Sleep duration and vascular inflammation using hybrid positron emission tomography/magnetic resonance imaging: results from the Multi-Ethnic Study of Atherosclerosis

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Study Objectives: Short sleep duration (SD) is associated with cardiovascular disease. We investigated the relationship between objective SD and subclinical atherosclerosis employing hybrid positron emission tomography/magnetic resonance imaging with 18F-FDG tracer in the MESA cohort.

Methods: We utilized data from Multi-Ethnic Study of Atherosclerosis-SLEEP and Multi-Ethnic Study of Atherosclerosis-PET ancillary studies. SD and sleep fragmentation index (SFI) were assessed using 7-day actigraphy. The primary and secondary outcomes were carotid inflammation, defined using target-to-background ratios, and measures of carotid wall remodeling (carotid wall thickness), summarized by SD category. Multivariable linear regression was performed to assess the association between SD and SFI with the primary/secondary outcomes, adjusting for several covariates including apnea-hypopnea index, and cardiovascular disease risk.

Results: Our analytical sample (n = 58) was 62% female (mean age 68 ± 8.4 years). Average SD was 5.1 ± 0.9 hours in the short SD group (≤6 h/night, 31%), and 7.1 ± 0.8 hours in the normal SD group (69%). Prevalence of pathologic vascular inflammation (maximal target-to-background ratio > 1.6) was higher in the short SD group (89% vs 53%, P = .01). Those with short SD had a higher maximal target-to-background ratio (1.77 vs 1.71), although this was not statistically significant (P = .39). Carotid wall thickness was positively associated with SFI even after adjusting for covariates (Beta [standard error] = 0.073 ± [0.032], P = .03).

Conclusions: Prevalence of pathologic vascular inflammation was higher among those who slept ≤6 hours, and vascular inflammation was higher among those with a SD of ≤6 hours. Interestingly, SFI was positively associated with carotid wall thickness even after adjustment for covariates. Our results are hypothesis generating but suggest that both habitual SD and SFI should be investigated in future studies as potential risk factors for subclinical atherosclerosis.

Keywords: actigraphy, sleep duration, sleep apnea, PET/MRI, vascular inflammation, TBR, atherosclerosis, MESA


INTRODUCTION

The American Academy of Sleep Medicine and Sleep Research Society recommend an average of 7–8 hours of sleep per night to promote optimal health.1,2 Despite this, the Centers for Disease Control and Prevention reports that 35% of the general population—an estimated 86.3 million US adults—sleep less than 7 hours in a 24-hour period.3 Additionally, a bedroom poll conducted by the National Sleep Foundation revealed over 40% of adults reporting a habitual sleep time below the recommended 7 hours of sleep.4 These data underscore the widespread epidemic of chronic sleep deprivation and habitual short sleep duration (SD) in the United States.

Sleep is fundamental in regulating the autonomic nervous system, metabolism, and endocrine functions, and the impact of short SD on cardiometabolic health is an emerging area of interdisciplinary research.5 Although both excessively short SD and long SD are associated with cardiovascular disease (CVD),6–11 experimental evidence validating mechanisms by which long SD may increase CVD risk remains unclear. On the other hand, several experimental studies have investigated mechanisms resulting in increased cardiometabolic risk due sleep restriction. Proposed
Mechanisms include inflammation, metabolic dysregulation, and increased autonomic instability, which may over time lead to accelerated atherosclerosis and result in the development of hypertension, diabetes, or CVD. For instance, short SD is associated with obesity (odds ratio 1.55, CI 1.43–1.68), diabetes (relative risk 1.28, CI 1.03–1.60), and CVD (odds ratio 2.20, CI 1.03–1.60), including coronary heart disease (relative risk 1.48, CI 1.22–1.80) and stroke (relative risk 1.15, CI 1.0–1.31). Short SD (5–6 hours) is also associated with endothelial dysfunction and subclinical atherosclerosis, which may increase the risk of CVD events.

Although the aforementioned evidence suggests an independent association between short SD and CVD, most studies are limited by subjective (eg, self-reported) assessments of SD. Objectively measured SD using actigraphy provides a more robust and reliable method of assessing habitual SD. Additionally, these studies do not concomitantly assess for sleep apnea, which is an important confounder of the relationship between SD and CVD.

Lastly, assessment of atherosclerosis in existing studies evaluates the association between SD and atherosclerosis, which is often limited by use of vascular ultrasound, used to measure carotid intima media thickness (CIMT). Of note, CIMT may not accurately predict CVD risks and is not a measure of plaque inflammation, which is a more robust predictor for future risk of CVD events. Arterial FDG uptake indicates increased proinflammatory macropage activity within the arterial wall, and is therefore a robust measure of inflammation within atherosclerotic plaques. Furthermore, studies have shown that FDG uptake has proven to be a useful prognostic tool in identifying patients most at risk for early CVD recurrence.

In 2016, the American Heart Association released a scientific statement emphasizing the importance of short SD in the development of adverse cardiometabolic risk. The statement also called for more observational and clinical studies examining the link between SD and disorders of cardiometabolic health while prioritizing diverse populations with women and minorities, as well as objective measures of sleep behavior. Therefore, our study attempts to address important knowledge gaps in this field by utilizing novel ways to assess subclinical atherosclerosis in an ethnically diverse population with objective measures of habitual SD. Our study utilizes the Multi-Ethnic Study of Atherosclerosis (MESA) cohort to investigate the relationship between objectively measured SD and subclinical carotid vascular inflammation using hybrid FDG PET/MRI in patients with objective assessments for sleep apnea.

MESA is a multisite prospective cohort study designed to investigate the prevalence and progression of subclinical CVD and identify CVD risk factors in a diverse sample. A total of 6,814 men and women between the ages 45 and 84 years were recruited from 2000 to 2002 across the 7 US communities. Participants were either non-Hispanic white, Chinese-American, Hispanic, or black, and were free of clinically apparent CVD at the time of recruitment. The current analysis uses data from the MESA SLEEP (2010–2013) and MESA PET ancillary study (2016–2020), detailed below.

**METHODS**

The MESA PET ancillary study (MESA Exam 6) recruited patients between November 2016 to December 2020. The study was approved by the Columbia University institutional review board (IRB AAAQ1318), and the participants provided written informed consent. The primary focus of the MESA PET study was to examine cholesterol efflux capacity in relation to plaque inflammation and morphology measured using PET/MRI. The study recruited 215 individuals from 3 sources: 1) the Icahn School of Medicine at Mount Sinai (n = 37), 2) the MESA cohort (n = 100), and 3) the Columbia University Neurovascular Laboratory (n = 78) (Figure 1), all of whom underwent a PET/MRI scan. The inclusion criteria for all 3 recruitment sources included presence of carotid plaque on a prior ultrasound study. One patient (recruited from Columbia University) dropped out of the study 1-year following the scan. There were no dropouts among those recruited from the MESA cohort or from Mount Sinai.

**Image acquisition/analysis**

Eligibility for PET/MR imaging in the participants recruited from the original MESA cohort required presence of carotid plaque on the original MESA ultrasound scan. In the current analysis, we included patients from the MESA cohort recruitment source (who underwent PET/MRI), and also had prior PSG/actigraphy data as a part of the MESA Sleep Ancillary Study.

**Figure 1—Flow chart of analytic cohort.**

MESA PET recruited 215 patients from three sources. In the current analysis, we included patients from the MESA cohort recruitment source (who underwent PET/MRI), and also had prior PSG/actigraphy data as a part of the MESA Sleep Ancillary Study. MESA = Multi-Ethnic Study of Atherosclerosis; PET/MRI = positron emission tomography/magnetic resonance imaging; PSG = polysomnography.
prior MESA ultrasound examination. Image acquisition and analysis (PET/MRI imaging studies of the extracranial carotid arteries) was conducted at the Biomedical Engineering and Imaging Institute) at Mount Sinai. PET/MRI scans were done using a single machine (Siemens Biograph 3T mMR scanner) that acquires the PET and MRI images simultaneously. Participants were injected with $^{18}$F-FDG radiotracer (10 millicurie [mCi]) for a circulation time of 90 minutes prior to PET scanning. PET data were obtained for both the carotid arteries, and the imaging protocol lasted for approximately 60 minutes. Vascular inflammation in the carotid arteries was quantified using target-to-background ratios (TBR), a well-validated method of measuring global vascular inflammation. TBR reflects arterial wall FDG uptake normalized to venous blood pool mean uptake, obtained by measuring mean and maximum standardized uptake values in the arterial walls (at the carotid bifurcation), divided by the mean standardized uptake value of the background, measured in the venous lumen blood. Previous analysis by Biomedical Engineering and Imaging Institute has demonstrated high intraobserver (0.93 and 0.98) and interobserver (0.90 to 0.97) agreement for this approach.

TBR$_\text{mean}$, TBR$_\text{max}$, and TBR$_\text{most-diseased segment}$ scores were calculated for each of the participants in the carotid arteries. The primary outcome for this study was average TBR$_\text{max}$ of the left and right carotid arteries. Additionally, MRI measurements for mean carotid wall thickness (CWT), wall area, and total vessel area were also obtained for the left and right carotid arteries as a secondary outcome measure. On all images deemed to be of sufficient quality, inner and outer vessel wall boundaries were traced for both the common carotids. Mean lumen diameter, vessel diameter, lumen area, wall area, total vessel area, mean wall thickness, and normalized wall thickness for each slice were calculated based on the contours drawn using a customized software program. Wall thickness measurements were obtained at evenly spaced positions along the circumference of the vessel wall. The normalized wall index (NWI) is the wall area divided by total vessel area used to account for differences in size of the arteries within each patient in an attempt to normalize wall areas for patient size.

In the analysis reported in our study, we included only individuals from the MESA cohort recruitment source who also had sleep data as part of the MESA protocol. This resulted in a total of 58 individuals with data for plaque inflammation and morphology (PET/MRI scans) from MESA PET, with actigraphy/PSG data from the MESA SLEEP ancillary study (Figure 1).

**MESA SLEEP**

The MESA SLEEP ancillary study was conducted between 2010 and 2013 as a part of MESA Exam 5 and collected PSG and actigraphy data in participants of the MESA cohort. Details regarding MESA PSG and actigraphy methodology were previously published. Participants who reported not regularly using treatment for sleep-disordered breathing were invited to participate in the MESA SLEEP ancillary study, which consisted of PSG, actigraphy, and sleep questionnaires collected during in-home examination.

**Actigraphy**

Actiwatch Spectrum wrist actigraphy (Philips Respironics, Murrysville, PA) was used on the nondominant wrist for 7 consecutive days in conjunction with a sleep diary. A minimum of 4 weekdays and 1 weekend day was required for analysis. Actigraphic data were scored in 30-second epochs as sleep or wake using Actiware-Sleep version 5.59 software as previously described. SD was calculated as the sum of epochs scored as sleep in each main sleep interval (identified based on a self-actuated event marker, sleep diary, and light sensor) averaged over all days of recording. Poor sleep quality was defined as having sleep maintenance efficiency (percentage of sleep time after sleep onset/sleep period) $<$ 85%. Sleep fragmentation is measured as an index of restlessness during the sleep period. It is the sum of the percent mobile epochs and the percent immobile bouts $<$ 1 minute in duration, to the number of immobile bouts for a given interval. The sleep fragmentation index (SFI) was defined as the percentage of average fragmentation index during main sleep across all days.

**PSG**

The Compumedics Somte devices (Compumedics Ltd, Abbotsville, Australia) were used to conduct in-home PSG using procedures previously described. The apnea-hypopnea index (AHI) definition was used based on the 2007 American Academy of Sleep Medicine alternative hypopnea criteria. An apnea was defined as 90% reduction in airflow lasting for 10 seconds or longer. Hypopneas were defined as a 50% or more reduction in airflow for 10 seconds or longer in association with at least a 3% desaturation or arousal. The AHI was defined as the sum of all apneas plus hypopneas divided by total sleep time. Presence of sleep apnea was defined based on an AHI cut-off of 5 events/h or greater.

**Sleep questionnaires**

A portion of the MESA SLEEP questionnaires included the Women’s Health Initiative Insomnia Rating Scale (WHIIRS) to measure insomnia. The WHIIRS is a validated 5-item insomnia scale, which assesses insomnia symptoms, including long sleep latency, sleep maintenance insomnia, early morning awakening, and poor sleep quality over the past 4 weeks. The score ranges from 0 to 4 for each item (0 to 20 total score range). Insomnia was defined as a WHIIRS score $\geq$ 10.

**Sample size and statistical analysis**

As previously reported, we analyzed data for participants recruited from the original MESA cohort for the MESA PET ancillary study, who also had actigraphy and PSG data available from MESA SLEEP. This resulted in a sample size of $n = 58$, which included all participants with available data on both sleep and plaque measures. All participants also had self-reported sleep data (including WHIIRS) obtained via sleep questionnaires. Baseline characteristics as well as the outcome measures (TBR values, carotid wall measurements) of the study sample were summarized using descriptive statistics. For the purpose of our analysis, participants were categorized into those with short SD ($\leq$ 6 h/night) or normal/longer SD ($>$ 6 h/night), with baseline characteristics and outcomes compared using unpaired t-tests.
We used a 6-hour cut-off because prior studies have demonstrated that < 6 h/night is associated with atherosclerosis and endothelial dysfunction.\textsuperscript{22–25,48} A TBR value of > 1.6 has been shown to be an independent predictor for the occurrence of a vascular event.\textsuperscript{34} Therefore, presence of pathologic vascular inflammation in both SD groups was defined as TBR > 1.6. These groups were then compared using the chi-square test.

Multivariable linear regression was used to assess the association between continuous measures of SD and SFI with TBR and carotid wall measurements, adjusting for a limited number of confounders. Model 1 was unadjusted; Model 2 was adjusted for age, sex, race/ethnicity, body mass index (BMI), and AHI (3\% O\(_2\) desaturation and/or arousals, log transformed), and Model 3 was adjusted for the atherosclerotic cardiovascular disease (ASCVD) risk score and BMI. The ASCVD risk score is used to estimate 10-year ASCVD risk in adults 40 to 79 years of age who are free from CVD.\textsuperscript{49} All analyses were conducted at the .05 2-sided significance level.

RESULTS

Baseline characteristics

Demographics

A total of 58 participants from MESA PET had acceptable PET/MRI imaging, actigraphy, PSG data, and self-reported sleep data.
Table 1 reports the baseline characteristics of the cohort by SD category. Mean age was 68.0 ± 8.4 years, and the majority of the sample (62%) was female. The cohort was predominantly Hispanic (48%), with 26% white, and 26% black participants. Overall, there were no significant differences in the baseline characteristics between the 2 groups. However, those with short SD (≤ 6 hours) were more likely to have a lower mean BMI than those with longer SD (P = .04). The demographic distribution of our study was similar to the overall MESA and MESA SLEEP ancillary cohort, although our sample had a higher proportion of Hispanic participants.

### Sleep characteristics

Table 1 also provides sleep characteristics by SD category in our sample, where mean SD was 6.5 ± 1.2 hours. This was similar to the mean hours of sleep measured via actigraphy in the parent MESA SLEEP ancillary cohort, 6.5 ± 1.2 hours, normally distributed. The prevalence of short SD (≤ 6 hours) was 31% (18/58) in our sample. Those in the short SD group had an average total SD of 5.1 ± 0.9 hours compared to those in the long SD group, with an average total SD of 7.1 ± 0.8 hours. The average SFI in the overall sample was 20.2 ± 6.9. A majority of the sample (88%) had a clinically adequate sleep efficiency (≥ 85%) and did not have insomnia based on the WHIIRS (67%). The prevalence of sleep apnea was 83% (AHI ≥ 5 events/h), 52% of whom had a mean BMI than those with longer SD (P = .02), and adjusted analyses (Model 2, CWT Beta [SE] = 0.069 ± [0.032], P = .03; and Model 3, CWT Beta [SE] = 0.073 [SE 0.032], P = .03). Normalized wall index (representing arterial wall area normalized for the difference in size of arteries) was weakly and positively associated with SFI in adjusted analysis (Table S1 in the supplemental material; Model 3, normalized wall thickness Beta [SE] 0.016 ± [0.0092] P = .09). There was no significant correlation between SD (continuous) and CWT (Table 3) or other structural carotid wall measures (Table S1).

### Objective sleep duration and vascular inflammation using hybrid PET/MRI

CWT was positively associated with the SFI in both unadjusted (Table 3; Model 1, CWT Beta [SE] = 0.075 [SE 0.031], P = .02), and adjusted analyses (Model 2, CWT Beta [SE] = 0.069 ± [0.032], P = .03; and Model 3, CWT Beta [SE] = 0.073 [SE 0.032], P = .03). Normalized wall index (representing arterial wall area normalized for the difference in size of arteries) was weakly and positively associated with SFI in adjusted analysis (Table S1 in the supplemental material; Model 3, normalized wall thickness Beta [SE] 0.016 ± [0.0092] P = .09). There was no significant correlation between SD (continuous) and CWT (Table 3) or other structural carotid wall measures (Table S1).

### DISCUSSION

This is the first study to evaluate the association between habitual objective SD and subclinical vascular inflammation in this racially diverse, majority female, community-based sample. Our study demonstrated that the prevalence of pathologic vascular inflammation was higher among those who slept ≤ 6 hours. Additionally, among those with a habitual SD of 6 hours or less, vascular inflammation as measured by FDG PET/MRI was higher compared to those who had a SD of more than 6 hours, although our results did not reach statistical significance. Furthermore, we found that sleep fragmentation was positively associated with CWT, even after adjustment for additional covariates, including AHI. Our results are hypothesis generating and suggest that both habitual SD and SFI are potentially important risk factors for subclinical atherosclerosis and should be investigated using multimodality imaging in future studies.

Our study is novel, and conceptually innovative for several reasons. First, we investigated the association between SD and vascular inflammation in an ethnically diverse, majority female sample from the MESA cohort. Most studies to date have assessed this relationship in a majority male population. Second, ours was one of the few studies to evaluate measures of objective habitual SD using actigraphy, in association with novel measures of subclinical atherosclerosis. Prior evidence suggests an association between short SD and subclinical atherosclerosis, although many of these studies are limited by self-reported assessments of SD. However, self-reported SD has demonstrated a tendency for overestimation of time asleep by up to 1 hour. Actigraph devices are worn over a period of days and provide a more robust and reliable method of assessing habitual SD, with a more accurate estimate of total sleep time and sleep efficiency. Third, no studies have investigated the association between SD and subclinical atherosclerosis in patients with sleep apnea, a group that is at increased risk of accelerated atherosclerosis and CVD.

Our sample included patients who had undergone PSG, with objective diagnoses of sleep apnea, which often serves as a confounder in the association between sleep studies and atherosclerosis. We adjusted for sleep apnea in our analyses.
Lastly, we investigated the association between SD, SFI, and vascular inflammation utilizing hybrid FDG PET/MRI. Quantification of atherosclerosis in existing studies is limited by the use of carotid vascular ultrasound for the measurement of CIMT in studies evaluating this association with SD.\textsuperscript{23}–\textsuperscript{25} CIMT may not accurately predict CVD risk\textsuperscript{29}–\textsuperscript{31} and is not a measure of plaque inflammation. Although CIMT provides structural assessments of atherosclerosis, measurement of plaque inflammation provides a metabolic assessment of large vessel atherosclerosis. Hybrid PET/MRI is a validated imaging technique to measure intraplaque inflammation in large arterial vascular beds (carotid arteries and aorta),\textsuperscript{41,56} which can serve as an origin for atheroembolic strokes.\textsuperscript{37,58} 18F-FDG is a radioactive tracer and a glucose analog, taken up by cellular glucose transporters that are upregulated during atherogenesis.\textsuperscript{59,60} The fate of an atherosclerotic plaque is determined largely by the actions of macrophages, as macrophages are found in increased density in unstable atherosclerotic plaques.\textsuperscript{37,61,62} FDG signal therefore indicates increased proinflammatory macrophage activity resulting in atherosclerotic plaque inflammation and correlates with macrophage burden.\textsuperscript{35,36} A recent study in the Progression of Early Subclinical Atherosclerosis cohort utilizing hybrid FDG PET/MRI showed significant associations between objective sleep duration and vascular inflammation.

Table 2—Carotid vascular inflammation and structural wall measurements by sleep duration category.

<table>
<thead>
<tr>
<th>Vascular inflammation</th>
<th>Total Sample (n = 58)</th>
<th>≤ 6 h (n = 18)</th>
<th>&gt; 6 h (n = 40)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of TBR &gt; 1.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avg. TBR\textsubscript{max} &gt; 1.6, n, %</td>
<td>37, 63.8%</td>
<td>16, 88.9%</td>
<td>21, 52.5%</td>
<td>.01</td>
</tr>
<tr>
<td>Avg TBR\textsubscript{mds} &gt; 1.6, n, %</td>
<td>44, 75.9%</td>
<td>16, 88.9%</td>
<td>28, 70.0%</td>
<td>.40</td>
</tr>
<tr>
<td>Average (SD) TBR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avg. TBR\textsubscript{max}</td>
<td>1.73 (0.25)</td>
<td>1.77 (0.22)</td>
<td>1.71 (0.26)</td>
<td>.40</td>
</tr>
<tr>
<td>Avg. TBR\textsubscript{mean}</td>
<td>1.47 (0.21)</td>
<td>1.50 (0.49)</td>
<td>1.45 (0.22)</td>
<td>.47</td>
</tr>
<tr>
<td>Avg. TBR\textsubscript{mds}</td>
<td>1.90 (0.33)</td>
<td>1.97 (0.36)</td>
<td>1.86 (0.32)</td>
<td>.29</td>
</tr>
<tr>
<td>Structural carotid wall measurements</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avg. (SD) CWT, mm</td>
<td>1.44 (0.16)</td>
<td>1.48 (0.16)</td>
<td>1.42 (0.16)</td>
<td>.19</td>
</tr>
<tr>
<td>Carotid wall area, mm\textsuperscript{2}</td>
<td>33.29 (6.37)</td>
<td>34.95 (7.42)</td>
<td>32.59 (5.84)</td>
<td>.20</td>
</tr>
<tr>
<td>Carotid total vessel area, mm\textsuperscript{2}</td>
<td>60.98 (12.58)</td>
<td>63.30 (14.51)</td>
<td>60.00 (11.73)</td>
<td>.37</td>
</tr>
<tr>
<td>Carotid NWI</td>
<td>0.55 (0.05)</td>
<td>0.56 (0.04)</td>
<td>0.55 (0.05)</td>
<td>.60</td>
</tr>
</tbody>
</table>

Avg. = average, CWT = carotid wall thickness, NWI = normalized wall index, SD = standard deviation, TBR = target-to-background ratio(s), TBR\textsubscript{mds} = target-to-background ratio most-diseased segment.

Table 3—Multivariate linear regression analyses: vascular inflammation and carotid wall thickness by sleep duration and sleep fragmentation index (continuous).

<table>
<thead>
<tr>
<th>Vascular inflammation (mean TBR\textsubscript{max})</th>
<th>Sleep Duration (minutes)</th>
<th>Continuous per 10-Minute Increase</th>
<th>P for Linear Trend</th>
<th>Sleep Fragmentation Index (%)</th>
<th>Continuous per 10% Increase</th>
<th>P for Linear Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>-0.00031 (0.0046)</td>
<td>.95</td>
<td>.0083 (0.048)</td>
<td>.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>-0.0026 (0.0047)</td>
<td>.58</td>
<td>0.056 (0.050)</td>
<td>.27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>0.00055 (0.0047)</td>
<td>.91</td>
<td>0.075 (0.051)</td>
<td>.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean CWT (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>-0.0024 (0.0032)</td>
<td>.45</td>
<td>0.075 (0.031)</td>
<td>.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>-0.0047 (0.0033)</td>
<td>.16</td>
<td>0.069 (0.032)</td>
<td>.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>-0.0027 (0.0033)</td>
<td>.42</td>
<td>0.073 (0.032)</td>
<td>.03</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Model 1: Unadjusted. Model 2: Age, sex, race/ethnicity, Log normal AHI (LNAHI) + BMI. Model 3: ASCVD + BMI. ASCVD = atherosclerotic cardiovascular disease, BMI = body mass index, CWT = carotid wall thickness, SE = standard error, TBR = target-to-background ratio(s). Bold values denote statistical significance.
MRI to characterize multiterritorial atherosclerosis demonstrated that FDG uptake was also present in plaque-free arterial segments, suggesting an arterial inflammatory state even at early stages of atherosclerosis, preceding plaque formation.63 Prior studies have also demonstrated that vascular PET imaging is a useful prognostic imaging tool shown to improve incident CVD risk prediction and identify patients at risk for early stroke recurrence.32,34,35 Moreover, this imaging modality has been used as a surrogate endpoint in clinical trials detecting early treatment effects of statins in patients with atherosclerosis.64–66 Therefore, utilizing hybrid FDG PET/MRI provides a novel way of investigating subclinical atherosclerosis in association with objective sleep measures.

We observed several novel findings in our study. The prevalence of pathologic vascular inflammation (TBRmax) was higher among those who slept ≤ 6 hours (90% vs 53%). Additionally, vascular inflammation as measured by TBRmax was approximately 4–5% higher among those with a habitual SD of 6 hours or less, although our results did not reach statistical significance. As a comparison, this average difference in vascular inflammation (TBR) between the groups is similar to the reduction in carotid TBRmax observed in our pilot study in patients with sleep apnea post-CPAP (6.2%)67 and similar to the magnitude of reduction in TBR observed after 12 weeks of statin therapy (6.7%).68 Therefore, a TBR value that is 4–5% higher in the short SD group may potentially represent a clinically significant difference in subclinical atherosclerosis, although these results must be confirmed in larger prospective studies.

In addition to these findings, we also report that actigraphic SFI was positively associated with CWT even after adjustment for additional covariates, including age, sex, race, BMI, AHI, and ASCVD risk score. While SFI was weakly associated with AHI (Pearson’s correlation coefficient 0.281, P = .03), the above relationship held true even after adjustment for AHI. Therefore, SFI—a measure of restlessness during sleep—may represent a higher intensity of arousals and longer periods of wake accompanied by movement not typically captured by the AHI during a single-night PSG. Given our results, we believe that that sleep fragmentation maybe a stronger risk factor for the development of arterial wall hypertrophy (increased CWT and reduced distensibility) and hypertension over time (independent of sleep apnea),68 while habitually short SD and chronic sleep deprivation may result in increased vascular inflammation, together contributing to the progression of subclinical atherosclerosis.

The results of our study are hypothesis generating but are the first of its kind, highlighting that short SD and sleep fragmentation may serve as important underlying risk factors for accelerated subclinical atherosclerosis and set the stage for future research in this area. These results also underscore the importance of differentiating between structural endpoints (CIMT and CWT) and metabolic endpoints (vascular inflammation) for atherosclerosis. Specific sleep measures may uniquely impact the acceleration of atherosclerosis and vascular remodeling via different mechanisms, i.e., habitually short SD (chronic sleep deprivation) may be more inflammatory, while sleep disturbances/sleep fragmentation may result in increased autonomic perturbations leading to accelerated arterial wall remodeling. These mechanisms need to be explored in future studies that investigate the association between sleep and subclinical atherosclerosis.

Limitations
Several methodological limitations should be considered in the interpretation of our study results. First, the small sample size limited the statistical power for associations. However, ours is the largest study to date and the first of its kind in utilizing multimodality imaging (hybrid PET/MRI) to investigate an independent association between sleep duration and vascular inflammation. Additionally, we recognize that MESA is a racially diverse cohort, and race has been shown to have a varying association with sleep apnea and SD.39 Notably however, there was no statistically significant differences in race/ethnicity, ASCVD risk score, or the prevalence of diabetes, hypertension, or smoking between the 2 SD groups (Table 1).

Second, eligibility for MESA PET required presence of carotid plaque on prior MESA ultrasound exam. This may render our findings less generalizable to those with less advanced atherosclerosis and potentially bias the results, reducing the ability to detect differences in the outcome measures between the sleep duration categories. However, the focus of the analysis was on the relationship of sleep duration with plaque inflammation (not the presence of carotid plaque). Future studies investigating this relationship should assess vascular inflammation in all-comers (those with and without arterial plaque).

Third, due to the limited sample size, we were unable to assess the effect of “long” SD (> 9 hours) on vascular inflammation, given that prior studies have demonstrated an association between long SD with CVD.6–11 Future studies should assess this relationship in a larger sample of patients.

Fourth, we were unable to assess atherosclerotic plaque inflammation in other large vascular beds. For the purposes of this study, we evaluated plaque inflammation in a single vascular bed (carotid arteries) due to limited quantification of other large vascular beds in the MESA-PET ancillary study. Assessment of multivessel subclinical atherosclerosis should be conducted in future studies investigating this relationship.

Lastly, the study was a cross-sectional analysis of objective SD and vascular inflammation over 2 different time periods and does not allow for causal inference. However as stated previously, the results of the study are hypothesis generating and can inform a larger prospective study assessing multivessel subclinical atherosclerosis in the large arteries (carotids, aorta, and femoral arteries) to aid in further investigating the relationship between objective sleep measures and vascular inflammation.

Conclusions
In this racially diverse, community-based, majority female sample, we found that prevalence of pathologic vascular inflammation was higher among those who slept < 6 hours. We also found that those with habitually short SD of < 6 h/night appear to have increased vascular inflammation as measured by hybrid FDG PET/MRI compared to those who had a SD of 6 hours or more. Furthermore, actigraphic sleep fragmentation was positively
associated with CWT independent of other risk factors, including sleep apnea. This study provides important preliminary data to address the poorly understood links between objective habitual SD, sleep fragmentation, and subclinical atherosclerosis in an ethnically diverse sample of patients, controlling for sleep apnea. Our results are hypothesis generating and highlight that short SD and sleep fragmentation may serve as important underlying risk factors for accelerated subclinical atherosclerosis. Larger prospective trials should further investigate these relationships utilizing multimodality imaging. Assessments of both arterial wall remodeling and plaque inflammatory activity as measures of subclinical atherosclerosis may provide novel insights into how sleep impacts vascular health on a variety of fronts.

**ABBREVIATIONS**

AHI, apnea-hypopnea index  
ASCVD, atherosclerotic cardiovascular disease  
BMI, body mass index  
CI, confidence interval  
CIMT, carotid intima media thickness  
CVD, cardiovascular disease  
CWT, carotid wall thickness  
FDG, fluorodeoxyglucose  
MES A, Multi-Ethnic Study of Atherosclerosis  
PET/MRI, positron emission tomography/magnetic resonance imaging  
PSG, polysomnography  
SD, sleep duration  
SE, standard error  
SFI, sleep fragmentation index  
TBR, target-to-background ratio(s)  
WHIIRS, Women’s Health Initiative Insomnia Rating Scale

**REFERENCES**


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Objective sleep duration and vascular inflammation using hybrid PET/MRI

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DISCLOSURE STATEMENT

All authors have seen and approved this manuscript. Work for this study was performed at Division of Pulmonary, Critical Care, and Sleep Medicine, Icahn School of Medicine at Mount Sinai, New York, NY. Imaging studies were performed at the Biomedical Engineering and Imaging Institute (BMEII) at Mount Sinai, NY. Participants were recruited at the Columbia University Field Center, NY, through Dr. Steven Shea’s MESA PET Ancillary Study (R01HL127637) for MESA Exam 6. Manuscript preparation was conducted at the Icahn School of Medicine at Mount Sinai, NY. Dr. Ayappa reports grants from the Centers for Disease Control/National Institute for Occupational Safety and Health, National Institutes of Health, and Fisher Paykel Healthcare outside the submitted work. In addition, Dr. Ayappa has patents for modifications of continuous positive airway pressure that result in royalties paid through New York University unrelated to the submitted work. Dr. Redline reports consulting fees and a grant from Jazz Pharma, and consulting fees from Eisai Inc and Respicardia Inc., unrelated to the submitted work. This study was funded by contracts HHSN268201500003I, N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168 and N01-HC-95169 from the National Heart, Lung, and Blood Institute (NHLBI), and by grants UL1-TR-000040, UL1-TR-001079, and UL1-TR-001420 from the National Center for Advancing Translational Sciences (NCATS). The MESA SLEEP study was supported by NHLBI grant HL56984. Dr. Susan Redline was partially supported by R35 HL135818. The MESA PET study is supported by R01HL127637 (principal investigator: Dr. Steven Shea). Dr. Neomi A. Shah has funding from the NHLBI (1R03HL140273, 1R01HL143221). Dr. Vaishnavi Kundel has funding from the American Academy of Sleep Medicine Foundation Physician Scientist Training Award (210-PA-19). The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the NHLBI, the National Institutes of Health, or the US Department of Health and Human Services. The other authors report no conflicts of interest.