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Retina

Association Between Fatty Acid Intakes and Age-Related Macular Degeneration in a Japanese Population: JPHC-NEXT Eye Study

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Purpose: To determine the associations between fatty acid intakes and the prevalence of age-related macular degeneration (AMD) under a population-based cross-sectional study.

Methods: Residents of Chikusei City aged ≥40 years underwent systemic and eye screening. AMD was graded according to a modified version of the Age-Related Eye Disease Study classification. Dietary intake was assessed using a food frequency questionnaire and was adjusted for total energy intake.

Results: Altogether, 10,788 eyes of 5394 participants, 2116 men (mean [standard deviation (SD)] age, 62.4 [9.4] years) and 3278 women (60.6 [9.5] years), were included. The mean daily total fat intakes were 52.8 g and 59.0 g in men and women, respectively. After adjustments for potential confounders, saturated fatty acid (SFA) intake was inversely associated with the prevalence of any AMD in men (for each energy-adjusted 1-SD increase: odds ratio [OR], 0.86; 95% confidence interval [CI], 0.74–1.00). Significant trends were found for decreasing odds ratios of AMD with increasing SFA, monounsaturated fatty acid (MUFA), and polyunsaturated fatty acid (PUFA) intake (P for trend = 0.02, 0.04, and 0.04, respectively). In women, only a significant association was observed between the second quartile of linolenic acid intake and the prevalence of any AMD (OR, 0.78; 95% CI, 0.62–0.99).

Conclusions: We found an inverse association of SFA intake and a weak inverse association of MUFA and PUFA intakes with the prevalence of any AMD in a Japanese population.

Translational Relevance: Adequate fatty acid intake may be necessary to prevent or decelerate AMD.

Introduction

Age-related macular degeneration (AMD) is a leading cause of vision loss among elderly people worldwide,[1] including Asians.[2] Asians currently constitute 60% of the world's population and are likely to be the greatest contributors to the global prevalence of AMD by 2040.[3] Therefore, AMD is becoming an increasingly important health care problem in Asia. Understanding the pathogenesis of AMD, including the influence of genetics and lifestyle, is essential for preventing the development of late AMD and the consequent visual disturbance.

Epidemiologic studies and meta-analyses have suggested that n–3 polyunsaturated fatty acid (PUFA) intake and fish intake can reduce the risks of early and late AMD.[4–9] The Age-Related Eye Disease Study (AREDS), a large multicenter clinical trial, found that participants with the highest n–3 PUFA intake were 30% less likely to develop advanced AMD than those with the lowest intake.[10] However, in AREDS2, the addition of n–3 PUFAs to the AREDS supplement did not further reduce the risk of progression to advanced AMD.[11] The Mediterranean diet, which is high in plant-based foods, such as fruit, grain, nuts, seeds, and olive oil, and low in red meat and dairy products,[12] has been shown to be inversely associated with AMD.[13] Olive oil contains substantial amounts of monounsaturated fatty acids (MUFAs), and nuts additionally contain n–6 PUFAs.[14] However, studies examining the association of AMD with MUFA[5,8,15–17] or n–6 PUFA[6,17,18] intake have been limited and conflicting. Similarly, studies examining the association between saturated fatty acid (SFA) intake and AMD have been limited, with inconsistent results.[4,5,8,19,20] In short, associations of fatty acid intakes and AMD risks have not yet been comprehensively investigated, and the results of previous studies are not always consistent.[4–9,15–20]

Racial and ethnic differences in AMD have been recognized between Western and Asian populations.[21,22] For example, polypoidal choroidal vasculopathy is more common in Asians than in white populations,[21] whereas geographic atrophy is more frequent in white populations than in Asians.[22] In addition, genotypes and dietary patterns also differ between Western and Asian populations.[23,24] These differences may partly explain the discrepancies among studies investigating the associations between fatty acid intakes and AMD. Although the associations between dietary fatty acid intakes and AMD have been extensively studied in Western populations, few such studies have been conducted among Asians.[25] Therefore, we aimed to comprehensively examine the cross-sectional associations of dietary fatty acid intakes with the prevalence of AMD in a large Japanese cohort from the Japan Public Health Center-based Prospective Study for the Next Generation (JPHC-NEXT) Eye Study.

Methods

Study Population

The JPHC-NEXT Eye Study is an ancillary study conducted under the protocol of the JPHC-NEXT Study.[26] In Chikusei City, Ibaraki Prefecture, residents aged ≥40 years underwent a systemic and ophthalmologic survey. The present study involved 7090 individuals who had participated in the survey between 2013 and 2015, and 5691 (80.3%) had completed the food frequency questionnaire (FFQ). After excluding 14 participants owing to missing fundus images or suboptimal fundus image quality (i.e., poor focus, eyelash artifacts, or uneven illumination) and 110 men and 173 women at the extreme high and low 2.5% of energy intake by sex, the remaining 5394 participants (10,788 eyes) were included in the analysis (2116 men and 3278 women).

This study was conducted in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects, Japan, and approved by the Medical Ethics Committees of the School of Medicine, Keio University, Tokyo; the University of Tsukuba, Ibaraki; the University of Osaka, Osaka; and the National Cancer Center, Tokyo. Written informed consent was obtained from all participants.

Data and Sample Collection

Nonmydriatic fundus photographs of both eyes were obtained using a 45° nonmydriatic fundus camera (Canon CR-1; Canon Inc., Tokyo, Japan) as part of the ocular examinations. The images were centered on the optic disc and macula.

Blood pressure (BP) was measured twice on the right upper arm while the participant was seated. The mean value was used for analysis. The body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Blood samples were collected to measure serum glucose (fasting or nonfasting), glycated hemoglobin (HbA1c) (%), total cholesterol (TC) (mmol/L), high-density lipoprotein cholesterol (HDL-C) (mmol/L), low-density lipoprotein cholesterol (LDL-C) (mmol/L), and triglyceride (TG) (mmol/L) levels. The nonfasting state was <8 hours

after the last meal. Hypertension was defined as the use of an antihypertensive medication, or a systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg.[27] Diabetes was defined as the use of an antidiabetic medication, or a fasting serum glucose ≥7.0 mmol/L or nonfasting serum glucose ≥11.1 mmol/L, or HbA1c ≥6.5% (National Glycohemoglobin Standardization Program).[28] Dyslipidemia was defined as the use of a lipid-lowering medication, LDL-C ≥3.6 mmol/L or HDL-C <1.0 mmol/L, or TG ≥1.7 mmol/L.[29]

Grading of Fundus Photographs for AMD

Nonmydriatic fundus photographs of both eyes of each participant were evaluated to determine whether their quality was sufficient for the grading of AMD lesions. The prevalence of AMD was determined by two blinded ophthalmologists each year (TK, HT, EY, YK, KM, and HK); disagreements regarding diagnosis were resolved through diagnosis by a third ophthalmologist (YT or NO). Photograph grading for the severity of AMD classification was performed according to a modified version of the protocol used in the AREDS,[30] which was based on fundus lesions assessed within two disc diameters of the fovea and was defined as follows: grade 1 (normal), two or fewer hard drusen (diameter <63 µm); grade 2 (early AMD), three or more hard drusen and/or two or fewer soft drusen (diameter ≥63 but <125 µm) and/or a retinal pigment epithelium abnormality; grade 3 (intermediate AMD), any large drusen (diameter ≥125 µm) and/or three or more soft drusen and/or geographic atrophy within the grid but none at the center of the macula; and grade 4 (late AMD), neovascular AMD and/or geographic atrophy in the central subfield. Neovascular AMD was defined as the presence of fibrovascular/serous pigment epithelial detachment, serous (or hemorrhagic) sensory retinal detachment, subretinal/subretinal pigment epithelial hemorrhage, subretinal fibrous tissue (or fibrin), or photocoagulation for AMD.[30] Geographic atrophy was defined as a sharply demarcated, usually circular, zone of partial or complete depigmentation of the retinal pigment epithelium, typically with exposure of the underlying large choroidal blood vessels.[30]

Dietary Assessment

Dietary intake was assessed using a long-form FFQ for the JPHC-NEXT study.[31] The long-form FFQ comprises 172 food and beverage items and nine frequency categories, ranging from almost never to seven or more times per day, or to ≥10 glasses per day for beverages. The questionnaire involves questions concerning the usual consumption of the listed foods and beverages during the previous year.[31] The nutrients including fatty acids that each item contained were estimated by the Japan Food Table Fifth version.[32] Then, the fatty acid intakes were calculated by multiplying the frequency scores and estimated SFA for each food and summing across all items. All dietary variables were adjusted for energy intake using the nutrient residual model.[33] The validity of the FFQ in the assessment of the fatty acid intakes was confirmed using 12-day weighed food records (12d-WFR). Spearman's correlation coefficients between the energy-adjusted intake of the fatty acids calculated from the FFQ and from dietary records ranged from 0.38 (for n–3 PUFA) to 0.55 (for MUFA) for men and from 0.21 (for MUFA) to 0.46 (for SFA) for women, respectively,[31] indicating moderate validity for the fatty acids. Percentage differences in the fatty acid intakes with the 12d-WFR varied from −11% (for n–3 PUFA) to +5% (for n–6 PUFA) in men and +16% (for n–3 PUFA) to +26% (for SFA) in women.

Statistical Analysis

All analyses were performed separately for men and women. Dietary intakes of fatty acids and other nutrients were adjusted for total energy intake using the residual method.[33] Then, energy-adjusted fatty acid intakes, intakes of SFA and PUFA, were categorized into quartiles and calculated with the lowest quartile as the reference group. Baseline participant characteristics were summarized and stratified according to quartiles of intakes of SFAs and PUFAs (Table 1) and the severity of AMD classification (Supplementary Table S1). Differences between the lowest quartile and other quartiles were tested using the Wilcoxon rank-sum test for continuous variables and the χ^2 test for categorical variables. The associations between energy-adjusted fatty acid intakes (as continuous variables and quartiles) and the prevalence of any AMD were assessed using generalized estimating equations (GEEs) with PROC GENMOD in SAS software (SAS Institute Inc., Cary, NC, USA), considering the nested structure of the data such as both eyes of a participant, and are expressed as odds ratios (ORs) with 95% confidence intervals (CIs) (Table 2). The associations between energy-adjusted fatty acid intakes (as continuous variables) and severity of AMD classification were assessed by using GEEs and are expressed as ORs with 95% CIs per 1–standard deviation (SD) increase (Supplementary Table S2). The first model was adjusted for age. The second model was further adjusted for BMI, smoking status (current or noncurrent smokers), hyperten-

Table 1. Baseline Characteristics Stratified by Quartiles of Intakes of SFA and PUFA

	SFA (Quartiles of Intake)					PUFA (Quartiles of Intake)				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4		Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Variable	No. (%) or Mean (SD)				*P* Value	No. (%) or Mean (SD)				*P* Value
Men										
Age, y	62.3 (9.1)	62.4 (9.1)	62.7 (9.2)	62.0 (10.3)	0.78	60.8 (9.8)	62.5 (9.1)	62.9 (9.1)	63.3 (9.6)	**<0.0001**
Body mass index, kg/m^2	23.7 (3.1)	24.0 (3.0)	24.0 (3.4)	23.9 (3.2)	0.27	23.8 (3.1)	23.7 (3.1)	24.2 (3.1)	24.0 (3.4)	0.13
Smoking status, % current	142 (26.8)	136 (25.7)	116 (21.9)	124 (23.4)	0.24	154 (29.1)	139 (26.3)	109 (20.6)	116 (21.9)	**0.004**
Hypertension	298 (56.3)	292 (55.2)	262 (49.5)	240 (45.4)	**0.0008**	273 (51.6)	264 (49.9)	291 (55.0)	264 (49.9)	0.30
Dyslipidemia	306 (57.8)	323 (61.1)	341 (64.5)	334 (63.1)	0.13	319 (60.3)	322 (60.9)	339 (64.1)	324 (61.3)	0.59
Diabetes	95 (18.0)	82 (15.5)	93 (17.6)	71 (13.4)	0.16	80 (15.1)	70 (13.2)	94 (17.8)	97 (18.3)	0.08
Total cholesterol, mmol/L	5.1 (0.9)	5.2 (0.8)	5.2 (0.9)	5.3 (0.9)	**0.0004**	5.2 (0.9)	5.2 (0.9)	5.2 (0.9)	5.2 (0.9)	0.78
HDL cholesterol, mmol/L	1.5 (0.4)	1.5 (0.4)	1.5 (0.4)	1.5 (0.3)	0.05	1.5 (0.4)	1.5 (0.4)	1.5 (0.4)	1.5 (0.3)	0.18
LDL cholesterol, mmol/L	3.0 (0.8)	3.1 (0.8)	3.2 (0.8)	3.3 (0.8)	**<0.0001**	3.1 (0.8)	3.1 (0.8)	3.2 (0.8)	3.2 (0.8)	0.06
Triglycerides, mmol/L	1.5 (1.0)	1.4 (0.9)	1.4 (0.9)	1.4 (0.9)	0.27	1.5 (1.0)	1.5 (1.0)	1.4 (0.8)	1.3 (0.8)	0.06
Total calories, kcal	2328.9 (757.0)	2398.7 (758.5)	2384.3 (724.2)	2267.1 (738.6)	**0.01**	2325.1 (812.3)	2376.5 (729.4)	2389.1 (716.1)	2288.4 (719.7)	**0.03**
Total fat, g	35.0 (8.7)	48.0 (6.9)	56.6 (7.6)	71.6 (12.6)	**<0.0001**	38.6 (13.1)	49.4 (10.9)	56.3 (10.6)	67.0 (14.7)	**<0.0001**
SFA, g	10.0 (2.3)	14.8 (1.1)	18.9 (1.4)	26.7 (5.0)	**<0.0001**	14.3 (7.4)	17.0 (5.9)	18.5 (5.5)	20.6 (6.6)	**<0.0001**
MUFA, g	14.2 (4.0)	20.0 (3.8)	23.6 (4.3)	29.9 (7.6)	**<0.0001**	15.7 (5.8)	20.6 (5.6)	23.6 (5.6)	27.9 (7.8)	**<0.0001**
PUFA, g	10.8 (3.6)	13.1 (3.3)	14.0 (3.6)	15.0 (4.1)	**<0.0001**	8.6 (1.7)	11.8 (0.7)	14.1 (0.7)	18.4 (2.9)	**<0.0001**
n–3 PUFA, g	1.9 (0.8)	2.3 (0.8)	2.5 (0.9)	2.6 (1.0)	**<0.0001**	1.5 (0.5)	2.1 (0.5)	2.5 (0.6)	3.3 (0.8)	**<0.0001**
Linolenic acid, mg	1277.1 (531.5)	1511.5 (497.1)	1591.8 (544.6)	1675.7 (582.2)	**<0.0001**	928.3 (241.6)	1328.2 (187.4)	1604.8 (232.8)	2194.8 (505.1)	**<0.0001**
EPA, mg	187.3 (154.1)	243.5 (171.6)	259.7 (185.7)	268.7 (198.2)	**<0.0001**	153.3 (124.1)	226.7 (149.8)	257.2 (169.5)	322.1 (222.8)	**<0.0001**
DHA, mg	330.2 (258.4)	428.0 (283.2)	463.2 (303.8)	473.6 (323.9)	**<0.0001**	271.9 (206.5)	402.7 (245.2)	464.0 (288.8)	556.4 (357.8)	**<0.0001**
n–6 PUFA, g	8.9 (3.0)	10.7 (2.7)	11.5 (3.0)	12.3 (3.4)	**<0.0001**	7.1 (1.4)	9.6 (0.7)	11.6 (0.8)	15.1 (2.5)	**<0.0001**
Alcohol, % current	371 (70.1)	302 (57.1)	253 (47.8)	167 (31.6)	**<0.0001**	338 (63.9)	307 (58.0)	265 (50.1)	183 (34.6)	**<0.0001**
Protein intake, g	65.3 (14.7)	75.3 (11.1)	81.1 (11.5)	88.2 (13.3)	**<0.0001**	65.3 (14.4)	74.8 (10.4)	81.0 (11.4)	88.7 (13.7)	**<0.0001**
Carbohydrate intake, g	327.8 (64.2)	325.5 (51.1)	312.2 (46.4)	285.7 (45.2)	**<0.0001**	324.6 (63.4)	319.9 (52.6)	311.1 (49.4)	295.8 (48.5)	**<0.0001**
β-carotene intake, µg	2326.5 (2037.5)	2585.5 (2189.9)	2650.6 (1816.1)	2527.2 (1965.3)	**<0.0001**	1607.7 (1121.0)	2223.4 (1452.5)	2574.2 (1726.1)	3684.5 (2745.4)	**<0.0001**
Vitamin C intake, mg	117.9 (82.8)	121.5 (76.0)	126.1 (73.7)	120.6 (70.5)	**0.01**	88.2 (60.1)	112.3 (63.5)	125.0 (69.3)	160.5 (88.8)	**<0.0001**
Vitamin E intake, mg	6.0 (2.7)	7.5 (2.6)	8.0 (2.7)	8.5 (2.9)	**<0.0001**	5.0 (1.7)	6.8 (1.6)	8.0 (1.8)	10.2 (3.1)	**<0.0001**

Table 1. Continued

Variable	SFA (Quartiles of Intake)					PUFA (Quartiles of Intake)				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* Value	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* Value
	No. (%) or Mean (SD)					No. (%) or Mean (SD)				
Women										
Age, y	61.2 (9.1)	61.7 (9.1)	59.7 (9.7)	59.8 (9.6)	**<0.0001**	59.1 (9.7)	60.3 (9.4)	60.7 (9.6)	62.3 (8.8)	**<0.0001**
Body mass index, kg/m^2	23.0 (3.5)	22.9 (3.5)	22.4 (3.4)	22.4 (3.3)	**<0.0001**	22.8 (3.5)	22.8 (3.4)	22.6 (3.4)	22.7 (3.4)	0.48
Smoking status, % current	54 (6.6)	33 (4.0)	44 (5.4)	39 (4.8)	0.11	70 (8.6)	48 (5.9)	25 (3.1)	27 (3.3)	**<0.0001**
Hypertension	323 (39.4)	300 (36.6)	286 (34.9)	258 (31.5)	**0.01**	282 (34.4)	291 (35.5)	269 (32.8)	325 (39.7)	**0.03**
Dyslipidemia	542 (66.2)	562 (68.5)	553 (67.4)	533 (65.1)	0.47	577 (70.5)	549 (67.0)	532 (64.9)	532 (65.0)	0.06
Diabetes	65 (7.9)	69 (8.4)	64 (7.8)	57 (7.0)	0.74	60 (7.3)	72 (8.8)	70 (8.5)	53 (6.5)	0.26
Menopausal status	647 (83.4)	654 (84.4)	601 (77.5)	611 (79.2)	**0.0008**	594 (76.5)	626 (80.7)	623 (80.6)	670 (86.7)	**<0.0001**
Hormone replacement therapy	27 (3.3)	25 (3.1)	26 (3.2)	30 (3.7)	0.91	27 (3.4)	25 (3.1)	24 (3.0)	32 (4.0)	0.68
Total cholesterol, mmol/L	5.6 (0.9)	5.6 (0.9)	5.6 (0.9)	5.6 (0.9)	0.19	5.6 (0.9)	5.7 (0.9)	5.6 (0.9)	5.6 (0.9)	0.51
HDL cholesterol, mmol/L	1.7 (0.4)	1.8 (0.4)	1.8 (0.4)	1.8 (0.4)	**0.02**	1.7 (0.4)	1.7 (0.4)	1.8 (0.4)	1.8 (0.4)	0.37
LDL cholesterol, mmol/L	3.3 (0.8)	3.4 (0.8)	3.4 (0.8)	3.4 (0.8)	0.26	3.4 (0.8)	3.5 (0.9)	3.4 (0.8)	3.3 (0.8)	0.09
Triglycerides, mmol/L	1.3 (0.8)	1.2 (0.6)	1.2 (0.6)	1.2 (0.7)	**0.01**	1.3 (0.8)	1.2 (0.6)	1.2 (0.7)	1.1(0.6)	**<0.0001**
Total calorie, kcal	2086.8 (741.1)	2156.7 (691.5)	2121.6 (696.4)	2063.9 (757.8)	**0.001**	2103.9 (788.2)	2112.0 (705.0)	2123.0 (690.3)	2090.2 (704.4)	0.34
Total fat, g	45.4 (8.8)	55.9 (6.8)	61.9 (7.1)	72.7 (11.0)	**<0.0001**	49.3 (11.9)	56.5 (10.2)	61.4 (10.1)	68.7 (11.7)	**<0.0001**
SFA, g	13.2 (2.3)	17.9 (1.0)	21.4 (1.2)	28.3 (4.4)	**<0.0001**	19.4 (7.3)	19.9 (5.8)	20.4 (5.3)	21.0 (5.5)	**<0.0001**
MUFA, g	18.8 (4.4)	23.4 (4.0)	26.0 (4.5)	29.8 (7.0)	**<0.0001**	19.8 (5.2)	23.6 (5.2)	25.9 (5.5)	28.7 (6.4)	**<0.0001**
PUFA, g	13.3 (3.8)	14.6 (3.4)	14.5 (3.2)	14.5 (3.9)	**<0.0001**	10.1 (1.5)	12.9 (0.6)	15.0 (0.7)	18.9 (2.8)	**<0.0001**
n–3 PUFA, g	2.4 (0.9)	2.7 (0.9)	2.6 (0.9)	2.6 (0.9)	**<0.0001**	1.8 (0.5)	2.3 (0.5)	2.8 (0.6)	3.4 (0.9)	**<0.0001**
Linolenic acid, mg	1673.8 (592.1)	1777.0 (530.5)	1725.4 (471.1)	1704.1 (565.6)	**<0.0001**	1163.7 (261.7)	1540.8 (226.5)	1831.8 (264.3)	2344.3 (495.6)	**<0.0001**
EPA, mg	229.1 (165.7)	277.6 (184.4)	260.7 (200.5)	247.6 (206.1)	**<0.0001**	181.0 (144.2)	232.9 (147.6)	283.7 (179.9)	317.5 (244.5)	**<0.0001**
DHA, mg	393.4 (272.7)	483.0 (309.6)	461.9 (334.2)	439.1 (337.1)	**<0.0001**	317.0 (226.9)	408.5 (242.5)	499.3 (297.7)	552.6 (410.9)	**<0.0001**
n–6 PUFA, g	10.9 (3.2)	11.8 (2.8)	11.8 (2.7)	11.9 (3.2)	**<0.0001**	8.2 (1.3)	10.6 (0.7)	12.2 (0.8)	15.5 (2.5)	**<0.0001**
Alcohol, % current	125 (15.3)	78 (9.5)	76 (9.3)	67 (8.2)	**<0.0001**	127 (15.5)	89 (10.9)	61 (7.4)	69 (8.4)	**<0.0001**
Protein intake, g	71.8 (12.6)	78.4 (11.6)	79.0 (12.0)	85.2 (13.3)	**<0.0001**	71.6 (12.4)	76.1 (10.3)	80.7 (10.5)	86.1 (14.7)	**<0.0001**
Carbohydrate intake, g	322.3 (37.5)	296.0 (28.7)	280.2 (28.7)	249.7 (34.1)	**<0.0001**	309.3 (44.7)	295.6 (34.1)	282.0 (33.1)	261.3 (38.3)	**<0.0001**
β-carotene, µg	4096.5 (3483.3)	3735.7 (2235.3)	3514.7 (2233.4)	3206.7 (2149.3)	**<0.0001**	2742.7 (1982.9)	3261.0 (1971.2)	3861.6 (2342.8)	4688.4 (3428.3)	**<0.0001**
Vitamin C intake, mg	197.7 (103.2)	181.7 (81.8)	164.4 (81.1)	148.8 (78.0)	**<0.0001**	150.6 (89.7)	164.9 (80.2)	179.5 (83.4)	197.7 (93.4)	**<0.0001**
Vitamin E intake, mg	8.9 (3.5)	9.3 (2.8)	9.3 (2.7)	9.0 (2.8)	**<0.0001**	7.0 (2.2)	8.4 (1.9)	9.5 (2.0)	11.7 (3.3)	**<0.0001**

Significant values are in presented in bold.

Intakes of total fat, SFA, MUFA, PUFA, n–3 PUFA, linolenic acid, EPA, DHA, n–6 PUFA, protein, carbohydrate, vitamin C, vitamin E, and β carotene are expressed as energy adjusted values.

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.

Table 2. Associations Between Fatty Acid Intakes and the Prevalence of Any AMD

Fatty Acid Intake	OR, Per Energy-Adjusted 1-SD Increase	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* Value for Trend
Men						
Total fat						
Median (range) intake, energy adjusted, g		35.2 (2.8–42.0)	47.2 (42.0–51.8)	56.4 (51.8–62.3)	71.2 (62.3–136.4)	
Number of eyes with outcome/at risk		269/1058	255/1058	199/1058	180/1058	
Model 1, OR (95% CI)	**0.79 (0.71–0.88)**	Reference	0.86 (0.67–1.11)	**0.65 (0.50–0.84)**	**0.57 (0.44–0.75)**	**<0.0001**
Model 2, OR (95% CI)	**0.81 (0.68–0.97)**	Reference	0.91 (0.68–1.20)	**0.69 (0.49–0.98)**	**0.64 (0.42–0.98)**	**0.02**
Saturated fatty acids						
Median (range) intake, energy adjusted, g		10.5 (0.9–12.9)	14.8 (12.9–16.6)	18.8 (16.7–21.4)	25.1 (21.4–52.3)	
Number of eyes with outcome/at risk		286/1058	240/1058	188/1058	189/1058	
Model 1, OR (95% CI)	**0.79 (0.71–0.88)**	Reference	0.78 (0.61–1.01)	**0.56 (0.43–0.73)**	**0.58 (0.44–0.75)**	**<0.0001**
Model 2, OR (95% CI)	**0.86 (0.74–1.00)**	Reference	0.84 (0.64–1.11)	**0.64 (0.47–0.88)**	0.71 (0.49–1.01)	**0.02**
Monounsaturated fatty acids						
Median (range) intake, energy adjusted, g		13.9 (0.8–16.8)	19.1 (16.8–21.3)	23.5 (21.3–26.1)	30.4 (26.1–62.2)	
Number of eyes with outcome/at risk		271/1058	245/1058	204/1058	183/1058	
Model 1, OR (95% CI)	**0.81 (0.73–0.91)**	Reference	0.83 (0.64–1.07)	**0.67 (0.51–0.86)**	**0.59 (0.45–0.77)**	**<0.0001**
Model 2, OR (95% CI)	0.87 (0.74–1.02)	Reference	0.88 (0.67–1.16)	0.74 (0.54–1.02)	0.68 (0.46–1.01)	**0.04**
Polyunsaturated fatty acids						
Median (range) intake, energy adjusted, g		9.1 (1.0–10.6)	11.8 (10.6–13.0)	14.1 (13.0–15.4)	17.7 (15.4–38.8)	
Number of eyes with outcome/at risk		266/1058	235/1058	198/1058	204/1058	
Model 1, OR (95% CI)	**0.84 (0.76–0.94)**	Reference	0.78 (0.61–1.01)	**0.62 (0.47–0.80)**	**0.62 (0.48–0.81)**	**0.0001**
Model 2, OR (95% CI)	0.90 (0.75–1.08)	Reference	0.81 (0.61–1.08)	**0.66 (0.47–0.92)**	0.67 (0.44–1.02)	**0.04**
n–3 polyunsaturated fatty acids						
Median (range) intake, energy adjusted, g		1.4 (0.1–1.7)	2.0 (1.7–2.2)	2.5 (2.2–2.8)	3.4 (2.8–8.2)	
Number of eyes with outcome/at risk		245/1058	232/1058	212/1058	214/1058	
Model 1, OR (95% CI)	**0.86 (0.78–0.95)**	Reference	0.88 (0.68–1.14)	**0.71 (0.55–0.93)**	**0.68 (0.52–0.89)**	**0.002**
Model 2, OR (95% CI)	0.94 (0.80–1.12)	Reference	0.95 (0.71–1.26)	0.79 (0.57–1.08)	0.82 (0.55–1.22)	0.20
Linolenic acid						
Median (range) intake, energy adjusted, mg		926.0 (67.3–1155.0)	1301.2 (1155.2–1447.9)	1614.0 (1448.2–1791.9)	2120.6 (1792.3–6874.9)	
Number of eyes with outcome/at risk		252/1058	223/1058	210/1058	218/1058	
Model 1, OR (95% CI)	0.89 (0.80–1.00)	Reference	0.81 (0.63–1.05)	**0.75 (0.58–0.97)**	**0.74 (0.57–0.96)**	**0.02**
Model 2, OR (95% CI)	0.95 (0.85–1.12)	Reference	0.87 (0.66–1.15)	0.84 (0.62–1.13)	0.86 (0.60–1.23)	0.37
Eicosapentaenoic acid						
Median (range) intake, energy adjusted, mg		65.0 (0–114.2)	159.1 (114.3–202.8)	256.8 (203.7–321.1)	428.9 (321.2–1647.9)	
Number of eyes with outcome/at risk		227/1058	244/1058	220/1058	212/1058	
Model 1, OR (95% CI)	**0.87 (0.79–0.96)**	Reference	0.99 (0.77–1.29)	0.78 (0.60–1.02)	**0.72 (0.55–0.95)**	**0.006**
Model 2, OR (95% CI)	0.96 (0.87–1.09)	Reference	1.07 (0.82–1.40)	0.90 (0.68–1.20)	0.95 (0.69–1.30)	0.49
Docosahexaenoic acid						
Median (range) intake, energy adjusted, mg		132.7 (0–216.7)	291.8 (216.9–367.9)	451.3 (368.6–561.7)	727.9 (562.1–2752.4)	
Number of eyes with outcome/at risk		236/1058	241/1058	214/1058	212/1058	
Model 1, OR (95% CI)	**0.86 (0.79–0.97)**	Reference	0.98 (0.76–1.27)	**0.75 (0.57–0.98)**	**0.70 (0.54–0.92)**	**0.002**
Model 2, OR (95% CI)	0.97 (0.86–1.09)	Reference	1.06 (0.81–1.38)	0.86 (0.65–1.16)	0.92 (0.66–1.28)	0.37

Table 2. Continued

Fatty Acid Intake	OR, Per Energy-Adjusted 1-SD Increase	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* Value for Trend
n–6 polyunsaturated fatty acids						
Median (range) intake, energy adjusted, g		7.4 (1.0–8.7)	9.7 (8.7–10.5)	11.5 (10.6–12.7)	14.4 (12.7–31.3)	
Number of eyes with outcome/at risk		266/1058	235/1058	202/1058	200/1058	
Model 1, OR (95% CI)	**0.85 (0.76–0.94)**	Reference	0.82 (0.64–1.06)	**0.66 (0.51–0.86)**	**0.64 (0.49–0.83)**	**0.0003**
Model 2, OR (95% CI)	0.91 (0.77–1.08)	Reference	0.88 (0.67–1.16)	0.73 (0.53–1.00)	0.72 (0.49–1.06)	0.06
Women						
Total fat						
Median (range) intake, energy adjusted, g		45.0 (14.2–50.6)	54.7 (50.6–58.4)	62.4 (58.4–66.8)	73.6 (66.8–118.2)	
Number of eyes with outcome/at risk		352/1638	364/1640	360/1640	377/1638	
Model 1, OR (95% CI)	1.01 (0.94–1.09)	Reference	1.04 (0.83–1.29)	1.07 (0.86–1.33)	1.10 (0.88–1.37)	0.38
Model 2, OR (95% CI)	0.90 (0.76–1.07)	Reference	1.00 (0.78–1.28)	1.03 (0.77–1.38)	1.05 (0.71–1.55)	0.80
Model 3, OR (95% CI)	0.91 (0.76–1.09)	Reference	1.03 (0.80–1.33)	1.04 (0.77–1.42)	1.04 (0.69–1.57)	0.84
Saturated fatty acids						
Median (range) intake, energy adjusted, g		13.7 (3.1–16.0)	17.9 (16.0–19.5)	21.4 (19.5–23.5)	26.9 (23.6–51.3)	
Number of eyes with outcome/at risk		370/1638	363/1640	337/1640	383/1638	
Model 1, OR (95% CI)	1.02 (0.95–1.11)	Reference	0.94 (0.75–1.16)	0.98 (0.79–1.22)	1.16 (0.93–1.44)	0.17
Model 2, OR (95% CI)	0.99 (0.87–1.11)	Reference	0.93 (0.74–1.19)	0.99 (0.77–1.28)	1.17 (0.85–1.61)	0.31
Model 3, OR (95% CI)	0.98 (0.86–1.11)	Reference	0.92 (0.72–1.18)	0.98 (0.75–1.28)	1.16 (0.84–1.62)	0.34
Monounsaturated fatty acids						
Median (range) intake, energy adjusted, g		17.7 (5.3–20.2)	22.2 (20.2–24.0)	25.9 (24.0–28.2)	31.6 (28.2–58.8)	
Number of eyes with outcome/at risk		360/1638	370/1640	369/1640	354/1638	
Model 1, OR (95% CI)	0.97 (0.90–1.05)	Reference	1.05 (0.84–1.30)	1.11 (0.89–1.38)	0.95 (0.76–1.19)	0.80
Model 2, OR (95% CI)	**0.85 (0.73–0.97)**	Reference	0.97 (0.77–1.23)	0.98 (0.75–1.28)	0.79 (0.56–1.11)	0.24
Model 3, OR (95% CI)	0.87 (0.75–1.01)	Reference	0.99 (0.77–1.26)	1.04 (0.79–1.37)	0.84 (0.58–1.20)	0.48
Polyunsaturated fatty acids						
Median (range) intake, energy adjusted, g		10.5 (2.3–11.8)	12.9 (11.8–14.0)	15.0 (14.0–16.2)	18.1 (16.2–34.1)	
Number of eyes with outcome/at risk		345/1638	319/1640	335/1640	454/1638	
Model 1, OR (95% CI)	1.05 (0.97–1.13)	Reference	0.83 (0.66–1.03)	0.85 (0.68–1.06)	1.18 (0.95–1.46)	0.11
Model 2, OR (95% CI)	1.05 (0.93–1.18)	Reference	0.82 (0.65–1.04)	0.86 (0.67–1.10)	1.25 (0.93–1.68)	0.17
Model 3, OR (95% CI)	1.04 (0.92–1.18)	Reference	0.81 (0.64–1.04)	0.85 (0.66–1.11)	1.18 (0.87–1.61)	0.30
n–3 polyunsaturated fatty acids						
Median (range) intake, energy adjusted, g		1.7 (0.2–2.0)	2.3 (2.0–2.5)	2.7 (2.5–3.1)	3.5 (3.1–9.4)	
Number of eyes with outcome/at risk		297/1638	348/1640	362/1640	446/1638	
Model 1, OR (95% CI)	1.05 (0.97–1.13)	Reference	1.10 (0.87–1.38)	1.07 (0.86–1.35)	1.21 (0.97–1.51)	0.13
Model 2, OR (95% CI)	1.03 (0.92–1.15)	Reference	1.07 (0.84–1.35)	1.04 (0.81–1.33)	1.16 (0.87–1.56)	0.39
Model 3, OR (95% CI)	1.00 (0.89–1.13)	Reference	1.08 (0.85–1.38)	0.98 (0.76–1.27)	1.12 (0.82–1.53)	0.68

Table 2. Continued

Fatty Acid Intake	OR, Per Energy-Adjusted 1-SD Increase	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* Value for Trend
Linolenic acid						
Median (range) intake, energy adjusted, mg		1144.2 (173.2–1351.1)	1506.9 (1351.3–1669.0)	1835.6 (1669.2–2015.0)	2302.9 (2015.6–4932.0)	
Number of eyes with outcome/at risk		356/1638	300/1640	386/1640	411/1638	
Model 1, OR (95% CI)	1.06 (0.95–1.11)	Reference	**0.76 (0.60–0.95)**	1.04 (0.84–1.29)	1.05 (0.85–1.31)	0.18
Model 2, OR (95% CI)	1.06 (0.95–1.18)	Reference	**0.76 (0.60–0.95)**	1.03 (0.82–1.30)	1.06 (0.82–1.38)	0.27
Model 3, OR (95% CI)	1.06 (0.95–1.18)	Reference	**0.78 (0.62–0.99)**	1.04 (0.82–1.32)	1.07 (0.82–1.41)	0.27
Eicosapentaenoic acid						
Median (range) intake, energy adjusted, mg		84.7 (0.1–132.9)	175.1 (133.0–216.3)	264.1 (216.4–324.2)	434.1 (324.7–2407.8)	
Number of eyes with outcome/at risk		286/1638	328/1640	394/1640	445/1638	
Model 1, OR (95% CI)	1.04 (0.96–1.10)	Reference	0.99 (0.79–1.25)	1.13 (0.90–1.42)	1.13 (0.90–1.42)	0.17
Model 2, OR (95% CI)	0.98 (0.89–1.08)	Reference	0.96 (0.76–1.22)	1.08 (0.85–1.38)	1.04 (0.80–1.36)	0.54
Model 3, OR (95% CI)	0.96 (0.88–1.06)	Reference	1.01 (0.79–1.29)	1.09 (0.85–1.40)	1.02 (0.77–1.35)	0.74
Docosahexaenoic acid						
Median (range) intake, energy adjusted, mg		162.2 (0.0–246.6)	312.4 (246.9–385.2)	461.9 (385.3–564.8)	745.1 (565.0–3989.3)	
Number of eyes with outcome/at risk		283/1638	326/1640	414/1640	430/1638	
Model 1, OR (95% CI)	1.03 (0.94–1.10)	Reference	1.01 (0.80–1.27)	1.25 (1.00–1.56)	1.12 (0.89–1.40)	0.15
Model 2, OR (95% CI)	0.97 (0.88–1.07)	Reference	0.97 (0.76–1.23)	1.19 (0.94–1.50)	1.02 (0.78–1.33)	0.52
Model 3, OR (95% CI)	0.97 (0.85–1.07)	Reference	1.05 (0.82–1.34)	1.21 (0.95–1.55)	1.01 (0.76–1.34)	0.66
n–6 polyunsaturated fatty acids						
Median (range) intake, energy adjusted, g		8.5 (2.1–9.7)	10.5 (9.7–11.4)	12.15 (11.4–13.2)	14.9 (13.2–27.9)	
Number of eyes with outcome/at risk		353/1638	332/1640	330/1640	438/1638	
Model 1, OR (95% CI)	1.04 (0.96–1.12)	Reference	0.87 (0.70–1.09)	0.84 (0.67–1.06)	1.17 (0.94–1.45)	0.18
Model 2, OR (95% CI)	1.04 (0.93–1.16)	Reference	0.87 (0.69–1.09)	0.84 (0.65–1.07)	1.22 (0.92–1.61)	0.25
Model 3, OR (95% CI)	1.04 (0.93–1.16)	Reference	0.92 (0.72–1.16)	0.85 (0.65–1.09)	1.23 (0.92–1.65)	0.27

Significant values are presented in bold.

Model 1: adjusted for age.

Model 2: adjusted for age, body mass index, smoking history, hypertension, dyslipidemia, diabetes, alcohol habit, total calorie intake, and energy-adjusted intakes of protein, carbohydrate, vitamin C, vitamin E, and β-carotene.

Model 3: adjusted for age, body mass index, smoking history, hypertension, dyslipidemia, diabetes, alcohol habit, total calorie intake, and energy-adjusted intakes of protein, carbohydrate, vitamin C, vitamin E, β-carotene, status of menopause, and hormone replacement therapy.

sion, dyslipidemia, diabetes, alcohol intake (current or noncurrent drinkers), total calorie intake, and energy-adjusted intakes (continuous variables) of protein, carbohydrate, vitamin C, vitamin E, and β-carotene. The third model was further adjusted in women for menopausal status (nonmenopausal or menopausal) and hormone replacement therapy (never or ever user). P values <0.05 were considered statistically significant. All statistical analyses were performed with SAS for Windows, version 9.4 (SAS Institute Inc.).

Results

Among 10,788 eyes of 5394 participants, 1421 eyes (13.2%) of 863 participants (16.0%) had early AMD, 906 eyes (8.4%) of 633 participants (11.7%) had intermediate AMD, and 29 eyes (0.46%) of 25 participants (0.3%) had late AMD. Baseline characteristics stratified by the quartiles of intakes of SFAs and PUFAs are presented in Table 1. Concerning the risk factors, in men, significant differences were found in hypertension and levels of TC and LDL-C across the quartiles of SFA intake, whereas significant differences were found in age and smoking status across the quartiles of PUFA intake. In women, significant differences were found in age, BMI, hypertension, menopausal status, and levels of HDL-C and TG across the quartiles of SFA intake, whereas significant differences were found in age, smoking status, hypertension, menopausal status, and level of TG across the quartiles of PUFA intake. Most dietary factors were correlated with energy-adjusted SFA and PUFA intakes in men and women (Table 1). In women, SFA intake was negatively correlated with β-carotene and vitamin C intake, whereas PUFA intake was positively correlated. A high positive correlation was found between SFA and MUFA intakes (Pearson's $r = 0.79$ for men and 0.64 for women, respectively). In addition, there were positive correlations between the intakes of n–6 PUFAs and n–3 PUFAs, MUFAs and PUFAs, MUFAs and n–3 PUFAs, and MUFAs and n–6 PUFAs in both men and women.

Associations Between Fatty Acid Intakes and the Prevalence of Any AMD

The associations between energy-adjusted fatty acid intakes (as continuous variables and quartiles) and the prevalence of any AMD were assessed using GEEs (Table 2). In men, an inverse association was observed between total fat and SFA intake and the prevalence of any AMD (for each energy-adjusted 1-SD increase: OR, 0.81; 95% CI, 0.68–0.97 for total fat; OR, 0.86; 95% CI, 0.74–1.00 for SFAs) (Table 2, model 2). When fatty acid intake was categorized into quartiles, the third and fourth quartiles of total fat intake were inversely associated with the prevalence of any AMD compared with that of the first quartile (third quartile: OR, 0.69; 95% CI, 0.49–0.98; fourth quartile: OR, 0.64; 95% CI, 0.42–0.98). We found a significant trend of decreasing odds ratios of AMD with increasing total fat intake (P for trend = 0.02). Moreover, the third quartiles of SFA and PUFA intake were inversely associated with the prevalence of any AMD compared with that of the first quartile (SFAs: OR, 0.64; 95% CI, 0.47–0.88; PUFAs: OR, 0.66; 95% CI, 0.47–0.92), and similar significant trends were found with increasing SFA, MUFA, and PUFA intakes (P for trend = 0.02, 0.04, and 0.04, respectively). Meanwhile, a significant association was observed in women only between the second quartile of linolenic acid intake and the prevalence of any AMD compared with that of the first quartile (OR, 0.78; 95% CI, 0.62–0.99).

Associations Between Fatty Acid Intakes and Severity of AMD Classification

Baseline characteristics stratified by severity of AMD classification are presented in Supplementary Table S1. Among 4232 eyes of 2116 men, 516 (12.2%), 375 (8.9%), and 12 (0.3%) had early, intermediate, and late AMD, respectively. There were significant differences in age, hypertension, dyslipidemia, levels of HDL-C and TG, and intakes of total fat, SFA, MUFA, PUFA, n–6 PUFA, protein, β-carotene, and vitamin C among the severities of AMD. Among 6556 eyes in women, 905 (13.8%), 531 (8.1%), and 17 (0.3%) had early, intermediate, and late AMD, respectively. There were significant differences in age, smoking status, hypertension, menopausal status, levels of HDL-C and TG, and intakes of PUFA, n–3 PUFA, linolenic acid, eicosapentaenoic acid, docosahexaenoic acid, n–6 PUFA, protein, β-carotene, vitamin C, and vitamin E among the severities of AMD.

The associations between energy-adjusted fatty acid intakes (as continuous variables) and severity of AMD classification were assessed using GEE (Supplementary Table S2). In men, increasing intakes of total fat, SFAs, and MUFAs were associated with reduced prevalence of intermediate AMD (grade 3) (for each energy-adjusted 1-SD increase: OR, 0.63; 95% CI, 0.47–0.85 for total fat; OR, 0.71; 95% CI, 0.55–0.92 for SFAs; and OR, 0.71; 95% CI, 0.54–0.94 for MUFAs) (Supplementary Table S2, model 2). In contrast, no associations were found between any fatty acid intake and the prevalence of early AMD (grade 2) or late AMD (grade 4).

In women, there were no associations between any fatty acid intake and the prevalence of any grades of AMD.

Discussion

We examined the cross-sectional associations of dietary fatty acid intakes with the prevalence of AMD by sex in a Japanese population with 5394 participants. A significant inverse association of SFA intake and a weak inverse association of MUFA and PUFA intakes with the prevalence of any AMD in men were noted. Regarding severity of AMD classification, SFA and MUFA intakes were inversely associated with the prevalence of intermediate AMD, whereas any fatty acid intake was not associated with that of early or late AMD in men. In women, only a marginal association was observed between the second quartile of linolenic acid intake and the prevalence of any AMD.

Studies on the association between SFA intake and the risk of AMD have been limited, and the results have been inconsistent. Several cohort studies reported that high SFA intake was associated with increased risk of any stage of AMD[20] or early AMD,[19] whereas others found no significant associations with early or late AMD.[4,5,8] Recently, the Tsuruoka Metabolomics Cohort Study reported that increased SFA intake was associated with reduced risk of early AMD, which used a nearly equal definition of the intermediate AMD in the AREDS classification.[25] Our finding supports their results in a larger population and with different methods—namely, a validated FFQ for quantitatively assessing fatty acid intakes and another AMD classification system.

Asians are known to consume less SFA-containing foods compared to that of Western populations.[24,34] According to the 2017 to 2018 National Health and Nutrition Examination Survey, the mean SFA intake was 33.0 g/d and 24.7 g/d for American men and women aged ≥20 years, respectively.[35] According to the 2018 National Health and Nutrition Survey, Japan, the mean SFA intake was 19.0 g/d and 16.4 g/d for Japanese men and women aged ≥20 years, respectively.[36] In the present study, the mean SFA intake was 17.6 g/d and 20.2 g/d for men and women, respectively. We should be careful in comparing these SFA intakes between surveys using different assessing methods of nutritional intakes. However, the SFA intakes among our study participants, especially men, were very low compared with those among Westerners, which may partly explain these disparate results. These findings suggest that SFA intake might be below the optimal level in the Japanese population and that the associations of fatty acid intakes with AMD could differ among populations with different genetic backgrounds or dietary patterns. Therefore, the optimal fatty acid intake amounts should be analyzed in the population of interest, with consideration of their source.

Yamagishi et al.[37] found that there was an inverse association between SFA intake and the risk of stroke, mainly deep intraparenchymal hemorrhage and lacunar infarction, in Japanese populations. The high incidence of both intraparenchymal hemorrhage and lacunar infarction among low SFA consumers could be caused by arteriolosclerosis,[34] which was associated with very low blood total cholesterol levels,[38] primarily owing to low SFA intake.[39] Meanwhile, increasing evidence supports the hypothesis that localized choroidal dysfunction and abnormal hemodynamics could be part of the pathogenesis of AMD.[40] Degeneration and functional disorders in the choriocapillaris result in outer retinal hypoxia, which may lead to the development of AMD.[41] In the choroid, arterioles/venules are found in the middle Sattler's layer. Similar to that of the cerebral small vessels, very low SFA intake may lead to arteriolosclerosis and, eventually, dysfunction of choroidal perfusion.

In addition, we found an inverse association of the prevalence of intermediate AMD with MUFA intake and a weak inverse association of the prevalence of any AMD with MUFA and PUFA intakes. Similarly, in a case-control study in the United States and Portugal, Roh et al.[17] reported inverse associations of the intakes of MUFAs and PUFAs, predominantly n–6 PUFAs with the prevalence of AMD, and a marginal association of SFA intake with it.

MUFAs exert anti-inflammatory effects through various biological pathways, including inhibition of nuclear factor–kappa B (NF-κB) via peroxisome proliferator–activated receptor (PPAR).[42] However, studies examining the association of MUFA intake and AMD have been conflicting. A few studies have demonstrated a positive effect of MUFAs on AMD,[15,16] whereas others found the opposite.[5,8] Interestingly, Roh et al.[17] showed an association of MUFA with AMD in Portuguese participants but not in American participants. The main source of MUFAs in the United States is meat and dairy products.[43] However, Portugal is known for the predominantly plant-based Mediterranean diet, which has high proportions of fruit, grain, seeds, nuts (high in MUFAs and n–6 PUFAs), and olive oil (high in MUFAs).[12,14] AMD has been inversely associated with a higher intake of olive oil,[16,18] adherence to the Mediterranean diet,[13] and nut consumption.[4] Thus, the source of MUFAs could be important, which may explain this discrepancy. In Japan, the sources of MUFAs are similar to those of SFAs,[44] and

there was a high correlation between the intakes of SFAs and MUFAs in the present study (Pearson's $r = 0.79$). Additionally, in the present study, there were sex differences in associations between the intakes of SFAs and MUFAs and the prevalence of AMD. It may be partly attributed to the fact that a small number of women had very low intakes of SFAs and MUFAs, which were associated with the observed higher odds of AMD in men.

PUFAs are one of the ligands responsible for the activation of PPAR-α,[45,46] which exerts a potent anti-inflammatory effect through NF-κB suppression.[47] Epidemiologic studies and meta-analyses have demonstrated that intake of n–3 PUFA and its main source (fish) could reduce the risks of early and late AMD.[4–9] We speculated that the lack of an association between n–3 PUFA intake and the prevalence of AMD in our results might be partly attributed to the high consumption of marine n–3 PUFA and a threshold effect.[25] However, an inverse association between n–3 PUFA intake and risk of neovascular AMD was reported in a case-control study in Japan.[48] As the present study did not include many individuals with late AMD, there may not have been enough participants to analyze associations with late AMD. Additionally, few studies that examined the association between n–6 PUFA intake and AMD have obtained inconsistent results.[6,17,18] Further studies are needed to clarify the associations between MUFA and PUFA intakes and AMD risk.

The strengths of this study include its large sample size; the use of standardized grading protocols to define the severity of AMD assessed by ophthalmologists, including retinal specialists; and the use of validated questionnaires to gather lifestyle and medical history information, which allowed us to perform a detailed analysis stratified by sex and AMD classification. The validated FFQ permitted the calculation of specific intakes of fatty acids.

We also recognize some limitations. First, the study had a cross-sectional observational design, without temporal information regarding associations. Second, as it did not include many participants with late AMD, the number of participants may have been low to analyze associations with late AMD. Third, we could not include AMD-related supplementary intake as a variable owing to the lack of data. However, according to the Council for Responsible Nutrition Consumer Survey, the prevalence of dietary supplement use is 74% and 79% among American men and women, respectively.[49] In contrast, according to the National Health and Nutrition Survey, the prevalence of dietary supplement use is 30.2% and 38.2% among Japanese men and women, respectively,[50] which is less than half that of the Westerners. Moreover, Sasaki et al.[51] reported that 34.5% of patients diagnosed as having AMD received AREDS-related supplements properly, which was lower than the corresponding proportion reported in the United States (67%).[52] Therefore, we speculate that supplement intake may have less of an impact on the association between fatty acid intake and AMD in a Japanese population compared with that in Western populations.

In summary, we found a significant inverse association of SFA intake and a weak inverse association of MUFA and PUFA intakes with the prevalence of any AMD in men. Additionally, intakes of SFAs and MUFAs were inversely associated with the prevalence of intermediate AMD in men. Although prospective longitudinal studies are needed to confirm this observation, these findings would help us better understand the pathogenesis of AMD and reveal interventional options to prevent or decelerate disease incidence or progression.

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