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## Sleep Duration is Associated with White Matter Hyperintensity Volume in Older Adults: The Northern Manhattan Study

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### Summary

Self-reports of long or short sleep durations have indicated an association with cardiovascular morbidity and mortality, but there are limited data evaluating their association with white matter hyperintensity volume (WMHV), a marker of cerebral small vessel disease. We conducted a cross-sectional analysis of self-reported sleep duration to test for a correlation with white matter hyperintensities, measured by quantitative MRI in the Northern Manhattan Study. We used multivariable linear regression models to assess associations between both short (< 6 hours) and long (≥ 9 hours) sleep durations and log-transformed WMHV, adjusting for demographic, behavioral and vascular risk factors. A total of 1244 participants, mean age 70 ± 9 years, 61% women and 68% Hispanics were analyzed with magnetic resonance brain imaging and self-reported sleep duration. Short sleep was reported by 23% (n = 293), and long sleep by 10% (n=121) of the sample. Long sleep ( $\beta = 0.178$ ;  $p = 0.035$ ), but not short sleep ( $\beta = -0.053$ ;  $p = 0.357$ ), was associated with greater log-WMHV in fully adjusted models. We observed an interaction between sleep duration, diabetes mellitus, and log-WMHV ( $p = 0.07$ ). In fully adjusted models, stratified analysis showed that long sleep duration was associated with greater WMHV only in those with diabetes ( $\beta = 0.78$ ;  $p = 0.0314$ ), but not in non-diabetics ( $\beta = 0.022$ ;  $p = 0.2$ ), whereas short sleep was not associated with white matter hyperintensities in those with diabetes or non-diabetics. In conclusion, long sleep duration was associated with a greater burden of white

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matter lesions in this stroke-free urban sample. The association was mainly seen among those with diabetes mellitus.

### Keywords

Elderly; Multi-ethnic; Short sleep; Long sleep; White Matter Hyperintensities; Leukoaraiosis; Diabetes

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## INTRODUCTION

Sleep is an important component of a healthy lifestyle (Grandner et al., 2012). Self-reported short and long sleep durations are associated with increased mortality (Mesas et al., 2010) ischemic stroke, diabetes mellitus, and hypertension (Cappuccio et al., 2011; Gallicchio and Kalesan, 2009).

In a meta-analysis of 15 population-based studies, both short ( 5–6 hours per night) and long (>8–9 hours per night) sleep durations were associated with stroke (Cappuccio et al., 2011); however, the mechanistic pathways for these relationships remain unclear.

One potential pathway linking sleep duration and stroke could be that short and/or long sleep duration results in cerebral small vessel damage. White matter hyperintensities visible on T2-weighted magnetic resonance imaging (MRI) is a subclinical marker of cerebral small vessel damage (Gardener et al., 2012). Of importance, increased white matter hyperintensities predicts future stroke and dementia (Debette et al., 2010)

In our sample, self-reported sleep duration have been associated with subclinical measures of vascular disease (Ramos A, 2013), but this association has not been observed with other sleep symptoms (i.e. snoring), (Ramos-Sepulveda A, 2010). Despite the relation between sleep duration, stroke and subclinical vascular disease, a correlation between sleep duration and white matter hyperintensities has not been investigated. This is of particular relevance to the elderly, where a high prevalence of vascular risk factors and sleep symptoms (i.e., daytime sleepiness and snoring) affect sleep duration (Mesas et al., 2011). In this study, we evaluated the association between sleep duration and white matter hyperintensity volume (WMHV) quantitatively, in a multi-ethnic cohort of elderly, stroke-free people. We hypothesized that short and long sleep durations are associated with greater white matter hyperintensity volume.

## METHODS

### Original Study Population

The Northern Manhattan Study (NOMAS) is a population-based study designed to determine stroke incidence, risk factors, and outcomes in a multi-ethnic cohort (Sacco et al., 2001). The original NOMAS community cohort of 3298 subjects was assembled from a population-based, random sample with the following eligibility criteria: (1) residence in Northern Manhattan for at least 3 months; (2) telephone present in household; (3) age 40 or older at the time of first in-person assessment; and (4) no baseline history of stroke.

## MRI Cohort

Participants remaining clinically free of stroke were recruited sequentially during annual telephone follow-up of the sample using the following criteria: (1) age older than 55; (2) no contraindications to MRI; and (3) willingness to sign written informed consent (Gardener et al., 2012). Of the 3298 NOMAS participants, 2636 were alive and free of stroke in 2003 when the study began recruiting for the MRI sub-cohort. A total of 1290 participants were scanned using a 1.5 tesla MRI system (Phillips, Best, The Netherlands). NOMAS was approved by the Columbia University Medical Center Institutional Review Board and by the University of Miami Institutional Review Board. All participants gave written informed consent.

## White Matter Hyperintensity Volume (WMHV)

The processing of MRI scans to quantitate WMHV has been described previously (Gardener et al., 2012). Briefly, we used axial Fluid-Attenuated Inversion Recovery (FLAIR) images and applied semi-automated measurements of pixel intensity distributions for cerebrospinal fluid and brain white and gray matter in order to identify the optimal threshold to distinguish cerebral spinal fluid from brain matter, using a custom-designed image analysis package (QUANTA 6.2 using a Sun Microsystems Ultra 5 workstation). Inter-rater reliabilities for the MRI measures of intracranial volume (0.97), brain volume (0.97), and WMHV (0.99) from NOMAS images were high (Gardener et al., 2012).

## Sleep symptoms: sleep duration and risk for sleep-disordered breathing

As part of NOMAS, questions about sleep duration, snoring symptoms and daytime sleepiness were administered during annual follow up in 2004–2005 (Boden-Albala et al., 2012). Self-reported sleep duration, was assessed through the following question: “During the past four weeks, how many hours, on average, did you sleep each night?” Responses were noted in 30 minute increments.

Symptoms of sleep-disordered breathing were estimated by constructing the Berlin questionnaire (Netzer et al., 1999) based on reports of frequent snoring and daytime sleepiness, along with information on hypertension and obesity in NOMAS. Sleep variables included categorical responses by the participants to the question, “Do you know, or were you told that you snore?” Questions from the Epworth sleepiness scale (ESS) were adapted for relevance to the northern Manhattan population (Boden-Albala et al., 2012). Participants were asked, on a scale of 0–3, “How often would you say you doze while: (1) sitting and reading, (2) watching TV, (3) sitting inactive in a public place, (4) as a passenger in a car, train or bus, (5) sitting and talking to someone, (6) sitting quietly after lunch without alcohol, and (7) as a driver in a car while stopped for a few minutes in traffic?”

We used a maximum score of 21, instead of 24, for the ESS. The question “How often would you say you doze as a driver in a car while stopped for a few minutes in traffic?” was not applicable to the NOMAS population and not used in our questionnaire. We used a score of 10 to define daytime sleepiness (Boden-Albala et al., 2012).

Habitual snoring was defined as self-reported snoring > 3 times per week, based on prior definitions (Young et al., 2002).

The presence of two out of the three following items was used to classify participants into high-risk for sleep disordered breathing following the criteria of the Berlin questionnaire: (1) frequent snoring (snoring > 3 times per week), (2) daytime sleepiness (summed score  $\geq 10$ ), and/or (3) presence of hypertension or obesity, defined as body mass index (BMI) > 30 kg/m<sup>2</sup>.

### Risk Factor Assessments

Data were collected through interviews by trained bilingual (English and Spanish) research assistants using standardized data collection instruments. Standard techniques were used to measure blood pressure, height, weight and fasting serum glucose, as described elsewhere (Sacco et al., 2001). Race and ethnicity were defined by self-identification based on questions modeled after the US census and categorized into mutually exclusive groups (Black, White, and Hispanic). Education was measured continuously as years of completed formal education. Moderate alcohol use was defined as current drinking of more than one drinks per month but fewer than or equal to 2 drinks per day. Smoking was categorized as never, former, and current. Obesity was defined by a body mass index (BMI) of  $\geq 30$  Kg/m<sup>2</sup>. Hypertension was defined as a systolic BP > 140 mmHg or a diastolic BP > 90 mmHg (average of 2 measurements obtained in sitting position) or use of antihypertensive medications. Diabetes mellitus was defined as fasting blood glucose  $\geq 126$  mg/dl, or the patient's self-report of diabetes or use of insulin or hypoglycemic medications. Cardiac disease included reports of angina pectoris, myocardial infarction, coronary artery disease (CAD), atrial fibrillation or heart failure. We also controlled for sedative medications. We created a dichotomous variable (yes vs. no) based on the use of any of the following medications: antidepressants, antiepileptic, pain, and antipsychotic medications.

### Statistical Analysis

The Chi-Square test was used to compare proportions, while ANOVA was used to compare means for continuous variables. White matter hyperintensity volume (WMHV) was expressed as a proportion of total cranial volume to correct for head size and was log-transformed (log-WMHV) to create a normal distribution. To evaluate the association between white matter hyperintensities and sleep duration, we performed linear regression with log-WMHV as the outcome, sleep duration as the main exposure, and other covariates as independent variables. We performed linear regression to evaluate the association with white matter hyperintensities for the categories of short-duration sleep, defined as < 6 hours, and long-duration sleep, defined as  $\geq 9$  hours, using 6 to < 9 hours of sleep as the reference group (Gallicchio and Kalesan, 2009, Cappuccio et al., 2011). In our models, we adjusted for the covariates that have been associated with increased white matter hyperintensities in NOMAS or that differ among the sleep duration groups. We first evaluated the unadjusted relation between sleep duration, centered at 7 hours of sleep, and log-WMHV. We sequentially adjusted for age, race/ethnicity, Medicaid or no insurance status, years of education and obesity (Model 2). We further adjusted for the following behavioral and vascular risk factors: former and current tobacco use, moderate alcohol consumption,

diabetes mellitus, hypertension and cardiac disease (Model 3). Finally, we adjusted for habitual snoring and daytime sleepiness (Model 4). We fitted logistic regression models with white matter hyperintensity volumes  $> 1$  standard deviation (SD) above the age-predicted mean, defined it as “large” white hyperintensity volumes, and analyzed as a binary outcome to calculate the odds ratio (OR) and 95% confidence interval (CI) (Hudson et al., 2011). We explored interactions between sleep duration and each covariate on log-WMHV. Stratified analysis was done at  $p < 0.1$ . All statistical analyses were performed using SAS version 9.3 (Cary, North Carolina).

## RESULTS

Data on sleep duration and white matter hyperintensity volumes were available for 1244 participants. The mean sleep duration was  $6.7 \pm 1.6$  hours. In our sample, long sleepers were older, had fewer years of formal education and had a greater frequency of having Medicaid or no insurance, diabetes mellitus, cardiac disease, and increased white matter hyperintensities (Table 1). We did not observe differences in race-ethnicity across the sleep duration groups. In addition, there were no differences in the frequency of hypertension, smoking status, obesity and the use of sedative/psychoactive medications such as antidepressants, antiepileptic, pain and antipsychotic across the sleep duration groups. There were no differences in the mean daytime systolic and/or diastolic blood pressure (BP).

When examined continuously, there was a bivariate association between longer sleep, centered at 7 hours, and greater log-WMHV ( $\beta = 0.042$ ; standard error (SE) = 0.015,  $p = 0.011$ ). This association remained after adjustments were made for age at MRI (Model 1), or sex, race/ethnicity, years of education, insurance status and obesity (Model 2). We further adjusted for former and current tobacco use, moderate alcohol consumption, hypertension, diabetes, and history of cardiac disease (Model 3). The association remained after final adjustments were made by including habitual snoring and daytime sleepiness in the final model (Model 4; Table 2). Examining categories of sleep duration revealed an association between long sleep duration ( $\geq 9$  hours) with greater white matter hyperintensity volume compared to 6 –  $< 9$  hours of sleep ( $\beta = 0.32$ ; SE = 0.091,  $p = 0.004$ ). There was an association between long sleep duration and “large” white matter hyperintensity (odds ratio: 1.67; 95% CI, 1.17–2.32) that remained after adjustment for demographic factors, but was mildly attenuated when adjusting for vascular risk factors and sleep symptoms. There was no association between short sleep duration and WHMV in bivariate ( $\beta = -0.35$ ; SE = 0.063,  $p = 0.57$ ) or adjusted models, when compared to the reference (Table 2). We performed a sensitivity analysis evaluating the differences between controlled and uncontrolled blood pressure (BP) in those with hypertension ( $n = 918$ ) among the sleep duration groups. Uncontrolled BP was defined as systolic BP  $> 140$  mm Hg or diastolic BP  $> 90$  mm Hg at the time of MRI in those with hypertension. We did not observe a difference between controlled and uncontrolled BP among the sleep duration groups ( $p = 0.248$ ). We further evaluated for differences in the risk for sleep disordered breathing by evaluating for an interaction between long sleep duration and obesity as a surrogate for sleep disordered breathing, provided that snoring symptoms may have been underestimated in our sample. We did not observe an interaction between long sleep duration and obesity in our sample ( $p = 0.875$ ). There was evidence of diabetes mellitus being an effect modifier between sleep

duration and white matter hyperintensity volumes in our fully adjusted model (sleep hours in DM,  $\beta = 0.077$ ;  $SE = 0.042$ ,  $p = 0.07$ ). After stratifying by diabetes status, longer sleep duration was associated with greater white matter hyperintensity volume only in those with diabetes, but not in those without diabetes (Table 3). The median number of years since the initial diagnosis of diabetes was 12.0 (range = 1 – 55). The duration of diabetes ( $p = 0.17$ ) was not associated with both long sleep and log-WMHV. There was no interaction between sleep duration and the other covariates associated with log-WMHV.

## DISCUSSION

To the best of our knowledge this is the first study to examine the association between sleep duration and white matter hyperintensity volume. In this analysis, those that reported 9 hours of sleep had increased white matter hyperintensity volume, a marker of cerebral small vessel disease and predictor of future stroke and dementia (DeBette et al., 2010). In elderly cohorts, long sleep is predictive of mortality independent of demographic and vascular risk factors, and cognitive function (Mesas et al., 2010, Cohen-Mansfield and Perach, 2012). Some suggest that the association between long sleep with adverse health outcomes and stroke is confounded by measures of sleep-disordered breathing, obesity, low socioeconomic status (SES) and race/ethnicity (Youngstedt et al., 2013, Zizi et al., 2012). In our study these factors did not modify the relation between long sleep duration and white matter hyperintensity volume.

We observed increased white matter hyperintensities in those with longer sleep and diabetes mellitus but not in those without diabetes. Several studies have found associations between diabetes and white matter hyperintensities (van Harten et al., 2006, Zizi et al., 2010) while others have not (van Harten et al., 2006, Biessels et al., 2006). In addition, long sleep duration (9 hours) has been linked to type-2 diabetes, impaired glucose tolerance and increased HbA1c levels (Gangwisch et al., 2007, Nakajima et al., 2008). A prospective study of 1139 men showed that long sleepers (>8 hours), when compared to average sleepers (6–8 hours), were three times more likely to develop diabetes over 15 years (Yaggi et al., 2006). In NOMAS, white matter hyperintensities has been associated with glycation end-products (Hudson et al., 2011) and with markers of inflammation (Wright et al., 2009). These factors have been associated with extremes of sleep duration by others (Patel et al., 2009, Zizi et al., 2010) and could contribute to increased white matter hyperintensities in diabetes and long sleep.

The presence of white matter hyperintensities provides indirect evidence of an ischemic process, but the mechanism by which long sleep duration might be linked to white matter hyperintensities is not defined. In our study, measures of daytime BP did not modify the association between long sleep duration and white matter hyperintensity volume, but we did not measure nocturnal BP. In a different study, long sleepers had increased nocturnal systolic BP and increased frequency of ‘non-dipping’ of BP during sleep measured by 24-hour ambulatory blood pressure monitoring (Ramos, J.Z., Rundek et al., 2013). Increased nocturnal systolic BP is a strong predictor of stroke and vascular events in diabetics (Nakano et al., 2004), and ‘non-dipping’ of BP during sleep predicts cardiovascular mortality and stroke (Kim et al., 2011, Ohkubo et al., 2002). It is plausible that in our cohort, long sleepers

may have increased nocturnal systolic BP and ‘non-dipping’ of BP during sleep, factors that are associated to increased white matter hyperintensities (Schwartz et al., 2007).

Sleep Fragmentation could also explain the association between long sleep and white matter hyperintensities. Sleep fragmentation has been associated to long sleep duration and to increased sympathetic tone and nocturnal hypertension - factors that may lead to increased white matter hyperintensities. (Barone and Menna-Barreto, 2011, Shaw et al., 2008).

In addition, impaired cerebrovascular function during sleep could also account for the results of our study. Decreased cerebrovascular perfusion, increased cerebrovascular resistance and impaired vasomotor reactivity by transcranial doppler ultrasound, along with “non-dipping” of blood pressure, have been correlated with white matter hyperintensities in diabetes (Perk et al., 2002, Novak et al., 2006).

We did not observe an association between short sleep duration and white matter hyperintensity volume. Short sleep is linked to an increased sympathetic tone, hypertension and insulin resistance in studies composed mostly of young to middle age adults (Gangwisch et al., 2006, Gottlieb et al., 2006). These traditional vascular risk factors, which were highly prevalent in our sample, could explain most of the variance between short sleep and white matter hyperintensity volume in our elderly cohort.

The strengths of our study are the evaluation of a large, multiethnic, community-based cohort with reliable and systematically applied measures of cardiovascular risk and white matter hyperintensities by magnetic resonance imaging. However, our study is cross-sectional, which prevents us from drawing any causal inferences. We did not obtain objective measurements of sleep time and sleep fragmentation (i.e., actigraphy or polysomnography), but epidemiologic studies of long sleep and adverse health outcomes are mainly based on subjective reports from questionnaires (Youngstedt and Kripke, 2004). Self-reported sleep duration does not allow differentiating between total sleep time and time in bed. However, time in bed and objective measures of total sleep time are highly correlated, and reported long-duration sleep could be indicative of physiologic sleep in the elderly (Youngstedt et al., 2013, Patel et al., 2012). Moreover, studies that have discriminated between total time in bed and total sleep time have found similar mortality associations with both measures (Kojima et al., 2000; Gale and Martyn, 1998).

In conclusion, we found a cross-sectional association between self-reported long sleep duration and increased WMHV after adjusting for demographic, behavioral and vascular risk factors. Diabetes mellitus modified the association between long sleep duration and white matter hyperintensities, but longitudinal studies are needed to understand the interplay between long sleep, impaired glucose and cerebral small vessel disease.

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**Table 1**

Demographics, vascular risk factors and sleep symptoms across the sleep duration groups

Mean ± SD or n (%)	Total N = 1244	< 6 h 293 (23)	6 –<9 h 830 (67)	9 h 121 (10)
<b>Demographics</b>				
Age, years, mean ± SD	70.0 ± 9.0	70.0 ± 9.0	70 ± 9.0	73 ± 9.0 **
Women	756 (61)	186 (64)	503 (61)	67 (55)
Education, years, mean ± SD	9.6 ± 5.1	9.4 ± 4.9	9.9 ± 5.2	8.6 ± 4.7 *
Medicaid or no insurance	410 (33)	89 (31)	265 (32)	56 (46) **
<b>Race/Ethnicity</b>				
Non-Hispanic white	180 (15)	43 (15)	121 (15)	16 (14)
Non-Hispanic Black	210 (17)	52 (18)	140 (17)	18 (15)
Hispanic	826 (68)	192 (67)	550 (68)	84 (71)
<b>Behavioral and Medical Factors</b>				
Moderate Alcohol	511 (41)	96 (33)	370 (45) **	45 (38)
Current smoker	203 (16)	40 (14)	135 (16)	28 (23)
Former smoker	452 (36)	113 (39)	299 (36)	40 (33)
Obesity (BMI ≥ 30 Kg/m <sup>2</sup> )	424 (34)	107 (37)	275 (33)	42 (35)
Diabetes Mellitus	191 (15)	39 (13)	120 (15)	32 (27) ***
Hypertension	918 (74)	216 (73)	613 (74)	89 (74)
Systolic BP, mm Hg, mean ± SD	136.3 ± 17.5	135.8 ± 17.2	136.5 ± 17.4	135.7 ± 18.6
Diastolic BP, mm Hg mean ± SD	78.0 ± 9.6	78.5 ± 9.4	78.0 ± 9.8	77.3 ± 9.1
Psychoactive medications <sup>^</sup>	263 (21)	72 (25)	161 (20)	30 (25)
Cardiac Disease	207 (17)	50 (17)	126 (15)	31 (25) *
High Risk for SDB	164 (13)	39 (14)	109 (13)	16 (13)
Frequent snoring	272 (22)	62 (21)	181(22)	29 (24)
Daytime Sleepiness	160 (13)	40 (14)	108 (13)	12 (9)
<b>WMHV, mean ± SD<sup>£</sup></b>	<b>0.66 ± 0.81</b>	<b>0.61 ± 0.72</b>	<b>0.65 ± 0.82</b>	<b>0.82 ± 0.85 **</b>

SDB: Sleep Disordered Breathing

\* p &lt; 0.05,

\*\* p &lt; 0.001,

\*\*\* p &lt; 0.0001

WMHV: White matter hyperintensity volume

<sup>£</sup>The p value is based on the comparison of log-WMHV<sup>^</sup>Psychoactive medications: self-reported use of antidepressant, antiepileptic, pain and/or antipsychotic.

**Table 2**

Association between Sleep Duration and White Matter Hyperintensity Volume.

	Model 1		Model 2		Model 3		Model 4	
Outcome: Log-WMHV	$\beta$ (SE) per hour	p	$\beta$ (SE) per hour	p	$\beta$ (SE) per hour	p	$\beta$ (SE) per hour	p
<b>Sleep duration</b>								
Centered at 7 h	0.035 (0.015)	0.022	0.034 (0.015)	0.022	0.035 (0.015)	0.023	0.034 (0.015)	0.027
<b>Categorical</b>								
< 6 hours	-0.054 (0.058)	0.354	-0.046 (0.057)	0.418	-0.046 (0.057)	0.421	-0.045 (0.057)	0.43
6- < 9 hours	--	--	--	--	--	--	--	--
9 hours	0.217 (0.084)	0.010	0.202 (0.083)	0.015	0.185 (0.084)	0.027	0.176 (0.084)	0.035
<b>Outcome: Large WMH</b>								
< 6 hours	OR 0.87	95% CI 0.66-1.13	OR 0.88	95% CI 0.67-1.16	OR 0.88	95% CI 0.66-1.15	OR 0.88	95% CI 0.66-1.16
6- < 9 hours	--	--	--	--	--	--	--	--
9 hours	1.55	1.13-2.28	1.56	1.15-2.31	1.47	0.98-2.19*	1.43	0.96-2.14 <sup>^</sup>

Model 1: Adjusted for age at MRI.

Model 2: As Model 1, sex, year of education, race/ethnicity, Medicaid or no insurance and obesity.

Model 3: As Model 2, moderate alcohol, former smoker, current smoker, diabetes, hypertension and cardiac disease.

Model 4: As Model 3, habitual snoring and daytime sleepiness.

\* p=0.058

<sup>^</sup> p=0.07

**Table 3**

Sleep Duration and WHMV in diabetics and non-diabetics

	Diabetes			No diabetes		
	$\beta$	SE	<i>p</i>	$\beta$	SE	<i>p</i>
Centered at 7 hours	0.078	0.036	0.0314	0.022	0.017	0.20
< 6 h hours	- 0.138	0.159	0.386	- 0.0353	0.063	0.577
6- < 9 hours		-----			-----	
9 hours	0.323	0.156	0.039	0.067	0.083	0.415

Adjusted for age at MRI, sex, years of education, race/ethnicity, Medicaid or no insurance, obesity, moderate alcohol, former and current smoker, hypertension, cardiac disease, snoring symptoms and daytime sleepiness.