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Dietary Fat in Relation to Risk of Multiple Sclerosis among Two Large Cohorts of Women

Shumin M. Zhang,[1,3] Walter C. Willett,[1–3] Miguel A. Hernán,[2] Michael J. Olek,[4] and Alberto Ascherio[1,2]

Ecologic correlations suggest that higher intake of saturated fat and lower intake of polyunsaturated fat might increase the risk of multiple sclerosis (MS), but the results of case-control studies have been inconsistent. Because no prospective data are available, the authors examined these associations in two large cohorts, the Nurses' Health Study, which consisted of 92,422 women with 14 years of follow-up (1980–1994) and the Nurses' Health Study II, which consisted of 95,389 women with 4 years of follow-up (1991–1995). They documented 195 new cases of MS. The pooled multivariate relative risks comparing women in the highest quintile with those in the lowest were 1.1 (95% confidence interval: 0.7, 1.7) for total fat, 0.7 (95% confidence interval: 0.5, 1.2) for animal fat, 1.2 (95% confidence interval: 0.7, 2.1) for vegetable fat, 0.8 (95% confidence interval: 0.5, 1.3) for saturated fat, 1.1 (95% confidence interval: 0.7, 1.7) for monounsaturated fat, 1.7 (95% confidence interval 1.0, 2.8) for n-6 polyunsaturated fat, 1.3 (95% confidence interval: 0.8, 2.0) for *trans* unsaturated fat, and 0.7 (95% confidence interval: 0.4, 1.1) for cholesterol. Omega-3 fatty acids from fish were also unrelated to risk. However, the authors observed a nonsignificantly lower risk of MS for a higher intake of linolenic acid. These findings do not support relations between intakes of total fat or major specific types of fat and the risk of MS. *Am J Epidemiol* 2000;152:1056–64.

diet; fats; multiple sclerosis

It has been hypothesized that diets high in animal fat or saturated fat and low in polyunsaturated fat or fish omega-3 fatty acids increase the risk of multiple sclerosis (MS) (1–3). Suggested mechanisms include increased platelet aggregation with consequent ischemic damage to the blood-brain barrier (4–7), changes in the fatty acid composition of the myelin sheath leading to increased susceptibility to demyelinization (4, 7, 8), and effects on the formation of prostanoids, resulting in alteration of immune responses (4, 7).

This hypothesis was supported by ecologic studies in which the prevalence or rate of MS was positively correlated with animal or saturated fat intake and inversely correlated with polyunsaturated fat intake (3). However, no association between intake of animal fat or saturated fat and the risk of MS was found in most case-control studies (9–14). Because no prospective data are available, we examined the associations between intakes of total and specific types of fat and the risk of MS in two large cohorts of women, the Nurses' Health Study (NHS) and the Nurses' Health Study II (NHS II).

MATERIALS AND METHODS

Study cohort

NHS. The NHS was established in 1976, when 121,700 female registered nurses aged 30–55 years living in 11 states completed a mailed questionnaire about their medical history and health-related behaviors. Biennially, questionnaires have been sent to cohort members to update information on potential risk factors and to ascertain newly diagnosed diseases. In 1980, a 61-item semiquantitative food frequency questionnaire was included to obtain dietary information. The food frequency questionnaire was expanded to 116 items in 1984. Similar questionnaires were used to update dietary intakes in 1986 and 1990. Through May 31, 1994, the follow-up was 98 percent complete as a percentage of potential person-years. For the analyses presented here, women were excluded from the 1980 baseline population if they completed a 1980 dietary questionnaire with an implausible total energy intake (i.e., <500 or >3,500 kcal/day) or if they left more than 10 food items blank. These exclusions left a total of 92,422 women

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Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MS, multiple sclerosis; NHS, Nurses' Health Study; NHS II, Nurses' Health Study II.

[1] Department of Nutrition, Harvard School of Public Health, Boston, MA.
[2] Department of Epidemiology, Harvard School of Public Health, Boston, MA.
[3] Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA.
[4] Center for Neurological Diseases—Multiple Sclerosis Unit, Brigham and Women's Hospital and Harvard Medical School, Boston, MA.
Reprint requests to Dr. Shumin M. Zhang, Department of Nutrition, Harvard School of Public Health, 665 Huntington Avenue, Boston, MA 02115 (e-mail: Shumin.Zhang@channing.harvard.edu).

for the analyses. The study was approved by the Human Research Committee at the Brigham and Women's Hospital.

NHS II. The NHS II was established in 1989, when 116,671 female registered nurses aged 25–42 years who were living in 14 states responded to a mailed questionnaire on their lifestyle and other health- related information. Follow-up questionnaires were sent to cohort members every 2 years. The response rate was 90 percent through May 31, 1995. In 1991, a 133-item semiquantitative food frequency questionnaire was included to obtain dietary information. For the analyses presented here, women were excluded from the 1991 baseline population if they completed a 1991 dietary questionnaire with an implausible total energy intake (i.e., <800 or >4,200 kcal/day) or if they left more than 70 food items blank. These exclusions left a total of 95,389 women for the analyses. The study was approved by the Human Research Committees at the Harvard School of Public Health and the Brigham and Women's Hospital.

Dietary assessment

The validity and reliability of the food frequency questionnaires used in the NHS have been described elsewhere (15–18). For each food, a commonly used unit or portion size (i.e., one egg or one slice of bread) was specified, and women were asked how often, on average, over the previous year they had consumed that amount of each food. There were nine possible responses, ranging from "never" to "six or more times per day." Nutrient intakes were computed by multiplying the frequency response by the nutrient content of the specified portion sizes. We also asked questions about the types of fat or oil used in the preparation of foods and at the table. Values for the specific types of fat and protein in the foods were obtained from the Harvard University Food Composition Database (updated on November 22, 1993), derived from US Department of Agriculture sources (19) and supplemented with information from manufacturers. Total *trans* isomers of unsaturated fat were based upon values analyzed by Enig et al. (20) and Slover et al. (21).

We also conducted analyses by using food groups. The following food groups were defined: red meats (beef, pork, or lamb as a main dish; beef, pork, or lamb as a sandwich or mixed dish; hamburgers; hot dogs; processed meats; and bacon), poultry (chicken with skin, chicken without skin, and turkey (only for the NHS II)), processed meats (hot dogs, processed meats, and bacon), low-fat dairy products (skim or low-fat milk; yogurt; cottage or ricotta cheese; and sherbet, ice milk, and frozen yogurt (only for the NHS II)), high-fat dairy products (whole milk, ice cream, hard cheese, butter, sour cream (only for the NHS II)), and cream cheese (only for the NHS II)), and fish and other seafood. The calculations of the red meats, poultry, and processed meats took into account the gram weights of each serving. Because the 1984 NHS dietary questionnaire provided greater detail needed to calculate intakes of some specific fatty acids, the analysis of linolenic acid, arachidonic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) in relation to the risk of MS in the NHS was started in 1984.

Nutrient and food intakes calculated from the 1980 food frequency questionnaire in the NHS were reasonably correlated with those recorded by 173 Boston participants who kept diet diaries for four 1-week periods over 1 year (15–18). The Pearson correlation coefficients between energy-adjusted nutrient estimates from the 1980 food frequency questionnaire and from the four 1-week dietary records were 0.53 for total fat, 0.59 for saturated fat, 0.48 for polyunsaturated fat, and 0.61 for cholesterol (15). The Pearson correlation coefficient between the calculated dietary intake of *trans* unsaturated fatty acids and the proportion of *trans* unsaturated fatty acids in adipose tissue was 0.51 (22). Nutrient intakes calculated from the 1986 food frequency questionnaire, which consisted of 136 items in the NHS, were also reasonably correlated with those recorded by 191 participants who kept diet diaries for two 1-week periods over 1 year (18). The Pearson correlation coefficients between energy-adjusted nutrient estimates from the 1986 food frequency questionnaire and the two 1-week dietary records were 0.57 for total fat, 0.68 for saturated fat, 0.58 for monounsaturated fat, 0.48 for polyunsaturated fat, and 0.73 for cholesterol (18).

Ascertainment of MS cases

New cases of MS were identified by self-report on each biennial questionnaire from 1982 to 1994 for the NHS and from 1993 to 1995 for the NHS II. Deaths in the cohort were identified by reports from family members, the postal service, and a search of the National Death Index; we estimated that 98 percent of all deaths were identified (23). We asked women who reported MS for permission to obtain hospital records. We then sent a questionnaire to the treating neurologists and asked about the certainty of their diagnosis (definite, probable, possible, not MS), the clinical history, and the results of laboratory tests. We sent the questionnaire to each participant's internist if the neurologist did not respond to us or if a neurologist was not involved. For the analyses presented here, we included the cases that were definite and probable according to the treating physicians. As previously described, the validity of these diagnoses was confirmed by applying the Poser criteria (24) to the clinical and laboratory data provided by the treating physicians and by review of a sample of medical records (25). We documented 121 new cases of MS during 14 years of follow-up in the NHS and 74 new cases of MS during 4 years of follow-up in the NHS II.

Data analysis

Person-years of observation for each participant were calculated from the date of returning the dietary questionnaire to the date of diagnosis of MS, death, or end of follow-up, whichever came first. The end of follow-up was May 31, 1994, for the NHS and May 31, 1995, for the NHS II. For nutrient analyses, women were categorized by quintile of the baseline dietary intake of specific types of fat.

For each category of nutrient intake, we calculated the incidence rate by dividing the number of MS cases by the

TABLE 1. Relative risks of multiple sclerosis and 95% confidence intervals according to baseline quintiles of intakes of total energy, total fat, and specific types of fat in the NHS* (1980–1994) and in the NHS II* (1991–1995)

Study	Quintile of nutrient intake†									*p* for trend
	1 (RR*)	2		3		4		5		
		RR	95% CI*	RR	95% CI	RR	95% CI	RR	95% CI	
Total energy										
NHS										
No. of cases	30		27		22		18		24	
Intake (kcal)	968		1,270		1,508		1,777		2,237	
Age-adjusted RR	1.0	0.9	0.5, 1.5	0.7	0.4, 1.3	0.6	0.3, 1.1	0.8	0.5, 1.3	0.21
Multivariate RR‡	1.0	0.9	0.5, 1.5	0.7	0.4, 1.2	0.6	0.3, 1.0	0.8	0.5, 1.4	0.22
NHS II										
No. of cases	17		11		18		13		15	
Intake (kcal)	1,125		1,462		1,732		2,035		2,540	
Age-adjusted RR	1.0	0.7	0.3, 1.4	1.1	0.6, 2.1	0.8	0.4, 1.6	1.0	0.5, 1.9	0.96
Multivariate RR‡	1.0	0.6	0.3, 1.4	1.1	0.5, 2.1	0.8	0.4, 1.6	0.9	0.5, 1.8	0.92
Pooled										
Multivariate RR‡	1.0	0.8	0.5, 1.2	0.8	0.6, 1.3	0.7	0.4, 1.0	0.8	0.5, 1.3	0.33
p value for heterogeneity			0.51		0.38		0.55		0.77	0.46
Total fat										
NHS										
No. of cases	26		24		17		25		29	
Intake (% energy)	28.7		34.9		39.1		43.1		48.7	
Age-adjusted RR	1.0	0.9	0.5, 1.6	0.6	0.4, 1.2	0.9	0.5, 1.6	1.1	0.6, 1.8	0.82
Multivariate RR§	1.0	0.9	0.5, 1.6	0.6	0.3, 1.2	0.9	0.5, 1.6	1.1	0.6, 1.9	0.68
NHS II										
No. of cases	12		15		19		14		14	
Intake (% energy)	24.5		28.7		31.6		34.5		38.7	
Age-adjusted RR	1.0	1.3	0.6, 2.7	1.6	0.8, 3.2	1.2	0.5, 2.5	1.1	0.5, 2.5	0.83
Multivariate RR§	1.0	1.2	0.6, 2.6	1.6	0.8, 3.2	1.1	0.5, 2.5	1.1	0.5, 2.3	0.94
Pooled										
Multivariate RR§	1.0	1.0	0.6, 1.6	0.9	0.6, 1.5	1.0	0.6, 1.6	1.1	0.7, 1.7	0.70
p value for heterogeneity			0.51		0.07		0.70		0.96	0.89
Animal fat										
NHS										
No. of cases	25		21		30		20		25	
Intake (% energy)	18.6		24.5		28.8		33.4		40.1	
Age-adjusted RR	1.0	0.8	0.5, 1.5	1.2	0.7, 2.0	0.8	0.4, 1.4	1.0	0.6, 1.7	0.87
Multivariate RR§	1.0	0.8	0.4, 1.4	1.2	0.7, 2.0	0.8	0.4, 1.4	1.0	0.6, 1.7	0.95
NHS II										
No. of cases	18		17		16		16		7	
Intake (% energy)	11.9		15.1		17.3		19.6		23.3	
Age-adjusted RR	1.0	1.0	0.5, 1.8	0.9	0.5, 1.8	0.9	0.5, 1.7	0.4	0.2, 1.0	0.05
Multivariate RR§	1.0	0.9	0.5, 1.8	0.9	0.4, 1.7	0.9	0.4, 1.7	0.4	0.2, 0.9	0.03
Pooled										
Multivariate RR§	1.0	0.9	0.6, 1.3	1.1	0.7, 1.6	0.8	0.5, 1.3	0.7	0.5, 1.2	0.39
p value for heterogeneity			0.72		0.51		0.83		0.06	0.05

Table continues

number of person-years of follow-up. Relative risks were calculated by dividing the incidence rate in an exposure category by the corresponding rate in the reference category. Age-adjusted relative risks were calculated with the use of 5-year age categories by the Mantel-Haenszel method (26). In multivariate analysis using pooled logistic regression with 2-year time increments (27, 28), we simultaneously adjusted for age (5-year categories), geographic tier of the United States at birth (North, Middle, or South), pack-years of smoking (never, >0 to <10, ≥10 to <25, ≥25 to <45, or ≥45), length of follow-up, and total energy intake (quintiles). Age and tier at birth are risk factors for MS (7, 29),

TABLE 1. Continued

Study	Quintile of nutrient intake†									*p* for trend
	1 (RR*)	2		3		4		5		
		RR	95% CI*	RR	95% CI	RR	95% CI	RR	95% CI	
					Vegetable fat					
NHS										
No. of cases	19		26		21		38		17	
Intake (% energy)	4.0		6.7		9.0		11.7		16.2	
Age-adjusted RR	1.0	1.3	0.7, 2.4	1.0	0.6, 1.9	1.9	1.1, 3.3	0.8	0.4, 1.6	0.99
Multivariate RR§	1.0	1.3	0.7, 2.4	1.1	0.6, 2.0	2.0	1.1, 3.4	0.9	0.5, 1.7	0.92
NHS II										
No. of cases	7		16		21		14		16	
Intake (% energy)	9.3		11.8		13.8		15.8		19.3	
Age-adjusted RR	1.0	2.3	0.9, 5.5	3.0	1.3, 7.0	1.9	0.8, 4.7	2.1	0.9, 5.1	0.24
Multivariate RR§	1.0	2.3	1.0, 5.6	3.0	1.3, 7.1	2.0	0.8, 5.0	2.2	0.9, 5.4	0.23
Pooled										
Multivariate RR§	1.0	1.6	1.0, 2.6	1.5	0.9, 2.6	2.0	1.2, 3.2	1.2	0.7, 2.1	0.46
p value for heterogeneity			0.32		0.06		0.96		0.10	0.35
					Saturated fat					
NHS										
No. of cases	25		22		20		28		26	
Intake (% energy)	11.0		13.7		15.6		17.4		20.1	
Age-adjusted RR	1.0	0.8	0.5, 1.5	0.8	0.4, 1.4	1.1	0.6, 1.8	1.0	0.6, 1.7	0.76
Multivariate RR§	1.0	0.9	0.5, 1.5	0.8	0.4, 1.4	1.1	0.6, 1.9	1.0	0.6, 1.8	0.65
NHS II										
No. of cases	17		18		16		14		9	
Intake (% energy)	8.2		10.0		11.1		12.3		14.3	
Age-adjusted RR	1.0	1.1	0.6, 2.1	0.9	0.5, 1.9	0.8	0.4, 1.7	0.6	0.2, 1.2	0.11
Multivariate RR§	1.0	1.0	0.5, 2.0	0.9	0.5, 1.8	0.8	0.4, 1.6	0.5	0.2, 1.1	0.07
Pooled										
Multivariate RR§	1.0	0.9	0.6, 1.4	0.8	0.5, 1.3	1.0	0.6, 1.5	0.8	0.5, 1.3	0.67
p value for heterogeneity			0.65		0.73		0.49		0.14	0.07
					Monounsaturated fat					
NHS										
No. of cases	26		24		16		25		30	
Intake (% energy)	11.1		13.9		15.9		17.9		20.8	
Age-adjusted RR	1.0	0.9	0.5, 1.5	0.6	0.3, 1.1	0.9	0.5, 1.6	1.1	0.7, 1.9	0.67
Multivariate RR§	1.0	0.9	0.5, 1.6	0.6	0.3, 1.1	0.9	0.5, 1.6	1.2	0.7, 2.0	0.53
NHS II										
No. of cases	11		13		21		17		12	
Intake (% energy)	8.9		10.7		12.0		13.2		15.1	
Age-adjusted RR	1.0	1.2	0.5, 2.6	1.9	0.9, 4.0	1.5	0.7, 3.3	1.1	0.5, 2.4	0.70
Multivariate RR§	1.0	1.2	0.5, 2.6	1.9	0.9, 3.9	1.5	0.7, 3.2	1.0	0.5, 2.3	0.78
Pooled										
Multivariate RR§	1.0	1.0	0.6, 1.5	1.0	0.6, 1.6	1.1	0.7, 1.7	1.1	0.7, 1.7	0.49
p value for heterogeneity			0.60		0.02		0.34		0.82	0.97

Table continues

and smoking was associated with the risk of MS in these two cohorts. We controlled for total energy to control for confounding and to reduce measurement errors due to general over- or underreporting of food items (18). Log relative risks from the two studies were pooled by the inverse of their variances. Tests for trend were conducted by using the median values for quintiles of nutrient intake as a continuous variable for nutrient analyses or by using the frequency responses in servings per day as a continuous variable for food analyses.

In separate analyses that incorporated repeated dietary measurements, the incidence of MS was related to the cumulative updated average intake from all available dietary questionnaires up to the start of each 2-year follow-

TABLE 1. Continued

Study	Quintile of nutrient intake†									*p* for trend
	1 (RR*)	2		3		4		5		
		RR	95% CI*	RR	95% CI	RR	95% CI	RR	95% CI	
					n-*6 Polyunsaturated fat*					
NHS										
No. of cases	15		26		24		28		28	
Intake (% energy)	2.5		3.4		4.1		4.8		6.2	
Age-adjusted RR	1.0	1.7	0.9, 3.2	1.5	0.8, 2.8	1.8	1.0, 3.4	1.7	0.9, 3.3	0.16
Multivariate RR§	1.0	1.7	0.9, 3.1	1.5	0.8, 2.9	1.7	0.9, 3.3	1.7	0.9, 3.1	0.20
NHS II										
No. of cases	7		18		14		22		13	
Intake (% energy)	3.4		4.2		4.8		5.4		6.5	
Age-adjusted RR	1.0	2.5	1.1, 6.1	1.9	0.8, 4.7	2.9	1.2, 6.7	1.7	0.7, 4.1	0.32
Multivariate RR§	1.0	2.6	1.1, 6.2	2.0	0.8, 4.9	3.1	1.3, 7.3	1.8	0.7, 4.5	0.32
Pooled										
Multivariate RR§	1.0	1.9	1.2, 3.2	1.7	1.0, 2.8	2.1	1.3, 3.5	1.7	1.0, 2.8	0.10
p value for heterogeneity			0.42		0.62		0.28		0.90	0.90
					Trans *unsaturated fat*					
NHS										
No. of cases	19		23		27		26		26	
Intake (% energy)	1.3		1.8		2.2		2.6		3.2	
Age-adjusted RR	1.0	1.2	0.6, 2.1	1.4	0.8, 2.4	1.3	0.7, 2.3	1.3	0.7, 2.3	0.38
Multivariate RR§	1.0	1.2	0.7, 2.2	1.4	0.8, 2.5	1.4	0.7, 2.5	1.4	0.7, 2.5	0.31
NHS II										
No. of cases	12		17		14		17		14	
Intake (% energy)	0.9		1.3		1.5		1.9		2.4	
Age-adjusted RR	1.0	1.4	0.7, 3.0	1.2	0.5, 2.5	1.4	0.7, 3.0	1.2	0.6, 2.5	0.73
Multivariate RR§	1.0	1.4	0.7, 2.9	1.2	0.5, 2.5	1.4	0.7, 3.0	1.2	0.5, 2.5	0.75
Pooled										
Multivariate RR§	1.0	1.3	0.8, 2.0	1.3	0.8, 2.1	1.4	0.9, 2.2	1.3	0.8, 2.0	0.30
p value for heterogeneity			0.75		0.69		0.93		0.76	0.79
					Cholesterol					
NHS										
No. of cases	27		23		23		26		22	
Intake (% energy)	133.8		172.3		201.8		234.7		297.1	
Age-adjusted RR	1.0	0.8	0.5, 1.5	0.8	0.5, 1.5	1.0	0.6, 1.6	0.8	0.5, 1.4	0.64
Multivariate RR§	1.0	0.9	0.5, 1.5	0.9	0.5, 1.5	1.0	0.6, 1.6	0.8	0.5, 1.4	0.56
NHS II										
No. of cases	20		13		14		16		11	
Intake (% energy)	92.2		114.9		131.7		150.4		182.6	
Age-adjusted RR	1.0	0.7	0.3, 1.3	0.7	0.4, 1.4	0.8	0.4, 1.5	0.6	0.3, 1.2	0.17
Multivariate RR§	1.0	0.7	0.3, 1.3	0.7	0.4, 1.4	0.8	0.4, 1.5	0.5	0.3, 1.1	0.16
Pooled										
Multivariate RR§	1.0	0.8	0.5, 1.2	0.8	0.5, 1.2	0.9	0.6, 1.4	0.7	0.4, 1.1	0.27
p value for heterogeneity			0.56		0.63		0.66		0.39	0.29

* NHS, Nurses' Health Study; NHS II, Nurses' Health Study II; RR, relative risk; CI, confidence interval.

† Values for intake are medians for each quintile of nutrient intake.

‡ The multivariate models were adjusted for age (5-year categories), tier at birth (North, Middle, or South), and pack-years of smoking (never, >0–<10, ≥10–<25, ≥25–<45, or ≥45).

§ The multivariate models were adjusted for age (5-year categories), tier at birth (North, Middle, or South), pack-years of smoking (never, >0–<10, ≥10–<25, ≥25–<45, or ≥45 pack-years), and total energy (quintiles).

up interval or to the most recent intake at the start of each 2-year follow-up interval (30). Indicator variables were used to denote any time period for which a questionnaire was not available. For all relative risks, we calculated 95 percent confidence intervals. All *p* values were two-tailed.

TABLE 2. Multivariate relative risks of multiple sclerosis and 95% confidence intervals by intakes of total energy, total fat, and specific types of fat as continuous variables in different models in the Nurses' Health Study, 1980–1994

Nutrient increment per day	Baseline diet (1980) (121 cases)		Cumulative average diet (121 cases)		Most recent diet (121 cases)	
	Multivariate RR*,†	95% CI*	Multivariate RR†	95% CI	Multivariate RR†	95% CI
Total energy (400 kcal‡)	1.0	0.8, 1.1	0.9	0.8, 1.1	1.0	0.8, 1.1
Total fat (10% of energy)	1.0	0.8, 1.3	0.9	0.7, 1.2	0.8	0.6, 1.0
Animal fat (10% of energy)	1.0	0.8, 1.2	1.0	0.7, 1.3	0.9	0.6, 1.1
Vegetable fat (10% of energy)	1.0	0.7, 1.4	0.8	0.5, 1.3	0.9	0.6, 1.3
Saturated fat (10% of energy)	1.0	0.6, 1.7	0.9	0.5, 1.7	0.7	0.4, 1.2
Monounsaturated fat (10% of energy)	1.1	0.7, 1.8	1.1	0.6, 2.0	0.9	0.5, 1.7
n-6 Polyunsaturated fat (5% of energy)	1.2	0.7, 2.2	0.9	0.5, 1.8	0.8	0.4, 1.5
Trans unsaturated fat (2% of energy)	1.2	0.8, 2.0	1.2	0.6, 2.1	1.1	0.6, 2.0
Cholesterol (200 mg/1,000 kcal)	0.9	0.6, 1.5	0.6	0.3, 1.3	0.5	0.3, 1.1

* RR, relative risk; CI, confidence interval.

† Values were adjusted for age (5-year categories), total energy (continuous), tier at birth (North, Middle, or South), and pack-years of smoking (never, >0–<10, ≥10–<25, ≥25–<45, or ≥45 pack-years).

‡ To convert kilocalories to joules, multiply by 4.184.

RESULTS

Table 1 presents the associations between the intakes of total energy, total fat, and specific types of fat, and the risk of MS. Intakes of total energy, total fat, animal fat, vegetable fat, saturated fat, monounsaturated fat, n-6 polyunsaturated fat, *trans* unsaturated fat, and cholesterol were not significantly associated with the risk of MS. In the pooled multivariate analyses controlling for age and other nondietary risk factors, none of the tests for trend across quintiles approached statistical significance. Animal fat intake had a significant inverse association with the risk of MS in the NHS II, but not in the NHS. However, the tests for heterogeneity between the two studies were not significant for comparisons of relative risks in the highest quintile, suggesting that the pooled relative risks are an appropriate summary of the data for the nutrients in table 1. Additional adjustment for protein and alcohol intake did not appreciably change the results.

To address the possibility that women might have changed their diet due to clinical symptoms of MS before they were diagnosed, we examined dietary intake in 1980 in relation to incidence of MS between 1984 and 1994 for the NHS ($n = 92$ cases) and dietary intake in 1991 in relation to incidence of MS between 1993 and 1995 for the NHS II ($n = 41$ cases); the estimates were similar (data not shown). The multiple measures of diet in the NHS provided an opportunity to examine various temporal relations between diet and the risk of MS (30). Neither the cumulative average intakes nor the most recent intakes was significantly associated with the risk of MS (table 2). In addition, the results did not appreciably change when we limited analyses to women who were less than age 50 years in the NHS.

Table 3 presents the relative risks for MS with oleic acid, linolenic acid, arachidonic acid, and omega-3 fatty acids. Linolenic acid intake was associated with a nonsignificantly

TABLE 3. Multivariate relative risks of multiple sclerosis and 95% confidence intervals according to intakes of oleic acid, linolenic acid, arachidonic acid, and fish omega-3 fatty acids

Nutrient increment per day	NHS* (80 cases)		NHS II* (74 cases)		Pooled (154 cases)	
	Multivariate RR*,†	95% CI*	Multivariate RR†	95% CI	Multivariate RR†	95% CI
Oleic acid (10% of energy)	0.5	0.2, 1.2	1.1	0.4, 2.9	0.7	0.4, 1.4
Linolenic acid (1.0% of energy)	0.3	0.1, 1.5	0.3	0.1, 2.2	0.3	0.1, 1.1
Arachidonic acid (0.05% of energy)	0.9	0.7, 1.4	1.0	0.7, 1.3	0.9	0.7, 1.2
Fish omega-3 fatty acids (0.1% of energy)	1.1	0.8, 1.3	1.1	0.9, 1.4	1.1	0.9, 1.3
Eicosapentaenoic acid (0.1% of energy)	1.1	0.6, 2.1	1.4	0.8, 2.3	1.3	0.9, 1.9
Docosahexaenoic acid (0.1% of energy)	1.1	0.8, 1.6	1.2	0.9, 1.6	1.1	0.9, 1.5

* NHS, Nurses' Health Study, dietary assessment in 1984, follow-up in 1984–1994; NHS II, Nurses' Health Study, dietary assessment in 1991, follow-up in 1991–1995; RR, relative risk; CI, confidence interval.

† Values were adjusted for age (5-year categories), total energy (continuous), tier at birth (North, Middle, or South), and pack-years of smoking (never, >0–<10, ≥10–<25, ≥25–<45, or ≥45 pack-years).

TABLE 4. Relative risks of multiple sclerosis and 95% confidence intervals according to intakes of food groups in the NHS* (1990–1994) and the NHS II* (1991–1995)

Study	Categories																		*p* for trend
	<1/week			1–2.9/week			3–4.9/week			5–6.9/week			1/day			≥2/day			
	No.	Multivariate RR*,†	95% CI*	No.	Multivariate RR†	95% CI	No.	Multivariate RR†	95% CI	No.	Multivariate RR†	95% CI	No.	Multivariate RR†	95% CI	No.	Multivariate RR†	95% CI	
Low-fat dairy products																			
NHS	40	1.0		24	0.9	0.6, 1.5	9	0.7	0.3, 1.4	6	0.6	0.2, 1.3	25	0.8	0.5, 1.3	17	0.9	0.5, 1.6	0.49
NHS II	13	1.0		10	0.7	0.3, 1.5	11	0.8	0.4, 1.8	3	0.3	0.1, 1.0	19	0.6	0.3, 1.1	18	0.6	0.3, 1.2	0.26
Pooled		1.0			0.8	0.5, 1.3		0.7	0.4, 1.2		0.4	0.2, 0.9		0.7	0.5, 1.0		0.7	0.5, 1.2	0.21
p for heterogeneity					0.52			0.74			0.36			0.50			0.39		0.65
High-fat dairy products																			
NHS				24	1.0		19	1.1	0.6, 2.0	16	1.1	0.6, 2.1	35	1.2	0.7, 2.0	27	1.1	0.6, 2.0	0.74
NHS II				28	1.0		12	0.6	0.3, 1.1	13	0.9	0.5, 1.8	15	0.5	0.3, 1.1	6	0.4	0.2, 1.0	0.05
Pooled								0.8	0.5, 1.3		1.0	0.6, 1.6		0.9	0.6, 1.3		0.8	0.5, 1.4	0.43
p for heterogeneity								0.15			0.64			0.08			0.07		0.06
Fish and other seafood																			
NHS	57	1.0		45	0.9	0.6, 1.4	19	0.9	0.5, 1.5										0.70
NHS II	24	1.0		32	1.3	0.7, 2.1	18	0.9	0.5, 1.7										0.48
Pooled		1.0			1.0	0.8, 1.4		0.9	0.6, 1.3										0.45
p for heterogeneity					0.37			0.99											0.79

	Quintile of food intake														
	1			2			3			4			5		
	No.	Multivariate RR†	95% CI	No.	Multivariate RR†	95% CI	No.	Multivariate RR†	95% CI	No.	Multivariate RR†	95% CI	No.	Multivariate RR†	95% CI
Red meats															
NHS	27	1.0		25	0.9	0.5, 1.6	20	0.8	0.4, 1.4	27	1.1	0.6, 2.0	22	1.0	0.5, 1.9
NHS II	10	1.0		18	1.8	0.8, 3.9	12	1.2	0.5, 2.8	24	2.4	1.1, 5.2	10	1.0	0.4, 2.6
Pooled		1.0			1.2	0.7, 1.8		0.9	0.5, 1.5		1.5	0.9, 2.4		1.0	0.6, 1.7
p for heterogeneity					0.16			0.40			0.11			0.91	
Poultry															
NHS	21	1.0		48	1.0	0.6, 1.7	6	0.7	0.3, 1.6	5	0.5	0.2, 1.2	41	1.2	0.7, 2.1
NHS II	16	1.0		12	0.6	0.3, 1.3	19	0.9	0.5, 1.8	18	1.2	0.6, 2.4	9	0.6	0.3, 1.4
Pooled		1.0			0.9	0.6, 1.3		0.8	0.5, 1.4		0.9	0.5, 1.5		1.0	0.6, 1.6
p for hetergenity					0.29			0.54			0.12			0.15	
Processed meats															
NHS	21	1.0		24	1.1	0.6, 2.0	29	1.0	0.6, 1.8	26	1.1	0.6, 1.9	21	0.8	0.4, 1.6
NHS II	9	1.0		18	1.7	0.8, 3.8	19	1.9	0.8, 4.1	14	1.8	0.8, 4.3	14	1.5	0.6, 3.6
Pooled		1.0			1.3	0.8, 2.1		1.2	0.8, 2.0		1.3	0.8, 2.1		1.0	0.6, 1.7
p for heterogeneity					0.41			0.23			0.32			0.30	

* NHS, Nurses' Health Study; NHS II, Nurses' Health Study II; RR, relative risk; CI, confidence interval.
† Values were adjusted for age (5-year categories), total energy (quintiles), tier at birth (North, Middle, or South), and pack-years of smoking (never, >0–<10, ≥10–<25, ≥25–<45, or ≥45 pack-years).

lower risk of MS in both cohorts; the pooled relative risk was 0.3 (95 percent confidence interval: 0.1, 1.1) for an increment of 1.0 percent of energy. Intakes of oleic acid, arachidonic acid, omega-3 fatty acids, EPA, and DHA were unrelated to risk of MS. The associations between the food groups high in fat and the risk of MS are presented in table 4. Intakes of dairy products, fish or other seafood, red meats, poultry, and processed meats were also not significantly associated with the risk of MS.

DISCUSSION

In these two large cohorts of women, we found no evidence that higher intake of saturated fat or lower intakes of polyunsaturated fat and fish omega-3 fatty acids were associated with an increased risk of MS. Intakes of dairy products, fish, red meats, poultry, and processed meats were also unrelated to risk of MS.

Because of the prospective design, recall or selection biases are unlikely in this study, and the high follow-up rates minimize the concern that differential follow-up rates have effected our results. The estimates of total fat and specific types of fat derived from the dietary questionnaires used in this study reasonably reflect long-term intakes of study subjects (15–18). The fact that they have predicted risk of coronary heart disease in the NHS (31) further supports their validity.

Symptoms of MS might have caused some women to reduce their saturated fat intake (or increase their polyunsaturated fat intake) before diagnosis. However, the results relating intakes of nutrients at baseline to incidence of MS 2 or 4 years later did not support this explanation. Finally, confounding by unknown variables cannot be excluded, but it seems unlikely because adjustment for the risk factors for MS, including age, latitude at birth, and smoking had minimal effect on the relative risks.

Findings from the population-based case-control studies that have examined dietary fat intake and foods contributing to dietary fat in relation to the risk of MS have been inconsistent; most of them suggest a null association with intakes of fat, meat, and dairy products (9–13). In the first case-control study of diet and MS, no significant difference in milk consumption was seen between 112 cases and 123 population-based controls (9). Contrary to expectations, butter consumption was lower among patients than among controls, but the difference was not significant (9). In another study that included 241 MS patients, which constituted 92 percent of all Israeli MS patients at that time, no significant differences between cases and controls were found for intakes of dairy foods, all types of meat and fish, eggs, and nuts (10). In a Polish study, MS patients had lower fat and meat consumption compared with the controls, but they had a similar milk consumption (11). In a study in New Zealand, a higher percentage of MS patients than of controls had stopped drinking milk by age 15 years (12). Intakes of meat, fat, milk, dairy products, and fish were unrelated to the prevalence of MS in a French investigation, although MS patients consumed more delicatessen foods than did controls (13). In an Italian study that used both hospital and population controls, an increased risk of MS was associated with higher consumption of butter, lard, and horse meat only before age 15 years and with higher intake of eggs after age 15 years (32). Finally, a study that included 197 cases of MS and 202 normal controls in Canada revealed a twofold increase in risk of MS for an increment of 33 g/day of animal fat (33). In this case-control study, saturated fat was nonsignificantly associated with a higher risk of MS, and linoleic acid was associated with a nonsignificantly lower risk (33). Hospital-based case-control studies also yielded mixed results (14, 34, 35). The weaknesses of case-control studies in addressing diet-disease hypotheses are well documented (18), but overall results of these investigations do not support an association between dietary fat and MS incidence.

Findings from three randomized clinical trials that have examined the effectiveness of linoleic acid in the treatment of MS in individuals with a remitting-relapsing course have been inconclusive (36–38), although a reanalysis of pooled data concluded that the intervention was beneficial among patients with minimal or no disability at entry (39). The effectiveness of long-chain omega-3 fatty acids on the treatment of MS was tested in a double-blind clinical trial among 312 patients with a diet low in saturated fat and high in polyunsaturated fat (40). Supplementation with fish oils providing 1.71 g/day of EPA (20:5, n-3) and 1.14 g/day of DHA (22:6, n-3) nonsignificantly reduced severity and duration of relapses at the end of 2 years of intervention (40). High doses of fish oils were reported to be beneficial in an uncontrolled study (41). Although the levels of intake were much lower, consumption of omega-3 fatty acids from fish including EPA and DHA was unrelated to risk of MS in this study.

In summary, in these prospective investigations, we found no evidence that the amount and type of dietary fat affect the risk of developing MS.

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