HHS Public Access

Author manuscript

Mult Scler. Author manuscript; available in PMC 2018 December 01.

Published in final edited form as:

Mult Scler. 2017 December ; 23(14): 1830–1838. doi:10.1177/1352458517691150.

Polyunsaturated fatty acids and the risk of multiple sclerosis

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Abstract

Background—Results from previous studies on PUFA intake and multiple sclerosis (MS) risk are conflicting.

Objective—To prospectively investigate the association between dietary intake of PUFA and MS risk.

Methods—We followed 80,920 women from Nurses' Health Study (1984–2004) and 94,511 women from Nurses' Health Study II (1991–2009) who reported on diet using a validated food frequency questionnaire every 4 years, and identified 479 incident MS cases during follow-up. We used Cox regression to estimate hazard ratios (HR) and 95% confidence intervals (CI), for the effect of PUFA intake on MS risk adjusting for age, latitude of residence at age 15, ancestry, cigarette smoking, supplemental vitamin D intake, body mass index, and total energy intake.

Results—Higher intake of total PUFA at baseline was associated with a lower risk of MS (HR top vs. bottom quintile: 0.67, 95% CI: 0.49–0.90, p trend=0.01). Among the specific types of PUFA, only α-linolenic acid (ALA) was inversely associated with MS risk (HR top vs. bottom

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Disclosures

K. Bjørnevik reports no relevant disclosures.
T. Chitnis reports no relevant disclosures.
A. Ascherio reports no relevant disclosures.
K.L. Munger reports no relevant disclosures.

quintile: 0.61, 95% CI: 0.45–0.83, p trend=0.001). The long-chain fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) were not associated with MS risk.

Conclusion—Low dietary PUFA intake may be another modifiable risk factor for MS.

Keywords

Multiple sclerosis; polyunsaturated fatty acids; alpha-linolenic acid; epidemiology; risk factors

Introduction

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system whose etiology is unknown. In the 1950s, some ecological studies reported geographical differences in MS prevalence independent of latitude.[1, 2] This was initially attributed to differences in saturated fat intake from animal sources, but later hypothesized to be due to differences in intake of polyunsaturated fatty acids (PUFA).[3] Results from recent studies on PUFA intake and MS risk have, however, been inconsistent. While several studies have reported an inverse association between food sources or supplements rich in PUFA, including fish[4–6] and cod liver oil,[7] and MS risk, one study observed no significant association.[8] A recent case-control study that estimated PUFA intake from the overall diet reported an inverse association between marine long-chain n-3 PUFA, but not for plant-derived PUFA.[9] Still, the only prospective study on PUFA and MS risk reported an inverse non-significant trend for the plant derived PUFA α-linolenic acid (ALA).[10]

As retrospective studies on diet are especially prone to bias,[11] the inconsistencies observed could to some extent be attributed to methodological limitations in previous research. We conducted a follow-up study of the first prospective study on PUFA and MS risk, and sought to prospectively examine the association in two large cohort studies with several decades of follow-up time.

Methods

Study population

The Nurses' Health Study (NHS) and the Nurses' Health Study II (NHSII) are two prospective cohort studies comprised of female nurses living in the United States. During follow-up, the participants completed biennial questionnaires on medical history and health-related behavior. NHS began in 1976 with 121,700 women aged 30 to 50 years. NHSII began in 1989 and enrolled 116,671 women aged 25 to 42 years. For the current analyses, the baseline year was the first year for which an expanded semi-quantitative food frequency questionnaire (FFQ) was available (1984 for NHS and 1991 for NHSII). In these years, 81,575 women in NHS and 95,452 women in NHSII completed the FFQ. Women who had incomplete baseline FFQs, implausible caloric intakes (<500 or >3,500 kcal/day) or who were diagnosed with MS prior to baseline were excluded. In a study comparing women excluded due to implausible energy intake with those included in NHS, the baseline characteristics were similar, although underreporters had higher BMI and overreporters reported higher levels of physical activity.[12] After these exclusions, 80,920 women in NHS and 94,511 women in NHSII were available for the analyses.

Standard protocol approvals, registrations, and patient consents

The institutional review board of Brigham and Women's Hospital approved this study.

Ascertainment of MS cases

The procedure of MS ascertainment in NHS and NHSII, including the validity of this approach, has previously been described.[13] In short, incident MS cases were identified by self-report on the biennial questionnaires. We confirmed the diagnosis by sending a questionnaire on the certainty of the diagnosis (definite, probable, possible, not MS) and the clinical history to the treating neurologist. Since 2003, our study neurologist (TC) reviewed the medical history if consent was given and the medical records were available. Patients defined as definite or probable cases were included in the study. Using this approach, we documented 130 and 349 new MS cases during follow up in NHS and NHSII, respectively.

Dietary assessment

The validity and reproducibility of the FFQs used in NHS and NHSII have been documented elsewhere.[14, 15] Women completed a comprehensive semi-quantitative FFQ in 1980, 1984, 1986, 1990, 1994, 1998, and 2002 in NHS and in 1991, 1995, 1999, 2003 and 2007 in NHSII. They were asked to report how often, on average, over the previous year they had consumed certain food items, measured on a nine-point scale (ranging from “never” to “six or more times per day”). The nutrient values were then calculated by multiplying the frequency response by the nutrient content of specific portion sizes according to the Harvard University food-composition database, which is derived from US Department of Agriculture sources[16] and supplemented with information from manufacturers. The first dietary assessment was done in 1980 by a 61-item questionnaire, and this questionnaire was expanded to 116 items in 1984. As the expanded questionnaire provided more detail needed to estimate intakes of specific fatty acids of interest, 1984 was considered baseline for NHS in the current analyses. For NHSII, the FFQ administered in 1991, which included 133 food items, was used to estimate baseline intakes of the fatty acids included in the analyses.

In validation studies, the intake of PUFAs estimated by the FFQ used in our study were modestly, but significantly, correlated with 1-week dietary records (r=0.48 for total PUFA)[17] and adipose tissue levels [r=0.40 ($p<0.001$) for total PUFA, r=0.34 ($p<0.001$) for ALA, r=0.37 ($p<0.001$) for linoleic acid (LA; 18:2n-6), r=0.47 ($p<0.001$) for eicosapentaenoic acid (EPA; 20:5n-3)].[18, 19] The top contributors to total PUFA at baseline were mayonnaise (NHS: 14.2%; NHSII: 12.3%), margarine (NHS: 9.3%; NHSII: 6.5%) and oil and vinegar dressing (NHS: 9.0%, NHSII: 6.6%). In the last FFQ during follow up, walnuts were the main contributors of PUFAs in both cohorts (NHS: 6.4%; NHSII: 8.5%). The top contributors to intake of LA and ALA at baseline were mayonnaise and oil and vinegar dressing in both cohorts, while fish contributed to most of the intake of EPA and docosahexanoic acid (DHA; 22:6n-3).

Covariates

Women reported their state of residence at age 15 and ancestry in 1992 (NHS) and 1993 (NHSII) and these were categorized as previously described.[13] Smoking status and number of cigarettes per day were reported biennially, and pack-years of smoking were derived

using this information. Further, the women reported height on the questionnaires in 1976 (NHS) and 1989 (NHSII) and their weight at age 18 in 1980 (NHS) and 1989 (NHSII). Their body mass index (BMI) at age 18 was calculated using this information, and they were categorized according to the World Health Organization's BMI definitions (<18.5, 18.5–<25, 25.0–<30, >=30 kg/m^2).[20]

Statistical analysis

The participants contributed person-years from the date of returning the baseline dietary questionnaire until MS diagnosis, time of death, loss to follow-up, or end of follow-up (June 1, 2004, NHS; June 1, 2009, NHSII), whichever occurred first. We primarily used date of diagnosis to increase the power in the analyses. We also did sensitivity analyses using date of onset as end date, and 289 of the patients were available for these analyses.

We modeled the effect of PUFA intake on MS risk using nutrient intakes as both categorical and continuous variables. For the categorical analyses, we estimated nutrient densities and categorized the women by quintile of dietary intake of the specific types of PUFA as a percentage of total energy intake (TEI). The primary analyses were based on the baseline intakes, but we also conducted analyses using the cumulative average intakes from all dietary questionnaires up to the start of each follow-up interval. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals. In a multivariable analysis, we adjusted for age (5 year intervals), latitude of residence at age 15 (north, middle, south), ancestry (South European, Scandinavian, other Caucasian, other), smoking (never smoker, 1–9, 10–24, and >=25 pack-years), BMI at age 18 (<18.5, 18.5–<25, 25.0–<30, >=30 kg/m^2), vitamin D supplementation (0, >0–<400, >=400 IU/day), and TEI (continuous). In a second multivariable model, we included both ALA and LA in the same model. We tested for linear trend across the quintiles by modeling the median intake of each quintile as a continuous variable.

We included TEI and nutrient densities of macronutrients and PUFAs as continuous variables in isocaloric substitution models to estimate the effect of substituting part of the TEI from one dietary source with a different dietary source on MS risk.[17] Further, we estimated the association between intakes of specific food items contributing to a substantial part of PUFA intake (ALA and LA; mayonnaise and oil and vinegar dressing, EPA and DHA; dark fish, canned tuna and other fish) by modeling the intake as a categorical variable (<1 per month, 1–3 times per month, 1 per week, ≥ 2–4 times per week). Lastly, we examined whether there is evidence for a non-linear relationship between ALA and MS risk non-parametrically with restricted cubic splines[21] by comparing a model with only the linear term with a model with the linear and cubic spline terms using the likelihood ratio test.

All analyses were conducted in each cohort separately, and the effect estimates were then pooled by the inverse of their variance using a fixed effects model,[22] as we observed no significant heterogeneity between the two cohorts. The analyses were conducted using SAS 9.4 and the figure was made in R 3.3.0. All p-values are two-tailed. The α-level was set at 0.05.

Results

Table 1 presents the distribution of baseline characteristics according to quintiles of PUFA and ALA intake. Women in the top quintile of both total PUFA intake and ALA intake had a lower vitamin D intake compared to the bottom quintiles in both cohorts. Further, women with the highest intake of ALA reported more pack-years of smoking and were more likely to live in the North tier at age 15 years. The other characteristics were similarly distributed across the quintiles. The median age at first symptom and median age at diagnosis for the incident MS cases were 41.4 and 47.0. The median time from baseline to MS diagnosis was 7.5 years.

Total PUFA intake at baseline was inversely associated with MS risk (Table 2). In the age-adjusted pooled analysis, the HR comparing the top and bottom quintile was 0.68 (95% CI: 0.50–0.93, p for trend=0.02). The estimates remained similar in the fully adjusted model (HR 0.67, 95% CI: 0.49–0.90, p for trend=0.01). The point estimates were similar in both cohorts. The wider confidence intervals for the estimates in NHS reflect the lower number of cases in this cohort.

We found a statistically significant inverse association between the plant-derived PUFAs LA and ALA in the age and energy adjusted analysis (Table 3). In the multivariable adjusted pooled analysis, the HR comparing women in the highest and lowest quintile were 0.71 (95% CI: 0.52–0.96, p for trend=0.02) and 0.61 (95% CI: 0.45–0.83, p for trend= 0.001) for LA and ALA, respectively. When we further adjusted LA for intake of ALA, LA was no longer significantly associated with MS risk (HR top vs. bottom quintile: 0.91, 95% CI: 0.63–1.30, p trend=0.75; Figure 1). The association between ALA and MS risk remained similar after adjusting for LA (HR top vs. bottom quintile: 0.65, 95% CI: 0.45–0.93, p trend=0.02; Figure 1). We found no evidence of non-linearity in the relation between ALA and MS risk (NHS: p=0.86; NHSII: p=0.51). We observed no significant associations between baseline intakes of the marine long chain n-3 fatty acids EPA and DHA and MS risk.

We observed a significant association between intake of the top contributor to ALA and LA intake, mayonnaise, when comparing women with the highest intake (2–4 times per week or more) with women with the lowest intake (less than once per month) (HR pooled multivariable analysis: 0.79, 95% CI: 0.58–1.07, p trend= 0.03); no significant associations were found between other top contributors to PUFA intake and MS risk, including fish intake (data not shown).

The analyses of cumulative intake during follow-up were consistent with the baseline analyses. Total PUFA intake was inversely associated with MS risk (HR top vs. bottom quintile, pooled multivariable analysis: 0.69, 95% CI: 0.51–0.93, p trend= 0.03). While ALA was significantly associated lower MS risk (HR top vs. bottom quintile, pooled multivariable analysis: 0.62, 95% CI: 0.46–0.84, p trend=0.009), neither of the other types of PUFAs (LA, EPA, DHA) was significantly associated with MS risk (data not shown).

In isocaloric substitution models, the strongest reductions in MS risk was observed for the substitution of carbohydrates with ALA (HR pooled multivariable analysis, for 0.5 % of

total energy: 0.60, 95% CI: 0.36–0.99) or other types of fat with ALA (HR pooled multivariable analysis, for 0.5 % of total energy: 0.65, 95% CI: 0.44–0.97). In sensitivity analyses using date of onset as end date for the cases, the effect estimates were similar compared analyses using date of diagnosis. In the multivariable adjusted pooled analysis, the HR comparing the top and bottom quintile were 0.65 (95% CI: 0.44–0.97, p for trend=0.01) and 0.77 (95% CI: 0.52–1.15, p for trend= 0.09) for total PUFA intake and ALA, respectively.

Discussion

In this large prospective study, we found an inverse association between dietary PUFA intake and MS risk. With 20 additional years of follow-up, we had more statistical power to further examine the association compared to the first study on PUFAs and MS in NHS,[10] and observed that only the plant-derived ALA was significantly associated with lower MS risk. We found no significant association between the intake of marine n-3 fatty acids and the risk of MS.

Most of the previous studies on PUFA intake and MS risk have focused on marine n-3 fatty acids, and our findings are not consistent with these. Several case-control studies have reported an inverse association between fish[4–6] or cod liver oil[7] and MS risk. However, these associations could be mediated by vitamin D, an established risk factor for MS.[23] Marine n-3 fatty acids have also been inversely associated with MS risk independent of vitamin D,[9] which is not consistent with our findings. Given that the women in the highest quintile of these fatty acids in our study had a median intake that was considerably lower (0.38g/day in both cohorts) than the amount that may be necessary to achieve an anti-inflammatory effect (>1–2 g/day),[24, 25] the intake might have been too low to affect MS risk. Still, the suggested threshold for an anti-inflammatory effect of marine n-3 fatty acids is also higher than that normally obtained through diet in most countries.[26] Further, both animal studies and intervention studies in MS patients examining the role of marine n-3 fatty acids are inconsistent.[27, 28] Thus, it remains unclear whether these fatty acids play a role in MS pathogenesis.

A significant inverse association between ALA and MS risk has not been previously reported. ALA is an essential fatty acid that the body cannot produce itself, and it can be metabolized to the long chain n-3 fatty acid EPA and further to DHA by saturation and elongation.[24] Thus, the association we observed between ALA and MS risk could be mediated by its derivatives rather than reflecting an effect of ALA itself. Still, only a small proportion of dietary ALA is metabolized to EPA (<6%)[29] and ALA may have biological effects independently of its downstream derivatives,[25] which would be consistent with our findings, as we did not observe an association between EPA or DHA and MS risk. We initially observed an association between LA and MS risk, which was no longer present after adjusting for ALA, likely reflecting the high correlation between LA and ALA intake. LA depends on the same enzymes as ALA to form long chain fatty acids,[24] and there is some evidence that a higher LA intake inhibits the conversion of ALA to EPA.[30] We did not observe any difference in the effect estimates after adjusting ALA for LA intake. This could reflect that LA is not affecting the conversion of ALA to EPA in our study, which is

consistent with previous analyses on biochemical markers in NHS,[31] but could also reflect that the association we are observing is due to ALA and is not mediated by its derivatives. Lastly, we only observed a lower risk in the top quintile of ALA intake, which may suggest that there is a threshold for a possible beneficial effect.

ALA may affect immune pathways relevant to the pathogenesis of MS. Lower levels of several inflammation markers have been reported in some,[32, 33] but not all,[34] clinical trials on ALA, including IL-6, IL-1β and TNF-α. IL-6 promotes, in combination with IL-1β and TNF-α, T helper 17 (Th17) cell differentiation,[35] and can also suppress regulatory T (Treg) cells and is thus an important modulator of the Treg/Th17 balance.[36] Interestingly, in two recent metabolomics studies in two different murine experimental autoimmune encephalitis (EAE) models (B6 and SJL), the authors identified only one common pathway in the two models.[37] This was related to PUFA metabolism and specifically to the metabolism of ALA and LA.

Our study has some limitations. We rely on self-reported information on diet, and did not have biochemical markers of PUFAs in the current study. While the intake of fatty acids estimated by the FFQ has been specifically validated against multiple week diet records and biochemical markers[17–19], the correlations are modest and indicate measurement error in the estimated intakes of nutrients. Still, because of the prospective design, this measurement error is most likely independent from disease risk, and thus tend to bias the relative risk estimates towards null. NHS and NHSII only enrolled women, and the great majority are white. Further studies are thus needed to generalize the findings to groups with other demographic characteristics. We did not have information on date of first symptom in all cases, and therefore used date of diagnosis in the main analyses. However, results from sensitivity analyses using date of first symptom were similar. Lastly, we cannot exclude the possibility of residual confounding by unknown factors.

In conclusion, in these large prospective studies we found a significant inverse association between PUFA intake and MS risk. The effect estimates were only significant for the plant-derived n-3 ALA, and not for marine n-3 fatty acids. Low PUFA intake may be another modifiable risk factor for MS.

Acknowledgments

The authors thank Leslie Unger, Harvard T.H. Chan School of Public Health, for technical assistance.

Funding

This work was supported by the US National Institutes of Health (grants UM1 CA186107, UM1 CA176726, R01NS046635).

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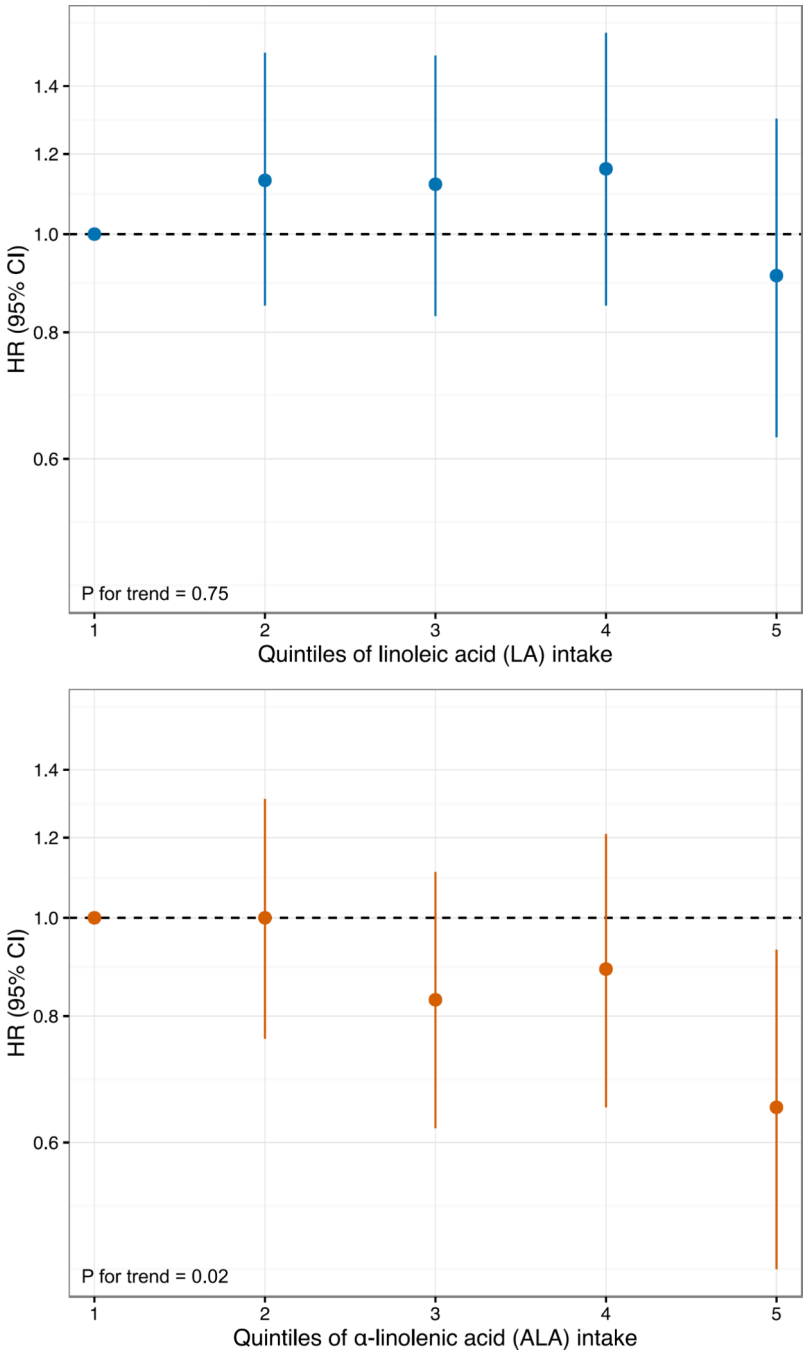

Figure 1.

The hazard ratio (HR) of multiple sclerosis according to intake of α-linolenic acid (ALA) and linoleic acid (LA) in NHS and NHS II when adjusting the intake of each fatty acid for the intake of the other fatty acid.

* The figure illustrates the association between intake of ALA, LA and MS risk when ALA and LA are included in the same model. The hazard ratios are plotted on the log scale.

Table 1

Age and Age-standardized Participant Characteristics in 1984 (NHS) and 1991 (NHSII) by Quintiles of Polyunsaturated Fatty Acid (PUFA) and α-linolenic Acid (ALA) Intake as a Percentage of Total Energy Intake.

	Total PUFA intake			ALA intake		
	Q1	Q3	Q5	Q1	Q3	Q5
NHS						
Median PUFA intake, %TEI	4.6	6.5	8.8	0.4	0.6	0.8
No. of women	16,140	16,209	16,206	16,167	16,195	16,202
Age, years, mean	51.5	50.5	50.5	50.6	50.5	51.2
Smoking, pack-years, mean	12.8	11.3	12.6	11.5	11.4	13.4
Vitamin D intake, IU/day, mean	346.5	329.3	311.0	336.3	334.8	311.2
BMI at age 18, kg/m^2, mean	21.3	21.3	21.6	21.3	21.3	21.6
Residence in North tier at age 15 y, %	36.6	36.6	37.2	33.3	37.1	40.2
Scandinavian ancestry, %	4.1	3.9	3.8	3.7	4.1	4.2
NHSII						
Median PUFA intake, %TEI	4.1	5.5	7.3	0.4	0.5	0.7
No. of women	18,869	18,917	18,898	18,876	18,902	18,907
Age, years, mean	35.6	36.1	36.9	35.7	36.1	36.8
Smoking, pack-years, mean	4.0	3.9	4.4	3.8	3.9	4.7
Vitamin D intake, IU/day, mean	430.3	377.2	331.1	396.7	382.1	350.1
BMI at age 18, kg/m^2, mean	21.0	21.2	21.6	20.9	21.2	21.6
Residence in North tier at age 15 y, %	31.4	30.2	30.6	28.7	30.4	32.8
Scandinavian ancestry, %	4.5	4.6	4.2	4.3	4.5	4.4

Values are standardized to the age distribution of the study population.

Table 2

Hazard ratio (HR) of multiple sclerosis (MS) according to quintiles of baseline intake of total polyunsaturated fatty acid (PUFA) in Nurses' Health Study (NHS, 1984–2004) and Nurses' Health Study II (NHSII, 1991–2009) as a percentage of total energy intake (TEI).

	NHS			NHSII			Pooled	
	Median PUFA %TEI	Cases/ person-years	HR (95% CI)[a]	Median PUFA %TEI	Cases/ person-years	HR (95% CI)[a]	HR (95% CI)[a]	HR (95% CI)[b]
Q1	4.6	27/295,105	Ref.	4.1	74/316,787	Ref.	Ref.	Ref.
Q2	5.7	29/299,780	1.02 (0.60–1.73)	4.9	79/318,750	1.07 (0.78–1.47)	1.06 (0.80–1.39)	1.06 (0.81–1.39)
Q3	6.5	22/302,656	0.76 (0.43–1.34)	5.5	71/319,177	0.94 (0.68–1.31)	0.89 (0.67–1.19)	0.90 (0.68–1.19)
Q4	7.3	31/302,646	1.09 (0.65–1.84)	6.2	75/319,902	1.00 (0.73–1.38)	1.03 (0.78–1.35)	1.02 (0.77–1.34)
Q5	8.8	21/302,360	0.72 (0.41–1.28)	7.3	50/319,797	0.67 (0.47–0.96)	0.68 (0.50–0.93)	0.67 (0.49–0.90)
p, trend			0.35			0.03	0.02	0.01
p, het							0.52	0.43

[a] Adjusted for age (5 year intervals) and total energy intake (continuous).

[b] Further adjusted for latitude age 15 (north, middle, south), ancestry (South European, Scandinavian, other Caucasian, other), smoking (never smoker, 1–9, 10–24, and >25 pack-years), body mass index (<18.5, 18.5–<25, 25–<30, >30) and vitamin D supplementation (none, <400 and >400 UI/day).

Table 3

Hazard ratio (HR) of multiple sclerosis (MS) according to quintiles of baseline intake of specific polyunsaturated fatty acids (PUFAs) in NHS (1984–2004) and NHSII (1991–2009) as a percentage of total energy intake.

	NHS		NHSII		Pooled	
	Median %TEI	Cases/ person-years	Median %TEI	Cases/ person-years	HR (95% CI)[a]	HR (95% CI)[b]
LA						
Q1	3.8	26/294,426	3.4	72/316,330	Ref.	Ref.
Q2	4.8	28/300,217	4.2	78/318,786	1.08 (0.82–1.42)	1.09 (0.82–1.43)
Q3	5.6	24/302,603	4.8	78/319,283	1.02 (0.77–1.34)	1.02 (0.77–1.35)
Q4	6.4	29/302,604	5.4	71/319,981	1.00 (0.76–1.33)	1.00 (0.76–1.33)
Q5	7.7	23/302,696	6.5	50/320,033	0.72 (0.53–0.97)	0.71 (0.52–0.96)
p, trend					0.03	0.02
p, het					0.40	0.31
ALA						
Q1	0.42	28/298,147	0.37	78/316,396	Ref.	Ref.
Q2	0.50	26/300,090	0.43	85/318,507	1.03 (0.79–1.34)	1.02 (0.78–1.33)
Q3	0.57	29/301,516	0.48	66/319,711	0.88 (0.66–1.16)	0.85 (0.65–1.13)
Q4	0.65	29/301,421	0.55	69/320,131	0.93 (0.71–1.23)	0.91 (0.69–1.20)
Q5	0.78	18/301,372	0.66	51/319,668	0.65 (0.48–0.88)	0.61 (0.45–0.83)
p, trend					0.005	0.001
p, het					0.39	0.34
EPA						
Q1	0.01	26/299,104	0.01	58/319,212	Ref.	Ref.
Q2	0.01	30/302,566	0.01	73/319,749	1.22 (0.92–1.64)	1.21 (0.91–1.62)
Q3	0.02	21/301,619	0.02	84/318,961	1.25 (0.93–1.67)	1.21 (0.91–1.62)
Q4	0.04	26/300,552	0.03	81/318,965	1.30 (0.97–1.73)	1.26 (0.94–1.68)
Q5	0.07	27/298,705	0.07	53/317,526	0.99 (0.73–1.35)	0.96 (0.70–1.31)
p, trend					0.53	0.41
p, het					0.30	0.50
DHA						

	NHS		NHSII		Pooled	
	Median %TEI	Cases/ person-years	Median %TEI	Cases/ person-years	HR (95% CI)[a]	HR (95% CI)[b]
Q1	0.02	28/299,742	0.02	60/319,247	Ref.	Ref.
Q2	0.04	25/301,703	0.04	78/319,273	1.18 (0.88–1.57)	1.16 (0.87–1.55)
Q3	0.06	26/300,958	0.06	82/319,470	1.24 (0.94–1.65)	1.22 (0.92–1.62)
Q4	0.08	27/301,019	0.09	68/319,353	1.11 (0.83–1.49)	1.08 (0.80–1.45)
Q5	0.14	24/299,124	0.14	61/317,070	1.00 (0.74–1.35)	0.95 (0.70–1.29)
p, trend					0.57	0.39
p, het					0.79	0.92

[a] Adjusted for age (5 year intervals) and total energy intake (continuous).

[b] Further adjusted for latitude age 15 (north, middle, south), ancestry (South European, Scandinavian, other Caucasian, other), smoking (never smoker, 1–9, 10–24, and >25 pack-years), body mass index (<18.5, 18.5–<25, 25–<30, >30), and vitamin D supplementation (none, <400 and >400 UI/day).