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Long-term Dietary Quality and Risk of Developing Rheumatoid Arthritis in Women

Yang Hu[1], **Jeffrey A. Sparks**[2], **Susan Malspeis**[2], **Karen H. Costenbader**[2], **Frank B. Hu**[3,4], **Elizabeth W. Karlson**[2], and **Bing Lu**[2]

[1]Departments of Nutrition, Harvard School of Public Health, Boston, MA, USA

[2]Division of Rheumatology, Immunology and Allergy, Brigham & Women's Hospital and Harvard Medical School, Boston, MA, USA

[3]Departments of Nutrition and Epidemiology, Harvard School of Public Health, USA

[4]Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School (FBH), Boston, MA, USA

Abstract

Objectives—To evaluate the association between long-term dietary quality, measured by the 2010 Alternative Healthy Eating Index (AHEI-2010), and risk of rheumatoid arthritis in women.

Methods—We prospectively followed 76,597 women in the Nurses' Health Study aged 30–55 years and 93,392 women in the Nurses' Health Study II aged 25–42 years at baseline and free from rheumatoid arthritis or other connective tissue diseases. The lifestyle, environmental exposure and anthropometric information were collected at baseline and updated biennially. Cumulative follow-up rates were more than 90% for both cohorts. The primary outcome was rheumatoid arthritis alone with two subtypes of the disease: seropositive and seronegative rheumatoid arthritis.

RESULTS—During 3,678,104 person-years, 1,007 RA cases were confirmed. In the multivariable-adjusted model, long-term adherence to healthy eating patterns was marginally associated with reduced RA risk. To assess potential effect modification by age at diagnosis, we stratified by age. Among women ≤ 55 years old, better quality diet was associated with lower RA risk ($HR_{Q4\ vs\ Q1}$: 0.67; 95% CI: 0.51 to 0.88; p trend: 0.002), but no significant association was found for women >55 years (p interaction: 0.005). When stratifying by serostatus, the inverse association among those aged ≤55 years was strongest for seropositive RA ($HR_{Q4\ vs\ Q1}$: 0.60; 95% CI: 0.42 to 0.86; p-trend: 0.003).

Correspondence to: Bing Lu, Division of Rheumatology, Immunology and Allergy, Brigham & Women's Hospital and Harvard Medical School, Boston, Massachusetts. 75 Francis Street, PBB-B3, Boston, MA, USA. blu1@rics.bwh.harvard.edu.

Contributors: YH and BL designed the study, analyze the data and wrote the first draft. SM contributed to the data analysis. BL, EWK, KHC, JAS and FBH were involved in data collection. All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. YH and BL 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.

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Conclusion—A healthier diet was associated with a reduced risk of RA occurring at 55 years of age or younger, particularly seropositive RA.

INTRODUCTION

Rheumatoid arthritis (RA) is a common autoimmune disease, affecting approximately 1.3 million Americans including 2.5 times as many women as men.[1] Although the etiology of RA is not completely understood, it is widely recognized that both genetic and environmental exposures including lifestyle and dietary risk factors contribute to the development of RA. Our group and others have reported that high intake of alcohol, fish, olive oil and cooked vegetables confer a protective effect against the development of RA,[2–6] whereas red meat and sugar-sweetened soda intake may increase the risk of RA.[7, 8] However, not all studies confirmed such associations.[9–11] One explanation for the inconsistent findings may be that individual food/nutrients only confer modest beneficial effects, so that any protective effects would not be observed unless groups of dietary factors are consumed together. Dietary pattern analysis in relation to disease risk addresses these limitations as it integrates the complexity of overall diet.[12]

The 2010 Alternative Healthy Eating Index (AHEI-2010) is a dietary quality score based on the recent Dietary Guidelines for Americans composed of 11 foods and nutrients that have been consistently associated with risk of chronic diseases.[13] Among 11 foods/nutrients included in the dietary index, fruits, vegetables, whole grains, nuts, long-chain (n-3) fat (% of total energy), polyunsaturated fat (% of total energy) and moderate alcohol consumption were considered as healthy items while sugar-sweetened beverages (including fruit juice), red/processed meat, trans fat (% of total energy) and sodium intake were deemed as unhealthy components. Higher scores of AHEI-2010 have been strongly associated with reduced risk for major chronic diseases including cardiovascular diseases (CVD), type 2 diabetes (T2D) and certain types of cancer.[14–19] No study has investigated the associations between overall dietary quality and risk of autoimmune diseases, such as RA. Our primary aim was to investigate associations between AHEI-2010 score and risk of RA in two large prospective cohort studies of women: Nurses' Health Study and Nurses' Health Study II.

Previous studies on CVD have showed that the influence of established risk factors such as smoking, BMI, hypertension, diabetes, hyperlipidemia diminished with advancing age,[20–22] which is likely due to blunted response to autonomic nervous system stimuli [23, 24] that is triggered by these modifiable factors. Similar phenomenon was observed in our previous analysis that demonstrated a significant trend toward increased risk of RA diagnosed at age ≤55 years among overweight and obese women, but not in women >55 years.[25] Moreover, literature suggest that RA occurred at younger and older age are etiologically different in many respects. [26, 27] Thus, our secondary aim was also to examine the diet quality and RA associations in both younger (age≤ 55) and older age (>55 years).

METHODS

Study population

In 1976, NHS was initiated and included 121,700 female registered nurses aged 30 to 55 years. In 1989, 116,671 female registered nurses aged 25–42 years enrolled in NHSII. Participants from both prospective cohorts provided information regarding lifestyle behaviors, medical history, and diseases through self-administered questionnaires at entry and updated every 2 years. The response rate was maintained over 90% for every 2 year period in both cohorts.[29, 30] The baselines for NHS and NHS II in the current study were 1984 and 1991 when a comprehensive Food Frequency Questionnaire (FFQ) was introduced in each cohort. A total of 76,597 and 93,392 participants from each cohort were included in the final analysis after excluding those who did not answer the FFQ and those who had RA or other connective tissue diseases at baseline. We censored all women who reported psoriasis, psoriatic arthritis or other connective tissue diseases at the self-reported date, unless the diagnosis was subsequently confirmed as RA. Women lost to follow-up were censored at their last response to questionnaires. The institutional review board at Partners Healthcare approved the study protocol.

Assessment of dietary factors and AHEI-2010

We used a 133-item semi-quantitative FFQ to collect dietary data approximately every 4 years from 1984–2010 in the NHS and 1991–2011 in NHSII. [28] About 84% of NHS participants and 90% of NHS II participants answered FFQ at respective baseline. Participants who returned FFQ with more than 70 missing items, total energy intake less than 500 kcal/day or greater than 3500 kcal/d were excluded from the analysis.[8] Validation studies from two parallel cohorts showed high correlation coefficients between FFQ and multiple dietary records for the dietary factors.[28, 31] We calculated nutrient intakes by multiplying the frequency of intake for each food by its nutrient content and summing nutrient contributions across all food items, using previously validated methods.[32]

As a scoring system, the AHEI-2010 integrates the dietary data to evaluate the overall dietary quality. The rationale of food items selection and score criteria of AHEI-2010 has been discussed elsewhere.[13] Women with moderate alcohol intake defined as 0.5–1.5 drinks/d received a maximum score of 10 but non-drinkers or heavy drinkers were assigned lower scores, reflecting the U-shaped association of alcohol consumption with chronic diseases.[13] All AHEI-2010 components are scored from 0 (worst) to 10 (best), and the total AHEI-2010 score can range from 0 to 110 (non to perfect adherence). A higher AHEI-2010 score indicates better diet quality. In order to investigate the potential cumulative effect of a long-term diet, we calculated cumulative average AHEI-2010 from all of the preceding measures over the study period.[8, 33] The missing cycles of FFQ were excluded from the estimates of cumulative average dietary measures.

Identification of RA

The identification of RA cases consisted of two steps. In the first step, participants who self-reported a physician diagnosis of RA received the connective tissue disease (CTD) screening questionnaire (CSQ) through mail. For those with positive screening for RA or other CTDs based on CSQ, medical records were requested.[34] In the second step, two rheumatologists independently reviewed medical records according to the 1987 American College of Rheumatology classification.[35] The serologic phenotype of RA was determined from medical records by positive rheumatoid factors (RF) (available since baseline) or cyclic citrullinated peptide (CCP) antibodies (available since the early 2000s).[34, 36]

Assessment of time-varying covariates

Information regarding participants' demographic, reproductive, clinical and behavioral factors has been collected with the biennial follow-up questionnaires. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters and was categorized into 5 levels: <18.49, 18.5–22.9, 23–24.9, 25–30, and ≥30 kg/m^2. Four categories were created for smoking status: never, past, current 1–14 cigarettes/day, current ≥15 cigarettes/day. Recreational physical activity levels were categorized as: 0–2.9, 3–8.9, 9–17.9, 18–26.9 and ≥27 metabolic equivalents (METs) /week. [37] Parity and breastfeeding status were jointly defined as: nulliparous, parous/no breastfeeding, parous/1–12 months breastfeeding, parous/ >12 months breastfeeding. Age at menarche was classified into 3 categories: <12, 12, >12 years and we defined the hormone use status as: pre-menopausal, post-menopausal with never use, current use and past use. Census tract median family income and total energy intake were ranked using quartiles and quintiles respectively.

Statistical analysis

Baseline characteristics were expressed as mean (SD) or median for continuous variables and percentage was used for categorical variables according to quartiles of AHEI-2010 score. In order to assess age-specific effects and potential effect modifiers, we pooled the data from both cohorts to include a wide-range of age groups. To control for possible cohort effects given secular trends in food supply according to calendar year, an indicator variable for cohorts was used in model stratification. For the primary analysis, time-varying Cox proportional hazards models were employed to assess the association between AHEI-2010 and risk of RA. All RA, seropositive and seronegative RA were separate outcomes in the analysis. Cumulative averaged AHEI-2010 score was included in the model as a time-varying exposure for which the values were updated during the follow-up. The proportional hazard assumption was evaluated by including an interaction term between continuous AHEI-2010 and logarithm of person-time and was met in all analyses. The main model adjusted for potential risk factors of RA that are also associated with AHEI including age, smoking, age at menarche, parity/breastfeeding, hormone use and total energy intake. We additionally adjusted for BMI to assess its potential mediation effects in a separate model. The median value of each quartile was used as a continuous variable to calculate the p-value for trend.

For the secondary aim, we stratified the participants by age rounded to integer (age ≤55 and age >55 years) based on our pre-specified hypotheses.[8, 25] Women were followed up from baseline to age 55 years, and from age 56 years to the end of cohorts respectively. The interaction was tested by comparing two β coefficients for the continuous AHEI-2010 score from respective multivariable models in a χ^2 test. We also conducted an exploratory analysis to evaluate the effect of each individual component score of AHEI-2010 in relation to RA risk.

In addition, we performed sensitivity analyses to examine the robustness of our findings. First, to maximally control for residual confounding effects, we further included variables that varied by AHEI but are less associated with RA in the NHS including census tract median family income, physical activity, multivitamin use and self-reported T2D. Secondly, after we identified that red meat and alcohol were two individual components of AHEI-2010 that showed particular beneficial effects against RA risk for women at age 55 years old or younger, we repeated the analysis using AHEI-2010 without either of these two components, to assess whether the observed associations were driven by single food item. Missing covariate data was carried forward one questionnaire cycle. All statistical tests were 2-sided with significant level of 0.05 and performed using SAS 9.3 (SAS Institute, Cary, NC).

RESULTS

A total of 1,007 RA cases (624 seropositive, 383 seronegative) were identified during 3,678,104 person-years of follow-up. The mean follow-up time was 21.6 years. The ranges of AHEI-2010 score were 15.6–100.1 and 13.7–95.8 at baseline for NHS and NHS II respectively. In both cohorts, higher baseline AHEI-2010 score was positively associated with desirable lifestyle and socioeconomic status including family median income, physical activity, alcohol consumption and multivitamin use (Table 1). Participants with higher AHEI-2010 score also tended to have lower BMI and total energy intake, and were less likely to be parous and current smokers. BMI and AHEI were significantly negatively correlated but the Spearman correlation coefficient was small (−0.08, p<0.001).

In multivariable-adjusted model, women in the highest quartile of AHEI-2010 had 15% reduced risk ($HR_{Q4\ vs\ Q1}$= 0.85, 95% CI: 0.70 to 1.02; *p* for trend 0.08) compared to the women in the lowest quartile. The association was slightly attenuated after additional adjustment for BMI ($HR_{Q4\ vs\ Q1}$= 0.87, 95% CI: 0.73 to 1.05; *p* trend 0.16). Results for both serologic subtypes of RA suggested an inverse association, but neither was statistically significant. In analyses restricted to women at age 55 years or younger (444 RA cases), a significant inverse dose-response relationship was found between AHEI-2010 and RA incidence (Table 3). Women in the top quartile of AHEI-2010 had 33% ($HR_{Q4\ vs\ Q1}$= 0.67, 95% CI: 0.51 to 0.88; *p* trend 0.002) lower risk of RA compared with those in the lowest quartile and the observed association remained statistically significant after additional BMI adjustment ($HR_{Q4\ vs\ Q1}$= 0.71, 95% CI: 0.54 to 0.94; *p* for trend 0.009). Further stratification analysis by two serologic subtypes of RA showed significant inverse associations for seropositive RA. No significant associations were detected for women at age over 55 years (p for age by AHEI-2010 interaction 0.005).

As an exploratory analysis, we further examined the association between each AHEI component and RA risk among women at 55 years or younger age (Table 4). A higher score of alcohol (moderate intake) or red meat consumption (lower intake) was significantly associated with a reduced RA risk independent of current BMI and other covariates, while no significant associations were observed for other AHEI components.

In sensitivity analyses that additionally adjusted for census tract median family income, physical activity, multi-vitamin use and diabetes history, the results were unchanged. Both alcohol-excluded and red meat-excluded AHEI-2010 yielded comparable estimates to the primary stratified analysis, so it is unlikely that these items alone were responsible for the findings.

DISUCSSION

Data from these two large cohort studies of women suggest that long-term adherence to higher dietary quality guidelines was associated with reduced RA risk, in particular for seropositive RA with onset at age 55 years or earlier. Among the individual components of AHEI-2010 score, moderate alcohol consumption and lower red meat intake were found to be most associated with decreased early-onset RA risk, while the associations of other components with RA risk were not strong enough to reach statistical significance. These results indicate that an overall healthy diet quality may be more beneficial for RA risk reduction than individual foods and nutrients, particularly for early-onset seropositive RA.

The observed inverse associations between AHEI-2010 score and RA risk are generally expected as most of the score's components are biologically relevant in reducing RA risk. Owing to the rich contents of dietary antioxidants, fruits and vegetables have long been suggested as healthy foods that may be effective for RA prevention. In our previous study evaluating association of Alternate Mediterranean Diet Score (AMED) with RA risk, we did not observe a significant association of AMED score as well as the fruit and vegetable consumption components with overall RA risk, but did not investigate whether this was associated with earlier onset RA.[33] AMED is the simple sum of 9 dichotomized components at median, not including detailed amount of actual dietary intakes. We previously found another AHEI-2010 component, sugar-sweetened beverages, to be linked to increased risk of later onset RA (diagnosed after age 55 years) using different comparison groups from the current study.[8] While the EPIC-Norfolk study found an elevated risk of RA among people with higher red meat consumption,[7] our group assessed the red meat-RA association in NHS 9 years ago and did not confirm such associations.[38] However, our current findings do not necessarily contradict our previous report. In the current analysis, we combined data from two cohorts with more incident RA cases and longer follow-up of both younger and older women than the previous analyses, allowing us to detect potential differing effects of diet quality on RA occurred in younger and older age.

The polyunsaturated, particularly long-chain n-3 fatty acids, have been found to be effective in both reducing RA risk and improving symptoms in RA patients through the mechanism of promoting the anti-inflammatory eicosanoid synthesis.[39, 40] Additionally, we have also demonstrated a U-shaped association between alcohol consumption and RA risk, in which women with moderate alcohol consumption had the lowest risk of RA.[2] A recently published nested case-control studies reported that high sodium consumption was associated with increased risk of RA particularly among smokers,[41, 42] and experimental studies have suggested that sodium may be able to promote the development of autoimmune diseases through the induction of pathogenic T helper 17 (Th17) in a process mediated by serum glucocorticoid kinase 1 (SGK1).[43, 44] Finally, legumes, nuts and whole grains, which are abundant in dietary fiber and antioxidants may have potential to mitigate the RA risk.[33]

In the current study, we have found that the protective effects of higher diet quality on RA risk are strongest among women < age 55 years. This result is similar to our previous finding that the positive association between obesity and RA is also restricted among women with RA diagnosed at younger age. This may imply different risk factors for earlier and later onset RA. It is proposed that later onset RA may be different from earlier onset RA in terms of genetic predisposition and immune dysfunction, and hormonal changes with menopause can be a source of RA activation in older female patients.[45]

The strengths of our study include the use of two large cohort studies with long-term follow-up, dietary pattern analysis, repeated assessments of diet and potential confounders, and high rates of follow-up. There are several limitations in our study. First, residual confounding by other unmeasured or unknown factors might still exist, and better diet quality could be a marker for healthy lifestyle. However, because we have carefully adjusted for major lifestyle factors, it's unlikely that the residual confounding completely explain the observed inverse associations. Second, the AHEI-2010 is a hypothesis-driven dietary index based on observed associations between single dietary components and the risk of major diseases, [13] that was not specifically derived for RA. The AHEI-2010 did not incorporate all dietary items that may have beneficial effects for lowering RA risk. Thus it is not clear that AHEI-2010 is the optimal dietary index for RA prevention. Third, the pooled analysis may generate spurious results when the distribution of exposure variable are different in each study (Simpson's paradox). [46, 47] However, NHS and NHS II have the similar research designs, so it is unlikely that our findings were severely biased by Simpson's paradox. Fourth, since the dietary information was collected every 4 years, we were unable to capture the variation of diet intake within this interval. However, the use of cumulative average dietary intake largely reduced the impact of day-to-day variation and could better reflect the long-term intake. Fifth, the majority of RA cases in our cohorts were diagnosed from 45 to 65 years old, we were unable to have enough RA cases to repeat the analyses among more extreme age groups, such as age<45 years or >65 years. Lastly, the dietary quality within these cohorts of mostly white, well-educated health professionals may not be representative of the dietary quality in the United States and other countries. However, it is unlikely that the underlying biologic mechanisms differ substantially by race. The observed associations of AHEI with other chronic diseases in NHS cohorts are very similar to other studies around the world.[48]

CONCLUSIONS

In summary, the results from this study indicate that greater long-term adherence to a healthy dietary pattern may reduce RA risk in women, particularly seropositive RA diagnosis at age 55 years or younger. Further studies are warranted to replicate our findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Age-standardized baseline characteristics of participants from Nurses' Health Study (N=76,597 in 1984) and study participants from Nurses' Health Study II (N=93,392 in 1991) according to AHEI-2010 quartile*

	AHEI-2010 quartile, NHS				AHEI-2010 quartile, NHSII			
	Q1 (n=19,149)	**Q2 (n=19,149)**	**Q3 (n=19,150)**	**Q4 (n=19,149)**	**Q1 (n=23,348)**	**Q2 (n=23,348)**	**Q3 (n=23,348)**	**Q4 (n=23,348)**
AHEI-2010, median (range)†	34.6	43.6	50.7	60.0	36.0	44.5	51.7	61.6
Age (years)†	49.3(7.1)	50.3(7.1)	51.2(7.1)	52.4(6.9)	35.9(4.7)	36.4(4.6)	36.8(4.6)	37.3(4.5)
Body mass index (kg/m²)	25.4(5.2)	25.2(4.9)	25.0(4.6)	24.4(4.1)	25.3(6.0)	24.8(5.4)	24.5(5.1)	23.9(4.6)
Census tract median family income $ (*1000), mean (SD)	60.4(22.7)	63.1(24.5)	66.0(26.4)	69.6(28.8)	56.8(18.9)	59.9(21.2)	62.6(23.1)	66.1(25.4)
Physical activity(MET-h/wk)‡	4.6(1.9, 12.7)	6.5(2.4, 16.0)	8.3(2.9, 20.1)	11.1(4.0, 24.9)	8.3(3.2, 18.7)	10.9(4.4, 23.3)	13.8(5.8, 27.7)	19.4(8.6, 37.1)
Alcohol consumption (g/day) ‡	1.1(0, 5.3)	1.9(0, 7.8)	2.8(0, 9.9)	3.9(0.9, 11.0)	0.5(0, 1.8)	0.9(0, 2.8)	1.4(0, 4.2)	2.0(0.5, 6.3)
Current smoker, %	30.3	25.8	23.1	18.1	14.7	13.1	11.8	9.8
Multivitamin use, %	31.1	34.7	38.3	43.3	40.0	42.5	45.1	47.7
Menarche before age 12, %	21.3	22.5	23.9	25.3	22.3	24.0	25.4	26.0
Oral contraceptive use, %	47.9	48.5	48.8	50.9	83.6	83.6	83.5	83.2
Parous, %	93.4	93.0	92.7	91.0	75.8	73.1	68.4	60.6
Breastfeeding ≥ 12 months, %	16.0	16.5	17.6	18.0	24.6	27.1	26.8	25.8
Postmenopausal, %	48.8	48.5	49.0	49.0	3.3	3.3	3.2	3.2
Current postmenopausal hormone use, %	18.7	19.5	21.0	23.9	2.7	2.7	2.7	2.6
Total energy intake (Kcal/d)	1909(501)	1769(532)	1688(528)	1599(509)	1937(531)	1804(552)	1727(545)	1690(529)

*Values are means (SD) or percentages and are standardized to the age distribution of the study population.

†Value is not age adjusted

‡Values are median (interquartile range)

Table 2

Pooled hazard ratios (95% CI) for incident RA according to cumulative AHEI-2010 quartile in Nurses' Health Study (NHS, 1984–2012) and Nurses' Health Study II (NHSII, 1991–2013)

	AHEI-2010 quartile				*p*-for trend‡
	Q1	Q2	Q3	Q4	
All RA					
Case/person-years	253/917,059	261/919,818	255/920,405	238/920,822	
Age adjusted model 1	1.00	0.97(0.82 to 1.16)	0.96(0.81 to 1.15)	0.86(0.72 to 1.03)	0.11
Multivariable-adjusted model 2 (main)*	1.00	0.97(0.81 to 1.15)	0.95(0.80 to 1.14)	0.85(0.70 to 1.02)	0.08
Multivariable-adjusted model 3†	1.00	0.97(0.82 to 1.16)	0.97(0.81 to 1.15)	0.87(0.73 to 1.05)	0.16
Seropositive RA					
Case/person-years	155/904,493	161/907,167	160/907,363	148/909,298	
Age adjusted model 1	1.00	0.98(0.78 to 1.22)	1.00(0.80 to 1.24)	0.89(0.71 to 1.12)	0.35
Multivariable-adjusted model 2 (main)*	1.00	0.98(0.78 to 1.23)	1.00(0.80 to 1.25)	0.88(0.70 to 1.12)	0.34
Multivariable-adjusted model 3†	1.00	0.98(0.79 to 1.23)	1.02(0.81 to 1.27)	0.92(0.72 to 1.16)	0.53
Seronegative RA					
Case/person-years	97/914,049	100/917,055	95/917,425	90/918,075	
Age adjusted model 1	1.00	0.96(0.73 to 1.28)	0.91(0.68 to 1.20)	0.82(0.61 to 1.09)	0.15
Multivariable-adjusted model 2 (main)*	1.00	0.95(0.72 to 1.26)	0.88(0.66 to 1.17)	0.78(0.58 to 1.06)	0.10
Multivariable-adjusted model 3†	1.00	0.95(0.72 to 1.26)	0.89(0.66 to 1.18)	0.81(0.60 to 1.09)	0.14

Hazard ratios were calculated by using time-varying Cox proportional hazards models

*Adjustment for age, cohort, smoking (never, past, current 1–14 cigarettes/d, current ≥15 cigarettes/d), age at menarche (<12, 12, >12 years), parity and breast feeding (nulliparous, parous/no breastfeeding, parous/1–12 months breastfeeding, parous/ >12 months breastfeeding), hormone use (pre-menopausal, post-menopausal with never use, current use and past use) and total energy (quintiles)

†Additional adjustment for BMI (<20, 20–22.9, 23–24.9, 25–29.9, ≥30kg/m^2)

‡*p* for trend was derived from tests of linear trend across categories of AHEI scores by treating the median value of each category as a continuous variable

Table 3

Pooled hazard ratios (95% CI) for incident RA according to cumulative AHEI-2010 quartile in Nurses' Health Study (NHS, 1984–2012) and Nurses' Health Study II (NHS II, 1991–2013) stratified by age before or after 55 years

	AHEI Score, quartile				
	Q1	**Q2**	**Q3**	**Q4**	***p* for trend** ‡
Age ≤55 years					
			All RA		
Case/person-years	136/558,968	125/535,171	99/513,734	84/485,162	
Age adjusted model 1	1.00	0.90(0.70 to 1.15)	0.76(0.58 to 0.98)	0.68(0.52 to 0.89)	0.003
Multivariable model 2 (main)*	1.00	0.89(0.69 to 1.14)	0.75(0.57 to 0.97)	0.67(0.51 to 0.88)	0.002
Multivariable model 3†	1.00	0.90(0.70 to 1.15)	0.76(0.59 to 1.00)	0.71(0.54 to 0.94)	0.009
			Seropositive RA		
Case/person-years	87/548,349	83/525,054	70/503,397	47/476,102	
Age adjusted model 1	1.00	0.95(0.70 to 1.29)	0.81(0.58 to 1.11)	0.63(0.44 to 0.89)	0.005
Multivariable model 2 (main)*	1.00	0.93(0.68 to 1.27)	0.78(0.57 to 1.09)	0.60(0.42 to 0.86)	0.003
Multivariable model 3†	1.00	0.95(0.69 to 1.28)	0.81(0.58 to 1.12)	0.65(0.45 to 0.92)	0.011
			Seronegative RA		
Case/person-years	49/556,795	42/533,240	29/511,879	37/483,609	
Age adjusted model 1	1.00	0.80(0.52 to 1.23)	0.67(0.43 to 1.05)	0.77(0.50 to 1.18)	0.18
Multivariable model 2 (main)*	1.00	0.81(0.52 to 1.24)	0.68(0.43 to 1.07)	0.79(0.51 to 1.24)	0.26
Multivariable model 3†	1.00	0.81(0.52 to 1.24)	0.69(0.44 to 1.09)	0.83(0.53 to 1.29)	0.34
Age>55 years					
			All RA		
Case/person-years	116/365,249	136/390,708	156/412,404	154/440,769	
Age adjusted model 1	1.00	1.08(0.85 to 1.37)	1.10(0.87 to 1.40)	1.11(0.87 to 1.41)	0.39
Multivariable model 2 (main)*	1.00	1.08(0.85 to 1.37)	1.10(0.86 to 1.40)	1.10(0.86 to 1.41)	0.45
Multivariable model 3†	1.00	1.08(0.85 to 1.37)	1.10(0.87 to 1.41)	1.11(0.87 to 1.42)	0.40

	AHEI Score, quartile				
	Q1	Q2	Q3	Q4	*p* for trend [‡]
			Seropositive RA		
Case/person-years	68/363,288	78/388,184	90/409,690	101/438,302	
Age adjusted model 1	1.00	1.04(0.76 to 1.42)	1.13(0.83 to 1.54)	1.19(0.88 to 1.62)	0.21
Multivariable model 2 (main) [*]	1.00	1.06(0.77 to 1.45)	1.17(0.85 to 1.59)	1.22(0.89 to 1.68)	0.17
Multivariable model 3 [†]	1.00	1.06(0.77 to 1.45)	1.17(0.85 to 1.60)	1.23(0.90 to 1.69)	0.16
			Seronegative RA		
Case/person-years	48/364,396	58/389,885	66/411,265	53/439,561	
Age adjusted model	1.00	1.13(0.78 to 1.64)	1.07(0.73 to 1.56)	0.99(0.67 to 1.45)	0.87
Multivariable model 1 (main) [*]	1.00	1.09(0.75 to 1.58)	1.01(0.69 to 1.48)	0.91(0.62 to 1.36)	0.57
Multivariable model 2 [†]	1.00	1.09(0.75 to 1.58)	1.02(0.69 to 1.49)	0.93(0.63 to 1.39)	0.66

Hazard ratios were calculated by using time-varying Cox proportional hazards models

[*] Adjustment for age, cohort, smoking (never, past, current 1–14 cigarettes/d, current ≥15 cigarettes/d), age at menarche (<12, 12, >12 years), parity and breast feeding (nulliparous, parous/no breastfeeding, parous/1–12 months breastfeeding, parous/ >12 months breastfeeding), hormone use (pre-menopausal, post-menopausal with never use, current use and past use) and total energy (quintiles)

[†] Additional adjustment for BMI (<20, 20–22.9, 23–24.9, 25–29.9, ≥30kg/m^2)

[‡] *p* for trend was derived from tests of linear trend across categories of AHEI scores by treating the median value of each category as a continuous variable

Table 4

Pooled hazard ratios (95% CI) for incident RA according to cumulative AHEI-2010 individual component score quartile for women aged 55 years or younger in Nurses' Health Study (NHS, 1984–2012) and Nurses' Health Study II (NHS II, 1991–2013)*

	AHEI-2010				
	Q1	**Q2**	**Q3**	**Q4**	***p* for trend §**
Unhealthy food/nutrient					
		Red/processed meat			
Median, servings/d	1.50	1.04	0.72	0.37	
Cases/ Person-years	131/544,851	138/530,911	93/522,149	82/495,159	
Age adjusted model 1	1.00	0.93(0.73 to 1.18)	0.71(0.54 to 0.92)	0.61(0.46 to 0.81)	<0.001
Multivariable-adjusted model 2 (main)†	1.00	0.89(0.69 to 1.14)	0.67(0.50 to 0.88)	0.58(0.43 to 0.79)	<0.001
Multivariable-adjusted model 3‡	1.00	0.91(0.71 to 1.17)	0.70(0.53 to 0.93)	0.64(0.47 to 0.87)	0.002
		Sugar-sweetened beverages			
Median, servings/d	1.00	0.83	0.56	0.18	
Cases/ Person-years	127/647,550	85/402,430	124/517,586	108/525,503	
Age adjusted model 1	1.00	0.95(0.71 to 1.27)	1.10(0.86 to 1.40)	1.02(0.79 to 1.31)	0.71
Multivariable-adjusted model 2 (main)†	1.00	0.93(0.69 to 1.25)	1.07(0.83 to 1.38)	1.01(0.77 to 1.32)	0.76
Multivariable-adjusted model 3‡	1.00	0.90(0.67 to 1.21)	1.02(0.80 to 1.32)	0.96(0.74 to 1.26)	0.97
		Trans fat			
Median, % of total energy	2.0	1.6	1.4	1.0	
Cases/ Person-years	127/543,068	108/534,883	110/521,468	99/493,651	
Age adjusted model 1	1.00	0.95(0.74 to 1.22)	0.81(0.62 to 1.06)	0.86(0.66 to 1.12)	0.15
Multivariable-adjusted model 2 (main)†	1.00	0.94(0.73 to 1.21)	0.81(0.62 to 1.05)	0.86(0.65 to 1.12)	0.15
Multivariable-adjusted model 3‡	1.00	0.96(0.74 to 1.23)	0.84(0.64 to 1.10)	0.93(0.71 to 1.22)	0.39
		Sodium¶			
Cases/ Person-years	125/546,210	113/468,167	112/565,577	94/513,114	
Age adjusted model 1	1.00	1.04(0.81 to 1.35)	0.87(0.67 to 1.12)	0.79(0.60 to 1.03)	0.04
Multivariable-adjusted model 2 (main)†	1.00	0.92(0.69 to 1.23)	0.73(0.52 to 1.02)	0.65(0.44 to 0.98)	0.02

	AHEI-2010				
	Q1	**Q2**	**Q3**	**Q4**	***p* for trend** [§]
Multivariable-adjusted model 3[‡]	1.00	0.95(0.71 to 1.27)	0.77(0.55 to 1.08)	0.71(0.48 to 1.07)	0.07
Healthy food/nutrient					
		Nuts			
Median, servings/d	0.07	0.18	0.29	0.57	
Cases/ Person-years	125/552,650	101/527,416	109/508,006	109/504,997	
Age adjusted model 1	1.00	0.82(0.63 to 1.07)	0.84(0.65 to 1.09)	0.95(0.73 to 1.22)	>0.99
Multivariable-adjusted model 2 (main)[†]	1.00	0.80(0.61 to 1.04)	0.81(0.62 to 1.06)	0.92(0.70 to 1.20)	0.89
Multivariable-adjusted model 3[‡]	1.00	0.80(0.61 to 1.05)	0.82(0.62 to 1.07)	0.95(0.73 to 1.25)	0.88
		Vegetables			
Median, servings/d	1.4	2.3	3.2	4.4	
Cases/ Person-years	123/542,983	101/530,967	118/517,891	102/501,229	
Age adjusted model 1	1.00	0.83(0.63 to 1.08)	1.01(0.78 to 1.30)	0.90(0.69 to 1.17)	0.73
Multivariable-adjusted model 2 (main)[†]	1.00	0.80(0.61 to 1.05)	0.96(0.73 to 1.25)	0.84(0.63 to 1.12)	0.45
Multivariable-adjusted model 3[‡]	1.00	0.80(0.61 to 1.05)	0.95(0.73 to 1.24)	0.84(0.63 to 1.11)	0.43
		Fruits			
Median, servings/d	0.42	0.85	1.34	2.15	
Cases/ Person-years	130/553,732	114/539,303	97/510,931	103/489,103	
Age adjusted model 1	1.00	1.21(0.93 to 1.57)	0.85(0.64 to 1.13)	1.05(0.81 to 1.37)	0.73
Multivariable-adjusted model 2 (main)[†]	1.00	1.20(0.92 to 1.56)	0.83(0.62 to 1.11)	1.03(0.77 to 1.36)	0.62
Multivariable-adjusted model 3[‡]	1.00	1.20(0.92 to 1.56)	0.84(0.63 to 1.12)	1.05(0.79 to 1.39)	0.73
		Poly-unsaturated fat			
Median, % of total energy	4.3	5.2	5.9	7.0	
Cases/ Person-years	107/517,432	99/527,495	111/526,417	127/521,723	
Age adjusted model 1	1.00	0.92(0.69 to 1.23)	1.13(0.86 to 1.49)	1.15(0.88 to 1.51)	0.16
Multivariable-adjusted model 2 (main)[†]	1.00	0.92(0.69 to 1.22)	1.12(0.85 to 1.47)	1.13(0.86 to 1.49)	0.20
Multivariable-adjusted model 3[‡]	1.00	0.89(0.67 to 1.19)	1.08(0.82 to 1.42)	1.09(0.83 to 1.43)	0.32

	AHEI-2010				
	Q1	**Q2**	**Q3**	**Q4**	***p* for trend** [§]
		Alcohol[¶]			
Range, drinks/d	0	2.0–2.5	1.5–2.0	0.5–1.5	
Cases/ Person-years	153/685,795	87/307,692	120/637,042	84/462,539	
Age adjusted model 1	1.00	1.08(0.82 to 1.42)	0.86(0.68 to 1.10)	0.72(0.55 to 0.94)	0.006
Multivariable-adjusted model 2 (main)[†]	1.00	1.03(0.78 to 1.36)	0.84(0.66 to 1.06)	0.67(0.51 to 0.89)	0.002
Multivariable-adjusted model 3[‡]	1.00	1.03(0.78 to 1.36)	0.87(0.68 to 1.10)	0.73(0.55 to 0.96)	0.013
		Whole grain			
Median, g/d	6.5	13.9	22.2	36.1	
Cases/ Person-years	129/543,264	106/536,438	108/520,691	101/492,676	
Age adjusted model 1	1.00	0.85(0.66 to 1.09)	0.81(0.62 to 1.05)	0.84(0.64 to 1.10)	0.24
Multivariable-adjusted model 2 (main)[†]	1.00	0.84(0.65 to 1.09)	0.80(0.61 to 1.04)	0.84(0.64 to 1.11)	0.25
Multivariable-adjusted model 3[‡]	1.00	0.84(0.65 to 1.08)	0.81(0.62 to 1.06)	0.88(0.67 to 1.16)	0.44
		Long-chain (n-3) fats (EPA+DHA)			
Median, mg/d	63	120	178	250	
Cases/ Person-years	116/529,182	118/544,526	100/493,951	110/525,410	
Age adjusted model 1	1.00	0.93(0.72 to 1.21)	0.85(0.65 to 1.12)	0.90(0.69 to 1.17)	0.37
Multivariable-adjusted model 2 (main)[†]	1.00	0.91(0.70 to 1.18)	0.82(0.62 to 1.08)	0.86(0.66 to 1.13)	0.23
Multivariable-adjusted model 3[‡]	1.00	0.90(0.69 to 1.18)	0.81(0.62 to 1.07)	0.86(0.66 to 1.13)	0.24

Hazard ratios were calculated by using time-varying Cox proportional hazards models

[*] The AHEI-2010 score is reversely coded for red meat, sugar-sweetened beverages, *Trans* fat and sodium: higher score means lower intake. The AHEI-2010 score is directly coded for nuts, vegetables, fruits, poly-unsaturated fat, alcohol, whole grain and long-chain (n-3) fats: higher score means higher intake

[†] Adjustment for age, cohort, smoking (never, past, current 1–14 cigarettes/d, current ≥15 cigarettes/d), age at menarche (<12, 12, >12 years), parity and breast feeding (nulliparous, parous/no breastfeeding, parous/1–12 months breastfeeding, parous/ >12 months breastfeeding), hormone use (pre-menopausal, post-menopausal with never use, current use and past use) and total energy (quintiles)

[‡] Additional adjustment for BMI (<20, 20–22.9, 23–24.9, 25–29.9, ≥30kg/m^2)

[§] *p* for trend was derived from tests of linear trend across categories of AHEI scores by treating the median value of each category as a continuous variable

Sodium score was derived according to an empirical quintile cutoff in the repeated dietary assessment, so the unit was not available

Alcohol score was derived using pre-specified cutoff, so only range was available