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Mediterranean diet and incidence of rheumatoid arthritis in women

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Abstract

Objective—We examined the association between Mediterranean dietary pattern as measured by Alternate Mediterranean Diet Score (aMed) and risk of incident rheumatoid arthritis (RA) in US women.

Methods—We prospectively followed 83,245 participants from the Nurses' Health Study (NHS, 1980–2008) and 91,393 participants from NHS II (1991–2009) who were initially free of baseline connective tissue diseases. Dietary information was obtained via validated food frequency questionnaires (FFQ) at baseline and approximately every 4 years during follow-up. The aMed was calculated according to the consumption status of 9 food components using cumulative average value. Time-varying Cox proportional hazards models were used to calculate hazard ratios (HR) for RA, seropositive RA and seronegative RA after adjustment for potential confounding factors. Results from 2 cohorts were pooled by an inverse variance–weighted, fixed-effects model.

Results—During 3,511,050 person-years of follow-up, 913 incident cases of RA were documented in the two cohorts. After adjustment for several lifestyle and dietary variables, in both cohorts, greater adherence to Mediterranean dietary pattern was not significantly associated with altered risk of RA. The pooled HR for women in the highest quartile of aMed score was 0.98 (95% CI: 0.80–1.20) compared with those in the bottom quartile. Similar non-significant results

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AUTHOR CONTRIBUTIONS:

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. Mr. Hu and Dr. Lu 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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were observed for both seropositive and seronegative RA. We did not find significant associations between each individual food component (except for alcohol) of aMed score and risk of incident RA.

Conclusion—We did not find a significant association between Mediterranean dietary pattern and risk of RA in women.

The traditional Cretan Mediterranean diet characterized by a high consumption of fruit, vegetables, whole grains, legumes, fish, olive oil, less red meat and moderate alcohol is generally regarded as a healthy diet pattern (1). A meta-analysis of prospective cohort studies showed that greater adherence to a Mediterranean diet was associated with significantly lower mortality rate from cardiovascular disease, lower incidence of cancer, Parkinson's disease and Alzheimer's disease (2). It has been suggested that the beneficial effects of the Mediterranean diet pattern are mediated through improvements of inflammatory markers, lipid profile and blood pressure (3–5).

Several randomized controlled clinical trials have shown a beneficial effect of Mediterranean diet intervention on physical function and vitality among patients with existing RA (6,7). This beneficial effect was found to be associated with improved fatty acid profile but not related with levels of plasma antioxidants (8,9). Several case-control studies suggested that higher consumption of fish, olive oil and cooked vegetables all of which were key components of the Mediterranean diet was associated with reduced risk or lower severity of RA (10–12). However, recall bias may be a particular critical issue in the dietary assessment because individuals with RA may be more likely to misreport their actual food consumption in the past. The case-control design is also unable to measure the long-term effects of certain dietary factors. Reverse causation may be a possible bias in case-control studies because individuals with early symptoms might change their usual diet. In most cases, many important time-varying confounders are rarely sufficiently controlled.

To the best of our knowledge, no previous prospective cohort studies have evaluated the association between the overall Mediterranean dietary pattern and risk of developing RA. We therefore investigate the relationships between the Mediterranean diet dietary pattern represented by Alternate Mediterranean Diet Score (aMed) (13)and RA risk in 2 well-established large cohorts of middle-aged and old women, controlling for a series of lifestyle and dietary factors.

MATERIALS AND METHODS

Study design and participants

The Nurses' Health Study (NHS) was a cohort study including 121,700 female registered nurses of age 30 to 55 years initiated at 1976. The Nurse's Health Study II (NHS II) was a parallel cohort established in 1989 and consisted of 116,671 female registered nurses of age 25–42 years. The participants in both cohorts responded to a baseline questionnaire about their lifestyles and medical histories, and they were followed biennially through validated questionnaires that obtained updated information. Follow-up was complete for more than 90% for every 2-year period in the two cohorts (14,15). Dietary information was collected using a validated food-frequency questionnaire (FFQ) since 1980 in NHS and 1991 in NHS

II and the information was updated approximately every 4 years during the follow up period. We used 1980 as baseline for NHS and 1991 for NHS II when the dietary information was first collected.

For this analysis, we included women who completed the 1980 FFQ in NHS and 1991 FFQ in NHS II with <70 missing items and total energy intake between 500 and 3500 kcal/d. We censored all women who reported psoriasis, psoriatic arthritis and connective tissue diseases, in which the diagnosis was not subsequently confirmed as RA at self-reported date. Participants with missing aMed score were excluded. After exclusions, this left a total of 83,245 NHS participants and 91,393 NHS II participants for the analysis. Women lost to follow-up were censored at their last response to questionnaires because incident cases could not subsequently be identified. All aspects of this study were approved by the Partners HealthCare Institutional Review Board.

RA Case Identification

The ascertainment of RA cases in the NHS and NHS II was a 2-step process. The connective tissue disease (CTD) screening questionnaire (CSQ) was mailed to participants who self-reported a new physician diagnosis of RA (16). Two board-certified rheumatologists trained in chart abstraction conducted independent medical record reviews according to American College of Rheumatology classification 1987 version for RA (17). The serologic phenotype of RA was determined by positive rheumatoid factors (RF) (available since baseline) or cyclic citrullinated protein (CCP) antibodies in the medical record (available since the early 1990's). Seropositive RA comprises of the majority of RA cases, and about 50–80% of patients with RA have positive RF, ACPA,(anti-citrullinated peptide antibody) or both (18). Compared with seronegative RA, seropositive RA has been more strongly associated with environmental risk factors such as cigarette smoking, which may induce the immunologic reaction against citrullinated peptides (19) and is also associated with a poorer prognosis (20). Detailed RA assessment procedures have been described elsewhere (21,22).

Dietary Assessment

Self-reported FFQ were used to assess average food intake over the preceding year. Participants were asked the frequency of certain food consumption according to commonly used unit or portion size. Nine possible frequency of consumption responses, ranging from 'never or less than once per month' to ' ≥ 6 times per day' were provided for each food. Total energy and nutrient intakes were calculated by summing energy or nutrient intakes from all foods. A previous validation study among participants of NHS found reasonably high correlation coefficients between FFQ and multiple dietary records for most of the dietary factors including the 9 components of the aMed score (23).

The aMed score was a modified version of Mediterranean diet scale from a previously published study (24). There were 9 components in the aMed score including vegetables (excluding potatoes), fruits, nuts, whole grains, legume, fish, ratio of monounsaturated to saturated fat, red and processed meats and alcohol (13). Participants who consumed alcohol between 5 and 15g/d were assigned 1 point, and otherwise they received 0 point. This represents approximately one 12-oz can of regular beer, 5 oz of wine or 1.5 oz of liquor. For

other food components of the aMed score, women with intake above the median intake were assigned 1 point and they otherwise received 0 point. Therefore, participants would have maximum 9 points and minimum 0 point in aMed score and a higher score indicated stronger adherence to the Mediterranean diet. We used cumulative average estimates of aMed score to reflect long-term dietary habits and reduce measurement errors (25). Because patients with preclinical RA typically have early symptoms such as joint pain which may lead them to change their usual diet, we performed a lag analysis in which aMed score was used to predict incident RA that occurred at least 4 years later to reduce the possibility of such reverse causation. For example, to predict RA incidence during the 1994–1998 time period, we used cumulative aMed score calculated between 1980 and 1990 (excluding 1994 measure, the most recent exposure). We stopped updating dietary variables at the first report of cancer because changes in diet after development of cancer may confound the relation between diet and RA. In sensitivity analyses, however, we also examined the association for cumulative average intake that was continually updated even after the development of cancer.

Assessment of Covariates

All covariates information was self-reported on the mailed questionnaires administered every 2 years since 1976 in the NHS, and since 1989 in the NHS II. Information on age, body weight, height, smoking status, menopausal status, use of postmenopausal hormone therapy, multivitamin use, history of diabetes, physical activity, census tract family median income, parity, breast feeding status and age of menarche was collected in both cohorts. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters and it was categorized in 5 levels: <20, 20–22.9, 23–24.9, 25–29.9 and ≥ 30kg/m^2. Smoking status was categorized as never, past, current 1–14 cigarettes/day, current ≥ 15 cigarettes/day. As a proxy of socioeconomic status, we included the 2000 U.S. Census tract median income for the nurses' residence. The age at menarche was categorized as < 12 years old, 12 years old and >12 years old. The information about menopause status and hormone use was grouped into 4 levels: pre-menopausal, post-menopausal with never use, current use and past use. The parity and breast feeding status were also integrated into a single variable that had 4 levels: nulliparous, parous/no breastfeeding, parous/1–12 months breastfeeding and parous/>12 months breastfeeding. Both history of diabetes and multivitamin use was dichotomized as yes or no. In the NHS, recreational physical activity was measured biennially beginning in 1986 with a validated questionnaire asking about the average time spent on 10 common activities. In the NHS II, similar measures were performed in 1989, 1991, 1997, 2001 and 2005. The information was summed and calculated as weekly energy expenditure in metabolic equivalent hours weighting each activity by its intensity level (26). Coffee and sugar-sweetened soda consumption were assessed every 4 years using validated FFQ and were cumulatively averaged to represent the long-term intake. The frequency of soda consumption had 4 levels: <1 month, 1–4/month, 2–6/week and>1/day, and for coffee consumption, they were <1/day, 1–2/day, 3–4/day and ≥ 4/day.

Statistical Analysis

We used time-varying Cox proportional hazards models to assess the association between the aMed score and risk of RA, including separate models for individual food components of

this derived Mediterranean diet score. Total RA, seropositive and seronegative RA were separate outcomes in each analysis. Baseline characteristics were presented as mean±SD for continuous variables and percentage was used for categorical variables. Cumulative average aMed score was included in the model as time-varying exposure and updated until 2 questionnaires prior to RA diagnosis (excluding the most recent questionnaire), and similarly, age, smoking status, physical activity, postmenopausal hormone use, dietary variables, and BMI were included in the multivariate model as time-varying covariates. aMed score was first included in the model using quartiles and then the median value of each quartile was used as a continuous variable to calculate the p-value for trend. We adjusted for the following potential confounders which were updated every 2years: age, census tract median family income (quartiles), cigarette smoking pack-years (never, past, current 1–14 cigarettes/day, current ≥ 15 cigarettes/day), 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), physical activity (0–3, 3–9, 9–18, 18–27, ≥ 27 METs /week), body mass index (<20, 20–22.9, 23–24.9, 25–29.9, ≥ 30kg/m^2), diabetes history, multi-vitamin use, sugar-sweetened soda consumption, coffee consumption, and total energy (Kcal, quintiles). Two sensitivity analyses were performed to assess the robustness of the main results. First, we kept updating dietary information after self-reported cancer. Second, we used the baseline aMed score without updating to examine the association with RA risk.

Missing data was carried forward one cycle. The inverse-variance weighted fixed-effects model was used to combine the results from 2 cohorts. All statistical tests were 2-sided and performed by using SAS 9.2 for UNIX (SAS Institute Inc, Cary, NC).

RESULTS

During 3,516,236 person-years of follow-up (28 years for NHS and 20 years for NHS II), we documented 916 cases of RA (631 cases in NHS, 282 in NHS II). Table 1 shows the age-standardized baseline characteristics of the study population by quartiles of aMed score. For both cohorts, women who were in higher quartiles of aMed score tended to be older, have higher census tract median family income, higher levels of physical activity, higher total energy intake, and lower BMI. Participants with higher aMed scores were also more likely to start menarche before age 12, have multivitamin supplement, breast-feeding more than 12 month and have current hormone use and less likely be current smoker. Parous status and postmenopausal status tended to be similar across aMed score quartiles in both cohorts. As expected, the average red and processed meat consumption was lower in the higher aMed score quartiles, while fish, vegetable, fruit, legume and whole grain consumption was systematically higher in higher aMed score quartiles in both cohorts. The nuts consumption was very low in both cohorts and the variation between aMed score quartiles was small. The average values of monounsaturated to saturated fat ratio were also similar across aMed score quartiles.

After adjusting for potential confounders, we did not find a significant association between aMed score and RA among NHS and NHS II participants. In the pooled results, the HR was

0.98 (95%CI: 0.80–1.20, *p* for trend 0.85) for women in the highest quartiles of aMed score compared with those in the bottom quartiles. Similar insignificant results were observed for seropositive RA (HR: 1.10, 95%CI: 0.85–1.42, *p* for trend 0.51) and seronegative RA (HR: 0.80, 95%CI: 0.57–1.13, *p* for trend 0.60) (Table 2). We further examined the relationship between each component of the aMed score and risk of RA (Table 3). We found a modest association between greater legume intake and increased risk of developing RA (*p* for trend 0.04). In a separate study, we found that long-term moderate alcohol drinking was associated with a reduced risk of RA in NHS and NHSII (27). However, no other food components of aMed score were observed to be associated with RA in the multivariable adjusted models. In both sensitivity analyses that updated dietary information after diagnosis of cancer and use baseline aMed score, the estimates changed modestly but the associations remained unchanged (data not shown).

DISCUSSION

In the present large cohort of women with up to 28 years of follow-up, greater adherence to a Mediterranean dietary pattern, as measured by a higher aMed score, was not significantly associated with reduced risk of incident RA. Except for alcohol consumption, and legume intake, we did not observe significant associations between individual food component of the aMed score and risk of developing RA. The results for alcohol consumption were published elsewhere (27).

Although several studies have investigated the association between components of Mediterranean diet such as vegetables, fruits and fish and risk of RA, this is the first study, to our knowledge, specifically designed to examine whether the overall Mediterranean dietary pattern could play a role in RA development using two large prospective cohorts. The traditional Mediterranean diet is shown to be effective in lowering CVD risk and it is also hypothesized to have a possible protective effect for development of RA because of its anti-inflammatory properties (28). This anti-inflammatory effect is particularly relevant to the treatment and prevention RA which is a disease characterized by persistent synovitis, systematic inflammation, and auto-antibodies (18,29).

Red meat consumption may be biologically plausible to be associated with the development of RA, while fish, fruits and vegetables may be associated with decreased risk of RA, however, the epidemiological results are inconsistent. The link between red meat consumption and increased RA risk may be attributed to its rich source of iron, which has been shown to accumulate in rheumatoid synovial membrane and exacerbate synovial inflammation (30,31). A prospective nested case-control study found that higher intake of meat and total protein was associated with an increased risk of RA (32), but the results from NHS found that neither red meat nor total protein was associated with increased RA risk (33). Fruits and vegetables are two major sources of antioxidants and their anti-inflammatory effects may be relevant in RA prevention. Several case-control studies suggest that higher consumption of fruits and vegetables are associated with reduced risk of RA (11,12), however results from the Iowa Women’s Health Study, a large prospective cohort including 29,368 participants, did not observe a significant association for fruit intake, but a modest inverse association for cruciferous vegetables (34). Dietary fish and fish oil have

been suggested to be protective for development of RA because of their long-chain omega-3 fatty acids which are precursors of anti-inflammatory eicosanoids (35). A large case-control study with 1,889 incident RA cases found that those with higher oily fish consumption had 20% reduced risk of RA compared with those with never or seldom intake (10), while another prospective cohort study showed that the protective effects were only restricted to fat fish, and the medium fat fish was associated with significantly increased risk of RA (36). In our recently study, we found a modest association between long-term moderate alcohol drinking and reduced risk of RA in NHS and NHSII (27). Compared to non-drinkers, women who consumed alcohol 5–9.9 gram/day had 22% lower risk of developing RA (HR: 0.78, 95% CI, 0.61–1.00) and the association was stronger for seropositive RA (HR: 0.69, 95% CI, 0.50–0.95). The underlying mechanisms remain to be clarified, but several studies suggested that alcohol consumption might play a role in immunologic regulation, which is able to diminishing the response to immunogens in animals as well as in humans, and to significantly suppressing the synthesis of proinflammatory cytokines and chemokines, such as tumor necrosis factor (TNF-α), interleukin 6(IL-6), and interleukin 8 (IL-8), both *in vivo* and *in vitro* in alveolar macrophages and human blood monocytes (37,38).

In the current study, we also examined whether legume, nuts and whole grain consumption could play a role in RA development as very few studies have been conducted to examine the associations between these foods and RA risk. Prospective studies have found dietary fiber intake to be inversely associated with inflammation biomarkers such as IL-6, TNF-α-2, plasma fibrinogen and hs-CRP (39). Thus, nuts and whole grain consumption might be beneficial for RA prevention. In addition, whole grains are also rich in antioxidants, including vitamin E, phytic acid, and selenium (40) which may attribute to the anti-inflammatory process. However, we did not observe a significant inverse association between these food items and RA risk in the current analysis. These insignificant findings were possibly because dietary fibers might have small-to-modest effects on RA risk that could not be detected with our sample size. We found a modest association of legume intake with increased risk of developing RA, but it remains unclear whether this is due to chance. It is suggested that dietary staples such as cereal grains and legumes contain lectins that have the ability to interact with components of the immune system which may facilitate the autoimmune process (41). More studies are warranted to confirm our findings

There were several potential interpretations for the null findings which have been hypothesized to be protective against RA risk. First, a previous study suggested that only cooked vegetables but not raw were associated with reduced risk of RA (11). However, we were not able to differentiate whether it was cooked or raw in the current study. Second, we did not collect information on certain types of fish (e.g., fat or medium fish). Thus the insignificant findings for vegetables and fish consumption might reflect a mixed of food with opposite disease prevention properties. Olive oil, which contains rich oleic acid that can be metabolized to eicosattrienoic acid with anti-inflammatory properties, is the primary source of monounsaturated fat in the traditional Mediterranean diet, however, in our cohorts the major sources of monounsaturated fat come from beef and other meats (13). Therefore, because the red meat also has potential pro-inflammatory effects, the insignificant results from monounsaturated/saturated fat ratio might also reflect a mixed food effects. We did not

find fruit consumption was associated with reduced risk of RA in both cohorts. One possible explanation could be that not all kinds of fruits were effective in RA prevention. A recent study using our cohorts has found that only greater consumption of specific whole fruits such as blue berries, grapes and raisins were associated with reduced risk of type 2 diabetes while some others were even associated with increased type 2 diabetes risk (42). Another important reason that may contribute to our null findings is that the variation of aMed score is too small to detect any modest associations. This issue also applies to the individual food components as we found the mean values for nuts and monounsaturated to saturated fat ratio were very similar across aMed score quartiles.

Our study had several strengths. First, prospective assessment of diet and lifestyle information and high rate of follow-up reduces the possibility of selection and recall bias that may be the major methodological limitations in case-control studies. Second, a validated FFQ was used to collect dietary information every 4 years during the follow up and we cumulatively averaged the consumptions to reflect participants' long-term intake and reduce measurement error. Third, we performed a lag analysis that excluded the most recent dietary information to prevent the possible reverse causation that people with early symptoms of RA were likely to change their usual dietary. Finally, although residual confounding is unavoidable in observational study, given our detailed and updated adjustment for potential confounders, it was unlikely that the results would be severely flawed. Despite these advantages, interpretation of the current data should be cautious because the study population consisted of all women with higher health awareness. Actually, the incidence of RA in our cohorts was lower than prior estimates from the Olmsted County, Minnesota's hospital case-based reports (43). Hence our ability to assess the association with men and capture subjects with early symptoms, or who were not health professionals was limited, and the generalizability of our findings was limited to women with middle-age range. However, the rigorous assessment of cases and dietary information guaranteed the internal validity of the current analysis.

In conclusion, no significant association was found between overall Mediterranean dietary pattern and RA risk in these two large prospective cohorts. Because this is the first prospective report regarding the potential effects of Mediterranean diet on RA risk, our results need to be replicated in other populations.

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Significance & Innovations

- Mediterranean diet is associated with reduced risk of some inflammatory diseases because of its anti-inflammatory properties. Clinical trials suggested beneficial effects of this dietary pattern on patients with existing rheumatoid arthritis.
- This is the first study to evaluate the association between overall Mediterranean dietary pattern and risk of incident RA using prospective cohorts.
- The greater adherence to Mediterranean diet might not have substantial benefits in reducing RA risk that might reflect mixed effects of the components of this dietary pattern. Except alcohol consumption, none of the components of the Mediterranean diet was found to be significantly associated with RA risk.

Table 1

Age-standardized baseline characteristics according to quartiles of aMed scores*

	Nurses' Health Study (N=83,245)				Nurses' Health Study II (N=91,393)			
Variables	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
No. of participants	19,140	17,279	32,501	14,325	19,071	33,881	16,375	22,066
aMed score range	0–2	3	4–5	6–9	1–2	3–4	5	6–9
Age (years)	47.4±7.0	48.2±7.1	49.0±7.2	50.1±7.2	38.2±4.8	38.6±4.7	38.8±4.6	39.1±4.5
BMI (kg/m^2)	24.7±4.7	24.7±4.6	24.6±4.5	24.4±4.4	25.7±6.0	25.3±5.7	25.2±5.5	24.7±5.2
Census tract median family income $ (*1000)	62.4±24.7	63.9±25.2	65.3±26.1	67.9±27.6	59.7±20.5	62.2±22.7	63.4±23.3	64.8±24.5
Physical activity(MET-h/wk)	11.1±17.3	12.7±19.6	14.8±20.8	18.0±22.9	15.9±22.7	19.2±24.7	22.8±28.6	26.9±32.4
AHEI score	45.7±10.2	48.5±10.3	51.7±10.4	56.6±10.3	34.6±7.8	41.4±8.4	46.9±8.4	53.1±9.3
Alcohol consumption (g/d)	6.4±12.3	6.6±11.3	6.3±9.9	6.5±8.2	2.4±5.3	2.9±5.3	3.2±5.3	3.8±5.2
Current smoking, %	34.4	29.7	24.9	19.2	14.6	11.7	9.8	8.7
Multivitamin use, %	31.0	34.1	37.9	43.3	33.6	38.0	41.2	45.9
Menarche before age 12, %	21.7	22.5	23.7	24.0	23.4	24.0	25.1	25.2
Parous, %	92.4	92.7	92.4	92.8	69.9	69.8	70.0	68.2
Breastfeeding >= 12 months, %	14.1	16.2	18.4	22.9	20.5	24.7	28.5	31.4
Postmenopausal, %	41.2	41.5	41.7	41.2	5.2	4.6	4.7	4.5
Current hormone use, %	15.5	15.5	16.3	17.3	37.4	36.8	36.7	36.1
Total energy intake (Kcal/d)	1435±477	1498±493	1609±503	1717±482	1508±481	1705±507	1909±521	2087±525
Red/processed meat (servings/d)	1.8±1.0	1.7±1.0	1.6±1.0	1.4±0.9	1.2±0.7	1.2±0.7	1.2±0.7	1.1±0.7
Fish (servings/d)	0.2±0.2	0.3±0.3	0.4±0.5	0.7±0.7	0.2±0.2	0.3±0.2	0.3±0.3	0.4±0.3
Vegetable (servings/d)	1.1±0.5	1.4±0.8	1.9±1.0	2.4±1.1	1.8±1.0	2.8±1.6	3.8±1.9	4.8±2.2
Fruit (servings/d)	0.8±0.8	1.2±1.0	1.6±1.3	2.2±1.3	0.6±0.5	1.0±0.8	1.4±1.0	1.8±1.1
Legume (servings/d)	0.3±0.2	0.4±0.3	0.5±0.4	0.7±0.4	0.2±0.2	0.3±0.3	0.4±0.3	0.6±0.4
Whole grain (servings/d)	0.3±0.6	0.5±0.8	0.9±0.9	1.3±1.0	0.7±0.7	1.2±1.0	1.6±1.1	2.1±1.3
Nuts (servings/d)	0.1±0.2	0.1±0.3	0.2±0.4	0.3±0.5	0.0±0.1	0.0±0.1	0.1±0.1	0.1±0.2
Monounsaturated to saturated fat ratio	1.0±0.1	1.0±0.1	1.0±0.1	1.1±0.2	1.0±0.1	1.1±0.1	1.1±0.2	1.2±0.2

*Values (except age) are standardized to the age distribution of the study population. Mean ± SD unless otherwise indicated. aMed = Alternate Mediterranean Diet Score; BMI= body mass index (calculated as weight in kilograms divided by height in meters squared); MET=metabolic equivalent task; AHEI=Alternate Healthy Eating Index.

Table 2

Hazard ratios of RA by quartiles of aMED Score*

	aMed Score				
	Q1	**Q2**	**Q3**	**Q4**	***p* for trend**
All RA					
NHS					
Cases/ Person-years	164/510,785	139/508,567	173/531,429	155/524,681	
Age adjusted	1.00	0.85(0.68,1.07)	1.01(0.81,1.25)	0.89(0.71,1.11)	0.56
Multivariable adjusted	1.00	0.87(0.69,1.09)	1.04(0.83,1.30)	0.94(0.73,1.20)	0.91
NHS II					
Cases/ Person-years	75/315,806	72/460,984	54/300,158	81/358,641	
Age adjusted	1.00	0.65(0.47,0.91)	0.71(0.50,1.00)	0.88(0.64,1.21)	0.58
Multivariable adjusted	1.00	0.71(0.51,0.98)	0.80(0.55,1.16)	1.09(0.75,1.57)	0.60
NHS and NHS II pooled					
Age adjusted	1.00	0.78(0.65, 0.94)	0.91(0.76, 1.10)	0.89(0.74, 1.06)	0.43
Multivariable adjusted	1.00	0.81(0.67, 0.98)	0.97(0.80, 1.18)	0.98(0.80, 1.20)	0.85
Seropositive RA					
NHS					
Cases/ Person-years	103/481,583	90/479,660	98/497,621	100/429,830	
Age adjusted	1.00	0.89(0.67,1.19)	0.92(0.70,1.22)	0.94(0.71,1.24)	0.74
Multivariable adjusted	1.00	0.93(0.70,1.24)	0.98(0.73,1.31)	1.03(0.76,1.40)	0.79
NHS II					
Cases/ Person-years	50/310,102	48/452,201	30/295,056	58/352,392	
Age adjusted	1.00	0.66(0.44,0.98)	0.58(0.37,0.92)	0.96(0.66,1.41)	0.75
Multivariable adjusted	1.00	0.73(0.48,1.09)	0.70(0.43,1.12)	1.26(0.81,1.98)	0.43
NHS and NHS II pooled					
Age adjusted	1.00	0.81(0.64, 1.02)	0.81(0.64, 1.03)	0.95(0.76, 1.19)	0.65
Multivariable adjusted	1.00	0.85(0.68, 1.08)	0.89(0.69, 1.14)	1.10(0.85, 1.42)	0.51
Seronegative RA					
NHS					

	aMed Score				
	Q1	**Q2**	**Q3**	**Q4**	***p* for trend**
Cases/ Person-years	61/509,353	49/507,020	75/529,827	55/522,969	
Age adjusted	1.00	0.79(0.54,1.15)	1.15(0.82,1.62)	0.82(0.56,1.18)	0.64
Multivariable adjusted	1.00	0.78(0.53,1.15)	1.14(0.79,1.63)	0.80(0.53,1.20)	0.61
NHS II					
Cases /Person-years	25/315,231	24/460,221	24/299,590	23/357,938	
Age adjusted	1.00	0.64(0.36,1.12)	0.95(0.54,1.67)	0.73(0.41,1.29)	0.60
Multivariable adjusted	1.00	0.66(0.37,1.18)	0.99(0.54,1.80)	0.81(0.43,1.55)	0.87
NHS and NHS II pooled					
Age adjusted	1.00	0.74(0.54, 1.01)	1.09(0.82, 1.47)	0.79(0.58, 1.08)	0.50
Multivariable adjusted	1.00	0.74(0.54, 1.02)	1.10(0.80, 1.49)	0.80(0.57, 1.13)	0.60

aMed = Alternate Mediterranean Diet Score; NHS = Nurses' Health Study; NHS II =Nurses' Health Study II; RA= rheumatoid arthritis.

*Adjusted for age, census tract median family income (quartiles), cigarette smoking status (never, past, current 1–14 cigarettes/day, current ≥15 cigarettes/day), 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), physical activity (0–3, 3–9, 9–18, 18–27, ≥27 METs /week), body mass index (<20, 20–22.9, 23–24.9, 25–29.9, ≥30kg/m2), multi-vitamin use, diabetes history, sugar-sweetened soda (<1 month, 1–4/month, 2–6/week, >1/day), coffee consumption (<1/day, 1–2/day, 3–4/day, >=4/day) and total energy (Kcal, quintiles).

Table 3

Hazard ratios of RA by quartiles of each component of aMED Score*

	aMed Score				
	Q1	**Q2**	**Q3**	**Q4**	***p* for trend**
Red/processed meat					
NHS					
Cases/ Person-years	146/521,016	163/516,642	165/516,887	157/520,917	
Age adjusted	1.00	1.12(0.90,1.41)	1.14(0.91,1.43)	1.08(0.86,1.35)	0.60
Multivariable adjusted	1.00	1.09(0.86,1.37)	1.12(0.88,1.42)	1.10(0.85,1.43)	0.51
NHS II					
Cases/ Person-years	56/357,340	66/358,752	77/359,436	83/360,061	
Age adjusted	1.00	1.16(0.81,1.66)	1.35(0.96,1.91)	1.46(1.04,2.05)	0.02
Multivariable adjusted	1.00	1.05(0.73,1.51)	1.15(0.80,1.65)	1.12(0.76,1.65)	0.55
NHS and NHS II pooled					
Age adjusted	1.00	1.13(0.94, 1.37)	1.20(0.99, 1.45)	1.19(0.98, 1.43)	0.10
Multivariable adjusted	1.00	1.08(0.89, 1.31)	1.13(0.92, 1.37)	1.11(0.89, 1.37)	0.39
Fish					
NHS					
Cases/ Person-years	117/466,509	168/548,258	179/565,017	167/495,678	
Age adjusted	1.00	1.21(0.95,1.54)	1.26(1.00,1.60)	1.31(1.03,1.66)	0.07
Multivariable adjusted	1.00	1.18(0.93,1.51)	1.26(0.99,1.60)	1.29(1.00,1.64)	0.10
NHS II					
Cases/ Person-years	80/361,761	60/352,959	60/363,665	82/357,204	
Age adjusted	1.00	0.74(0.53,1.04)	0.70(0.50,0.98)	0.96(0.70,1.30)	0.91
Multivariable adjusted	1.00	0.74(0.53,1.03)	0.69(0.49,0.97)	0.95(0.69,1.32)	0.88
NHS and NHS II pooled					
Age adjusted	1.00	1.03(0.85, 1.25)	1.04(0.86, 1.26)	1.16(0.96, 1.40)	0.09
Multivariable adjusted	1.00	1.01(0.83, 1.23)	1.03(0.85, 1.26)	1.15(0.95, 1.40)	0.12
Vegetables					
NHS					

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	aMed Score				
	Q1	**Q2**	**Q3**	**Q4**	***p* for trend**
Cases/ Person-years	146/518,607	149/518,556	160/519,156	176/519,143	
Age adjusted	1.00	1.00(0.80,1.26)	1.07(0.85,1.34)	1.16(0.93,1.44)	0.15
Multivariable adjusted	1.00	0.99(0.78,1.25)	1.06(0.84,1.34)	1.18(0.92,1.50)	0.13
NHS II					
Cases /Person-years	72/357,029	66/358,288	60/359,973	84/360,299	
Age adjusted	1.00	0.86(0.62,1.21)	0.77(0.54,1.08)	1.03(0.75,1.41)	0.73
Multivariable adjusted	1.00	0.86(0.61,1.21)	0.76(0.53,1.10)	1.04(0.73,1.49)	0.67
NHS and NHS II pooled					
Age adjusted	1.00	0.96(0.79, 1.15)	0.97(0.80, 1.17)	1.11(0.93, 1.33)	0.18
Multivariable adjusted	1.00	0.94(0.78, 1.14)	0.96(0.79, 1.17)	1.13(0.92, 1.38)	0.15
			Fruit		
NHS					
Cases/ Person-years	153/520,416	164/515,583	181/519,863	133/519,600	
Age adjusted	1.00	1.04(0.84,1.30)	1.16(0.93,1.44)	0.84(0.66,1.06)	0.16
Multivariable adjusted	1.00	1.07(0.86,1.35)	1.21(0.97,1.52)	0.91(0.70,1.17)	0.48
NHS II					
Cases /Person-years	75/352,518	56/362,022	76/361,593	75/359,456	
Age adjusted	1.00	0.70(0.50,0.99)	0.95(0.69,1.31)	0.91(0.66,1.26)	0.90
Multivariable adjusted	1.00	0.74(0.52,1.05)	1.04(0.74,1.46)	1.05(0.73,1.50)	0.37
NHS and NHS II pooled					
Age adjusted	1.00	0.93(0.77, 1.12)	1.09(0.91, 1.30)	0.86(0.71, 1.04)	0.25
Multivariable adjusted	1.00	0.96(0.80, 1.16)	1.16(0.96, 1.40)	0.95(0.77, 1.17)	0.86
			Legume		
NHS					
Cases/ Person-years	145/516,719	160/535,523	176/505,554	150/517,666	
Age adjusted	1.00	1.07(0.86,1.34)	1.25(1.00,1.56)	1.04(0.83,1.31)	0.72
Multivariable adjusted	1.00	1.09(0.87,1.37)	1.29(1.03,1.62)	1.13(0.89,1.44)	0.31
NHS II					
Cases /Person-years	66/364,070	58/373,428	68/338,852	90/359,239	

	aMed Score				
	Q1	**Q2**	**Q3**	**Q4**	***p* for trend**
Age adjusted	1.00	0.82(0.57,1.16)	1.03(0.73,1.44)	1.28(0.93,1.76)	0.03
Multivariable adjusted	1.00	0.82(0.57,1.17)	1.02(0.72,1.44)	1.27(0.91,1.79)	0.04
NHS and NHS II pooled					
Age adjusted	1.00	0,99(0.82, 1.20)	1.18(0.98, 1.42)	1.12(0.93, 1.35)	0.11
Multivariable adjusted	1.00	1.00(0.83, 1.22)	1.20(0.99, 1.45)	1.18(0.97, 1.43)	0.04
Whole grain					
NHS					
Cases/ Person-years	158/533,912	159/530,808	148/472,824	166/539,917	
Age adjusted	1.00	1.00(0.80,1.25)	1.03(0.82,1.29)	1.01(0.81,1.27)	0.87
Multivariable adjusted	1.00	1.00(0.80,1.25)	1.06(0.84,1.34)	1.08(0.85,1.36)	0.49
NHS II					
Cases /Person-years	76/351,023	60/364,511	70/360,040	76/360,014	
Age adjusted	1.00	0.75(0.53,1.05)	0.86(0.62,1.20)	0.94(0.68,1.29)	0.90
Multivariable adjusted	1.00	0.76(0.54,1.07)	0.91(0.64,1.28)	1.04(0.73,1.48)	0.46
NHS and NHS II pooled					
Age adjusted	1.00	0.92(0.76, 1.10)	0.97(0.81, 1.17)	0.99(0.82, 1.18)	0.84
Multivariable adjusted	1.00	0.92(0.76, 1.11)	1.01(0.83, 1.22)	1.06(0.87, 1.30)	0.32
Nuts					
NHS					
Cases/ Person-years	151/529,925	128/384,444	197/639,686	155/521,407	
Age adjusted	1.00	1.14(0.89,1.44)	1.07(0.86,1.32)	1.02(0.81,1.27)	0.75
Multivariable adjusted	1.00	1.11(0.87,1.42)	1.08(0.87,1.34)	1.03(0.82,1.30)	0.90
NHS II					
Cases /Person-years	74/379,761	56/347,896	75/373,176	77/334,756	
Age adjusted	1.00	0.79(0.53,1.18)	0.98(0.70,1.36)	1.07(0.76,1.49)	0.24
Multivariable adjusted	1.00	0.78(0.52,1.16)	0.97(0.70,1.36)	1.11(0.78,1.56)	0.15
NHS and NHS II pooled					
Age adjusted	1.00	1.03(0.84, 1.27)	1.04(0.87, 1.25)	1.03(0.86, 1.24)	0.88
Multivariable adjusted	1.00	1.01(0.82, 1.24)	1.05(0.87, 1.25)	1.06(0.87, 1.28)	0.68

	aMed Score				
	Q1	**Q2**	**Q3**	**Q4**	***p* for trend**
Monounsaturated to saturated fat ratio					
NHS					
Cases/ Person-years	163/518,408	164/518,646	153/518,216	151/520,192	
Age adjusted	1.00	1.00(0.81,1.25)	0.94(0.76,1.18)	0.92(0.74,1.15)	0.39
Multivariable adjusted	1.00	1.00(0.80,1.24)	0.94(0.76,1.18)	0.93(0.74,1.16)	0.43
NHS II					
Cases /Person-years	73/358,162	60/359,484	72/358,987	77/358,956	
Age adjusted	1.00	0.79(0.56,1.12)	0.92(0.66,1.28)	0.95(0.69,1.32)	0.99
Multivariable adjusted	1.00	0.77(0.55,1.09)	0.90(0.65,1.24)	1.00(0.72,1.39)	0.75
NHS and NHS II pooled					
Age adjusted	1.00	0.94(0.78, 1.13)	0.94(0.78, 1.13)	0.93(0.77, 1.12)	0.50
Multivariable adjusted	1.00	0.93(0.77, 1.11)	0.93(0.77, 1.12)	0.95(0.79, 1.14)	0.66

aMed = Alternate Mediterranean Diet Score; NHS = Nurses' Health Study; NHS II =Nurses' Health Study II; RA= rheumatoid arthritis.

*Adjusted for age, census tract median family income (quartiles), cigarette smoking status (never, past, current 1–14 cigarettes/day, current ≥15 cigarettes/day), 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), physical activity (0–3, 3–9, 9–18, 18–27, ≥27 METs /week), body mass index (<20, 20–22.9, 23–24.9, 25–29.9, ≥30kg/m2), multi-vitamin use, diabetes history, sugar-sweetened soda (<1 month, 1–4/month, 2–6/week, >1/day), coffee consumption (<1/day, 1–2/day, 3–4/day, >=4/day) and total energy (Kcal, quintiles).