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### Title

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### Permalink

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### Journal

Sleep, 39(9)

### ISSN

0161-8105

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### Publication Date

2016-09-01

### DOI

10.5665/sleep.6104

Peer reviewed

# Sleep Duration and White Matter Quality in Middle-Aged Adults

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**Study Objectives:** Sleep duration has been associated with risk of dementia and stroke, but few studies have investigated the relationship between sleep duration and brain MRI measures, particularly in middle age.

**Methods:** In a prospective cohort of 613 black and white adults (mean age = 45.4 years) enrolled in the Coronary Artery Risk Development in Young Adults (CARDIA) study, participants reported typical sleep duration, dichotomized into moderate sleep duration (> 6 to ≤ 8 h) and short sleep duration (≤ 6 h) at baseline (2005–2006). Five years later, we obtained brain MRI markers of white matter including fractional anisotropy, mean diffusivity, and white matter hyperintensities.

**Results:** Compared to moderate sleepers, short sleepers had an elevated ratio of white matter hyperintensities to normal tissue in the parietal region (OR = 2.31, 95% CI: 1.47, 3.61) adjusted for age, race/sex, education, hypertension, stroke/TIA, depression, smoking status, and physical activity. White matter diffusivity was also higher, approximately a 0.2 standard deviation difference, in frontal, parietal, and temporal white matter regions, among those reporting shorter sleep duration in ( $P < 0.05$  for all).

**Conclusions:** Short sleep duration was associated with worse markers of white matter integrity in midlife. These mid-life differences in white matter may underlie the link between poor sleep and risk of dementia and stroke.

**Keywords:** sleep duration, white matter integrity, white matter hyperintensities, midlife

**Citation:** Yaffe K, Nasrallah I, Hoang TD, Lauderdale DS, Knutson KL, Carnethon MR, Launer LJ, Lewis CE, Sidney S. Sleep duration and white matter quality in middle-aged adults. *SLEEP* 2016;39(9):1743–1747.

## Significance

Despite increasing data linking sleep quality to risk of dementia and stroke, few studies have investigated whether sleep duration is associated with MRI measures of white matter. Among middle-aged adults, short sleep duration was prospectively associated with MRI measures of reduced white matter quality, including elevated white matter diffusivity and white matter hyperintensities. Results indicate that sleep duration could be an important marker of white matter integrity, even in midlife, and support a link between sleep and outcomes like dementia and stroke.

## INTRODUCTION

Abnormal sleep duration has been associated with an increased risk of stroke and dementia.<sup>1–4</sup> Some studies suggest a “j-shaped” pattern of risk in which short and long sleep duration are both associated with elevated risk,<sup>1–4</sup> and meta-analysis indicates that the risk of stroke may be 20% to 50% higher among those with short or long sleep.<sup>3</sup> A number of cross-sectional studies have also demonstrated associations between sleep duration and worse cognitive performance<sup>5–8</sup> with similar findings reported in prospective studies for risk of cognitive decline,<sup>9,10</sup> but with minimal data on associations with white matter quality.

Very few studies have examined structural brain changes in relation to sleep duration even though measures of white matter abnormalities, including greater white matter hyperintensity (WMH) volume, lower fractional anisotropy (FA), and increased mean diffusivity (MD), have been linked to cognitive deficits, dementia, and stroke.<sup>11–15</sup> In one cross-sectional study of older adults, long sleep was associated with worse cognitive function, and among participants with diabetes, increased white matter hyperintensities,<sup>16</sup> while short sleep duration was associated with both cognitive decline and atrophy in another prospective study of healthy older adults.<sup>17</sup> Moreover, it remains unclear how early in the life course these initial brain changes may begin. In this study, we examined the prospective association of sleep duration with MRI markers of white matter quality and cognitive function in a cohort of middle-aged adults. We

hypothesized that short sleep duration would be associated with decreased white matter integrity and worse cognitive function.

## METHODS

Participants were enrolled in the Coronary Artery Risk Development in Young Adults (CARDIA) study, a multi-site, longitudinal cohort of 5,115 adults aged 18–30 at baseline in 1985–1986.<sup>18</sup> At year 20 (our study baseline, 2005–06), 3,549 individuals were enrolled in CARDIA. The CARDIA MRI Ancillary Study (2010–11) included 3 of the 4 CARDIA sites: Birmingham, AL, Minneapolis, MN, and Oakland, CA, and the targeted enrollment for the substudy was 700 individuals with the goal of balancing the distribution of race and sex. A total of 643 participants had complete data for the sleep questionnaire at baseline and also underwent brain MRI and a cognitive assessment 5 years later.<sup>19</sup> Compared to those without MRI data at the 5-year follow up, participants with MRI data were more likely to be white (61.4% vs. 51.2%) and more likely to have a college education (46.2% vs 39.9%,  $P < 0.05$  for both) but not significantly different on gender (53.8% women vs. 57.3%) or age (mean age = 50.4 years vs 50.1 years,  $P > 0.05$  for both). Signed informed consent for participation in the MRI study was obtained separately from the main study with the approval of participating site IRBs.

At baseline, participants completed a questionnaire on sleep habits derived from the Sleep Heart Health Study.<sup>20</sup> Participants

were asked “During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spend in bed).” Sleep duration was recorded as a continuous variable and categorized according to standard criteria (short:  $\leq 6$  h, reference:  $> 6$  to  $\leq 8$  h).<sup>21</sup> The number of participants reporting long sleep duration,  $> 8$  hours per night, was small ( $n = 30$ ), and thus, excluded from this analysis.

The CARDIA MRI Ancillary Study acquired brain MRI markers on 3T MR scanners (Birmingham, AL: Philips 3T Achieva/2.6.3.6 platform; Minneapolis, MN: Siemens 3T Tim Trio/VB 15 platform; and Oakland, CA: Siemens 3T Tim Trio/VB 15 platform) with acquisition parameters and processing previously described in Launer et al.<sup>19</sup> Image processing was performed with an automated pipeline with pre-processing, intermediate, and post-processing quality control steps. Briefly, T1 images were parcellated into anatomical regions of interest (ROIs) by deformable registration to the Jakob Atlas using HAMMER.<sup>22,23</sup> White matter lesions were segmented using a multiparametric, automated algorithm using T1, T2, and FLAIR scans.<sup>23–25</sup> Standard tools were used to calculate FA and MD<sup>26</sup> using custom-developed Insight Toolkit software ([www.itk.org](http://www.itk.org)), with results registered to subject T1 space for segmentation using FSL (<http://www.fmrib.ox.ac.uk/fsl/>). We evaluated associations with white matter indices including FA, MD, and volume of white matter hyperintensities (WMH) for frontal, occipital, parietal, and temporal brain regions. All FA, MD, and volume measures were calculated by summing measurements from the left and right hemispheres. Aggregate measures of total brain WMH volumes were somewhat correlated with MD ( $r = -0.14$ ,  $P < 0.001$ ) but not FA ( $r = -0.07$ ,  $P > 0.05$ ).

Trained interviewers also administered a battery of 3 cognitive tests 5 years after baseline: the Digit Symbol Substitution Test (DSST) which assesses processing speed and executive function (higher scores indicating better cognitive function),<sup>27</sup> the Stroop Test which assesses executive function (an interference score was calculated with lower scores indicating better function),<sup>28,29</sup> and the Rey Auditory Verbal Learning Test (RAVLT) which assesses verbal memory (the delayed score was used with higher scores indicating better function).<sup>30,31</sup>

Baseline measures examined as potential confounders were age, race, sex, education, hypertension, diabetes, stroke/transient ischemic attack (TIA), myocardial infarction, body mass index (BMI), depression,<sup>32</sup> physical activity,<sup>33</sup> smoking, and alcohol consumption. A previous CARDIA study noted a strong interaction between sex and race with regard to sleep measures; thus, we have considered these variables jointly using a 4-level variable (black female, black male, white female, white male).<sup>34</sup> Medical comorbidities were defined from a combination of self-report, medication use and clinic assessments.<sup>19</sup>

Sleep duration categories were compared on a variety of demographic and health characteristics. MD, FA, and cognitive test scores were modeled using linear regression models with robust standard errors. Due to the relatively young age of the cohort, many individuals had no WMH and the distribution was right-skewed. To examine WMH, we used beta regression, which can model skewed distributions bounded between 0 and 1, exclusive. For each region, we took the volume which

was considered abnormal (volume of WMH) and divided by the total region-specific white matter volume, resulting in the proportion of the region considered hyperintense. From a beta regression analysis, an exponentiated regression coefficient of 1.5 would indicate that the ratio of hyperintense to normal volume is 1.5 times higher for the variable associated with the coefficient. Models controlled for age group and for variables that differed ( $P < 0.05$ ) between sleep duration groups. For FA, MD, and WMH volumes, separate models were run for each region. Statistical significance was set at  $P < 0.05$ .

## RESULTS

At baseline, the average age of participants was 45.4 years; 38% were black, and 46% had completed college. Sixty-three percent of participants ( $n = 388$ ) were classified as having moderate sleep duration, and 37% ( $n = 225$ ) had short sleep duration. There were significant differences in the race/sex distribution according to sleep duration, with black men and women representing a larger proportion of atypical sleep duration (Table 1). Short sleepers had higher prevalence of hypertension, stroke, depression, and smoking compared to moderate sleepers, and the average age of participants in the typical sleep duration group was slightly older than those reporting short sleep duration.

Short sleep was associated with abnormalities of white matter integrity (Table 2). In unadjusted models, short sleep was associated with increased MD in the frontal, occipital, parietal, and temporal regions along with decreased FA in the occipital and parietal regions compared to moderate sleep duration. In models adjusted for age, race/sex, education, hypertension, stroke/TIA, depression smoking status, and physical activity, this association persisted for frontal, parietal, and temporal white matter MD. The magnitude of the association was modest—approximately a 0.2 standard deviation difference in each region.

In unadjusted models, short sleep was also associated with increased ratio of abnormal to normal white matter in the parietal region ( $P < 0.001$ ). After multivariate adjustment, short sleep duration compared to moderate sleep duration was associated with increased WMH volume in the parietal region such that the ratio of WMH to normal white matter was 2.3 times higher in participants with short sleep (2.31, 95% CI: 1.47–3.61;  $P = 0.001$ ) (Figure 1). Sleep duration was not associated with WMH volume in frontal, occipital, or temporal regions ( $P > 0.05$  for all). There was no association between short sleep duration and cognitive performance on any of the three cognitive tests after multivariate adjustment (DSST adjusted mean [SD] score for short: 64.0 [1.4] digits vs moderate: 63.8 [1.3] digits; Stroop adjusted mean [SD] score for short: 25.0 [1.1] seconds+ errors vs. moderate: 25.7 [1.0] seconds+ errors; RAVLT adjusted mean score [SD] for short: 7.6 [0.3] words vs moderate: 7.5 [0.3] words;  $P > 0.05$  for all).

## DISCUSSION

We found an association between short sleep duration and MRI markers of white matter abnormality among middle-aged adults. In unadjusted analysis, our results link short sleep to greater MD and lower FA in several brain regions and to increased presence of WMH in the parietal region. After adjusting for age, race/sex, education, hypertension, stroke/TIA, depression

**Table 1**—Demographics and comorbidities of the 613 participants by sleep duration.

	≤ 6 hours (n = 225)	> 6 to ≤ 8 hours (n = 388)	P value
Age (years), mean (SD)	44.9 (3.7)	45.7 (3.3)	0.004
Race/Sex, n (%)			< 0.0001
Black/Female	71 (31.6)	58 (15.0)	
Black/Male	52 (23.1)	54 (13.9)	
White/Female	52 (23.1)	144 (37.1)	
White/Male	50 (22.2)	132 (34.0)	
Education, n (%)			< 0.0001
< 4 y college	143 (63.6)	186 (47.9)	
4 y college +	82 (36.4)	202 (52.1)	
Hypertension, n (%)	61 (27.1)	76 (19.6)	0.03
Diabetes, n (%)	20 (8.9)	23 (6.0)	0.18
Stroke/TIA, n (%)	4 (1.4)	0 (0)	0.02
CES-D > 16, n (%)	36 (16.2)	37 (9.8)	0.02
Body mass index (kg/m <sup>2</sup> ), n (%)			0.35
< 25	45 (20.0)	85 (21.9)	
25–30	91 (40.4)	179 (46.1)	
> 30	89 (39.6)	124 (32.0)	
Current smoking, n (%)	49 (22.0)	55 (14.2)	0.01
Alcohol (drinks/week), mean (SD)	6.0 (9.9)	5.7 (7.8)	0.72
Physical activity, n (%)			0.01
Low	106 (47.1)	148 (38.3)	
Moderate	69 (30.7)	109 (28.2)	
High	50 (22.2)	129 (33.4)	

TIA, transient ischemic attack; CES-D, Center for Epidemiologic Studies Depression Scale; SD, standard deviation.

**Table 2**—Short sleep duration (≤ 6 h) and markers of white matter integrity.

	Short Sleep			
	Unadjusted		Adjusted	
	Standardized Regression Coefficient (95% CI)	P value	Standardized Regression Coefficient (95% CI)	P value
Mean diffusivity				
Frontal	0.23 (0.07, 0.39)	0.006	0.29 (0.11, 0.48)	0.002
Occipital	0.18 (0.02, 0.35)	0.03	0.17 (−0.03, 0.37)	0.10
Parietal	0.21 (0.05, 0.37)	0.01	0.22 (0.02, 0.40)	0.02
Temporal	0.20 (0.04, 0.36)	0.01	0.26 (0.05, 0.45)	0.01
Fractional anisotropy				
Frontal	−0.13 (−0.29, 0.03)	0.10	−0.11 (−0.30, 0.08)	0.26
Occipital	−0.17 (−0.33, −0.01)	0.04	−0.17 (−0.37, 0.03)	0.09
Parietal	−0.24 (−0.40, −0.08)	0.003	−0.17 (−0.35, 0.02)	0.08
Temporal	−0.15 (−0.31, 0.01)	0.07	−0.12 (−0.31, 0.07)	0.23

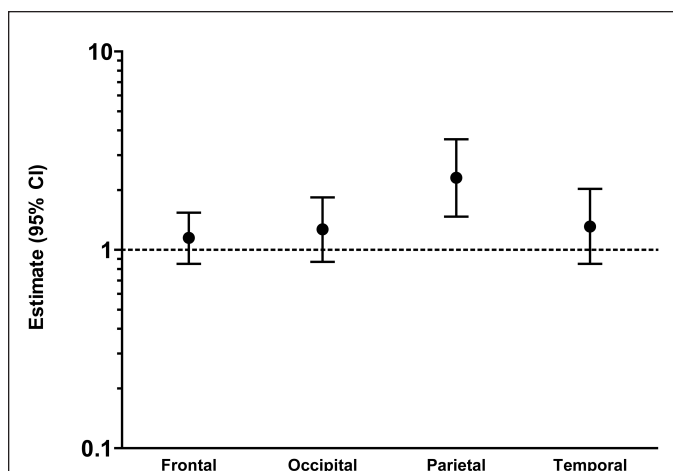
Short sleep duration, ≤ 6 h, was compared to the reference category, > 6 to ≤ 8 h. Estimates for diffusivity and fractional anisotropy (FA) differences from the reference category were derived from linear regression models. All models control for age, race/sex category, education, hypertension, stroke/TIA, depression, smoking, and physical activity.

smoking status, and physical activity, these results remained significant for both MD and WMH volume. We did not identify any cognitive differences between sleep duration groups.

While an increasing number of studies have demonstrated that abnormal sleep duration may be a critical marker for risk of dementia and stroke,<sup>2–4</sup> to our knowledge, this study is one of the first investigations to examine the association between sleep duration and white matter quality in middle-aged adults.

One study of community-dwelling older adults reported that long, but not short, sleep was associated with greater WMH volume but only among those with diabetes.<sup>16</sup> Compared to that cohort of older adults, the burden of cardiovascular disease in our younger study group was lower, and we were not able to assess an interaction with diabetes.

In contrast to our results on cognition, previous studies in older adults have reported significant associations between



**Figure 1**—Association between short sleep duration,  $\leq 6$  hours (reference:  $> 6$  to  $\leq 8$  h) and relative regional white matter hyperintensity volumes. Short sleep duration,  $\leq 6$  h, was compared to the reference category,  $> 6$  to  $\leq 8$  h. Estimates for white matter hyperintensities (WMH) differences from the reference category come from beta regression models and refer to the ratio of WMH in a particular region to the total white matter volume in that region. All models control for age, race/sex category, education, hypertension, stroke/TIA, depression, smoking, and physical activity.

sleep duration and cognitive performance.<sup>8</sup> Two such reports indicate that this relationship may differ with age.<sup>1,35</sup> Due to the relatively young age of our cohort, the pathological damage associated with abnormal sleep duration may not yet be sufficient to affect cognitive function.

We also found that short sleep was linked to elevated MD suggesting an association between sleep duration and regional white matter microstructural abnormalities. Elevated MD and decreased FA are well-established markers for chronic neuroaxonal degeneration, and similar changes have been observed in neurodegenerative processes associated with hypertension,<sup>36</sup> stroke,<sup>37</sup> and AD.<sup>38</sup> Although we found a reduction in white matter FA, the association was no longer significant after adjustment. This could be related to relatively early changes in our middle-aged population that have manifested predominantly as MD elevation, or MD may be a more sensitive marker of damage in cerebral small vessel disease.<sup>39</sup>

The white matter abnormalities associated with sleep duration in our cohort could be an early marker of processes that may intensify later in the life course resulting in further microstructural changes and cognitive impairment. While WMH, and in particular hyperintensities in the parietal lobe, have been associated with increased AD risk,<sup>40</sup> the mechanisms by which abnormal sleep duration may lead to reduced white matter integrity are unclear. Recent studies indicate that sleep is required for the clearance of neurotoxic metabolites such as  $\beta$ -amyloid,<sup>41</sup> and shortened sleep could disrupt this process as suggested in a study of older adults that found that self-reported short sleep was associated with increased  $\beta$ -amyloid deposition.<sup>42</sup> Sleep may also play an essential role in regulating oligodendrocyte proliferation and thus myelination.<sup>43</sup> In addition, abnormal sleep duration could increase metabolic risk factors

including insulin resistance<sup>44</sup> as well as inflammatory factors like c-reactive protein, interleukin-6, and TNF- $\alpha$ ,<sup>45</sup> affecting processes involved in maintenance of neuronal membranes and myelination.<sup>46,47</sup> Finally, data from long-term studies of sleep are limited, but acute sleep deprivation studies have reported disrupted cerebral perfusion and metabolism.<sup>48</sup>

Compared to previous sleep duration studies, the CARDIA study has several key strengths. In particular, this was a large study in a diverse cohort of black and white adults with five years of follow-up. In addition, we were able to adjust for important confounders including cardiovascular comorbidities. Limitations to consider include possible misclassification bias as sleep duration was self-reported. Although sleep duration and MRI outcomes were measured five years apart, assessment of MRI occurred at only one time point rather than over time, and we cannot be certain that MRI abnormalities were not preexisting. As a result, we cannot exclude the possibility of reverse causality. While a small group of studies have demonstrated a consistent association between change in sleep duration and increased risk of cognitive impairment,<sup>8</sup> additional studies are needed to evaluate the association between trajectories of sleep duration and changes in white matter integrity.

Our findings that short sleep duration was significantly associated with white matter quality in midlife suggest that the pathology associated with disturbed sleep duration may begin much earlier in life. These results highlight the potential role of sleep quality in prevention of cognitive aging and stroke across the life course

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## SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication January, 2016

Submitted in final revised form May, 2016

Accepted for publication May, 2016

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## DISCLOSURE STATEMENT

This was not an industry supported study. The Coronary Artery Risk Development in Young Adults Study (CARDIA) is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with the University of Alabama at Birmingham (HHSN268201300025C & HHSN268201300026C), Northwestern University (HHSN268201300027C), University of Minnesota (HHSN268201300028C), Kaiser Foundation Research Institute (HHSN268201300029C), and Johns Hopkins University School of Medicine (HHSN268200900041C). CARDIA is also partially supported by the Intramural Research Program of the National Institute on Aging (NIA) and an intra-agency agreement between NIA and NHLBI (AG0005). The CARDIA Cognitive Function Ancillary Study is supported by NHLBI HL122658. Dr. Yaffe is also supported by NIA K24 AG031155. This manuscript has been reviewed by CARDIA for scientific content. Drs. Yaffe, Carnethon, Lewis, and Sidney report grant support for the CARDIA study NHLBI HL122658, HHSN268201300027C, HHSN268201300025C & HHSN268201300026C, HHSN268201300029C. The other authors have indicated no financial conflicts of interest.