	292 (29.9%)	371 (38.1%)	181 (18.6%)	37 (3.8%)	
Past drinker	1463	164 (11.2%)	417 (28.5%)	501 (34.2%)	310 (21.2%)	71 (4.9%)	
<1 drink per day	4054	383 (9.4%)	1188 (29.3%)	1491 (36.8%)	858 (21.2%)	134 (3.3%)	
>1 drink per day	887	44 (5%)	235 (26.5%)	298 (33.6%)	253 (28.5%)	57 (6.4%)	
Moderate or strenuous activities ≥ 20min							0.0003
No activity	4334	432 (10%)	1270 (29.3%)	1519 (35%)	912 (21%)	201 (4.6%)	
Some activity	361	37 (10.2%)	92 (25.5%)	127 (35.2%)	82 (22.7%)	23 (6.4%)	
2–4 episodes/wk	1451	123 (8.5%)	416 (28.7%)	533 (36.7%)	338 (23.3%)	41 (2.8%)	
>4 episodes/wk	1287	102 (7.9%)	367 (28.5%)	507 (39.4%)	277 (21.5%)	34 (2.6%)	
Body mass Index (BMI)							0.0926
<25 kg/m^2	2158	182 (8.4%)	609 (28.2%)	833 (38.6%)	453 (21%)	81 (3.8%)	
25–29 kg/m^2	2695	250 (9.3%)	805 (29.9%)	950 (35.3%)	583 (21.6%)	107 (4%)	
≥30 kg/m^2	2548	262 (10.3%)	722 (28.3%)	883 (34.7%)	571 (22.4%)	110 (4.3%)	
HT use ever							0.3996
No	4055	360 (8.9%)	1170 (28.9%)	1495 (36.9%)	865 (21.3%)	165 (4.1%)	
Yes	3387	336 (9.9%)	979 (28.9%)	1192 (35.2%)	746 (22%)	134 (4%)	
History of Depression							<0.0001

	Hours of sleep per night						
	N[†]	≤5	6	7	8	≥9	p-value[‡]
No	6669	584 (8.8%)	1921 (28.8%)	2429 (36.4%)	1473 (22.1%)	262 (3.9%)	
Yes	604	97 (16.1%)	178 (29.5%)	192 (31.8%)	109 (18%)	28 (4.6%)	
Hypertension ever							0.0379
No	4462	391 (8.8%)	1257 (28.2%)	1657 (37.1%)	971 (21.8%)	186 (4.2%)	
Yes	2899	298 (10.3%)	865 (29.8%)	1000 (34.5%)	627 (21.6%)	109 (3.8%)	
Treated for diabetes							0.0397
No	6946	636 (9.2%)	2019 (29.1%)	2521 (36.3%)	1497 (21.6%)	273 (3.9%)	
Yes	484	60 (12.4%)	124 (25.6%)	163 (33.7%)	112 (23.1%)	25 (5.2%)	
High cholesterol requiring pills ever							0.3536
No	6009	550 (9.2%)	1761 (29.3%)	2169 (36.1%)	1293 (21.5%)	236 (3.9%)	
Yes	1339	137 (10.2%)	361 (27%)	483 (36.1%)	299 (22.3%)	59 (4.4%)	
History of CVD							0.0097
No	6054	540 (8.9%)	1720 (28.4%)	2217 (36.6%)	1335 (22.1%)	242 (4%)	
Yes	1280	149 (11.6%)	388 (30.3%)	436 (34.1%)	259 (20.2%)	48 (3.8%)	
Subcohort membership[§]							
E-alone control	1476	158 (10.7%)	470 (31.8%)	489 (33.1%)	297 (20.1%)	62 (4.2%)	0.4757
E-alone intervention	1461	169 (11.6%)	426 (29.2%)	482 (33%)	322 (22%)	62 (4.2%)	
E+P control	2290	187 (8.2%)	647 (28.3%)	875 (38.2%)	493 (21.5%)	88 (3.8%)	0.9333
E+P intervention	2217	182 (8.2%)	607 (27.4%)	842 (38%)	499 (22.5%)	87 (3.9%)	

[*] The data represented the number (row %) belonging to each level of sleep duration, given for each subcategory of personal characteristics.

[†] The total number of subjects summed up across each subcategory varies slightly because of missing values.

[‡] p-value for Chi-square test comparing the distribution of sleep duration across subcategories of each personal characteristics

[§] E-alone: conjugated equine estrogen alone; E+P: estrogen plus progestin (medroxyprogesterone acetate)

Table 2

Incidence Rates for Having Significant Cognitive Decline and MCI/Dementia by Sleep Duration in WHIMS Cohort, 1995–2008

≥8 points decrease in 3MS[†]	Hours of sleep per night				
	≤ 5	6	7	8	≥ 9
N	664	2078	2615	1562	286
Total person-years at risk	4549.26	15254.74	19776.87	11548.77	2036.58
Number of significant cognitive decline	88	269	246	169	30
Event rate (cases per 1000 person-years)[*]	19.34	17.63	12.44	14.63	14.73
MCI[‡]/dementia	**Hours of sleep per night**				
	≤ 5	**6**	**7**	**8**	**≥ 9**
N	693	2149	2686	1610	298
Total person-years at risk	4902.59	16352.33	21158.47	12387.62	2182.33
Number of MCI/dementia	65	188	163	110	23
Event rate (cases per 1000 person-years)[*]	13.26	11.50	7.70	8.88	10.54

[*] Poisson regression with Chi-square test: p=0.0003 for the difference in 3MS decline across the category of sleep duration; p=0.0003 for the difference in MCI/dementia incidence across the category of sleep duration

[†] 3MS: Modified Mini-Mental State Examination

[‡] MCI: mild cognitive impairment

Table 3

Cox Models for Having Significant Cognitive Decline and MCI/Dementia Associated with Sleep Duration in WHIMS Cohort, 1995–2008

	Hazard Ratios (95% confidence interval)			
≥8 points decrease in 3MS	**Hours of sleep per night**			
	≤ 6	**7**	**≥ 8**	**p-value**
Crude analysis	1.46 (1.24–1.72)	1.00	1.18 (0.98–1.42)	<0.01
Adjusted analyses				
[*]**Model-I**	1.35 (1.15–1.59)	1.00	1.22 (1.01–1.47)	<0.01
[†]**Model-II**	1.31 (1.11–1.55)	1.00	1.20 (0.99–1.44)	<0.01
[‡]**Model-III**	1.32 (1.12–1.56)	1.00	1.20 (0.99–1.45)	<0.01
[§]**Model-IV**	1.31 (1.10–1.56)	1.00	1.19 (0.98–1.45)	<0.01
[¶]**Model-V**	1.36 (1.14–1.62)	1.00	1.18 (0.96–1.45)	<0.01
MCI/dementia	**Hours of sleep per night**			
	≤ 6	**7**	**≥ 8**	**p-value**
Crude analysis	1.57 (1.29–1.91)	1.00	1.19 (0.95–1.50)	<0.01
Adjusted analyses				
[*]**Model-I**	1.36 (1.11–1.66)	1.00	1.23 (0.98–1.55)	<0.01
[†]**Model-II**	1.31 (1.07–1.60)	1.00	1.19 (0.94–1.50)	0.03
[‡]**Model-III**	1.31 (1.07–1.61)	1.00	1.23 (0.98–1.56)	0.03
[§]**Model-IV**	1.34 (1.07–1.67)	1.00	1.30 (1.01–1.67)	0.02
[¶]**Model-V**	1.36 (1.09–1.71)	1.00	1.27 (0.98–1.64)	0.03

[*]Model-I: adjusted for age and race

[†]Model-II: adjusted for age, race, and SES (education, family income, and employment status)

[‡]Model-III: adjusted for age, race, SES, and lifestyle factors (smoking, alcohol consumption, physical activities)

[§]Model-IV: adjusted for age, race, SES, lifestyle factors (smoking, alcohol consumption, physical activities), and depression

[¶]Model-V: adjusted for age, race, SES, lifestyle factors (smoking, alcohol consumption, physical activities), depression, and other relevant clinical characteristics (previous HT use, BMI, prior CVD history, hypertension, DM, hypercholesterolemia)

All p-values were from Chi-square tests examining the difference in hazard ratio across the category of sleep duration.

Table 4

Associations (Hazard Ratios) of Significant Cognitive Decline (3MS Decreased ≥ 8 points) with Sleep Duration in WHIMS, Stratified by History of Cardiovascular Disease, Hypertension, Diabetes Mellitus, and Obesity

	Cardiovascular Disease			**Hypertension**		
Sleep duration per night	**Yes (N=1228)**	**No (N=5872)**	**p-value***	**Yes (N=2786)**	**No (N=4338)**	**p-value***
Crude						
≤ 6 hrs	**1.63 (1.15–2.32)**	**1.41 (1.17–1.70)**		**1.63 (1.26–2.10)**	**1.36 (1.09–1.69)**	
7 hrs	1.00	1.00	<0.01	1.00	1.00	0.39
≥ 8 hrs	0.69 (0.42–1.14)	**1.32 (1.07–1.62)**		1.17 (0.86–1.57)	1.21 (0.94–1.54)	
Adjusted†						
<6 hrs	**1.61 (1.10–2.35)**	**1.28 (1.05–1.57)**		**1.47 (1.12–1.94)**	**1.28 (1.01–1.61)**	
7 hrs	1.00	1.00	<0.01	1.00	1.00	0.66
≥ 8 hrs	0.67 (0.39–1.14)	**1.32 (1.06–1.65)**		1.19 (0.86–1.64)	1.18 (0.91–1.54)	
	Diabetes Mellitus			**Obesity Status**		
	Yes (N=457)	No (N=6734)		Obese: BMI≥30 kg/m^2 (N=2482)	Non-obese: BMI<30 kg/m^2 (N=4684)	
Crude						
≤ 6 hrs	**1.77 (1.02–3.06)**	**1.42 (1.20–1.68)**		**1.68 (1.26–2.24)**	**1.38 (1.13–1.68)**	
7 hrs	1.00	1.00	0.75	1.00	1.00	0.07
≥ 8 hrs	1.36 (0.74–2.47)	1.15 (0.94–1.40)		0.99 (0.70–1.41)	**1.27 (1.02–1.59)**	
Adjusted†						
≤ 6 hrs	1.42 (0.80–2.52)	**1.35 (1.12–1.63)**		**1.50 (1.11–2.05)**	**1.28 (1.03–1.60)**	
7 hrs	1.00	1.00	0.87	1.00	1.00	0.03
≥ 8 hrs	1.07 (0.57–2.02)	1.20 (0.97–1.49)		0.91 (0.63–1.32)	**1.34 (1.05–1.72)**	

*Chi-square test p-value for interaction comparing the hazard ratios with potential effect modifier vs. hazard ratios without potential effect modifier

†adjusted for age, race, SES, lifestyle factors (smoking, alcohol consumption, physical activities), depression, and other relevant clinical characteristics (previous HT use, BMI, prior CVD history, hypertension, DM, hypercholesterolemia)

Table 5

The Associations (Hazard Ratios) of MCI/Dementia with Sleep Duration in WHIMS, Stratified by History of Cardiovascular Disease, Hypertension, Diabetes Mellitus, and Obesity

	Cardiovascular Disease			**Hypertension**		
Sleep duration per night	**Yes (N=1278)**	**No (N=6048)**	**p-value***	**Yes (N=2895)**	**No (N=4458)**	**p-value***
Crude						
≤ 6 hrs	**1.64 (1.09–2.46)**	**1.51 (1.2–1.89)**		**1.47 (1.09, 1.98)**	**1.61 (1.24, 2.11)**	
7 hrs	1.00	1.00	0.28	1.00	1.00	0.42
≥ 8 hrs	0.86 (0.50–1.47)	1.23(0.95–1.60)		1.32 (0.94, 1.85)	1.09 (0.80, 1.51)	
Adjusted†						
<6 hrs	**1.67 (1.06–2.64)**	1.27 (0.98–1.64)		1.35 (0.96, 1.89)	**1.39 (1.02, 1.88)**	
7 hrs	1.00	1.00	0.14	1.00	1.00	0.43
≥ 8 hrs	1.00 (0.56–1.78)	**1.35 (1.01–1.80)**		**1.46 (1.00, 2.12)**	1.12 (0.78, 1.6)	
	Diabetes Mellitus			**Obesity Status**		
	Yes (N=482)	No (N=6940)	p-value*	Obese: BMI≥30 kg/m^2 (N=2546)	Non-obese: BMI<30 kg/m^2 (N=4847)	p-value*
Crude						
≤ 6 hrs	1.82 (0.99, 3.35)	**1.54 (1.25, 1.90)**		**1.96 (1.36, 2.82)**	**1.45 (1.14, 1.84)**	
7 hrs	1.00	1.00	0.86	1.00	1.00	0.28
≥ 8 hrs	1.37 (0.70, 2.67)	1.16 (0.91, 1.48)		1.22 (0.79, 1.87)	1.20 (0.91, 1.57)	
Adjusted†						
≤ 6 hrs	1.42 (0.73, 2.76)	**1.35 (1.06, 1.72)**		**1.59 (1.06, 2.37)**	1.27 (0.97, 1.67)	
7 hrs	1.00	1.00	0.87	1.00	1.00	0.24
≥ 8 hrs	1.14n(0.56, 2.33)	1.29 (0.98, 1.71)		1.12 (0.70, 1.79)	**1.36 (1.00, 1.86)**	

*Chi-square test p-value for interaction comparing the hazard ratios with potential effect modifier vs. hazard ratios without potential effect modifier

†adjusted for age, race, SES, lifestyle factors (smoking, alcohol consumption, physical activities), depression, and other relevant clinical characteristics (previous HT use, BMI, prior CVD history, hypertension, DM, hypercholesterolemia)

Table 6

Summary of Longitudinal Studies Linking Sleep Duration with Cognitive Decline and Dementia

References	Study Design & Population	Measures of Sleep Duration	Neurocognitive Outcomes	Main Findings	Statistical Adjustment for Confounding
Studies on MCI or Dementia					
Benito-Leon et al. [13]	3.2-year (median) follow-up study on 3,286 participants (aged ≥65) in the Neurological Disorders in Central Spain cohort	Self-reported "total hours of sleep in a 24hour period" (nighttime sleep + daytime napping) at baseline; average daily total sleep duration grouped into five categories	Diagnosis of dementia based on DSM-IV; etiologic classification (e.g., AD); vascular dementia; dementia associated with Parkinson's disease) based on acceptable clinical criteria	**Adjusted RR (95% CI)** **All Dementia / AD** **≤5h**: 1.87 (0.85, 4.15) / 2.40 (0.86, 6.66) **6h**: 1.13 (0.48, 2.69) / 1.50 (0.50, 4.48) **7h**: 1 [Reference] / 1 [Reference] **8h**: 2.05 (0.97, 4.31) / 3.17 (1.22, 8.28) **≥9h**: 2.18 (1.09, 4.37) / 2.58 (1.02, 6.50)	- Adjusted for age, education, smoking, and drinking. - Not adjusted for physical activities, depression, and other CVD-related clinical characteristics
Yaffe et al. [15]	A 4.7-year (median) follow-up study on 298 women (aged 82.1 ±3.2 years) in the Study of Osteoporotic Fractures' Sleep and Cognition Study	Home-based polysomographic measure of total sleep time, coded into tertiles	- Centrally adjudicated diagnosis of dementia based on DSM-IV criteria; MCI based on the modified Petersen's criteria	Adjusted OR (95%CI) ***Sleep duration (min)*** **Low (median: 269.9)**: 1 [Reference] **Mid (median: 358.2)**: 0.58 (0.31, 1.09) **High (median: 425.5)**: 0.83 (0.46, 1.51)	- Adjusted for age, race, BMI, education, smoking, diabetes, hypertension, and medication (antidepressants, benzodiazepines, or nonbenzodiazepine anxiolytics) - Not adjusted for alcohol use, physical activities, and depressive symptoms
Hahn et al. [14]	9-year follow-up of 214 Swedish adults who were aged ≥75 years at baseline and participated in the phase-II clinical examination including sleep assessment for the Kungsholmen Project	Self-reported change in sleep pattern ("a subjective feeling of reduced duration or depth of sleep compared to the subject's own normal pattern") from Comprehensive Psychopathological Rating Scale at baseline	Diagnosis of dementia based on DSM-IIIR; Diagnosis of AD based on NINCDS-ADRDA criteria, excluding those with MMSE≤23 at baseline or diagnosed with dementia at 3-year visit	- Increased risk for all-cause dementia or AD associated with a self-reported change in sleep pattern (equivalent to a sleep reduction >2 hrs), which became non-significant when depressive symptoms were controlled. Adjusted HR (95% CI) Dementia: 1.50 (0.87, 2.59) AD: 2.77 (0.91, 3.14)	- Adjusted for age, sex, education, and depressive symptoms - Resulting associations unaffected by lifestyle factors (smoking, alcohol use, no physical activity, and living alone) and vascular factors (heart disease, stroke, hypertension, or diabetes)
Studies on Cognitive Declines					

References	Study Design & Population	Measures of Sleep Duration	Neurocognitive Outcomes	Main Findings	Statistical Adjustment for Confounding
Tworoger et al. [12]	2-year study on 1,884 women aged 70–81 years, free of stroke in the in the Nurses' Health Study, excluding antidepressants users and those with depression	Self-reported "total hours of sleep in a 24hour period" in 1986 and 2000	Cognitive impairment: TICS score <31; Other domains: immediate/delayed recalls of East Boston Memory Test; delayed recall of TICS 10-word; categorical fluency (animals); digit span backwards test for working memory and attention	No associations between sleep duration and defined cognitive impairment or declines in cognitive performance	- Adjusted for baseline score, age, education, smoking, physical activity, high blood pressure, living status, mental health index, tranquilizer use, and alcohol consumption. - Not adjusted for CVD-related clinical characteristics.
Potvin et al. [11]	1-year follow-up of 1,664 French-speaking adults aged 65–96 years in the Enquente sur la santé des aines (Survey on Elders' Health)	Sleep duration subscale of the French version of the Pittsburgh Sleep Quality Index at baseline	- MMSE at baseline and 1-year follow-up - Criteria for incident cognitive impairment: (1) follow-up MMSE score <15th percentile according to norms for age, education and sex (~1SD below normal); and (2) a loss of MMSE ≥2 points between baseline and follow-up interviews	**Adjusted OR (95% CI)** **General** / **Amnestic** ***Women*** **≤5 h** 1.31 (0.65, 2.65) / 1.60 (0.56, 4.61) **5–9h** [Reference] / [Reference] **≥9h** 2.10 (1.10, 4.00) / 3.70 (1.49, 9.17) ***Men*** **≤5h** 2.91 (1.24, 6.82) / 4.95 (1.72, 14.27) **5–9h** [Reference] / [Reference] **≥9h** 0.26 (0.03, 2.03) / 0.51 (0.06, 4.26) No statistically significant associations for nonamnestic cognitive impairment	- Adjusted for age, education, baseline MMSE score, anxiety, depressive episodes, psychotropic drug use, cardiovascular conditions score, and chronic diseases. - Not adjusted for lifestyle factors (smoking, alcohol consumption, physical activities)
Keage et al. [10]	10-year follow-up of 2012 cognitively unimpaired individuals ≥65 years from the Healthy Ageing Project subcohort of the MRC Cognitive Function and Ageing Study	Self-reported sleep duration calculated from individual's responses to a series of questions in the Healthy Ageing Project	- MMSE at baseline, 2-year (n=1,658), and 10-year (n=663) follow-up - Cognitive impairment: MMSE score ≤21	V-shaped association between sleep duration and cognitive declines Adjusted OR (95% CI) **2-year** / **10-year** **≤6.5h** 1.94 (1.01, 3.72) / 2.02 (1.17, 3.48) **6.5–8.5h** [Reference] / [Reference] **≥8.5h** 1.50 (0.72, 3.14) / 1.27 (0.64, 2.48)	- Adjusted for sex, age, BMI, and education and cognition at baseline - Not adjusted for lifestyle factors (smoking, alcohol consumption, physical activities), depression, and other CVD-related clinical characteristics
Devore et al. [9]	6.4-year (median) follow-up of 15,385 women ≥70 years and free of stroke	Self-reported "total hours of sleep in a 24hour period" in 1986 (midlife, n=13,052)	4 assessments (each with six tests) over 6 years (1995–2001), including: global function (average score of six tests; TICS	Inverse U-shaped association between late-life sleep duration and average cognition, but no association with trajectories of cognitive function over 6 years	- Adjusted for age, education, shift work history, smoking status, alcohol intake, physical

References	Study Design & Population	Measures of Sleep Duration	Neurocognitive Outcomes	Main Findings	Statistical Adjustment for Confounding
	and depression in the Nurses' Health Study	and 2010 (late-life sleep and depression in the Nurses' Health Study	score) and verbal memory (averaging immediate/delayed recalls from the East Boston Memory Test and TICS 10-word list)	after accounting for learning effects in repeated neuropsychological assessments.	activity, BMI, history of high blood pressure, mental health score, living alone, and tranquilizer use - Not adjusted for other CVD-related clinical characteristics

Abbreviations: AD – Alzheimer's Disease; BMI – Body Mass Index; CVD – Cardiovascular Disease; DSM-III/DSM-IV – Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition/4th Edition; HR – Hazard Ratio; HT – Hormone Therapy; MCI – Mild Cognitive Impairment; MMSE – Mini Mental State Examination; MRC–Medical Research Council; NINCDS-ARDA – National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; OR – Odds Ratio; RR – Relative Risk; TICS – Telephone Interview for Cognitive Status.

CVD-related clinical characteristics: hypertension, diabetes mellitus, hypercholesterolemia, and/or history of cardiovascular disease.