



ORIGINAL ARTICLE

# Association between diet quality and sleep apnea in the Multi-Ethnic Study of Atherosclerosis

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## Abstract

**Rationale:** Although short sleep duration has been linked to unhealthy dietary patterns, little is known about the association of obstructive sleep apnea (OSA), a disorder characterized by sleep fragmentation and diet.

**Study Objectives:** Investigate associations between diet quality and OSA in the Multi-Ethnic Study of Atherosclerosis and assess whether reductions in slow-wave sleep (stage N3) and rapid eye movement (REM) sleep are potential mediators for these associations.

**Methods:** A diverse population ( $N = 1813$ ) completed a food frequency questionnaire and underwent Type 2 in-home polysomnography, which included measurement of N3 and REM sleep and apnea-hypopnea index (AHI). Moderate-to-more severe OSA was defined as having an AHI  $> 15$  events/hr.

**Results:** Participants were 53.9% female with a mean age of 68.3 (SD 9.1) years. Approximately 33.8% were categorized as having moderate-to-more severe OSA. In adjusted analyses, OSA was associated with lower intakes of whole grains ( $\beta = -0.200$ , SE = 0.072,  $p < 0.01$ ), higher intakes of red/processed meat ( $\beta = -0.440$ , SE = 0.136,  $p < 0.01$ ), and lower overall diet quality ( $\beta = -1.286$ , SE = 0.535,  $p = 0.02$ ). Stage N3 sleep partially explained the associations between red/processed meat and overall diet quality score with OSA.

**Conclusions:** Moderate-to-more severe OSA is associated with a less healthy dietary profile that is partially explained by reduced N3 sleep. These findings suggest the opportunity to target sleep quality in interventions aimed at improving cardio-metabolic risk factors in patients with OSA.

## Statement of Significance

This paper investigates the associations between obstructive sleep apnea (OSA) and diet quality, characterized by the Alternative Healthy Eating Index-2010, and assesses sleep architecture, such as slow-wave sleep and rapid eye movement, as potential mediators of the association between OSA and diet quality. The study shows that OSA is associated with dietary intake of red/processed meat, whole grains, and overall diet quality and that reduced slow-wave sleep partially explains these associations. These findings raise the important possibility that by focusing on improving sleep quality, it may be possible to break the cycle of obesity–OSA–obesity and further suggests the need to address sleep quality as a way of improving OSA/CVD risk factors.

**Key Words:** OSA; diet quality; slow-wave sleep; Alternative Health Eating Index

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## Introduction

There is a growing literature linking sleep quality and duration to nutrient intake [1]. Individuals with insomnia, poor sleep quality, or curtailed sleep report unhealthy diets. For example, compared with individuals who report good sleep quality, those who report poor sleep quality report lower intakes of vegetables and fish and higher intakes of confectionary, sugar-sweetened beverages, energy drinks, and carbohydrates as well as more frequently report skipping breakfast and eating irregularly [2, 3]. Curtailed sleep or short sleep duration are also associated with high intakes of fatty foods, carbohydrates, total calories, and snacks [4–8]. Mechanisms linking insufficient sleep with dietary intake include hedonic and hormonal factors [9]. A period of restricted sleep has been shown to enhance activation of hedonic stimulus processing in the brain, particularly in the insular cortex, orbitofrontal cortex, and dorsolateral prefrontal cortex [10–13]. Poor sleep quality and short sleep duration have also been found to affect hunger and satiety hormones, ghrelin and leptin, which are implicated in a causal association between insufficient sleep and increased propensity to consume food [14–17].

Sleep quality and duration may not only reflect the impact of behavioral factors influencing sleep, but also may reflect underlying sleep disorders, which have not been systematically studied in relation to diet. In particular, obstructive sleep apnea (OSA), a condition characterized by intermittent upper airway obstruction [18], causes sleep fragmentation as well as exposure to intermittent hypoxemia, factors that trigger sympathetic nervous system activation, insulin resistance, and other neurohumoral responses [19, 20]. The Multi-Ethnic Study of Atherosclerosis (MESA) provides an opportunity to characterize the association between OSA and dietary intake. This diverse cohort allows for the examination of objective sleep measures and dietary quality using the Alternative Healthy Eating Index – 2010 (AHEI-10), a validated tool used to assess conformity based on Dietary Guidelines [21]. We hypothesized that OSA, via effects on sleep architecture, would be associated with less healthy dietary patterns.

## Methods

### Study design

The Multi-Ethnic Study of Atherosclerosis is a longitudinal assessment of risk factors for the incidence and progression of cardiovascular disease in a multiethnic cohort of adults. The study was comprised of a population-based sample of 6814 men and women aged 45–84 years who were free of clinically recognized cardiovascular disease at baseline. Participants were studied every 2 years with in-clinic examinations, starting in July 2000, as described elsewhere [22]. The current analyses used data from the MESA Exam 5 and an associated MESA Sleep ancillary study.

### Sleep measures

Between 2010 and 2013, participants who reported not regularly using oral devices, nocturnal oxygen, or nightly positive airway pressure devices were invited to participate in the MESA Sleep Ancillary Study. Of the 4077 potentially eligible individuals

participating in Exam 5, 2261 MESA participants agreed to participate in the sleep study [23]. As described before, compared with the overall MESA cohort, participants in the sleep exam were somewhat more likely to be white, older, smokers, and to have hypertension but had a comparable prevalence of self-reported doctor-diagnosed sleep apnea [23]. Participants underwent in-home polysomnography (PSG) using a 15-channel monitor. The sleep data were centrally scored [23] and provided quantitative levels of overnight hypoxemia, arousal indices, apneas and hypopneas, and sleep architecture which included sleep stage distributions and total sleep time, as described elsewhere [24]. The primary exposure variable was the apnea-hypopnea index (AHI), which was calculated as the average number of all apneas plus hypopneas associated with a 4% desaturation per hour of sleep [25]. Moderate-to-more severe OSA was defined as an AHI > 15 [24]. Short sleep duration (<6 hr/night) and long sleep duration (>9 hr/night) [26] were derived from the PSG assessment of total sleep time. Sleep staging was conducted following published guidelines by staff with high scorer reliability [27, 28]. Slow-wave sleep (stage N3) was defined as the percentage and absolute duration of total sleep time spent in stage N3 sleep. Rapid eye movement (REM) was defined as the percentage and total duration of total sleep time spent in stage REM sleep.

### Dietary measures

Participants attending Exam 5 (2010–2012) completed a detailed multiple-choice food frequency questionnaire (FFQ) [21] that assessed the participant's usual dietary intake over the past year. Dietary intake from the FFQ was then used to assess the dietary quality based on the AHEI-10 food group component and matrix score. The AHEI-10 uses a dietary scoring system that has been shown to predict risk of chronic diseases, such as cardiovascular disease [29–35]. The nutrient and food group components used to calculate the AHEI-10 were calculated at the MESA Coordinating Center blinded to other data. Briefly, the AHEI-10 represents the sum of 11 individual food components, each scored based on assessing the FFQ food group line item per day and then recalculated based on 1000 calories (kcal) of energy intake and the individual food components: vegetables, fruit, whole grains, sugar-sweetened beverages and fruit juices, nuts and legumes, red/processed meat, trans fat, long-chain fats, polyunsaturated fatty acids, sodium, and alcohol. Each food component is given a score that ranges from 0 to 10, with 10 considered the healthiest and summed for a total score [29, 30]. The following components: sugar-sweetened beverages and fruit juices, red/processed meat, trans fat, and sodium were reversed scored, meaning lower intake of these components received higher scores. The moderate category of alcohol intake received the maximum score. Those with too high or too low daily energy intake (>5000 or <500 kcal/day) were considered outliers and incomplete dietary questionnaires were excluded from the analysis [36].

### Covariates

At the clinic examination, height, weight, waist circumference, and hip circumference were directly measured using standardized approaches, and sociodemographic and comorbidity data were obtained from questionnaires as described previously [22]. Age, sex, race/ethnicity, education level, income, diabetes, and physical activity were considered as potential confounders and

were included in fully adjusted models. Age was assessed as a continuous variable. Race/ethnicity was categorized into four categories: non-Hispanic white, black, Hispanic, and Chinese. Education level was obtained using an 8-level scale and was further classified into the following four categories: less than high school, high school or graduate education diploma (GED), some college, and college degree or higher. Income was defined as the total gross family income. It was categorized into four categories: <\$25 000, \$25–49 999, \$50–74 999, and ≥\$75 000. Diabetes status was categorized into a dichotomous yes/no variable based on having a fasting glucose ≥126 mg/dL, taking insulin, or oral diabetes medication. Physical activity was derived from the Typical Week Physical Activity Survey (TWPAS), a validated questionnaire [37], that assesses daily activities associated with different physical intensity levels as well as the number of times this activity was performed and the average amount of time spent per day. Physical activity was categorized into three categories: low physical activity (<33% quartile), moderate physical activity (33%–67% quartile), and high physical activity (>67% quartile), using levels of moderate intensity physical activity, expressed as MET-min/day of energy expenditure [38].

### Statistical analysis

Multivariate linear regression analysis was used to estimate the associations of OSA with the overall AHEI-10 score as well as its individual components (i.e. the diet scores were considered as dependent variables). Covariate adjustments included age, sex, race/ethnicity, education, and income. We also adjusted for diabetes given that it is associated with OSA and may influence dietary choices, and physical activity, as a proxy for general health habits associated with both diet and OSA [39]. Secondary analyses also adjusted for sleep duration and considered AHI as a continuous variable. Mediation analysis was used to assess stages N3 and REM sleep as potential mediators of the association between OSA (dichotomized) or AHI (continuously measured) and diet scores. Mediated effects were estimated using the method of Baron and Kenny, which estimates the indirect (mediated) effects as the difference between the total and direct effects, based on hypothesized causal associations [40]. The point estimates and 95% confidence intervals for these estimates were calculated using resampling methods described by Mackinnon et al. [41]. All statistical analyses were conducted with SAS 9.4 statistical software.

Results with two-sided  $p < 0.05$  were considered statistically significant.

### Results

A total of 1813 individuals had both acceptable PSG studies and complete food intake data. The sample had a mean age of 68.3 years (standard deviation [SD] = 9.1 years); 37.8% were non-Hispanic white with the remaining black (27.5%), Hispanic (23.5%), and Chinese (11.2%); 53.9% were female. Approximately 33.8% of the study sample met the criterion for moderate-to-more severe OSA (AHI > 15). Individuals with OSA were more likely to be male, spend fewer minutes in N3 and REM sleep, and have shorter sleep duration, higher BMI, and greater waist circumference and waist-to-hip ratio relative to those without moderate-to-more severe OSA, all  $p < 0.01$  (Table 1).

In unadjusted analyses, moderate-to-more severe OSA was associated with a lower total AHEI-10 score ( $\beta = -2.278$ ,  $SE = 0.521$ ,  $p < 0.01$ ), lower intake of fruits ( $\beta = -0.354$ ,  $SE = 0.153$ ,  $p = 0.021$ ) and whole grains ( $\beta = -0.274$ ,  $SE = 0.069$ ,  $p < 0.01$ ), and higher intake of red/processed meats ( $\beta = -0.543$ ,  $SE = 0.133$ ,  $p < 0.01$ ), sugar-sweetened beverages and fruit juices ( $\beta = -0.433$ ,  $SE = 0.196$ ,  $p = 0.027$ ), trans fat ( $\beta = -0.068$ ,  $SE = 0.033$ ,  $p = 0.038$ ), and sodium ( $\beta = -0.521$ ,  $SE = 0.159$ ,  $p < 0.01$ ), compared with those without moderate-to-more severe OSA.

In adjusted models, moderate-to-more severe OSA was associated with lower intakes of whole grains ( $\beta = -0.200$ ,  $SE = 0.072$ ,  $p < 0.01$ ) and total AHEI-10 scores ( $\beta = -1.286$ ,  $SE = 0.535$ ,  $p = 0.02$ ), and higher intakes of red/processed meat ( $\beta = -0.440$ ,  $SE = 0.136$ ,  $p < 0.01$ ) (Table 2). These associations persisted when adjusting for both short and long sleep durations (long sleep duration not shown). Associations of OSA with fruits, sugar-sweetened beverages and fruit juices, trans fat, and sodium were no longer significant after adjusting for demographics, socioeconomic status, diabetes, and physical activity.

Similar associations were seen when modeling AHI as a continuous variable (Supplementary Table 1). Of note, the association between higher intake of sugar-sweetened beverages and fruit juices and AHI level remained significant in adjusted models using AHI as a continuous variable, whereas it was no longer significant when AHI was used as a dichotomous variable.

In the mediation analysis, we first examined whether duration of stage N3 and REM sleep mediated the association between AHI level and red/processed meat intake, when controlling for sex, race/ethnicity, education, income, age, physical activity, and diabetes. Percent sleep time spent in N3 sleep explained 9.25% of the association between AHI and red/processed meat score (95% CI:  $-0.021$ ,  $-0.0054$ ; Figure 1). A similar pattern was observed when OSA was based on a dichotomous definition (AHI > 15) (Figure 2). We also examined whether N3 and REM sleep duration explained the association between AHI and total AHEI-10 score. Our mediation analysis suggested that percent time in N3 sleep explained 7.4% of the association between AHI and overall diet score (Figure 3), with similar associations observed for OSA described as a binary variable (9.3% of the variation explained by N3; Figure 4). If we modeled N3 as absolute N3 sleep time in minutes rather than as a percentage of total sleep, N3 sleep explained 9.4% and 9.9% of the association between AHI and red/processed meat and total AHEI-10 score, respectively.

The mediation models did not identify significant explanatory associations for N3 sleep in the association between AHI and whole grain intake. REM sleep duration was not a significant explanatory variable between AHI and any measure of dietary intake.

Since the association between diet quality and risk of chronic diseases, such as cardiovascular disease, is mediated by adiposity [42], we also explored the consistency of our models after additionally adjusting for waist-to-hip ratio (Supplementary Table 2). When adjusting for waist-to-hip ratio, our results did not substantively change and OSA remained significantly associated with lower intake of whole grains ( $\beta = -0.815$ ,  $SE = 0.075$ ,  $p = 0.01$ ) and total AHEI-10 score ( $\beta = -1.084$ ,  $SE = 0.536$ ,  $p = 0.04$ ), and higher intake of red/processed meat ( $\beta = -0.431$ ,  $SE = 0.137$ ,  $p < 0.01$ ). This suggests that adiposity did not entirely explain the association, despite its correlation with both sleep and dietary quality.

**Table 1.** Study population characteristics by OSA (N = 1813), MESA Study 2010–2013

Characteristic	With moderate-to-severe OSA (AHI > 15; n = 613) mean (SD) or number (%)	Without moderate-to-severe OSA (AHI ≤ 15) (n = 1200) mean (SD) or number (%)	P*
Age, year	68.8 ± 8.9	68.1 ± 9.2	0.11
Race			0.02
Non-Hispanic white	210 (34.3%)	476 (39.7%)	
Black	161 (26.2%)	338 (28.1%)	
Hispanic	161 (26.3%)	264 (22.0%)	
Chinese	81 (13.2%)	122 (10.2%)	
Sex			<0.01
Male	381 (62.1%)	455 (37.9%)	
Female	232 (37.9%)	745 (62.1%)	
Education			0.12
Less than high school	96 (15.7%)	279 (23.8%)	
High school/GED	93 (15.2%)	338 (28.8%)	
Some college but no degree	164 (26.7%)	214 (18.3%)	
College degree or higher	260 (42.4%)	341 (29.1%)	
Income			0.12
<\$25 000	172 (28.6%)	279 (23.8%)	
\$25–49 999	150 (24.9%)	338 (28.8%)	
\$50–74 999	108 (17.9%)	214 (18.3%)	
≥\$75 000	172 (28.6%)	341 (29.1%)	
Sleep duration			
Short sleep (<6 hr per night)	218 (35.6%)	334 (27.8%)	<0.01
Long sleep (>9 hr per night)	12 (2.0%)	18 (1.5%)	0.47
Smoking status			0.12
Current smoker	33 (5.5%)	88 (7.4%)	
Former/never	573 (94.5%)	1104 (92.6%)	
Physical activity, hours per day			<0.01
Low	227 (37.1%)	335 (27.9%)	
Moderate	189 (30.8%)	417 (34.8%)	
High	197 (32.1%)	448 (37.3%)	
Body mass index, kg/m <sup>2</sup>	30.67 ± 5.94	27.78 ± 5.08	<0.01
Waist-hip ratio, cm	0.962 ± 0.066	0.926 ± 0.090	<0.01
Alcohol use (currently drink alcohol)			0.67
Yes	277 (45.3%)	530 (44.2%)	
No	335 (54.7%)	669 (55.8%)	
Diabetes			<0.01
Yes	155 (25.5%)	187 (15.7%)	
No	452 (74.5%)	1001 (84.3%)	
Time in N3 sleep, min	29.46 ± 29.55	40.90 ± 34.76	<0.01
Time in REM sleep, min	58.28 ± 29.29	71.00 ± 29.18	<0.01
Time in N3 sleep, %	8.26 ± 7.97	10.97 ± 9.15	<0.01
Time in REM sleep, %	16.29 ± 7.02	18.97 ± 6.29	<0.01

\*Chi-square or ANOVA tests for categorical or continuous variables (respectively).

## Discussion

This study provides novel data linking dietary quality with OSA. Compared with adults without moderate-to-more severe OSA, we found that individuals with moderate-to-more severe OSA had significantly poorer AHEI-10 total scores, due to lower whole grain intake and increased red/processed meat consumption. These associations persisted after adjusting for age, sex, race/ethnicity, education level, income, diabetes, and physical activity. Moreover, these findings were independent of sleep duration but were partially explained by reductions in stage N3 sleep, a sleep state associated with generally high parasympathetic tone, low sympathetic tone, and less fragmented sleep. These are the first data to the best of our knowledge that identify that a common sleep disorder (OSA) is associated with an unhealthy diet and suggest that reduced N3 sleep partially explains this association.

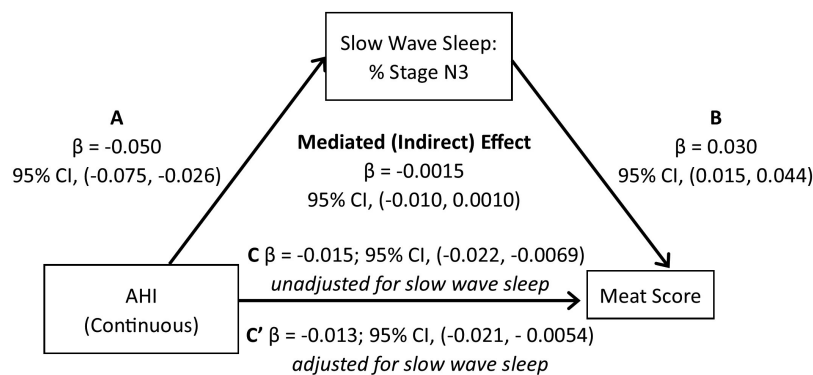
A growing literature indicates that adhering to the recommendation set forth in the Dietary Guidelines for Americans is associated with a lower risk of developing chronic diseases [21]. The recommendations show that adhering to a high consumption of high nutrient dense foods and low consumption of low density foods decreases the risk of developing cardiovascular disease and other major chronic diseases. The combination of low whole grain and high red/processed meat consumption is associated with numerous adverse health outcomes, such as cardiovascular disease, type-2 diabetes, and all-cause mortality [43–45].

Prior studies have shown associations between poor dietary habits and short sleep duration. A study of 410 female youths in Iran showed those who slept less than 6 hr per day were more likely to consume a lower amount of whole grains compared with those who slept more than 6 hr per night [46]. Individuals with symptoms of insomnia report lower intakes of vegetables and

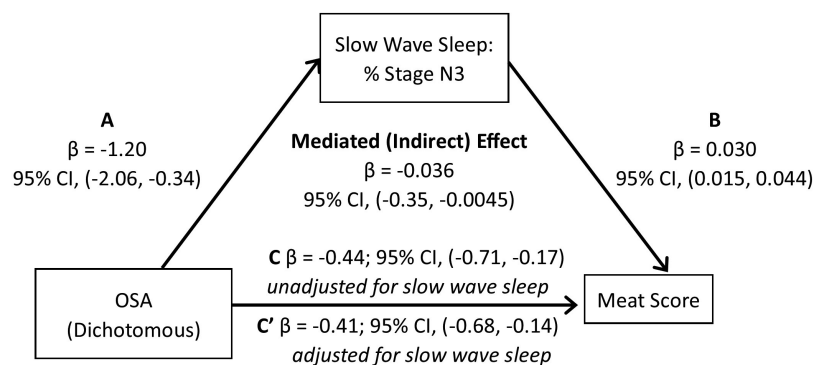
**Table 2.** Differences in the overall AHEI-10 score and its individual dietary components according to OSA status (AHI > 15 vs. AHI ≤ 15) using multivariate linear regression, MESA Study 2010–2013

	Moderate-to-severe OSA (AHI > 15) vs. without moderate-to-severe OSA (AHI ≤ 15)					
	Model 1, n = 1813		Model 2, n = 1752		Model 3, n = 1752	
	β (SE)	P	β (SE)	P	β (SE)	P
Vegetable score	-0.12 (0.14)	0.38	0.047 (0.14)	0.74	0.042 (0.14)	0.77
Fruit score	<b>-0.35 (0.15)</b>	<b>0.021</b>	-0.092 (0.16)	0.56	-0.087 (0.16)	0.58
Whole grain score	<b>-0.27 (0.069)</b>	<b>&lt;0.001</b>	<b>-0.20 (0.072)</b>	<b>0.0059</b>	<b>-0.20 (0.073)</b>	<b>0.0055</b>
Beverage score	<b>-0.43 (0.20)</b>	<b>0.027</b>	-0.39 (0.20)	0.055	-0.38 (0.20)	0.064
Nuts and legumes score	-0.20 (0.17)	0.25	-0.12 (0.18)	0.52	-0.17 (0.18)	0.56
Red/processed meat score	<b>-0.54 (0.13)</b>	<b>&lt;0.001</b>	<b>-0.44 (0.14)</b>	<b>0.0013</b>	<b>-0.43 (0.14)</b>	<b>0.0017</b>
Trans fat score	<b>-0.068 (0.033)</b>	<b>0.038</b>	-0.022 (0.034)	0.52	-0.022 (0.034)	0.53
Long-chain fats score	0.20 (0.11)	0.084	0.22 (0.12)	0.061	0.21 (0.12)	0.077
Polyunsaturated fatty acids score	-0.10 (0.15)	0.49	-0.047 (0.15)	0.76	-0.052 (0.15)	0.74
Sodium score	<b>-0.52 (0.16)</b>	<b>0.0011</b>	-0.30 (0.16)	0.063	-0.29 (0.16)	0.071
Alcohol score	0.14 (0.14)	0.32	0.057 (0.14)	0.69	0.062 (0.14)	0.66
Total AHEI-10 score	<b>-2.28 (0.52)</b>	<b>&lt;0.001</b>	<b>-1.29 (0.54)</b>	<b>0.016</b>	<b>-1.26 (0.54)</b>	<b>0.019</b>

Model 1: Unadjusted; Model 2: Adjusted for age, sex, race, education, income, diabetes, and physical activity; Model 3: Model 2 + short sleep duration. Bold p-values represent statistical significance at the 0.05 level.



**Figure 1.** Mediation Analysis: N3 as a mediator in the association of AHI or OSA with red/processed meat intake, MESA Study 2010–2013. (A–C) Mediation analysis demonstrating that the association of sleep apnea (modeled either as continuously or dichotomously expressed AHI) on meat score is partially mediated by slow-wave sleep. Sleep apnea is associated with both (A) N3 sleep and (C) meat score. (B) N3 sleep is also strongly associated with meat score. The mediated (indirect) effect is the total effect (pathway C) minus the direct effect (pathway C') or the difference in the point estimate of sleep apnea on meat score without and with adjustment for N3 sleep.

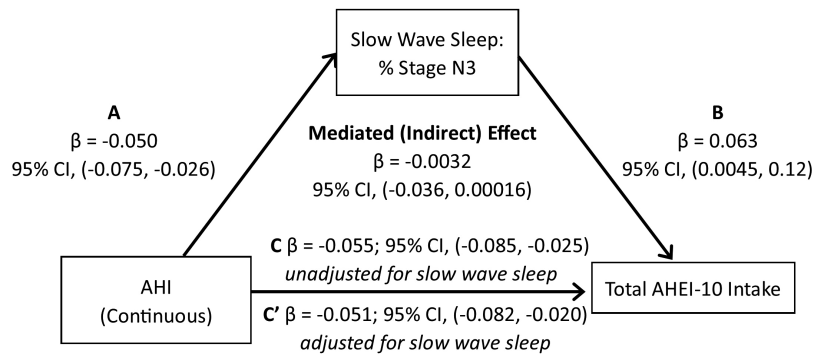


**Figure 2.** Mediation Analysis: N3 as a mediator in the association of AHI or OSA with red/processed meat intake, MESA Study 2010–2013. (A–C) Mediation analysis demonstrating that the association of sleep apnea (modeled either as continuously or dichotomously expressed AHI) on meat score is partially mediated by slow-wave sleep. Sleep apnea is associated with both (A) N3 sleep and (C) meat score. (B) N3 sleep is also strongly associated with meat score. The mediated (indirect) effect is the total effect (pathway C) minus the direct effect (pathway C') or the difference in the point estimate of sleep apnea on meat score without and with adjustment for N3 sleep.

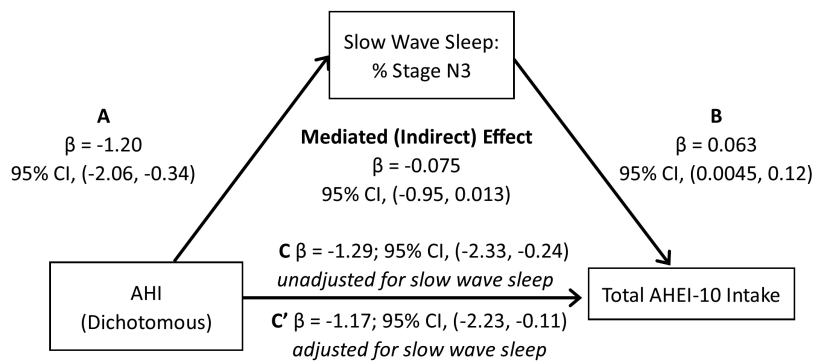
higher intakes of trans fat, sodium, and total energy consumption than individuals without symptoms of insomnia [2]. Several mechanisms have been invoked to explain this association between insufficient sleep and unhealthy eating, including dysregulation of appetite hormones and changes in central nervous system

responses to food stimuli [9–13]. However, prior research has not examined the association between OSA and dietary intake.

Adjusted analyses showed that the associations with OSA were significant for total AHEI-10 score and scores for red/processed meats and whole grains. Although unadjusted analyses



**Figure 3.** Mediation analysis: N3 as a mediator in the association of AHI or OSA with total AHEI-10 intake, MESA Study 2010–2013. A–C, Mediation analysis demonstrating that the association of sleep apnea (modeled either as continuously or dichotomously expressed AHI) on total AHEI score is partially mediated by slow-wave sleep. Sleep apnea is associated with both (A) N3 sleep and (C) total AHEI score. (B) N3 sleep is also strongly associated with total AHEI score. The mediated effect is the total effect (pathway C) minus the direct effect (pathway C') or the difference in the point estimate of sleep apnea on total AHEI score without and with adjustment for N3 sleep.



**Figure 4.** Mediation analysis: N3 as a mediator in the association of AHI or OSA with total AHEI-10 intake, MESA Study 2010–2013. A–C, Mediation analysis demonstrating that the association of sleep apnea (modeled either as continuously or dichotomously expressed AHI) on total AHEI score is partially mediated by slow-wave sleep. Sleep apnea is associated with both (A) N3 sleep and (C) total AHEI score. (B) N3 sleep is also strongly associated with total AHEI score. The mediated effect is the total effect (pathway C) minus the direct effect (pathway C') or the difference in the point estimate of sleep apnea on total AHEI score without and with adjustment for N3 sleep.

also showed associations with trans fat and sodium with OSA, those associations were attenuated after adjusting for age, sex, race/ethnicity, education level, income, diabetes, and physical activity. The clinical relevance of these associations is supported by the literature linking red/processed meat and whole grains with chronic diseases and mortality [43–45]. To the best of our knowledge, no study has previously reported an association between OSA and consumption of low whole grains and increased red/processed meat intake.

In adjusted analyses relating AHI and diet, we also observed associations with increasing AHI levels and higher consumption of sugar-sweetened beverages. Sugar-sweetened beverages have been identified as a significant contributor to rising rates of obesity [47]. Therefore, it is plausible that there are reinforcing mechanisms relating sleep apnea, high-caloric diets, and obesity.

Our study suggests that an important link between OSA and unhealthy diet may be through reduced N3 sleep. N3 sleep has long been recognized to play an important role in neurobehavioral functioning, including memory consolidation [48] and cognition [49]. In addition, N3 sleep significantly modulates a number of endocrine functions, including the hypothalamic-pituitary-adrenocortical system and growth hormone and prolactin release [50]. Experimental studies show that selective reductions in N3 sleep cause abnormalities in glucose tolerance

and insulin secretion [51, 52] consistent with a causal role in the development of diabetes. Epidemiological studies have also shown that independent of sleep duration, decreased N3 sleep is associated with increased adiposity [53]. Reduced N3 sleep has been found to be associated with poor diet intake in a small experimental study of young adults. In that study, percentage of time spent in N3 sleep was inversely associated with fat and carbohydrate intake [54].

Reductions in N3 sleep occur commonly with aging and secondary to sleep fragmentation. Individuals with OSA experience repetitive respiratory disturbances and arousals, which increase time in Stage N1 sleep and reduce time in N3 and prolong the latency to the first epoch of N3 and REM sleep compared with those without sleep apnea [55]. In our study, N3 sleep was 25%–28% lower in individuals with OSA compared with others. A formal mediation analysis showed that N3 sleep duration explained approximately 6% to 9% of the association between AHI and red/processed meat score and total AHEI-10 score. These associations suggest the importance of poor sleep quality as a contributor to unhealthy eating patterns in individuals with OSA, and possibly secondarily, as a risk factor for obesity and cardiovascular disease in those patients.

In contrast to N3 sleep, we found no statistical evidence to support a potential mediatory role of reduced REM sleep linking OSA and dietary pattern. Although REM sleep is the sleep state

associated with the highest sympathetic tone, which we postulated may associate with dietary patterns, there is little evidence that REM sleep patterns are strongly associated with endocrine function or appetite.

We carefully considered the challenge of covariate adjustment and adjusted for factors that a priori we considered to be common risk factors for diet and OSA. For example, sociodemographic factors are associated with both diet and OSA [23]. Prior analyses showed that increased physical activity was associated with OSA [56] and since physical activity may be a marker of other lifestyle factors, we also included this in our adjusted model. Diabetes was included as individuals with diabetes may alter their diet. Although we were reluctant to adjust for obesity (which may be an outcome of poor diet) due to concerns over introducing collider bias, in exploratory analysis inclusion of waist-hip ratio in exploratory analysis did not alter the results (Supplementary Table 2). Short sleep duration was adjusted for given its association with diet; however, its inclusion (models 3) did not appreciably influence the findings.

There are several clinical implications to our results that should be tested in future interventions. OSA is associated with obesity and weight loss may lead to significant improvements in the AHI [57]. However, behavioral interventions to improve energy balance have had limited success [58–60] and in fact, even with CPAP treatment, patients with OSA commonly gain weight [61]. OSA is associated with an increased prevalence of cardiovascular disease [62–64]. Therefore, it is important to identify modifiable factors that influence diet quality or otherwise influence cardiovascular risk factors in individuals with OSA. Diets characterized by increased intake of high-quality foods, such as whole grains, and decreased low-quality foods, such as red/processed meat, are ideal in reducing cardiovascular risk factors and other chronic diseases. The results of this analysis suggest that efforts to improve sleep quality, particularly N3 sleep duration, in OSA may be a potentially useful adjunctive strategy for addressing the chronic health problems associated with OSA.

Strengths of this study include the racial/ethnic diversity of the participants, relatively large sample size, and the use of rigorously collected objective sleep and standardized diet measures. The use of calculating dietary intake using the AHEI-10 guidelines corresponded to analyzing OSA, a chronic debilitating disease. Authors were blinded to the diet and sleep scoring.

The study also had several limitations. Although we used a well-validated dietary scoring tool, misclassification is possible and information on timing of meals was not available. As described earlier, we selected an a priori list of covariates in our adjusted model; nonetheless, we cannot exclude the possibility of unmeasured confounding, including those that may affect N3 sleep duration. We examined both total AHEI-10 score and its components, and it is possible that by examining multiple outcomes, we increase the likelihood of falsely rejecting the null hypothesis. Although less than 60% of the eligible participants participated in the sleep ancillary study, it is possible but unlikely that selection bias influenced the observed associations between sleep and diet [23]. The cross-sectional design limits causal inference and assessment of mediation [65]. A meta-analysis of data from the Nurses' Health Study, the Nurses' Health Study II, and the Health Professionals Follow-up Study showed that those who consume more unprocessed red meats and processed meats and consumed less whole grains experienced shorter sleep duration and increased weight gain

[66], consistent with a causal association between insufficient sleep and obesogenic behaviors. It is plausible that diet could influence N3 sleep (rather than the reverse). Supporting this hypothesis, a prior study of 10 healthy young males, randomized to either a high-carbohydrate dinner or high-fat dinner, found those who ingested a high-carbohydrate dinner spent significantly less time in N3 sleep compared with those who are a high-fat dinner [67]. This causal direction raises the provocative idea that an unhealthy diet may predispose to OSA via effects on reducing N3, the sleep stage when breathing is typically most stable (and AHI is lowest).

## Conclusion

This study provides novel evidence that sleep apnea is associated with dietary quality, with associations strongest for consumption of low whole grains, high red/processed meat, and overall low AHEI-10 score, and that the latter associations may be partially explained by reduction in N3 sleep. Although current interventions aim to reduce apnea and hypopnea frequency, our study suggests that additional efforts to improve sleep architecture may help improve the cardiovascular risk factor profile of patients with OSA. However, longitudinal studies and clinical trials are needed to clarify causal pathways and identify the effect of changes in N3 sleep on diet patterns in patients with OSA.

## Supplementary Material

Supplementary material is available at *SLEEP* online.

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