# Overall diet quality and proinflammatory diet in relation to risk of obstructive sleep apnea in 3 prospective US cohorts

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## ABSTRACT

**Background:** Inflammation-related mechanisms may be important in the development of obstructive sleep apnea (OSA), and diet plays a crucial role in modulating inflammation. Current epidemiologic evidence for the associations between dietary patterns and OSA risk is limited to cross-sectional studies.

**Objectives:** We investigated prospectively the associations of overall diet quality and proinflammatory diet with OSA risk.

**Methods:** We followed 145,801 participants in the Nurses' Health Study (NHS) (2002–2012), NHS II (1995–2013), and Health Professionals Follow-up Study (1996–2012). Alternative Healthy Eating Index 2010 (AHEI) and Empirical Dietary Inflammatory Pattern (EDIP) scores were calculated based on validated FFQs administered every 4 y. Cox models were used to estimate HRs and 95% CIs.

**Results:** We documented 8856 incident OSA cases during follow-up. In pooled analyses adjusted for potential confounders, higher diet quality (higher AHEI scores) was associated with lower OSA risk (HR comparing the highest with the lowest quintile of AHEI: 0.76; 95% CI: 0.71, 0.82; $P$-trend $< 0.001$), and higher dietary inflammatory potential (higher EDIP scores) was associated with significantly increased risk (HR comparing the highest with the lowest quintile of EDIP: 1.94; 95% CI: 1.81, 2.08; $P$-trend $< 0.001$). Additional adjustment for metabolic factors attenuated both associations. The association with AHEI score was no longer statistically significant (comparable HR: 0.98; 95% CI: 0.91, 1.05; $P$-trend $= 0.54$), whereas the association with EDIP score remained statistically significant (comparable HR: 1.31; 95% CI: 1.22, 1.41; $P$-trend $< 0.001$).

**Conclusions:** A healthier diet, particularly one with anti-inflammatory potential, was associated with lower OSA risk. *Am J Clin Nutr* 2022;116:1738–1747.

**Keywords:** diet quality, proinflammatory diet, obstructive sleep apnea, Alternative Healthy Eating Index, Empirical Dietary Inflammatory Pattern, prospective cohort study

## Introduction

Obstructive sleep apnea (OSA) is a common sleep disorder caused by repeated episodes of partial or complete obstruction of the upper airway during sleep, affecting 10%–20% of the US adult population and leading to increased morbidity and mortality (1–6). A growing number of prospective studies have linked poorer diet quality with worse pulmonary functions and increased risk of chronic health conditions comorbid with OSA (e.g., obesity, diabetes, cardiovascular disease, and chronic obstructive pulmonary disease) (7–10). Another line of evidence suggests a close relation of an unhealthy diet with shorter sleep duration and poorer sleep quality (11, 12), which are common among individuals with OSA. Therefore, it is highly plausible that the risk of OSA may also be modulated by diet. However,

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Abbreviations used: AHEI, Alternative Healthy Eating Index 2010; AHI, Apnea-Hypopnea Index; EDIP, Empirical Dietary Inflammatory Pattern; EDS, excessive daytime sleepiness; HPFS, Health Professionals Follow-up Study; HT, hormone therapy; NHS, Nurses' Health Study; OSA, obstructive sleep apnea; RRR, reduced rank regression; SSB, sugar-sweetened beverage.

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current epidemiologic evidence for the potential role of diet in OSA development remains limited. Although 4 cross-sectional studies reported consistent associations of lower diet quality with higher OSA prevalence (13–16), these results may reflect bidirectional relations and prospective studies are needed to clarify the directionality of the associations (17).

Diet also modulates inflammation, and higher diet quality has been associated with favorable inflammation profiles (18–21). Further, the dietary inflammatory index, which was developed to specifically assess the inflammatory potential of diet (22), has been robustly associated with increased risk of several inflammation-related diseases including diabetes (23), cardiovascular disease (24), and colorectal cancer (25). Given that elevated inflammation has been implicated in the pathogenesis of OSA (26–28), the inflammatory dietary pattern may be particularly relevant for OSA risk. There are initial clues from cross-sectional studies suggesting adverse associations between the inflammatory potential of diet and several OSA-related parameters [e.g., Apnea-Hypopnea Index (AHI) and daytime sleepiness] (16, 29).

We investigated the associations of overall diet quality and proinflammatory diet with OSA risk in the Nurses' Health Study (NHS), NHS II, and Health Professionals Follow-up Study (HPFS). We hypothesized that higher overall diet quality and lower dietary inflammatory potential may be associated with lower OSA risk, independently of confounders and major OSA predictors.

## Methods

### Study population

The NHS, NHS II, and HPFS are ongoing US prospective cohort studies, the details of which have been elaborated elsewhere (30–32). In brief, the NHS was initiated in 1976, enrolling 121,700 female nurses between 30 and 55 y of age (30), and NHS II in 1989, enrolling 116,429 female nurses aged 25–42 y (31). The HPFS began in 1986, when 51,529 male health professionals aged between 40 and 75 y were included (32). Demographics and disease history were collected at cohort enrollment. Through biennial follow-up using self-administered questionnaires, information on anthropometrics, lifestyle characteristics, diet, menstrual and reproductive history (females only), and medical history were assessed, with response rates exceeding 90% of eligible person-time. The study protocols were approved by the Institutional Review Boards of the Brigham and Women's Hospital and Harvard TH Chan School of Public Health. We excluded individuals who had no dietary information at the predefined analytic baseline (NHS: 2002, NHS II: 1995, and HPFS: 1996), reported implausible total energy intake (<500 or >3500 kcal/d for females and <800 or >4200 kcal/d for males), did not answer the question on sleep apnea diagnosis, or reported sleep apnea diagnosis before the analytic baseline, leaving 57,391 participants in the NHS, 69,180 in the NHS II, and 19,536 in the HPFS for analysis (**Supplemental Figure 1**).

### Dietary assessment

A semiquantitative FFQ was first administered in the NHS in 1980, with expanded 131-item FFQs in 1984, 1986, and every 4 y thereafter. Starting from 1991 in the NHS II and 1986 in the HPFS, the same 131-item FFQs were administered quadrennially. Participants were queried about their consumption frequency of each food during the previous year based on a specified standardized portion size or a commonly used unit, and responses included 9 categories ranging from "never or <1 time per month" to "≥6 times per day." The validity and reproducibility of the FFQs in our cohorts have been comprehensively reported (33–35). We estimated the average daily intake of nutrients by multiplying the consumption frequency of each food by the corresponding nutrient content (based primarily on the USDA Nutrient Database, and supplemented by other published sources). We further calculated energy-adjusted, cumulative average dietary intakes from repeated FFQs to capture long-term exposure and reduce random within-subject variation (36, 37).

The Alternative Healthy Eating Index 2010 (AHEI) was derived from 11 foods and nutrients predictive of chronic disease risk based on existing clinical and epidemiologic investigations (38), including information from the original Alternate Healthy Eating Index (39). The details of variable selection and scoring criteria for the AHEI have been elaborated elsewhere (38). Each component was scored from 0 (worst) to 10 (best), with a total score ranging from 0 (nonadherence to healthy eating) to 110 (perfect adherence to healthy eating). Components that receive a lower score with higher intake include sugar-sweetened beverages (SSBs), red and processed red meat, *trans* fat, sodium, and alcohol; components that receive a higher score with higher intake include fruits, vegetables, whole grains, nuts and legumes, PUFAs, and omega ($\omega$)-3 fatty acids (38).

The Empirical Dietary Inflammatory Pattern (EDIP) score was derived according to food groups' ability to predict plasma concentrations of 3 inflammatory markers (IL-6, CRP, and TNF $\alpha$ receptor 2) to assess the overall inflammatory potential of diet (18, 22). Using reduced rank regression (RRR; to identify an RRR dietary pattern based on linear functions of food groups simultaneously maximizing the explained variation in inflammatory markers) and stepwise linear regression (to identify the most important food group components contributing to the RRR dietary pattern), a data-driven index of dietary inflammatory potential was generated based on the weighted sum of 18 food groups, with higher scores indicating higher inflammatory potential (18, 22). Dietary components that contribute to higher EDIP scores with higher intake (proinflammatory) include processed meat, red meat, organ meat, fish other than dark-meat fish, vegetables other than green leafy or dark yellow vegetables, refined grains, high-energy beverages, low-energy beverages, and tomatoes. Components that contribute to lower scores with higher intake (anti-inflammatory) include beer, wine, tea, coffee, dark yellow vegetables, green leafy vegetables, snacks, fruit juice, and pizza. This EDIP score has been widely used in multiple cohorts with robust associations with risk of cardiometabolic disease and cancer (24, 25, 40, 41).

The AHEI and EDIP were moderately correlated (Spearman correlation = −0.34 in the pooled baseline sample) (**Supplemental Table 1**a). Supplemental Table 1b presents correlations of individual food/nutrient groups with the AHEI and EDIP. The scoring criteria for both indexes have previously been reported (18, 22, 38).

### Assessment of OSA and related symptoms

On the 2012 NHS questionnaire, participants reported whether they had sleep apnea diagnosed by a clinician or sleep study (yes or no), and (if yes) the year of first diagnosis (response categories: before 2002, 2002–2005, 2006–2007, 2008–2009, 2010–2011, and after 2012) (42–44). Therefore, the analytic baseline was 2002 in the NHS. In 2013 (NHS II) and 2012 (HPFS), clinical diagnoses of sleep apnea were assessed using a similar approach, with the analytic baseline determined as 1995 and 1996, respectively (42–44). The validity of self-reported sleep apnea in our cohorts has been studied previously and showed excellent reliability (42). Specifically, in 108 NHS/NHS II participants with self-reported sleep apnea, all diagnoses were confirmed by medical record review based on ≥1 objective monitoring method (92% by in-laboratory polysomnography, 98% were classified as obstructive, and 89% were considered as moderate-to-severe with AHI ≥15) (42). Moreover, the projected prevalence of moderate-to-severe OSA in the United States measured by polysomnography (1) was similar to that of self-reported OSA in our cohorts (42). Key OSA symptoms were assessed repeatedly throughout follow-up, including habitual snoring (defined as snoring every night or most nights) and excessive daytime sleepiness (EDS; defined as ≥4 d/wk of disrupted daily activities due to sleepiness) (4). We considered incidence of clinically diagnosed OSA as the primary outcome of interest, and incidence of symptomatic OSA with EDS (potentially more severe OSA) as a secondary outcome.

### Statistical analysis

The analytic baseline was 2002 in the NHS, 1995 in the NHS II, and 1996 in the HPFS, with follow-up until 2012 in the NHS, 2013 in the NHS II, and 2012 in the HPFS. We calculated person-years of follow-up from the return date of the baseline questionnaire until the date of OSA diagnosis or the return date of the 2012/2013 questionnaire, whichever arrived earlier.

We first performed analyses in each cohort, and then conducted pooled analyses with assessment of potential heterogeneity by cohort using meta-analysis. Multivariable-adjusted HRs and 95% CIs for OSA risk across quintiles of AHEI and EDIP scores were estimated using Cox proportional hazards models; we found no evidence for violation of the proportional hazards assumption. Dietary exposures and covariates (except race/ethnicity and cohort) were modeled as time-varying in the analysis. Tests for linear trend were conducted by modeling median values in each quintile of AHEI or EDIP score as a continuous variable.

The first multivariable model was stratified by cohort (NHS, NHS II, and HPFS, in the pooled analyses only), age (mo), and questionnaire cycle, and adjusted for race/ethnicity (white, nonwhite), smoking (never, past, current), pack-years of smoking (continuous), menopausal status (premenopausal, postmenopausal) (females only), duration of postmenopausal hormone therapy (HT) by type (never, <5, 5 to <10, ≥10 y for estrogen-only and estrogen + progestin HT separately) (females only), physical exams (yes, no), total energy intake (in quintiles; kcal/d), habitual sleep duration (≤5, 6, 7, 8, ≥9 h/d), and physical activity (<6.0, 6.0–11.9, 12.0–20.9, 21.0–35.9, ≥36.0 metabolic equivalent task hours per week). Details for assessment of these covariates can be found in **Supplemental Methods**. The second multivariable model further adjusted for metabolic factors including BMI (continuous; in kg/m$^2$), waist circumference (continuous; cm), history of diabetes (yes, no), and history of hypertension (yes, no), which were likely consequences of dietary patterns and considered as potential mediators in the analysis. We estimated the percentage of the association explained by these metabolic factors using the publicly available %Mediate macro (https://www.hsph.harvard.edu/donna-spiegelman/software/mediate/). The proportion was estimated by applying the partial likelihood function to 2 Cox models postulated on the same failure time variable, and the CIs were constructed by using the direct normal approximation to the point estimator (45). Secondarily, we repeated these analyses using OSA with EDS as the outcome.

We further explored the associations of individual foods/nutrients in each dietary score with OSA risk to understand what may drive potential differences in the results between the AHEI and EDIP. We also performed stratified analyses by age, sex, BMI, diabetes status, waist circumference, and physical activity to explore whether these factors modified the associations. Statistical significance of effect modification was assessed by testing multiplicative interactions using the likelihood ratio test. Finally, given the long time span of our exposure assessment, we repeated our primary analyses using AHEI and EDIP scores assessed 2–4 y before OSA diagnosis as the exposure to test the robustness of our findings based on the most recent diet.

To minimize missing data, information from the most recent previous questionnaire cycle was carried forward for imputation. Missing indicators were used if the data were still missing. This approach has been widely applied in prior studies in the NHS and HPFS (25, 46, 47).

Data analyses were conducted using SAS statistical software (version 9.4; SAS Institute Inc.), with 2-sided $P$ values $< 0.05$ considered statistically significant.

## Results

### Population characteristics

A total of 8856 incident cases of OSA (NHS: 1743, NHS II: 5022, and HPFS: 2091) were identified during ≤18 y of follow-up, encompassing 2,051,278 person-years. Participants with higher AHEI scores were more likely to be older and white, engaged in more physical activity, had lower BMI and waist circumference, reported lower total energy intake and fewer pack-years of smoking, and were less likely to be current smokers, or report habitual snoring and EDS (**Table 1**). They were also less likely to have a history of diabetes and hypertension, and were more likely to have regular physical exams or use estrogen + progestin HT. Largely similar differences were observed comparing individuals with lower EDIP with those with higher EDIP (**Table 2**).

### AHEI and OSA risk

In pooled analyses adjusted for potential confounders, higher AHEI score was associated with lower OSA risk (**Table 3**). The HR was 0.76 (95% CI: 0.71, 0.82) comparing participants in the highest with those in the lowest AHEI score quintile.

**TABLE 1** Age-adjusted baseline characteristics by AHEI score in the NHS, NHS II, and HPFS[1]

| Characteristic | AHEI score | | | | | |
|---|---|---|---|---|---|---|
| | NHS (2002) | | NHS II (1995) | | HPFS (1996) | |
| | Quintile 1, unhealthiest ($n$ = 11,534) | Quintile 5, healthiest ($n$ = 11,455) | Quintile 1, unhealthiest ($n$ = 13,825) | Quintile 5, healthiest ($n$ = 13,843) | Quintile 1, unhealthiest ($n$ = 4015) | Quintile 5, healthiest ($n$ = 3824) |
| AHEI score, median (range) | 40.8 (17.3–44.6) | 64.8 (60.4–94.7) | 35.8 (16.0–39.7) | 61.7 (56.9–95.4) | 40.1 (16.5–44.4) | 67.2 (62.3–94.3) |
| Age, y | 65.1 ± 6.4 | 67.8 ± 6.5 | 40.1 ± 4.7 | 41.7 ± 4.4 | 57.3 ± 6.7 | 60.6 ± 7.3 |
| Nonwhite | 4.8 | 7.2 | 4.1 | 5.5 | 3.4 | 3.8 |
| BMI,[2] kg/m$^2$ | 27.5 ± 5.6 | 25.8 ± 4.7 | 26.4 ± 6.4 | 24.6 ± 5.0 | 22.8 ± 9.7 | 21.8 ± 9.5 |
| Waist circumference, cm | 88.5 ± 11.8 | 84.1 ± 11.4 | 88.9 ± 14.4 | 83.9 ± 12.9 | 101.7 ± 10.7 | 97.6 ± 10.1 |
| Smoking status | | | | | | |
| Never smoked | 52.2 | 42.5 | 71.2 | 61.3 | 53.4 | 55.3 |
| Past smoker | 36.8 | 53.8 | 17.1 | 31.4 | 38.1 | 42.2 |
| Current smoker | 11.0 | 3.7 | 11.7 | 7.3 | 8.5 | 2.5 |
| Pack-years of smoking[3] | 21.7 ± 18.0 | 15.1 ± 13.8 | 13.6 ± 10.0 | 10.6 ± 7.7 | 23.5 ± 17.2 | 16.4 ± 12.8 |
| Habitual sleep duration, h | 7.2 ± 1.2 | 7.1 ± 1.1 | 7.0 ± 1.1 | 7.0 ± 1.0 | 7.2 ± 1.0 | 7.1 ± 1.0 |
| Habitual snoring, ≥4 nights/wk | 31.1 | 23.6 | 31.6 | 22.8 | 38.4 | 29.3 |
| Excessive daytime sleepiness, ≥4 d/wk | 3.9 | 2.9 | 12.1 | 9.3 | 11.2 | 8.6 |
| Physical activity,[4] MET-h/wk | 12.8 ± 13.2 | 25.2 ± 21.2 | 15.0 ± 19.0 | 31.6 ± 33.3 | 22.7 ± 19.3 | 36.3 ± 27.1 |
| Total energy intake, kcal/d | 1848 ± 441 | 1691 ± 434 | 1964 ± 491 | 1703 ± 491 | 2132 ± 531 | 1886 ± 522 |
| History of diabetes | 7.3 | 4.5 | 0.6 | 0.2 | 1.8 | 1.3 |
| History of hypertension | 52.8 | 44.3 | 10.3 | 7.8 | 29.3 | 26.3 |
| Physical exams in the past 2 y | 92.6 | 94.6 | 88.2 | 90.5 | 64.5 | 72.3 |
| Postmenopausal | 99.3 | 99.3 | 7.5 | 7.0 | — | — |
| Ever estrogen-only HT use | 40.1 | 44.8 | 4.8 | 3.5 | — | — |
| Ever estrogen + progestin HT use | 36.6 | 44.5 | 1.6 | 2.2 | — | — |

[1] Values are means ± SDs or percentages. AHEI, Alternative Healthy Eating Index 2010; HPFS, Health Professionals Follow-up Study; HT, hormone therapy; MET, metabolic equivalent task; NHS, Nurses' Health Study.

[2] Calculated as weight in kilograms divided by height in meters squared.

[3] Among ever smokers.

[4] Weekly energy expenditure in MET-hours per week from recreational and leisure-time physical activity.

However, the inverse trend was only evident in the NHS II, but not in the NHS or HPFS ($P$-heterogeneity by cohort < 0.001). The HR comparing the extreme quintiles of AHEI score was 0.97 (95% CI: 0.83, 1.14) in the NHS ($P$-trend = 0.33), 0.65 (95% CI: 0.59, 0.72) in the NHS II ($P$-trend < 0.001), and 0.90 (95% CI: 0.78, 1.04) in the HPFS ($P$-trend = 0.27). After in addition controlling for metabolic factors, no association was detected between AHEI score and OSA risk in the pooled sample ($P$-trend = 0.54) or individual cohorts; metabolic factors fully attenuated the association between AHEI score and OSA risk (proportion mediated: 91.9%; 95% CI: 35.1%, 99.6%).

### EDIP and OSA risk

Higher EDIP score was linearly associated with increased risk of OSA in the pooled analysis (**Table 4**). Compared with the lowest quintile of EDIP score, the HR for OSA was 1.18 (95% CI: 1.10, 1.27) for quintile 2, 1.38 (95% CI: 1.28, 1.48) for quintile 3, 1.54 (95% CI: 1.43, 1.65) for quintile 4, and 1.94 (95% CI: 1.81, 2.08) for the highest quintile ($P$-trend < 0.001). Significant positive trends were consistently observed across all 3 individual cohorts ($P$-trend < 0.001 for all), although the association appeared stronger in the NHS and NHS II than in the HPFS ($P$-heterogeneity by cohort < 0.001). The observed association was partially attenuated after further adjusting for metabolic factors but remained statistically significant (HR comparing the highest and lowest quintiles of EDIP score: 1.31; 95% CI: 1.22, 1.41; $P$-trend < 0.001). The percentage of the association between EDIP score and OSA risk explained by metabolic factors was 64.8% (95% CI: 58.2%, 70.8%).

### Stratified analyses

In subgroup analysis, we detected significant effect modification by sex ($P$-interaction < 0.001), age ($P$-interaction < 0.001), and BMI ($P$-interaction < 0.001) for the association between AHEI score and OSA risk, with stronger inverse associations observed specifically for females, those aged <65 y, or those with BMI ≥25 kg/m$^2$ than for their counterparts. In subgroup analysis of the association between EDIP score and OSA risk, we observed significant heterogeneity by sex ($P$-interaction = 0.005), age ($P$-interaction = 0.009), and diabetes status ($P$-interaction = 0.001). Dietary inflammatory potential

**TABLE 2** Age-adjusted baseline characteristics by EDIP score in the NHS, NHS II, and HPFS[1]

| Characteristic | EDIP score | | | | | |
|---|---|---|---|---|---|---|
| | NHS (2002) | | NHS II (1995) | | HPFS (1996) | |
| | Quintile 1, anti-inflammatory ($n$ = 11,743) | Quintile 5, proinflammatory ($n$ = 11,189) | Quintile 1, anti-inflammatory ($n$ = 13,852) | Quintile 5, proinflammatory ($n$ = 13,799) | Quintile 1, anti-inflammatory ($n$ = 3949) | Quintile 5, proinflammatory ($n$ = 3879) |
| EDIP score, median (range) | −0.4 (−3.5 to −0.2) | 0.3 (0.1–2.2) | −0.4 (−2.7 to 0.3) | 0.3 (0.2–2.4) | −0.4 (−3.2 to −0.3) | 0.3 (0.2–1.9) |
| Age, y | 66.5 ± 6.4 | 65.6 ± 6.4 | 41.9 ± 4.3 | 40.1 ± 4.8 | 58.6 ± 6.7 | 58.3 ± 7.2 |
| Nonwhite | 3.8 | 8.3 | 3.1 | 7.2 | 2.6 | 5.9 |
| BMI,[2] kg/m$^2$ | 25.2 ± 4.3 | 28.7 ± 5.9 | 24.5 ± 4.8 | 27.4 ± 6.7 | 22.1 ± 9.5 | 22.7 ± 10.1 |
| Waist circumference, cm | 83.8 ± 11.0 | 89.7 ± 12.4 | 84.3 ± 12.6 | 90.3 ± 15.1 | 99.7 ± 10.2 | 102 ± 11.3 |
| Smoking status | | | | | | |
| Never smoked | 37.2 | 54.1 | 55.2 | 73.3 | 43.7 | 62.8 |
| Past smoker | 54.0 | 38.6 | 31.4 | 18.3 | 50.0 | 32.3 |
| Current smoker | 8.8 | 7.3 | 13.4 | 8.4 | 6.3 | 4.9 |
| Pack-years of smoking[3] | 18.4 ± 16.1 | 19.5 ± 16.8 | 12.0 ± 8.6 | 12.7 ± 9.5 | 20.3 ± 14.6 | 21.0 ± 16.0 |
| Habitual sleep duration, h | 7.2 ± 1.1 | 7.1 ± 1.2 | 7.0 ± 1.0 | 6.9 ± 1.1 | 7.2 ± 1.0 | 7.1 ± 1.0 |
| Habitual snoring, ≥4 nights/wk | 24.5 | 33.0 | 25.6 | 32.4 | 34.9 | 38.2 |
| Excessive daytime sleepiness, ≥4 d/wk | 2.5 | 4.3 | 9.7 | 12.4 | 9.6 | 10.9 |
| Physical activity,[4] MET-h/wk | 21.5 ± 19.3 | 15.4 ± 15.1 | 25.4 ± 28.7 | 19.6 ± 24.7 | 30.4 ± 23.2 | 27.0 ± 24.6 |
| Total energy intake, kcal/d | 1746 ± 438 | 1893 ± 472 | 1803 ± 504 | 1966 ± 539 | 2007 ± 520 | 2199 ± 595 |
| History of diabetes | 2.4 | 11.6 | 0.2 | 1.1 | 1.1 | 2.9 |
| History of hypertension | 41.7 | 59.2 | 7.3 | 13.2 | 26.3 | 32.0 |
| Physical exams in the past 2 y | 93.8 | 93.7 | 89.3 | 89.4 | 71.7 | 66.8 |
| Postmenopausal | 99.4 | 99.2 | 6.8 | 8.5 | — | — |
| Ever estrogen-only HT use | 40.3 | 43.8 | 3.6 | 5.4 | — | — |
| Ever estrogen + progestin HT use | 45.1 | 35.3 | 2.2 | 1.9 | — | — |

[1] Values are means ± SDs or percentages. EDIP, Empirical Dietary Inflammatory Pattern; HPFS, Health Professionals Follow-up Study; HT, hormone therapy; MET, metabolic equivalent task; NHS, Nurses' Health Study.
[2] Calculated as weight in kilograms divided by height in meters squared.
[3] Among ever smokers.
[4] Weekly energy expenditure in MET-hours per week from recreational and leisure-time physical activity.

was more strongly positively associated with OSA risk in females, those aged <65 y, or individuals without diabetes than in their counterparts (**Supplemental Figure 2**).

### Dietary component analyses

In multivariable analyses examining individual dietary components in the AHEI, the strongest ones included positive associations with intakes of red and processed meat (HR per 1-SD increment: 1.18; 95% CI: 1.16, 1.21), sodium (1.18; 95% CI: 1.15, 1.20), and *trans* fat (1.10; 95% CI: 1.08, 1.13), and an inverse association with alcohol intake (0.86; 95% CI: 0.84, 0.88) (**Supplemental Figure 3**). Other AHEI components were either not associated with OSA risk (e.g., whole grains, $\omega$-3 fatty acids) or moderately associated with OSA risk in an unexpected direction (e.g., vegetables, PUFAs, SSBs). Given these unexpected associations, we conducted a post hoc analysis excluding vegetables, PUFAs, SSBs, and nuts/legumes from the AHEI, and the AHEI score showed a stronger association with OSA risk. The HR comparing extreme quintiles was 0.59 (95% CI: 0.55, 0.64) before adjusting for metabolic factors ($P$-trend < 0.001) and 0.88 (95% CI: 0.81, 0.94) after adjusting for metabolic factors ($P$-trend < 0.001). By contrast, the significant association observed for EDIP was mainly due to inverse associations with intakes of wine (HR per 1-SD increment: 0.84; 95% CI: 0.82, 0.87), coffee (0.90; 95% CI: 0.88, 0.92), and beer (0.93; 95% CI: 0.91, 0.95), and strong positive associations with intakes of red meat (1.14; 95% CI: 1.12, 1.16), processed meat (1.11; 95% CI: 1.09, 1.13), and low-energy beverages (1.15; 95% CI: 1.13, 1.17) (**Supplemental Figure 4**).

### Sensitivity analyses

Overall, the association patterns for OSA with EDS were similar to those observed in the primary analysis (**Supplemental Tables 2** and **3**). When using AHEI and EDIP scores assessed 2–4 y before OSA diagnosis as the exposure, our results remained essentially unchanged (**Supplemental Tables 4** and **5**).

## Discussion

In this large prospective cohort study, lower diet quality and higher dietary inflammatory potential were associated with increased OSA risk after rigorously controlling for potential

**TABLE 3** AHEI score and risk of incident obstructive sleep apnea in the NHS, NHS II, and HPFS[1]

| | AHEI score | | | | | |
|---|---|---|---|---|---|---|
| | Quintile 1, unhealthiest | Quintile 2 | Quintile 3 | Quintile 4 | Quintile 5, healthiest | *P*-trend[2] |
| NHS | | | | | | |
| Cases, *n* (total *n* = 1743) | 417 | 377 | 331 | 304 | 314 | |
| Person-years, *n* | 110,164 | 110,416 | 110,870 | 110,797 | 110,569 | |
| Multivariable[3] | 1.00 (Reference) | 0.96 (0.83, 1.10) | 0.89 (0.77, 1.03) | 0.85 (0.73, 0.99) | 0.97 (0.83, 1.14) | 0.33 |
| Multivariable + metabolic factors[4] | 1.00 | 0.98 (0.85, 1.13) | 0.93 (0.80, 1.08) | 0.94 (0.80, 1.09) | 1.16 (0.99, 1.35) | 0.21 |
| NHS II | | | | | | |
| Cases, *n* (total *n* = 5022) | 1266 | 1113 | 951 | 945 | 747 | |
| Person-years, *n* | 237,574 | 240,482 | 241,411 | 242,441 | 241,842 | |
| Multivariable[3] | 1.00 | 0.88 (0.81, 0.95) | 0.77 (0.70, 0.83) | 0.78 (0.71, 0.85) | 0.65 (0.59, 0.72) | <0.001 |
| Multivariable + metabolic factors[4] | 1.00 | 0.95 (0.88, 1.04) | 0.88 (0.80, 0.96) | 0.96 (0.88, 1.05) | 0.91 (0.82, 1.00) | 0.06 |
| HPFS | | | | | | |
| Cases, *n* (total *n* = 2091) | 473 | 438 | 404 | 414 | 362 | |
| Person-years, *n* | 60,144 | 59,005 | 58,858 | 58,642 | 58,064 | |
| Multivariable[3] | 1.00 | 0.96 (0.84, 1.10) | 0.92 (0.80, 1.05) | 0.99 (0.87, 1.14) | 0.90 (0.78, 1.04) | 0.27 |
| Multivariable + metabolic factors[4] | 1.00 | 0.99 (0.86, 1.13) | 0.95 (0.83, 1.09) | 1.08 (0.95, 1.24) | 1.04 (0.90, 1.20) | 0.34 |
| Pooled | | | | | | |
| Cases, *n* (*n* = 8856) | 2156 | 1928 | 1686 | 1663 | 1423 | |
| Person-years, *n* | 407,882 | 409,903 | 411,139 | 411,880 | 410,474 | |
| Multivariable[3] | 1.00 | 0.91 (0.86, 0.97) | 0.82 (0.77, 0.88) | 0.84 (0.79, 0.90) | 0.76 (0.71, 0.82) | <0.001 |
| Multivariable + metabolic factors[4] | 1.00 | 0.96 (0.91, 1.03) | 0.90 (0.85, 0.96) | 0.98 (0.92, 1.05) | 0.98 (0.91, 1.05) | 0.54 |

[1] Values are HRs and 95% CIs unless otherwise indicated. *P*-heterogeneity by cohort < 0.001. AHEI, Alternative Healthy Eating Index 2010; HPFS, Health Professionals Follow-up Study; HT, hormone therapy; NHS, Nurses' Health Study.

[2] *P*-trend was calculated using the midpoint of each category of AHEI score.

[3] HRs and 95% CIs were estimated by Cox proportional hazards analyses. Multivariate analyses were stratified by cohort (NHS, NHS II, and HPFS, in the pooled analyses only), age (mo), and questionnaire cycle; adjusted for race/ethnicity (white, nonwhite), smoking (never, past, current), pack-years of smoking (continuous), menopausal status (premenopausal, postmenopausal) (females only), duration of postmenopausal HT by type (never, <5, 5 to <10, ≥10 y for estrogen-only and estrogen + progestin HT separately) (females only), physical exams (yes, no), total energy intake (in quintiles; kcal/d), habitual sleep duration (≤5, 6, 7, 8, ≥9 h/d), and physical activity (<6.0, 6.0–11.9, 12.0–20.9, 21.0–35.9, ≥36.0 metabolic equivalent task hours per week).

[4] Metabolic factors included BMI (continuous; kg/m$^2$), waist circumference (continuous; cm), history of diabetes (yes, no), and history of hypertension (yes, no).

confounders. Additional adjustment for metabolic factors partly explained the association for EDIP score but fully attenuated the association with AHEI score. Our findings underscored the potential benefits of maintaining a healthier diet (particularly one with anti-inflammatory potential) in reducing OSA risk, and suggested the possible mediating role of metabolic factors in the association between diet and OSA risk. To our knowledge, we present the first prospective epidemiologic evidence to have characterized the magnitude of long-term excess risk of OSA in relation to overall diet quality and dietary inflammatory potential.

### Comparison with other studies

Prior population-based evidence regarding the association between overall diet quality and OSA risk remains sparse and is limited to 4 cross-sectional studies (13–16). In a subset of MESA (Multi-Ethnic Study of Atherosclerosis) participants who completed an FFQ and 1-night in-home polysomnography, OSA was cross-sectionally associated with lower overall diet quality as measured by the AHEI (13). Two other smaller studies in obese adolescents/adults reported that severe OSA may be cross-sectionally associated with poor diet quality independently of degree of obesity (14, 15). A more recent study linked high-quality and anti-inflammatory diets with lower OSA prevalence (16). Our prospective study, leveraging the repeated, validated, longitudinal dietary assessment and self-reported, validated OSA diagnosis, reported a similar inverse association between overall diet quality and OSA diagnosis; however, no association was observed after accounting for metabolic factors including BMI and waist circumference, which is inconsistent with results from previous cross-sectional investigations (13–15). On the other hand, few epidemiologic studies have focused on the role of proinflammatory diet in OSA development, and we reported a robust positive association between dietary inflammatory potential and OSA risk independent of obesity and a wide spectrum of potential confounders. Collectively, our study added important prospective evidence to the existing cross-sectional investigations, suggesting that a healthier diet, particularly diet with lower inflammatory potential, may be associated with lower risk of OSA.

**TABLE 4** EDIP score and risk of incident obstructive sleep apnea in the NHS, NHS II, and HPFS[1]

| | EDIP score | | | | | |
|---|---|---|---|---|---|---|
| | Quintile 1, anti-inflammatory | Quintile 2 | Quintile 3 | Quintile 4 | Quintile 5, proinflammatory | *P*-trend[2] |
| NHS | | | | | | |
| Cases, *n* (total *n* = 1743) | 233 | 260 | 351 | 406 | 493 | |
| Person-years, *n* | 113,860 | 112,312 | 110,619 | 109,270 | 106,753 | |
| Multivariable[3] | 1.00 (Reference) | 1.13 (0.94, 1.35) | 1.51 (1.28, 1.78) | 1.71 (1.45, 2.01) | 2.01 (1.72, 2.36) | <0.001 |
| Multivariable + metabolic factors[4] | 1.00 | 1.00 (0.84, 1.19) | 1.22 (1.03, 1.45) | 1.25 (1.06, 1.47) | 1.23 (1.04, 1.45) | 0.002 |
| NHS II | | | | | | |
| Cases, *n* (total *n* = 5022) | 663 | 839 | 966 | 1097 | 1457 | |
| Person-years, *n* | 242,210 | 243,059 | 241,969 | 240,417 | 236,096 | |
| Multivariable[3] | 1.00 | 1.26 (1.13, 1.39) | 1.44 (1.30, 1.59) | 1.64 (1.49, 1.81) | 2.18 (1.99, 2.40) | <0.001 |
| Multivariable + metabolic factors[4] | 1.00 | 1.16 (1.05, 1.29) | 1.21 (1.09, 1.34) | 1.21 (1.10, 1.34) | 1.31 (1.19, 1.44) | <0.001 |
| HPFS | | | | | | |
| Cases, *n* (total *n* = 2091) | 373 | 393 | 409 | 426 | 490 | |
| Person-years, *n* | 60,293 | 60,088 | 58,286 | 58,302 | 57,745 | |
| Multivariable[3] | 1.00 | 1.07 (0.93, 1.23) | 1.15 (1.00, 1.33) | 1.20 (1.04, 1.39) | 1.38 (1.20, 1.59) | <0.001 |
| Multivariable + metabolic factors[4] | 1.00 | 1.07 (0.93, 1.24) | 1.16 (1.00, 1.33) | 1.16 (1.01, 1.34) | 1.22 (1.06, 1.40) | 0.003 |
| Pooled | | | | | | |
| Cases, *n* (total *n* = 8856) | 1269 | 1492 | 1726 | 1929 | 2440 | |
| Person-years, *n* | 416,363 | 415,459 | 410,873 | 407,989 | 400,594 | |
| Multivariable[3] | 1.00 | 1.18 (1.10, 1.27) | 1.38 (1.28, 1.48) | 1.54 (1.43, 1.65) | 1.94 (1.81, 2.08) | <0.001 |
| Multivariable + metabolic factors[4] | 1.00 | 1.12 (1.04, 1.21) | 1.22 (1.13, 1.31) | 1.24 (1.15, 1.33) | 1.31 (1.22, 1.41) | <0.001 |

[1] Values are HRs (95% CIs) unless otherwise indicated. *P*-heterogeneity by cohort < 0.001. EDIP, Empirical Dietary Inflammatory Pattern; HPFS, Health Professionals Follow-up Study; HT, hormone therapy; NHS, Nurses' Health Study.

[2] *P*-trend was calculated using the midpoint of each category of EDIP score.

[3] HRs and 95% CIs were estimated by Cox proportional hazards analyses. Multivariate analyses were stratified by cohort (NHS, NHS II, and HPFS, in the pooled analyses only), age (mo), and questionnaire cycle; adjusted for race/ethnicity (white, nonwhite), smoking (never, past, current), pack-years of smoking (continuous), menopausal status (premenopausal, postmenopausal) (females only), duration of postmenopausal HT by type (never, <5, 5 to <10, ≥10 y for estrogen-only and estrogen + progestin HT separately) (females only), physical exams (yes, no), total energy intake (in quintiles; kcal/d), habitual sleep duration (≤5, 6, 7, 8, ≥9 h/d), and physical activity (<6.0, 6.0–11.9, 12.0–20.9, 21.0–35.9, ≥36.0 metabolic equivalent task hours per week).

[4] Metabolic factors included BMI (continuous; in kg/m$^2$), waist circumference (continuous; cm), history of diabetes (yes, no), and history of hypertension (yes, no).

Of note, in our further analyses exploring individual dietary components, we observed that increased OSA risk associated with a higher intake of red/processed meat and a lower intake of alcohol for both the AHEI and EDIP. Interestingly, 2 prior cross-sectional studies reported similar positive associations between intake of red/processed meat and OSA (13, 48). However, the association between alcohol consumption and OSA risk remains equivocal. Although acute alcohol ingestion before sleep is known to exacerbate OSA severity and alter sleep architecture (49), there is a lack of evidence on the long-term impact of alcohol consumption on OSA risk, particularly the potential benefits of moderate social drinking that have been observed for multiple cardiometabolic outcomes (50–52). Of note, the strong positive association observed for sodium intake in the current study was consistent with prior well-designed studies linking sodium intake with OSA (53, 54). High sodium consumption may induce peripheral fluid retention, which has been implicated in OSA pathogenesis (55–58). For other AHEI components, we observed increased OSA risk associated with higher intakes of PUFAs, vegetables, and nuts/legumes and lower SSB intake, which are considered to be part of a healthy dietary pattern. These counterintuitive findings may to some extent dilute the overall inverse association with the AHEI. In a post hoc analysis excluding these 4 components from the AHEI, we found a stronger inverse association between the new AHEI score (including red and processed red meat, *trans* fat, sodium, alcohol, fruits, whole grains, and $\omega$-3 fatty acids) and OSA risk, which remained statistically significant even after adjusting for metabolic factors. To our knowledge, the associations between individual dietary components (e.g., nuts/legumes) and OSA risk have been rarely studied and require further investigation.

For EDIP components, higher energy drink consumption and lower coffee consumption were associated with increased OSA risk. Prior cross-sectional studies have reported positive associations of carbonated and noncarbonated beverages with risk of OSA (13, 59), although our study suggests that low-energy drinks appear more strongly associated with the risk than do high-energy drinks. Similar to alcohol consumption, the long-term association between coffee intake and OSA risk is unclear despite evidence that caffeinated beverages may contribute to sleep disturbances such as prolonged sleep latency, reduced sleep duration, and poorer perceived sleep quality. However,

in the Jackson Heart Sleep Study, evening caffeine use was not associated with sleep parameters measured by concurrent actigraphy and sleep diary (60). Other coffee components, such as polyphenols and trigonelline, have been shown in experimental studies to reduce inflammation and improve insulin resistance (61, 62), which are potential pathogenic pathways for OSA. Because coffee consumption was not included in the AHEI, the inverse association with coffee intake may drive the overall more significant association observed for the EDIP. However, coffee intake was not correlated with OSA in a previous small case–control study (63). For coffee and alcohol intakes, additional studies are needed to understand their relations with OSA risk in more detail, such as timing of coffee/alcohol consumption and type of coffee/alcohol (e.g., caffeinated compared with decaffeinated coffee).

### Biological mechanisms

Increasing biological and epidemiologic evidence has recognized the role of chronic metabolic dysregulation and low-grade inflammation in the etiology of OSA (26, 27, 64). We consistently detected effect attenuation in the associations of both AHEI and EDIP with OSA risk after in addition accounting for metabolic factors in fully adjusted analyses, supporting that a healthier diet may lower OSA risk by reducing obesity, improving metabolic function, and mitigating chronic inflammation. Of note, although the EDIP was more strongly correlated with metabolic factors than was the AHEI in our study (Supplemental Table 1), adjustment for metabolic factors only partly explained the association with the EDIP but fully attenuated the association with the AHEI. Interestingly, the EDIP components associated with OSA risk, namely low-energy beverages, red meat, processed meat, wine, coffee, and beer, are also top food groups most strongly associated with circulating inflammatory biomarkers (18, 22), suggesting inflammatory pathways underlying the observed associations. Specifically, in our mediation analysis, 64.8% of the association between EDIP and OSA risk was explained by metabolic factors. We thus cannot exclude the possibility that a proinflammatory diet may influence OSA risk through other plausible biological mechanisms, such as lipid dysregulation and insulin resistance (40, 65, 66). In contrast, the mediation analysis indicated that the association of AHEI with OSA risk may be predominantly (91.9%) mediated by metabolic-related mechanisms. Given significant age and sex differences in OSA endotypes such as pharyngeal collapsibility and ventilator control (67, 68), future studies are warranted to elucidate whether the observed effect modification by age and sex for the associations between diet and OSA risk may be explained by the dietary impact on these OSA-related physiologic traits.

### Strengths and limitations

Our study had several notable strengths, including the prospective study design, large sample size, long-term follow-up, high follow-up rates, and a large number of documented OSA cases with high reliability. Repeated and validated longitudinal assessment of dietary information and a wide spectrum of covariates allowed us to accurately capture long-term dietary exposure and rigorously control for confounding in a time-varying manner. The nature of our study participants (all health care professionals) further ensured data quality and internal validity and minimized socioeconomic confounding.

Our study had several limitations. First, although a previous validation study showed higher accuracy of self-reported OSA diagnoses in our cohorts of health care professionals (42), the impact of clinically undiagnosed OSA and differential OSA diagnosis on our results cannot be completely ruled out; such misclassification may potentially lead to underestimation of the associations. Second, information on OSA severity and treatment was unavailable in our cohorts. Third, despite extensive control for confounding, residual and unmeasured confounding were still possible given the observational study design. Lastly, the homogeneities of our study population (which comprised only health care professionals and were predominantly of European ancestry) may limit generalizability of our findings to underrepresented groups.

## Conclusion

In summary, our prospective findings suggest that a healthier diet, particularly one with anti-inflammatory potential, may be associated with lower risk of OSA.

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The authors' responsibilities were as follows—YL and TH: conceived and designed the study, had full access to all the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis; YL: acquired, analyzed, and interpreted the data, drafted the manuscript, and performed the statistical analysis; FKT, MJS, SR, and TH: critically revised the manuscript for important intellectual content; SR and TH: obtained funding; MJS and TH: provided administrative, technical, or material support; TH: provided supervision; and all authors: read and approved the final manuscript.

## Data availability

Data described in the article, code book, and analytic code are available upon request pending approval by the Channing Division of Network Medicine at Brigham and Women's Hospital and Harvard Medical School, and Harvard TH Chan School of Public Health. Further information including the procedures to obtain and access cohort data is described at https://www.nurseshealthstudy.org/researchers (contact e-mail: nhsaccess@channing.harvard.edu) and https://sites.sph.harvard.edu/hpfs/for-collaborators/. The data are not publicly available owing to privacy or ethical restrictions.

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