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Associations of Sleep Duration and Sleep Wake Rhythm with Lung Parenchymal Abnormalities on Computed Tomography: the MESA Study

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Abstract

Impairment of the circadian rhythm promotes lung inflammation and fibrosis in pre-clinical models. We aimed to examine whether short and/or long sleep duration and other markers of sleep-wake patterns are associated with a greater burden of lung parenchymal abnormalities on computed tomography among adults. We cross-sectionally examined associations of sleep duration captured by actigraphy with interstitial lung abnormalities (n=1,111) and high attenuation areas (n=1,416) on CT scan in the Multi-Ethnic Study of Atherosclerosis at Exam 5 (2010–2013). We adjusted for potential confounders in logistic and linear regression models for interstitial lung abnormalities and high attenuation area, respectively. High attenuation area models were also adjusted for study site, lung volume imaged, radiation dose, and stratified by body mass index. Secondary exposures were self-reported sleep duration, sleep fragmentation index, sleep midpoint, and chronotype. The mean age of those with longer sleep duration (≥ 8 hours) was 70 years and the prevalence of interstitial lung abnormalities was 14%. Increasing actigraphy-based sleep duration among participants with ≥ 8 hours of sleep was associated with a higher adjusted odds of interstitial lung abnormalities (odds ratio of 2.66 per 1-hour increment, 95% CI 1.42 to 4.99). Longer sleep duration and higher sleep fragmentation index were associated with more high attenuation area on CT among participants with a body mass index < 25 kg/m² (p-value for interaction < 0.02). Self-reported sleep duration, later sleep midpoint, and evening chronotype were not associated with outcomes. Actigraphy-based longer sleep duration and sleep fragmentation were associated with a greater burden of lung abnormalities on CT scan.

Keywords

sleep duration; actigraphy; interstitial lung disease

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic form of interstitial lung disease (ILD) that leads to respiratory failure and death (Lederer & Martinez, 2018). Current treatments are limited in their therapeutic scope (Flaherty et al., 2019; King et al., 2014) as IPF and other fibrotic ILDs remain among the most common indications for lung transplantation. Repetitive parenchymal lung injury followed by aberrant wound healing that leads to irreversible scarring is believed to drive pulmonary fibrosis (Zoz, Lawson, & Blackwell, 2011). Identification of risk factors that cause recurrent harm and impair recovery may further our understanding of the underlying biology of this disease and inform prognostic and therapeutic strategies.

Under-studied potential risk factors for ILD are sleep and circadian disturbances. Prior studies have largely focused on the role obstructive sleep apnea may have in pulmonary fibrosis (Kim et al., 2017; Lancaster et al., 2009). However, other sleep-related pathologies may be critical in ILD including sleep disturbances or patterns that disrupt circadian rhythms. Short and long sleep durations (potential markers of circadian misalignment) have been linked to systemic inflammation and a higher risk of cardiovascular disease and mortality (Cappuccio, Cooper, D'Elia, Strazzullo, & Miller, 2011). While circadian rhythms have not been comprehensively investigated in adults with ILD, murine models and genome-

wide association studies suggest that both dysregulated sleep-wake patterns and circadian rhythm lead to disturbances in lipid metabolism (Noordam et al., 2019), adipogenesis, and collagen homeostasis (Chang et al., 2020; Cunningham et al., 2020), all of which are relevant to the pathogenesis of pulmonary fibrosis (Kim et al., 2020; Podolanczuk et al., 2017). However, prior studies that examined sleep duration with ILD relied on self-reporting (Cho, Teoh, Roberts, & Wheatley, 2019), which correlates poorly with objective assessments like actigraphy (Jackson, Patel, Jackson, Lutsey, & Redline, 2018).

Developments in computed tomography (CT)-based methods that detect lung parenchymal abnormalities (ex. reticular opacities, traction bronchiectasis) have facilitated investigations that bridge pre-clinical evidence of pathological mechanisms in pulmonary fibrosis to humans. These imaging-based methods include interstitial lung abnormalities (ILA) (Putman et al., 2016) and high attenuation areas (HAA) (Podolanczuk et al., 2016), which may capture evidence of early interstitial changes that precede the development of fulminant fibrosing disease. This is supported by their associations with ILD-related hospitalization and death, biomarkers of fibrogenesis, a lower forced vital capacity, genetic variants linked to a higher risk of ILD, a higher prevalence among 1st-degree adult relatives of patients with ILD, and correlations with lung biopsies (Hatabu et al., 2020; Hunninghake et al., 2013; Hunninghake et al., 2020; Manichaikul et al., 2017; Miller et al., 2018).

We hypothesized that long and/or short sleep duration captured by actigraphy would be associated with a greater burden of lung parenchymal abnormalities on CT scan in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort. We explored associations of lung CT findings with other markers of sleep and circadian rhythm available from actigraphy or questionnaire, including self-reported sleep duration, sleep fragmentation index, sleep midpoint, and chronotype.

METHODS

Study Design

We used data from MESA, a National Heart, Lung, and Blood Institute-sponsored longitudinal cohort study that was originally designed to examine subclinical cardiovascular disease (Bild et al., 2002). MESA enrolled 6,814 community-dwelling adults from six U.S. communities between 2000 and 2002 (Exam 1) who were the ages of 45 to 84 years and free of clinical cardiovascular disease. MESA Sleep was an ancillary study that was performed in conjunction with MESA Exam 5 between 2010 and 2013. All MESA participants were invited to participate in MESA Sleep, which collected polysomnography, actigraphy, and sleep questionnaires during an in-home examination. Inclusion and exclusion criteria have been previously described (Chen et al., 2015). Briefly, at Exam 5 all MESA participants were invited to participate in the MESA Sleep Ancillary study which consisted of PSG, actigraphy, and sleep questionnaire data collected. Participants who reported regular use of nocturnal oxygen, oral devices, or positive airway pressure devices were not invited. Of the eligible 3,879 participants, 2,261 enrolled in MESA Sleep.

Actigraphy

The Actiwatch Spectrum (PA, USA) was worn by participants on the non-dominant wrist for seven consecutive days. Data were scored in 30 second epochs as sleep or wake using the Actiware Sleep software (version 5.59) by a central sleep reading center (Brigham and Women's Hospital, Boston, MA, USA). Total sleep duration was calculated as the sum of epochs scored as sleep in each main sleep interval averaged over all days with valid recordings, as described before (Chen et al., 2015). Sleep intervals were manually identified based on sleep diary, light sensor, and self-actuated event marker. Calculation of sleep midpoint was defined as the clock time halfway between sleep onset and sleep offset, averaged over recording nights. An average sleep midpoint before 5:00 AM was defined as an "earlier midpoint" and past 5:00 AM was defined as a "later midpoint" (Roenneberg et al., 2007). The Sleep Fragmentation Index was determined by the sum of the sleep period percentage spent with movement and the percentage of the number of immobile phases that were less than 1 minute long (Knutson, Van Cauter, Zee, Liu, & Lauderdale, 2011). Intra and inter-scanner reliability was assessed with intra-class correlation coefficients. In the study, coefficients were greater than 90% for sleep duration and sleep midpoint.

Polysomnography

A 15-channel monitor (Compumedics Somte System; Compumedics Ltd., Abbotsford, AU) was used to conduct full in-home single-night polysomnography examinations as previously detailed (Chen et al., 2015). Recordings were scored by registered polysomnologists by a central reading center (Brigham and Women's Hospital, Boston, MA, USA) using similar methods as the Sleep Heart Health Study (Redline et al., 1998; Whitney et al., 1998). The apnea-hypopnea index (AHI, events/hour) was calculated as the average number of all apneas and hypopneas associated with a 4% desaturation per hour of sleep (Chen et al., 2015).

Sleep Questionnaire

A self-reported questionnaire adapted from the Hispanic Community Health Study/Study of Latinos questionnaire was used (Redline et al., 2014). Average self-reported sleep duration was computed by the difference between reported wake-up and bedtimes on weekdays and, separately, weekends. We used the weekday self-reported duration for the purposes of this study. The modified Horne-Östberg Morningness-Eveningness Questionnaire (MEQ) was used to determine chronotype for each participant (MEQ ≤ 11 for eveningness and MEQ > 11 for non-eveningness) (Horne & Ostberg, 1976).

CT Scan Measurements

Full lung non-contrast CT scans were performed at Exam 5 using the MESA Lung/SPIROMICS protocol (Sieren et al., 2016). ILA (present/absent) was assessed by one of five trained radiologists and defined as reticular abnormalities, honeycombing, non-emphysematous cysts, traction bronchiectasis, and/or ground-glass abnormalities with at least 5% of nondependent lung involvement (Hatabu et al., 2020). Scans with focal or unilateral reticular or ground-glass abnormalities or patch ground-glass abnormalities were labeled "indeterminate" and excluded from the analysis. HAA and percent emphysema

were measured using the Pulmonary Analysis Software Suite at the University of Iowa's Advanced Pulmonary Physiomic Imaging Laboratory as lungs were semi-automatically segmented and corrected by a trained technician. HAA and percent emphysema were defined as the percentage of voxels having attenuation values between -600 and -250 Hounsfield units (HU) (Podolanczuk et al., 2016) and below -950 HU (Barr et al., 2010), respectively.

Statistical Analysis

We initially considered categorizing actigraphy-based sleep duration based on recommendations for ideal sleep duration. However, these recommendations are largely based on studies that used self-reported sleep questionnaires, which have shown poor concordance with objective measures of sleep duration (Hirshkowitz et al., 2015; Jackson et al., 2018). Because our *a priori* hypothesis was that long and/or short duration would be linked to interstitial lung abnormalities, we used generalized additive models (GAMs) to plot the unadjusted association of sleep duration with ILA. We took this approach in order to divide the cohort into subgroups based on potential inflection points on the x-axis where the slope of the linear relationship changes.¹ We used logistic regression models to examine the cross-sectional association of sleep duration as a continuous measure with ILA within each subgroup. Therefore, results are reported per 1-hour increment in sleep duration. Model 1 was unadjusted and Model 2 was adjusted for covariates that are potentially linked to sleep duration and ILD including age, sex, race/ethnicity, smoking status (never, former, and current), cigarette pack-years, education attainment, body mass index (BMI, kg/m^2), AHI, percent emphysema, statin use, total intentional exercise, and anti-depressant use (a proxy for depressed mood). Due to potential confounding by concomitant co-morbidities leading to short or prolonged sleep duration, we also adjusted for systolic and diastolic blood pressures and diabetes (self-reported at Exam 5) (Whelton et al., 2018).

For HAA, which is a lung density-based quantitative assessment, body habitus may have a more confounding effect compared with ILA which is assessed qualitatively by a trained radiologist (Kliment et al., 2015). Therefore, we used GAMs by BMI category subgroup ($<25 \text{ kg}/\text{m}^2$, $25\text{--}30 \text{ kg}/\text{m}^2$, $30 \text{ kg}/\text{m}^2$) to identify inflection points in our HAA analysis. We then used linear regression models to examine associations of sleep duration with HAA by BMI subgroup. We transformed HAA as $(-1/\text{HAA}^2)$, which we have designated as “eta” (H), to model HAA to meet assumptions of linearity in our linear regression models (Kim et al., 2020). Model 1 was adjusted for study site, radiation dose, and lung volume imaged *a priori* (Podolanczuk et al., 2016). Model 2 was additionally adjusted for the same covariates as ILA model 2. We also included BMI (categorical) and “BMI (categorical) \times sleep duration” interaction term in our HAA model because we analyzed by BMI subgroup. We used similar ILA and HAA regression models with other secondary exposure variables which included self-reported sleep duration, sleep fragmentation index (continuous), sleep midpoint (before vs. after 5:00 AM), and chronotype (non-evening vs. evening). For sleep fragmentation index model, results are reported per one log-unit increment of the index.

We performed exploratory stratified analysis to examine whether the associations of actigraphy-based sleep duration with ILA were modified by other sleep metrics (sleep

fragmentation index, sleep midpoint, and chronotype). In other words, we were interested in whether the association of sleep duration varied in backgrounds of different sleep continuity, sleep timing, and timing preference. We tested for effect modification with the likelihood ratio test of models with and without interaction terms. Given the exploratory and hypothesis-generating nature of the stratified analyses, we did not adjust for multiple comparisons in our statistical testing. We used multiple imputation with chained equations for missing covariate data. We used SAS V9.4 (SAS Institute, Cary, NC, USA) for our analyses.

RESULTS

Study Participants

There were 1,949 MESA participants with actigraphy, polysomnography, and sleep questionnaire data, of whom 1,111 and 1,416 had Exam 5 CT ILA and HAA assessments, respectively (Figure 1). Baseline characteristics of participants with ILA assessments overall and by actigraphy-based sleep duration of less than 6 hours, 6 to 8 hours, and greater than 8 hours are summarized in Table 1. Characteristics of participants with HAA assessments are summarized in Table S1. MESA participants with ≥ 8 hours of sleep were older and had a higher prevalence of statin and antidepressant use, and a higher proportion were women.

Actigraphy-Based Sleep Duration

The continuous association between actigraphy-based sleep duration and ILA was U-shaped (p -value for non-linearity < 0.001) (Figure 2). Inflection points appeared to be at 6 and 8 hours. Among participants with a sleep duration less than 6 hours, shorter sleep duration was associated with a higher odds for ILA. In other words, in individuals with a sleep duration less than 6 hours per night, each 1-hour decrement was associated with a 1.54 unadjusted odds for ILA (95% CI 1.02 to 2.32); however, this association was attenuated after covariate adjustment. Participants with greater than 8 hours of sleep had an unadjusted odds ratio for ILA of 2.21 (95% CI 1.36 to 3.58) per 1-hour increased sleep duration increment, which did not appreciably change with covariate adjustment. No association was observed between sleep duration and odds of ILA among participants with a sleep duration of 6 to 8 hours (Table 2).

Sleep fragmentation index and chronotype did not modify associations between sleep duration and ILA (i.e., there was no statistical evidence of interaction; Table 2). Among participants with a sleep duration greater than 8 hours, sleep midpoint modified its association with ILA (p -value for interaction=0.02). For every 1-hour increment in sleep duration greater than 8 hours, there was a 3.71 odds of ILA (95% CI 1.80 to 7.63) among those with an earlier sleep midpoint compared with 0.38 (95% CI 0.03 to 4.90) among those with a later sleep midpoint.

Continuous associations of actigraphy-based sleep duration with HAA by BMI subgroup are shown in Figures 3A–C. The inflection point describing the association between HAA and sleep duration appeared to be at 7 hours among participants with a BMI < 25 kg/m². Among participants with a sleep duration less than 7 hours, incremental changes in sleep duration

were not associated with HAA among the BMI subgroups in unadjusted and adjusted analyses (p-value for BMI interaction = 0.22). Among participants with a sleep duration greater than 7 hours and after adjustment for covariates, a 1-hour increased increment was associated with a change in HAA of 33.13 (95% CI 13.16 to 53.09), -8.56 (95% CI -27.01 to 9.89), and -20.75 (95% CI -39.16 to -2.34) among those with a BMI <25 kg/m², 25 to 30 kg/m², ≥ 30 kg/m², respectively (p-value for BMI interaction <0.001) (Table 3).

Self-reported sleep duration was not associated with ILA in adjusted models (Tables S2). Longer self-reported sleep duration among participants who reported sleeping less than 7 hours and have a BMI ≥ 30 kg/m² was associated with less HAA (Table S3). This association was no longer significant after adjusting for covariates.

Additional Sleep and Chronotype Markers

Sleep fragmentation index, sleep midpoint after 5:00 AM, and evening chronotype were each not associated with ILA or HAA in the overall sample (Table S4–S5). A higher sleep fragmentation index was associated with more HAA among those with a BMI <25 kg/m² (p-value for BMI interaction = 0.02). A one natural log unit increment in sleep fragmentation index was associated with an HAA of 52.10 (95% CI 16.15 to 88.04) after adjustment for covariates (Table S3).

DISCUSSION

Among community-dwelling adults, there was a U-shaped association between actigraphy-assessed sleep duration and ILA in unadjusted analyses, where shorter sleep duration from 6 hours and less and increasing sleep duration greater than 8 hours were associated with more ILA. However, in fully adjusted analyses, only the association between increasing sleep duration beyond 8 hours per night remained associated with ILA. Among participants with a BMI <25 kg/m² and ≥ 30 kg/m², increasing sleep duration beyond 7 hours was associated with more and less HAA, respectively. Associations were not explained by consideration of ILD-related risk factors such as age, smoking, sex, and medication use. Higher sleep fragmentation index was associated with more HAA among adults with a BMI <25 kg/m². In contrast, self-reported sleep duration, later sleep midpoint, and evening chronotype were not associated with CT lung abnormalities.

Longer sleep duration has been identified as a risk factor for multiple chronic health conditions and increased mortality (Cappuccio et al., 2011). One hypothesis is that these associations reflect residual confounding by factors such as depression, cardiovascular disease, and lower socioeconomic status (Stamatakis & Punjabi, 2007). Adults with longer sleep durations have poorer health and social determinants that may put them at higher risk for worse clinical outcomes. Adults with ILD suffer from poor sleep quality and continuity as they have less deep sleep and reduced sleep efficiency (Cho et al., 2019). This link between perturbed sleep continuity and ILD may be driven by co-morbidity confounders (ex. mood disorders, smoking history). In our study, MESA participants with an actigraphy-based sleep duration ≥ 8 hours were older and had a higher prevalence of statin and anti-depressant use. However, a positive association between longer sleep and ILA

persisted after adjusting for multiple confounders, including AHI, and was not modified by sleep fragmentation or chronotype in stratified analyses.

Emerging data also have identified associations between long sleep duration and a higher odds of pulmonary fibrosis in the UK Biobank Cohort, even after accounting for risk factors including age and smoking (Cunningham et al., 2020). Variation in sleep duration may reflect key differences in circadian programming (Aeschbach et al., 2003). Individuals with prolonged sleep duration may experience misalignment between the timing of the biological clock with the timing of sleep and other activities (ex. physical activity and food intake), resulting in metabolic dysfunction and inflammation. Disruption of processes regulated by the human circadian clock, such as lipid homeostasis (Podolanczuk et al., 2017) and adipogenesis (Kim et al., 2020), which are both implicated in the pathogenesis of ILD, may have partly driven our findings. A prior genome-wide interaction study revealed significant interactions between prolonged sleep duration and variants linked to lipid-related genes, supporting the biologic plausibility of abnormal sleep-wake rhythms and patterns on diseases mediated by impaired lipid metabolism (Noordam et al., 2019). Adipokines, such as adiponectin, have been postulated to have a contributory role in ILD pathogenesis (Kim et al., 2020), as their gene expression and transcription demonstrate 24-hour rhythmicity with impairment of their signaling induced by mutations of key clock proteins, *ARNTL* and *CLOCK* (Gomez-Abellan et al., 2010).

In addition to its influence on these metabolic pathways, an impaired circadian clock may contribute to ILD risk more directly via effects on fibrogenesis and collagen production in experimental murine models. Deficiency in the 19th exon of the *clock* gene (*Clock*¹⁹) leads to an accumulation of collagen and alteration of the redox pathway via regulation of NRF2 in mice (Chang et al., 2020). Furthermore, deletion of *NR1D1* (*REVERBa*) leads to an increased fibrotic response and accumulation of α -smooth muscle actin positive myofibroblasts in bleomycin-exposed mouse models mediated by reduced expression of the downstream transcription factor, TBPL1 (Cunningham et al., 2020). Among the clock genes, *REVERBa* is highly expressed in human lung tissue from adults with IPF.

Our study adds to these murine and cell-based studies by linking objectively estimated long sleep duration with two unique CT-based assessments of lung parenchymal changes in humans. Discordance between the actigraphy-based and self-reported sleep duration findings is consistent with previous work that has compared these tools (Jackson et al., 2018). Sleep fragmentation and chronotype did not modify the association between sleep duration and ILA; however, power to detect small to modest interactions is limited. Longer sleep duration was more strongly associated with ILA among those with an earlier sleep midpoint. Earlier sleep timing is seen with aging, and it is possible that earlier sleep placement in this sample is a marker of more advanced chronological aging and subsequent susceptibility to the biological effects of circadian misalignment when sleep is prolonged. However, delayed phase is more commonly associated with chronic health conditions, and given the small number of individuals with long sleep duration and later sleep timing, these subgroup analyses are prone to type I error and we caution over-interpretation of this finding.

In addition to its association with ILA overall, we found that actigraphy-based longer sleep duration was differentially associated with HAA by BMI subgroup. Longer sleep was associated with more HAA on CT among those with a BMI <25 kg/m², whereas an inverse association was observed in those with a BMI ≥ 30 kg/m². A potential reason for this may be the confounding effects that body habitus (i.e., soft tissue and atelectasis) has on CT lung densities (Kliment et al., 2015). Compared with ILA, HAA may capture other characteristics not related to ILD which include atelectasis, increased attenuation from soft tissue, and reduced inspiratory volumes. This may be why we found a stronger association in the hypothesized direction among those with a lower BMI that is consistent with our ILA outcome. Alternatively, sleep continuity and circadian alignment may have distinct influences on lung injury resolution and remodeling by body habitus type. Further research and development in CT methods to account for the effects of body habitus on lung densities (ex. texture-based analysis) may help elucidate the complex relationship between sleep, early lung injury/scarring, and body habitus.

In addition to prolonged sleep duration, we found that a higher sleep fragmentation index was strongly associated with more HAA on CT scan in participants with a BMI <25 kg/m². The sleep fragmentation index measures the frequency of transitions from sleep to wakefulness, which usually is accompanied by altered sleep stage distributions. Changes in sleep continuity and depth can result in abnormalities in autonomic nervous system activation and elevated norepinephrine levels, resulting in elevations in blood pressure and abnormalities in cortisol secretion and glucose metabolism (Knutson et al., 2011; Mezick et al., 2009). These sympathetic system-related stresses triggered by disruption of sleep continuity may be pertinent to the lung (Heindl, Lehnert, Criege, Hasenfuss, & Andreas, 2001). The absence of effect modification by sleep fragmentation on duration and ILA suggests that measurement of sleep duration and fragmentation may capture unique causal pathways to lung injury that are not entirely overlapping or synergistic and require further investigation.

Although prior research suggests harmful effects of shorter sleep duration, later sleep midpoint, and evening chronotype, they were not associated with either ILA or HAA in our study in adjusted analyses. Many other population-based studies also have not shown consistent associations between short sleep duration and chronic cardiometabolic outcomes, potentially due to the variable reasons for short sleep across populations (Kwok et al., 2018). We did not have information on circadian phase, which would have better defined the influence of circadian markers on lung outcomes.

Our study has several limitations. Analyses were cross-sectional and reverse causality cannot be excluded. Our outcomes of ILA and HAA are possibly surrogate radiologic markers of subclinical disease in a general population cohort, which may attenuate the possible effect of reversal causation. While we carefully selected potential confounders to adjust for in our models, we cannot rule out the effect of residual confounding on our findings. Although the MESA cohort is racially and ethnically diverse and is derived from multiple U.S. communities, the generalizability of our findings is limited to older adults. Whether prolonged sleep duration is associated with a progression to fulminant ILD was not addressed by our study as our analyses were cross-sectional. Although

ILA and HAA are strongly associated with future ILD-related clinical events and genetic variants associated with ILD risk, it remains unknown what proportion of adults with these radiologic abnormalities will progress to fulminant disease and is an ongoing area of research (Hatabu et al., 2020). We acknowledge that our findings may still be due to chance. Particularly with our stratified analyses due to the multiple comparisons and smaller subgroup sizes. Taking into account the above limitations, we strongly caution extrapolating any clinical implications of this finding as longitudinal studies and trials that examine the effect of sleep duration on risk and progression of ILD are needed.

In conclusion, longer sleep duration was cross-sectionally associated with a greater burden of lung inflammation and scarring on CT scan. Future prospective cohort studies and sleep behavior modification interventional trials will further elucidate the potential role abnormal sleep-wake patterns have in the pathogenesis of ILD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of Interest Statement:

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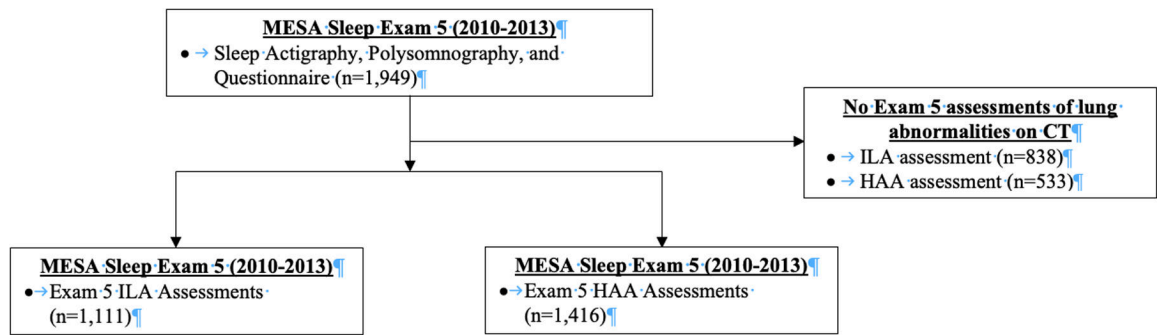


Figure 1.
Flow diagram of MESA participants with actigraphy-based sleep duration and interstitial lung abnormalities and high attenuation areas assessments.

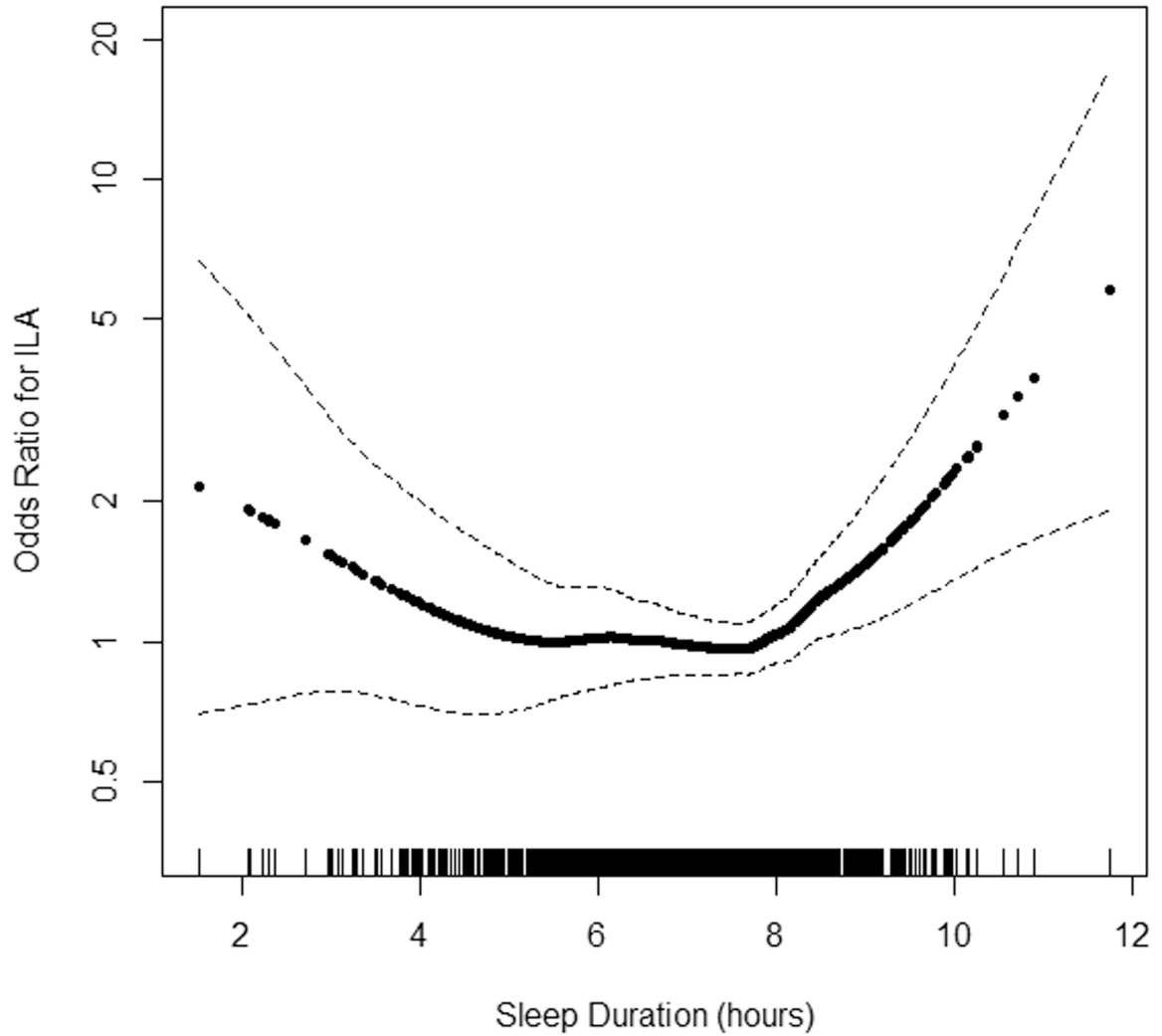
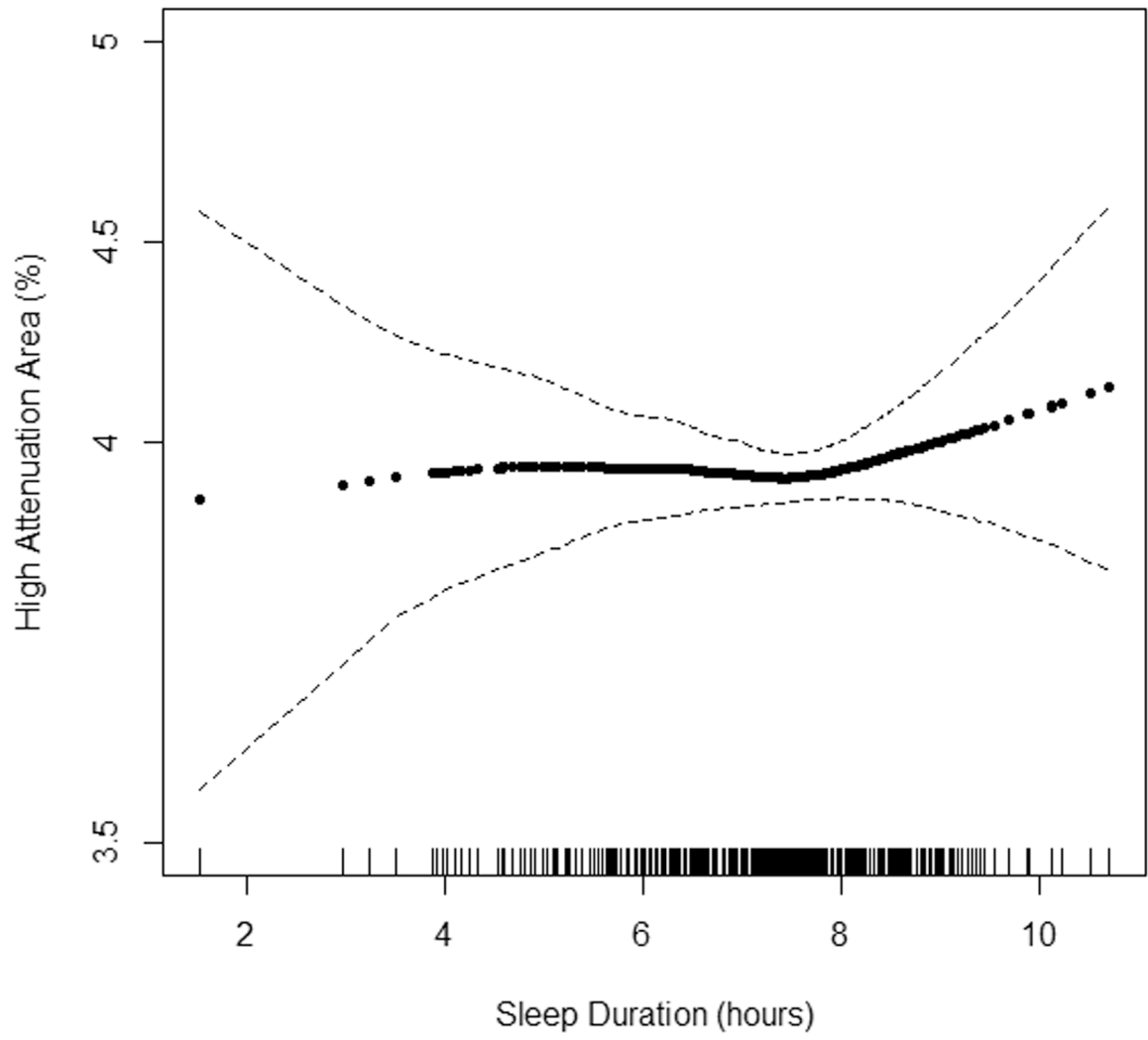
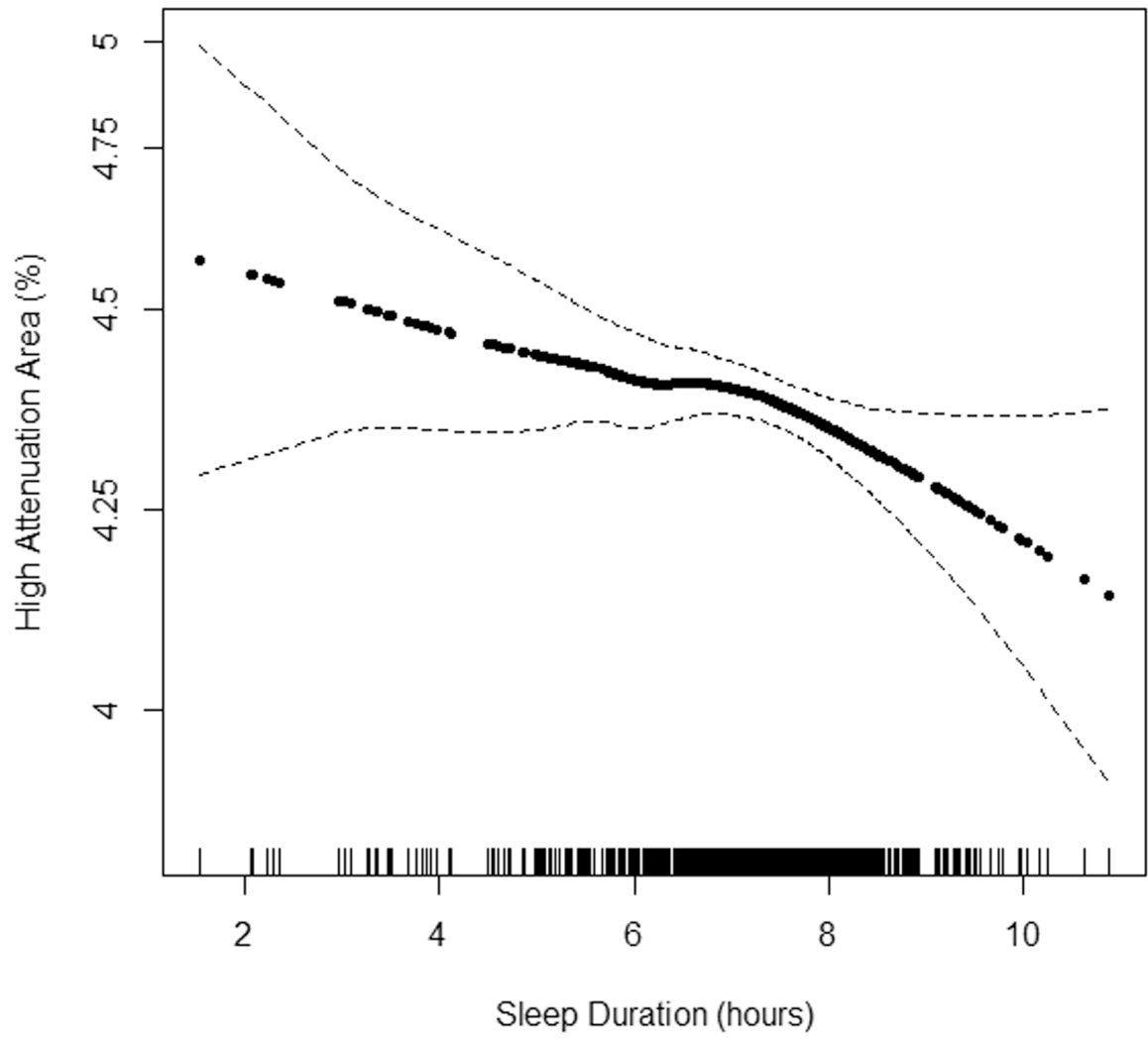


Figure 2. Continuous association of actigraphy-based sleep duration with odds ratio for interstitial lung abnormalities (n=1,111). P-values for linearity = 0.36 and for non-linearity <0.001. Model is unadjusted. The solid line is the overall effect estimate, thin dashed lines represent 95% confidence interval bands. Each vertical hashmark along the x-axis represents an individual participant.





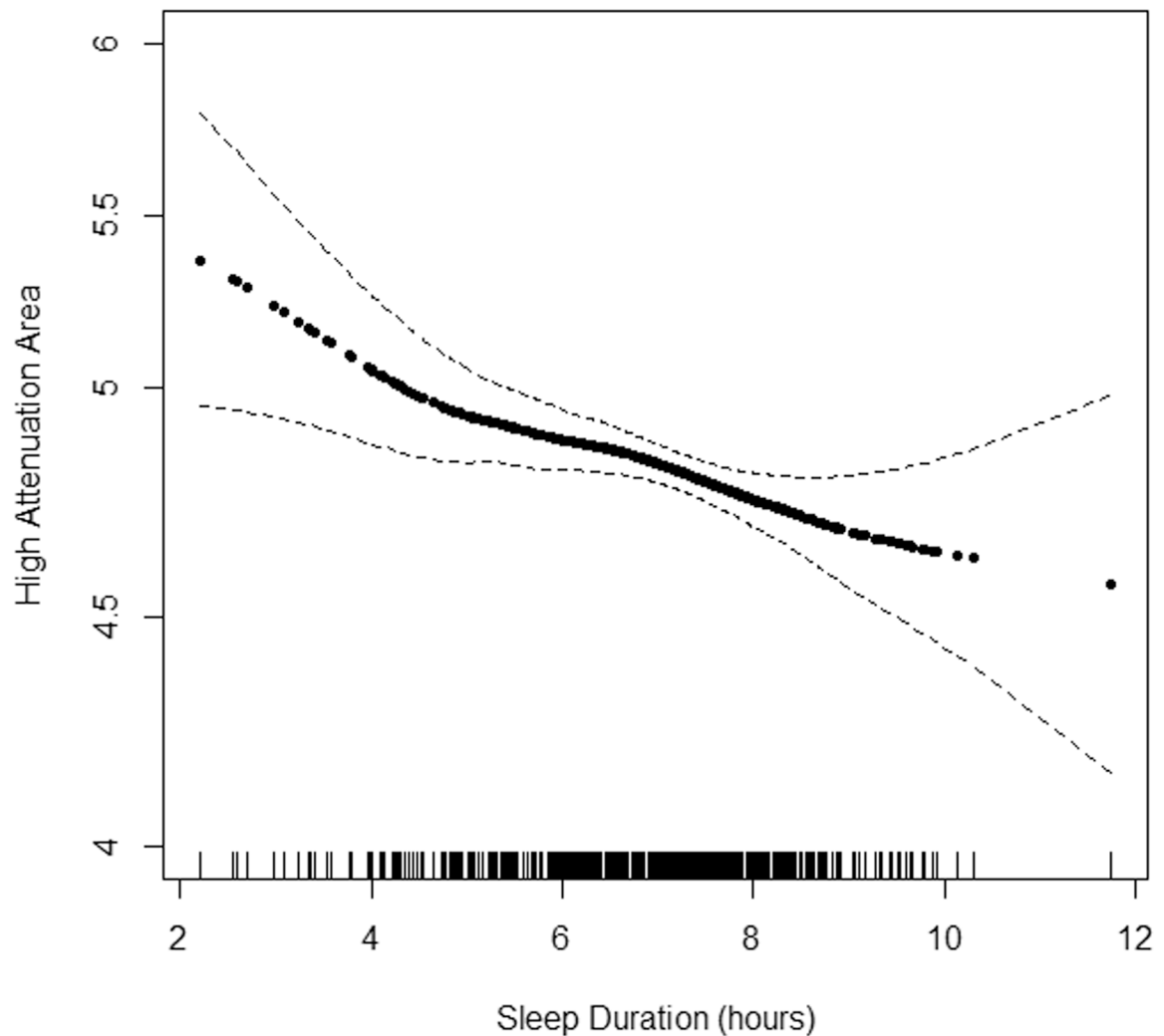


Figure 3. Continuous association of actigraphy-based sleep duration with high attenuation areas by body mass index (BMI) subgroup: A) BMI <25 kg/m² (n=371), B) BMI 25–30 kg/m² (n=537), and C) BMI ≥30 kg/m² (n=508). P-values for linearity were A) 0.68, B) 0.02, C) 0.001. P-values for non-linearity were A) 0.37, B) 0.49, and C) 0.72. Models adjusted for study site, lung volume imaged, and radiation dose. The solid line is the overall effect estimate, thin dashed lines represent 95% confidence interval bands. Each vertical hashmark along the x-axis represents an individual participant.

Table 1

Baseline characteristics of the analytical sample

Characteristic	Overall (n=1,111)	Less than 6 hours (n=199)	6 to 8 hours (n=625)	Greater than 8 hours (n=287)
Sleep Duration (h)	7 (1)	5 (1)	7 (1)	9 (1)
Age (years)	68 (9)	68 (10)	67 (9)	70 (9)
Female	54%	40%	52%	67%
Race/ethnicity				
White	35%	19%	36%	43%
Asian	14%	18%	12%	16%
Black	28%	44%	28%	18%
Hispanic	23%	19%	24%	23%
Smoking status				
Never Smoker	51%	46%	52%	53%
Former Smoker	42%	44%	43%	39%
Current Smoker	7%	10%	5%	8%
AHI (events/hr)	14 (16)	19 (18)	13 (15)	14 (17)
BMI (kg/m ²)	29 (6)	30 (6)	29 (5)	28 (6)
Systolic blood pressure (mmHg)	123 (20)	124 (22)	122 (19)	124 (19)
Diastolic blood pressure (mmHg)	69 (10)	70 (11)	69 (10)	68 (10)
Statin use	36%	28%	38%	38%
Antidepressant use	9%	10%	7%	13%
Diabetes	16%	17%	16%	15%
Total intentional exercise (min/wk)	2,952 (4,060)	3,146 (3,888)	3,091 (4,483)	2,591 (3,097)
Education attainment				
Less than high school	14%	10%	14%	18%
High school	45%	45%	46%	44%
College and beyond	41%	45%	40%	38%
Interstitial lung abnormalities	12%	11%	11%	14%

Continuous variables presented as mean (standard deviation) and categorical variables presented as percentages

Table 2

Associations of Actigraphy-Based Sleep Duration with ILA

Sleep Duration	No. Participants	Odds Ratio for ILA (95% CI) per 1-hour increment	P-value	P-value for Interaction
Model 1				
Less than 6 hours*	199	1.54 (1.02 to 2.32)	0.04	
6 to 8 hours	625	0.74 (0.47 to 1.15)	0.18	
Greater than 8 hours	287	2.21 (1.36 to 3.58)	0.001	
Model 2				
Less than 6 hours*	199	1.13 (0.66 to 1.92)	0.66	
6 to 8 hours	625	0.70 (0.42 to 1.15)	0.18	
Greater than 8 hours	287	2.66 (1.42 to 4.99)	0.002	
Stratified Analysis				
Fragmentation Index				
Less than 6 hours				0.34
Tertile 1	53	1.64 (0.58 to 4.62)	0.35	
Tertile 2	72	0.92 (0.27 to 3.09)	0.79	
Tertile 3	74	0.56 (0.22 to 1.44)	0.29	
6 to 8 hours				0.06
Tertile 1	206	0.46 (0.17 to 1.22)	0.12	
Tertile 2	214	0.43 (0.19 to 0.97)	0.04	
Tertile 3	205	1.61 (0.67 to 3.89)	0.29	
Greater than 8 hours				0.52
Tertile 1	111	4.63 (1.47 to 14.54)	0.01	
Tertile 2	85	2.30 (0.98 to 5.42)	0.06	
Tertile 3	91	2.05 (0.56 to 7.59)	0.28	
Chronotype				
Less than 6 hours				0.91
Non-evening	182	0.85 (0.50 to 1.46)	0.56	
Evening	17	1.90 (0.05 to 67.00)	0.72	
6 to 8 hours				0.80
Non-evening	571	0.69 (0.41 to 1.18)	0.17	

Sleep Duration	No. Participants	Odds Ratio for ILA (95% CI) per 1-hour increment	P-value	P-value for Interaction
Evening	54	0.87 (0.17 to 4.43)	0.87	
Greater than 8 hours				0.70
Non-evening	269	2.64 (1.37 to 5.07)	0.004	
Evening	18	4.46 (0.27 to 74.87)	0.30	
Sleep Midpoint				0.64
Less than 6 hours				
Before 5:00 AM	148	0.96 (0.50 to 1.85)	0.91	
After 5:00 AM	51	0.49 (0.13 to 1.82)	0.28	
6 to 8 hours				0.97
Before 5:00 AM	557	0.70 (0.40 to 1.20)	0.19	
After 5:00 AM	68	0.81 (0.24 to 2.72)	0.74	
Greater than 8 hours				0.02
Before 5:00 AM	268	3.71 (1.80 to 7.63)	<0.001	
After 5:00 AM	19	0.38 (0.03 to 4.90)	0.46	

Model 1: Unadjusted

Model 2: Adjusted for age, sex, race/ethnicity, smoking status, cigarette pack-years, body mass index, percent emptysema, systolic and diastolic blood pressures, statin use, apnea-hypopnea index, total intentional exercise, education attainment, diabetes, antidepressant use.

* Results are reported per 1-hour decrement in sleep duration

Table 3

Associations of Actigraphy-Based Sleep Duration with HAA

Sleep Duration	Less than 7 hours sleep duration			Greater than 7 hours sleep duration		
	No. Participants	Change in HAA per 1 hour increment in sleep duration (95% CI)	P-value	No. Participants	Change in HAA per 1 hour increment in sleep duration (95% CI)	P-value
Model 1						
Less than 25 kg/m ²	69	14.45 (-12.03 to 40.94)	0.28	302	22.98 (-3.91 to 49.88)	0.09
25–30 kg/m ²	132	-12.92 (-31.21 to 5.38)	0.17	405	-12.94 (-37.77 to 11.89)	0.31
Greater than 30 kg/m ²	121	-9.93 (-27.04 to 7.19)	0.26	387	-23.33 (-48.14 to 1.48)	0.07
Model 2						
Less than 25 kg/m ²	69	3.28 (-16.96 to 23.52)	0.75	302	33.13 (13.16 to 53.09)	0.001
25–30 kg/m ²	132	6.91 (-7.16 to 20.97)	0.34	405	-8.56 (-27.01 to 9.89)	0.36
Greater than 30 kg/m ²	121	-0.74 (-13.58 to 12.09)	0.91	387	-20.75 (-39.16 to -2.34)	0.03

Model 1: adjusted for study site, radiation dose, lung volume imaged.

Model 2: Model 1 + age, sex, race/ethnicity, smoking status, cigarette pack-years, percent emphysema, systolic and diastolic blood pressures, statin use, apnea-hypopnea index, total intentional exercise, education attainment, diabetes, and antidepressant use.

P-values for BMI interaction (Model 1): 0.22 (less than 7 hours sleep duration); 0.04 (greater than 7 hours sleep duration)

P-values for BMI interaction (Model 2): 0.72 (less than 7 hours sleep duration); <0.001 (greater than 7 hours sleep duration)