Intake of Vegetables, Fruit, and Fish is Beneficial for Age-Related Macular Degeneration

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- PURPOSE: What patients should eat to reduce their risk of age-related macular degeneration (AMD) is still unclear. We investigated the effect of a diet recommended by Health Councils on AMD.
- DESIGN: Prospective population-based cohort study.
- METHODS: Four thousand two hundred and two participants from the Rotterdam Study ≥55 years of age who were free of AMD at baseline were included and followed up for 9.1 ± 5.8 years. Incident AMD was graded on fundus photographs. Dietary data were collected using a validated 170-item food frequency questionnaire, and food intakes were categorized into food patterns based on guidelines from Health Councils. Associations with incident AMD were analyzed using Cox proportional hazards models that were adjusted for age, sex, total energy intake, smoking, body mass index, hypertension, education, and income.
- RESULTS: Seven hundred fifty-four people developed incident AMD. Intake of the recommended amounts of vegetables (≥200 g/day), fruit (2×/day), and fish (2×/week) were 30.6%, 54.9%, and 12.5%, respectively. In particular, the intake of fish (2×/week) decreased the risk of incident AMD (hazard ratio 0.76 [95% confidence interval 0.60-0.97]). Intake of the recommended amounts of all 3 food groups was only 3.7%, but adherence to this pattern showed a further reduction of the risk of incident AMD (hazard ratio 0.58 [95% confidence interval 0.36-0.93]). Younger age, higher income, and not smoking were associated with this food pattern, but the risk-lowering effects remained significant after additional adjustment for these factors.
- CONCLUSION: A diet of 200 grams per day of vegetables, fruit two times per day, and fish two times per week is associated with a significantly reduced risk of AMD. (Am J Ophthalmol 2019;198:70–79. © 2018 Elsevier Inc. All rights reserved.)

DESPITE RECENT THERAPEUTIC DEVELOPMENTS, age-related macular degeneration (AMD) is still the leading cause of visual impairment in the elderly of industrialized countries. In Europe, the number of affected persons is expected to increase with the aging population to 18.8 million in 2040.[1,2] Current therapeutic options are still unable to improve the long term visual prognosis, and therefore unraveling the etiology of AMD has become a strong research focus. The disease is caused by a complex interplay of many genetic and nongenetic factors,[3] and nutrition is a key player among the amendable lifestyle factors.

Nutrients with antioxidative properties, in particular lutein and zeaxanthin, zinc, vitamins C and E, and the polyunsaturated omega-3 fatty acids, have been shown to reduce risk of developing AMD. Evidence for these beneficial effects stems from trials with high-dose supplementation[4,5] and from reports on dietary intake.[6–13] A diet that combines multiple beneficial nutrients appears to be more protective against AMD than an unvaried diet.[10,14–16] A possible explanation is that the bioavailability and nutritional value of a nutrient depends on the concomitant uptake of other nutrients.

Although it is clear which micronutrients are important for AMD, clinicians and patients are still doubtful about the diet pattern that is beneficial for persons who are at risk of AMD. Several studies evaluated dietary patterns,[14–16] but just how to translate their findings into clinical recommendations remains challenging. In this study, we aimed to assess whether general dietary guidelines for a healthy lifestyle are associated with a reduced risk of AMD,[17] and in particular we searched for beneficial food patterns. We analyzed recommended minimum intake values for different food categories and food patterns that were based on general and easy accessible dietary recommendations from National Food Centers operating in many developed countries.[17] We also

calculated the proportion of the population who adhered to these recommendations, characterized their profile, and investigated their risk of AMD.

METHODS

THE ROTTERDAM STUDY IS A PROSPECTIVE, POPULATION-based cohort study investigating the frequencies and determinants of cardiovascular, neurologic, ophthalmologic, and locomotor diseases. The rationale and design have been described in detail elsewhere.[18] In brief, all inhabitants ≥55 years of age living in Ommoord, a city district of Rotterdam, The Netherlands, were invited to participate in the study (99% were of European descent). The ophthalmologic part of the study became operational after the pilot phase of the study had started and included 6780 participants. A baseline home interview and examinations at the study center were performed from 1990 to 1993 and 4 follow-up examinations were performed in 1993 to 1995, 1997 to 1999, 2002 to 2004, and 2009 to 2011. The Rotterdam Study was approved by the Medical Ethics Committee of the Erasmus MC and by the Ministry of Health, Welfare, and Sport of the Netherlands, implementing the Wet Bevolkingsonderzoek: ERGO (Population Studies Act: Rotterdam Study). All participants provided written informed consent to participate in the study and to obtain information from their treating physicians.

• STUDY SAMPLE: The cohort at risk consisted of 6780 persons with eye data. For the current analysis, participants were eligible if they had gradable fundus photographs at baseline, at least 1 follow-up eye examination, and valid dietary assessments, which resulted in a study population of 4202 persons (62% of persons with eye data) (Figure 1). Of these, persons with a diagnosis of dementia were excluded because of unreliable dietary recall; persons living in nursing homes were excluded because of the intake of standard meals; persons with macular pathology other than AMD hindering appropriate grading of the macula were excluded; and persons with prevalent early or late AMD at baseline were excluded. Therefore, only persons at risk of incident AMD were included in the analysis.

• ASSESSMENT OF AMD: Each participant underwent a comprehensive ophthalmic examination, including color fundus photography. Fundus photography of the macular area was performed after pupil dilation using a 35° fundus camera (Topcon TRV-50VT; Topcon Optical Company, Sha Tin, Hong Kong). This was replaced by a Topcon digital 35° color fundus camera (Topcon TRC 50EX with a Sony DXC-950P digital camera; 0.44 megapixel, Minato, Japan) during the third and fourth follow-up examinations. Grading procedures and graders were identical at baseline and follow-up. Graders were masked to nonocular

determinants, including dietary intake. Each eye was graded according to the Wisconsin Age-related Maculopathy Grading[19] and classified using the Rotterdam classification.[20] Classification of the person was based upon the eye with the most severe AMD stage. The outcome was incident AMD (ie, persons who developed signs of early or late AMD during the study period); no AMD was used as the reference. Early AMD was defined by the presence of soft distinct drusen with pigmentary changes, soft indistinct drusen with or without pigmentary changes, or reticular pseudodrusen with or without pigmentary changes. Late AMD was defined by the presence of geographic atrophy or neovascular AMD. No AMD was defined as no signs of early or late AMD.

• DIETARY ASSESSMENT: At baseline, dietary intake was assessed using a 2-stage approach: (1) a self-administered checklist at home in which subjects were asked which foods were consumed weekly, or at least twice a month during the preceding year, and (2) a structured interview with a trained dietician at the research center reviewing self-administered checklists for frequencies and amounts. The interview included a 170-item, validated semiquantitative food frequency questionnaire. This questionnaire was validated and adapted for use in the elderly.[21,22] The frequency of each intake was recorded as times per day, per week, or per month. The portion sizes in grams per day (g/day) were estimated using standardized household measures.[23] Using the computerized Dutch Food Composition Table (NEVO) of 1993, these dietary data were converted to macronutrient intakes.[24]

• STRATIFICATION INTO FOOD CATEGORIES AND FOOD PATTERNS: Health councils are national institutes that provide scientific substantiation for the government's development of public health policies and guidelines. The dietary guidelines and recommendations that they advocate for a healthy lifestyle are strikingly similar for many countries (eg, the United States, Germany, France, the United Kingdom, the Netherlands, and Japan), and are in accordance with advice from the United Nations Food and Agriculture Organization and the World Health Organization.[17] For the current analysis, we considered the guidelines from the Health Council in the Netherlands.[17,25,26] We defined food categories and patterns with recommended minimum intake values according to these guidelines (Supplemental Table 1; Supplemental Material available at AJO.com).

Intake of each food category was coded as "below recommended minimum intake values" and "equal to and above recommended minimum intake values" in grams per day. The National Food Center did not provide maximum intakes for the different food categories except for meat, for which a maximum of 500 grams per week was taken into account.[26] For the analysis, we calculated the equivalent intake per day (500 g/7 = 71 g/day). The minimal amount
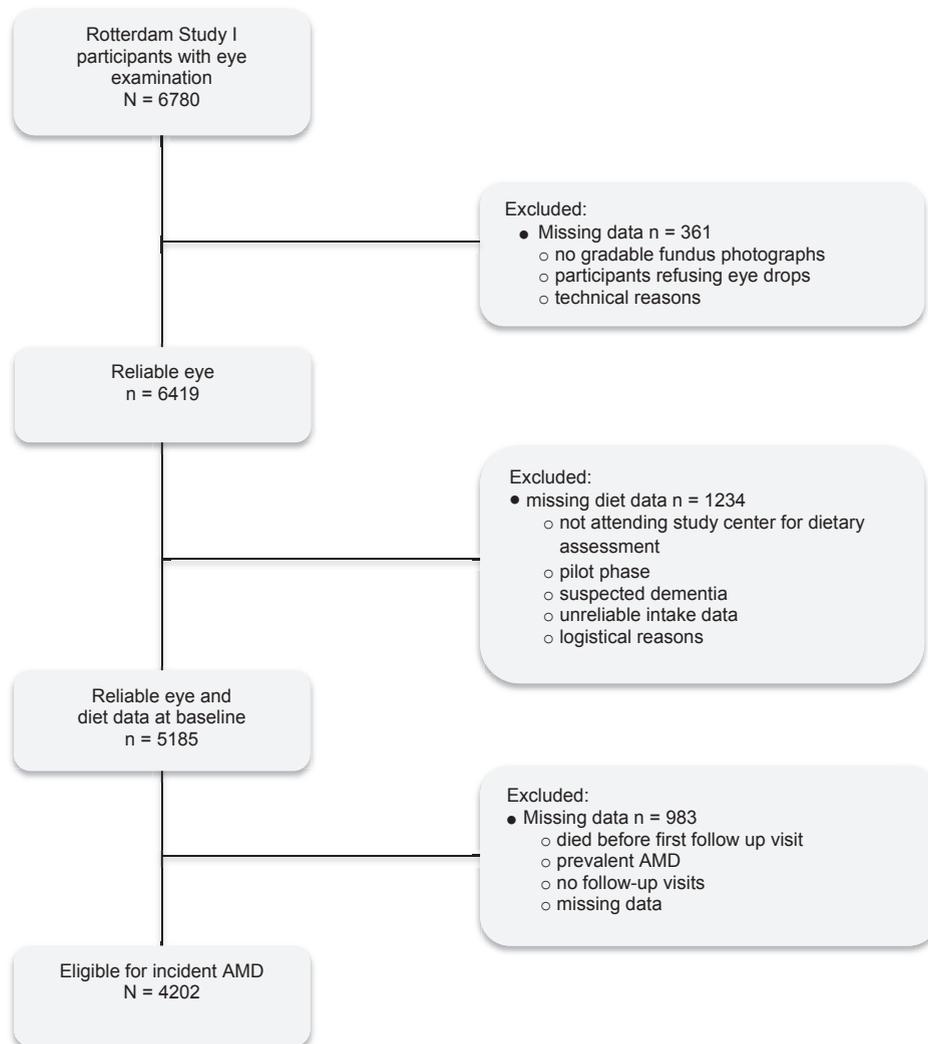
FIGURE 1. Diagram showing selection of participants at risk of any age-related macular degeneration of the Rotterdam Study I.

of meat per day (224 g/7 = 32 g/day) was based on 2 portions of meat per week. The recommended intake of vegetables was 200 grams per day; we further stratified this category according to the content of antioxidants previously associated with AMD.[4,5,10] Fruit intake was advised as 2 large pieces of fruit per day, which is equivalent to approximately 200 grams of fruit per day. The recommended fish intake was 2 potions a week; however, for our analysis, we calculated the equivalent intake of fish per day (224 g/7 = 32 g/day). For the intake of eggs, 2 eggs a week was recommended and the equivalent per day (112 g/7 = 16 g/day) was used in our analysis. We did not consider the recommended category beverages because data on this category were unreliable.

We first analyzed a pattern containing all food categories (food pattern 1; includes vegetables, fruit, fish, eggs, poultry, meat, dairy, potatoes, legumes, grains, and "fat products" like butter and margarine). Subsequently, we

aimed to assess the most protective dietary pattern for AMD and designed food patterns that included various food categories (Table 1). We particularly focused on foods with well-established associations with AMD (ie, lutein, zeaxanthin, omega-3 fatty acids) that can be found in vegetables, fruits, and fish. We then varied in adding other potentially healthy food categories, which resulted in 9 food patterns. Persons adhering to a food pattern were defined as those with intakes equal to and above the recommended minimum intake values in grams per day and were compared with persons who did not.

• ASSESSMENT OF COVARIATES: Information on covariates was collected through face-to-face, standardized interviews and physical examinations performed at baseline. Smoking was categorized as never, past, or current. Education variable was divided in 2 groups: ≤12 years of education and ≥13 years of education. Body mass index (BMI)

TABLE 1. Food Patterns Based on General Dietary Guidelines

Food Pattern	Food Type and Amount
1	Vegetables ≥200 g/day; fruit ≥200 g/day; fish ≥32 g/day; egg, poultry, or meat ≥80 g/day; dairy 150 g/day; potatoes, legumes, or grains ≥319 g/day; fat products ≥15 g/day
2	Vegetables ≥200 g/day; fruit ≥200 g/day; fish ≥32 g/day; egg, poultry, or meat ≥80 g/day
3	Vegetables ≥200 g/day; fruit ≥200 g/day; fish ≥32 g/day; egg or poultry ≥48 g/day
4	Vegetables ≥200 g/day; fruit ≥200 g/day; fish ≥32 g/day; poultry ≥16 g/day
5	Vegetables ≥200 g/day; fruit ≥200 g/day; fish ≥32 g/day; 32 g/day ≤ meat ≤ 71 g/day
6	Vegetables ≥200 g/day; fruit ≥200 g/day; poultry ≥16 g/day
7	Vegetables ≥200 g/day; fruit ≥200 g/day; egg ≥32 g/day
8	Vegetables ≥200 g/day; fruit ≥200 g/day; 32 g/day ≤ meat ≤ 71 g/day
9	Vegetables ≥200 g/day; fruit ≥200 g/day; fish ≥32 g/day

was calculated as weight in kilograms divided by height squared in meters. Blood pressure (systolic and diastolic) was calculated as the average of 2 consecutive measurements, using random-zero mercury sphygmomanometers. Hypertension was defined as a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg or the use of antihypertensive medication. Net annual income at baseline was classified low (≤35,999 Dutch guilders), average (36,000–48,999 Dutch guilders), and high (≥49,000 Dutch guilders). Registration of deceased persons during follow-up was complete until January 1, 2016.

• STATISTICAL ANALYSIS: Characteristics of participants with and without incident AMD were compared using analysis of covariance for continuous variables and logistic regression analysis for discrete variables, adjusted for age and sex. We investigated adherence of the daily food intake for each food category in our population and calculated the frequencies. The association of food categories and food patterns with incident AMD was analyzed using Cox proportional hazards models. Effect estimates for the food categories were adjusted for total energy intake (TEI), age, and sex. Intakes compliant with the recommended minimum intake values were compared with intakes that were below these values. All analyses were initially only adjusted for age and sex, and subsequently also for TEI, smoking, BMI, hypertension, education, and net annual income.

Profiles of persons who adhered to the beneficial food pattern and those who did not were further investigated. To this end, the variables age, sex, smoking, hypertension,

BMI, mortality, and TEI were compared between those adhering to food pattern 9 (intake per day for vegetables ≥200 g, fruit ≥200 g, and fish ≥32 g) and those not meeting these criteria using analysis of covariance for continuous variables and logistic regression analysis for discrete variables. All of these analyses were adjusted for age and sex.

We used $P < .05$ to denote statistical significance, and all tests were 2-sided. The proportional hazards assumption was checked using statistical tests and graphical diagnostics with scaled Schoenfeld residuals tests. All analyses were performed using SPSS software (version 21.0; IBM Corp., Armonk, NY) except for the tests and graphical diagnostics with scaled Schoenfeld residuals tests, which were performed using R software (version 3.0.2; Institute for Statistics and Mathematics, R Core Team, Vienna, Austria).

RESULTS

DURING A MEAN FOLLOW-UP OF 9.1 ± 5.8 YEARS, 754 PARTICipants developed incident AMD (681 early and 73 late). Baseline characteristics for those with and without incident AMD are shown in Table 2. Participants with incident AMD were less frequently diagnosed with hypertension (49.5% vs 52.8%; adjusted $P = .03$) and fish intake was lower compared with those without AMD (median intake fish, 7.4 g/day vs 6.6 g/day, adjusted $P = .03$). Other baseline characteristics were not significantly different between the 2 groups.

First, we assessed adherence to the previously defined food categories with recommended minimum intake values based on general dietary guidelines (Table 3). Daily food intake according to these food categories showed that only 2.0% of the population met the recommended intake of eggs, while 82.6% met the recommendations for legumes. For vegetables, fruit, and fish, the proportion of participants with minimum intakes was 30.6%, 54.9%, and 12.5%, respectively (Table 3). For the food patterns, only 0.3% of our population adhered to the complete pattern (food pattern 1); the most commonly followed (7.1%) food pattern was food pattern 6 (vegetables, fruit, and poultry). The food pattern that met the recommended minimal intake of vegetables, fruit, and fish (food pattern 9) was followed by only 3.7%.

Second, we calculated the risk of incident AMD for food categories and patterns (Table 3). Intake of fish was associated with a reduced risk of incident AMD by 24% (hazard ratio [HR] 0.76 [95% confidence interval {CI} 0.60-0.97], adjusted for age and sex), which remained significant after additional adjustment for smoking, BMI, hypertension, education, net annual income, and TEI (HR 0.77 [95% CI 0.60-0.97]). Associations with other single food categories did not reach statistical significance. With respect to food patterns, food pattern 9 (vegetables, fruit, and fish) was significantly associated with a reduced risk of incident

TABLE 2. Baseline Characteristics of the Study Population

Variable	No AMD n = 3448	Incident AMD n = 754	P Value[a]
Age at baseline (y), mean (SD)	66.5 (7.2)	67.0 (6.9)	.06
Male, n (%)	1402 (40.7)	309 (41.0)	.81
Smoking, n (%)			.44
Past	1480 (42.7)	341 (45.5)	
Current	3428 (22.9)	167 (22.3)	
BMI (kg/m^2), mean (SD)	26.4 (3.6)	26.2 (3.5)	.19
Hypertension, n (%)	1822 (52.8)	373 (49.5)	.03
>12 y of education, n (%)	2282 (66.2)	513 (68.0)	.18
Net annual income,[b] n (%)			.24
Low	890 (25.8)	180 (23.9)	
Average	1537 (44.6)	351 (46.6)	
High	1021 (29.6)	223 (29.6)	
Total energy intake (Kcal), mean (SD)	1970 (499)	2000 (522)	.08
Food categories (g/day), median (IQR)			
Total vegetables	164.7 (122–214)	167.3 (131–212)	.49
Cruciferous and green leafy	45.5 (31–63)	46.4 (33–62)	.84
Red and yellow	22.2 (14–33)	22.0 (13–33)	.78
Other vegetables	92.5 (64–126)	96.1 (69–128)	.25
Fruit	213.7 (135–295)	220.1 (144–303)	.06
Fish	7.4 (0.0–21)	6.6 (0.0–21)	.03
Fat products	24.9 (18–36)	25.4 (18–36)	.43
Meat	92.1 (67–123)	93.6 (68–143)	.77
Total grains	140.0 (107–182)	142.8 (109–184)	.60
Whole grains	120.0 (80–162)	120.6 (84–165)	.51
Refined grains	10.0 (0.3–30)	9.9 (0.0–25)	.69
Poultry	8.9 (3–18)	8.6 (4–17)	.24
Eggs	14.3 (7–14)	14.3 (7–14)	.64
Potatoes	121.8 (85–171)	117.5 (86–171)	.97
Legumes	38.1 (25–54)	39.3 (27–55)	.70
Dairy	351.8 (215–514)	369.4 (215–540)	.13

AMD = age-related macular degeneration; BMI = body mass index; IQR = interquartile range; Kcal = kilocalorie; SD = standard deviation.

[a]Calculated using analysis of covariance for continuous variables and logistic regression for discrete variables and adjusted for age and sex. P values for foods were beside adjustment for age and sex and were also adjusted for total energy intake.

[b]Defined as low (≤35,999 Dutch guilders), average (36,000-48,999 Dutch guilders), and high (≥49,000 Dutch guilders).

AMD (HR 0.56 [95% CI 0.35-0.89])—an association that remained significant in the full model (HR 0.58 [95% CI 0.36-0.93]). Other food patterns did not show a significant association with AMD.

Third, we aimed to investigate the characteristics of those who managed to adhere to food pattern 9 and studied the risk profiles of these individuals (Table 4). Persons who consumed the recommended intake of fish, vegetables, and fruit were younger than those who did not (adjusted P < .001), were less likely to smoke (adjusted P < .001), had a higher intake of total calories (adjusted P = .02), and had a higher intake of protein (adjusted P < .001). Further stratification showed a significant higher intake of vegetable and animal protein (both adjusted P < .001). Persons who adhered to food pattern 9 had a lower intake of fat products (mean ± SD 22.5 ± 18.9 g/day vs 25.1 ± 18.0 g/day, adjusted P < .001), a lower intake of meat (mean ± SD 85.2 ± 64.7 g/day vs 92.6 ± 55.2 g/day, adjusted P = .005), a lower intake of refined grains (mean ± SD 5.0 ± 19.9 g/day vs 10.0 ± 29.9 g/day, adjusted P = .02), and a lower intake of potatoes (mean ± SD 106.9 ± 73.4 g/day vs 121.8 ± 85.5 g/day, adjusted P = .01). However, they had a higher intake of poultry (mean ± SD 17.9 ± 15.0 g/day vs 8.9 ± 15.7 g/day, adjusted P < .001) and a higher intake of legumes (mean ± SD 43.8 ± 28.1 g/day vs 38.2 ± 28.3 g/day, adjusted P = .05). We conducted an additional risk analysis for food pattern 9 adjusting for these potential confounders; the association between food pattern 9 and AMD risk remained significant (HR 0.58 [95% CI 0.36-0.93]).

The proportional hazards assumption was checked using statistical tests and graphical diagnostics with scaled

TABLE 3. Risk of Age-Related Macular Degeneration for Those Following the Recommended Intakes of Food Categories and Patterns Versus Those With Lower Intakes

Variables	Following at Least the RMIV, n (%) +	Following at Least the RMIV, n (%) −	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)
Food categories				
Vegetables	1286 (30.6)	2916 (69.4)	0.99 (0.85–1.16)	1.01 (0.86–1.18)
Cruciferous and green leafy	1376 (32.7)	1826 (67.3)	0.99 (0.85–1.15)	0.98 (0.84–1.14)
Red and yellow	1371 (32.6)	2831 (67.4)	1.01 (0.87–1.17)	1.02 (0.87–1.19)
Other	1415 (33.7)	2787 (66.3)	0.99 (085–1.16)	1.00 (0.86–1.17)
Fruit	2305 (54.9)	1897 (45.1)	1.03 (0.89–1.19)	1.03 (0.89–1.20)
Fish	525 (12.5)	3678 (87.5)	0.76 (0.60–0.97)	0.76 (0.60–0.97)
Fat products	3521 (83.8)	681 (16.2)	1.08 (0.88–1.32)	1.00 (0.81–1.23)
Meat				
<32 g			1	1
32–71 g	920 (21.9)	3282 (78.1)	0.99 (0.71–1.38)	0.91 (0.65–1.28)
>71 g			1.11 (0.82–1.51)	1.11 (0.81–1.52)
Grains	1188 (28.3)	3014 (71.7)	1.06 (0.89–1.25)	1.00 (0.83–1.20)
Poultry	1155 (27.5)	3014 (72.5)	0.91 (0.77–1.07)	0.92 (0.78–1.09)
Eggs	83 (2.0)	4119 (98.0)	1.19 (0.74–1.93)	1.10 (0.67–1.78)
Potatoes	2217 (52.8)	1985 (74.8)	0.96 (0.83–1.11)	0.91 (0.78–1.06)
Legumes	3471 (82.6)	731 (17.4)	1.13 (0.92–1.38)	1.11 (0.90–1.36)
Dairy	870 (20.7)	3332 (79.3)	1.17 (0.99–1.39)	1.13 (0.95–1.35)
Food patterns				
1	11 (0.3)	4178 (99.4)	0.90 (0.23–3.62)	0.90 (0.22–3.64)
2	24 (0.6)	4178 (99.4)	0.95 (0.36–2.54)	0.96 (0.36–2.57)
3	25 (0.6)	4177 (99.4)	0.95 (0.35–2.53)	0.95 (0.35–2.56)
4	84 (2.0)	4118 (98.0)	0.64 (0.35–1.16)	0.65 (0.36–1.18)
5	40 (1.0)	4162 (99.0)	0.72 (0.32–1.60)	0.74 (0.33–1.66)
6	299 (7.1)	3903 (92.9)	0.81 (0.60–1.09)	0.81 (0.60–1.10)
7	18 (0.4)	4184 (99.6)	1.68 (0.70–4.10)	1.62 (0.67–3.92)
8	195 (4.6)	4007 (95.4)	0.97 (0.69–1.36)	1.01 (0.72–1.41)
9	155 (3.7)	4047 (96.3)	0.56 (0.35–0.89)	0.58 (0.36–0.93)

AMD = age-related macular degeneration, CI = confidence interval, HR = hazard ratio, RMIV = recommended minimum intake value.

[a]Adjusted for age and sex.

[b]Model 1 plus smoking, body mass index, hypertension, education, total energy intake, and net annual income.

Schoenfeld residuals tests and was met for all food patterns (Schoenfeld residuals tests, ρ ≤ 0.057 and $P \geq .163$; food pattern 9, ρ = 0.04 and $P = .775$).

DISCUSSION

OUR STUDY AIMED TO IDENTIFY A DIET THAT IS PROTECTIVE for AMD and that fits in general healthy dietary guidelines recommended by Health Councils. Many countries have established similar dietary guidelines, and all recommend 1 to 2 portions of (particularly fatty) fish per week, 200 to 250 grams of vegetables per day, and 200 grams of fruit per day. Only Germany recommends even higher minimum dosages (400 g/day of vegetables; 250 g/day of fruit).[17,26] Our data showed that adherence to these portions was associated with a 42% reduction in the risk of AMD. Following the recommendations for fish intake (twice a week) was sufficient for a risk reduction of 24%.

Of the 10 food categories, only the category fish reached statistical significance for association with AMD. Fish was not a frequently consumed food in our population—only 12.5% of people had a regular intake of fish. The most commonly eaten fish in the Netherlands are smoked salmon, salted herring, and canned salmon, with an average consumption of 3.6 kilograms per year.[26] In comparison, the average fish consumption per person in the rest of Western Europe was 26.0 kilograoms per year, and in Japan up to 66.0 kilograms per year.[27] Investigators of the Australian Blue Mountain Eye Study also reported a protective effect of fish.[7,28] Fish is a natural source of omega-3 poly unsaturated fatty acids, of which the highest concentrations are found in squid, cod, and tuna.[24] Almost 20% of the dry weight of the retina is accountable for lipids, mainly consisting of polyunsaturated fatty acids. These are highly

TABLE 4. Risk Profiles of Persons Who Consume the Recommended Amount of Fish, Vegetables, and Fruit (Food Pattern 9)

Variables	No Intake FVF (n = 4047)	Intake FVF (n = 155)	P Value[a]
Characteristics			
Age at baseline (y), mean (SD)	66.7 (7.2)	64.9 (6.6)	<.001
Male, n (%)	1650 (40.8)	61 (39.4)	.65
Total energy intake (Kcal), mean (SD)	1972 (501)	2060 (546)	.02
Total protein intake (Kcal), mean (SD)	81.2 (19.2)	94.4 (24.0)	<.001
Intake vegetable protein (Kcal), mean (SD)	28.2 (8.2)	31.6 (9.7)	<.001
Total carbohydrates intake (Kcal), mean (SD)	212.1 (61.1)	219.3 (68.4)	.13
Total fat intake (Kcal), mean (SD)	80.4 (27.2)	80.3 (28.5)	1.00
Smoking, n (%)			<.001
Past	1747 (43.2)	74 (47.7)	
Current	935 (23.1)	22 (14.2)	
Hypertension, n (%)	2110 (52.4)	85 (54.8)	.16
BMI (kg/m^2), mean (SD)	26.3 (3.6)	26.7 (3.3)	.12
>12 y of education, n (%)	2687 (67.3)	108 (73.0)	.29
Net annual income,[b] n (%)			.05
Low	1039 (25.7)	31 (20.0)	
Average	1827 (45.1)	61 (39.4)	
High	1181 (29.2)	63 (40.6)	
Deceased during follow-up, n (%)	2085 (51.5)	63 (40.6)	.29
Food categories (g/day), median (IQR)			
Total vegetables	162.5 (122–208)	246.5 (224–287)	<.001
Cruciferous and green leafy	45.1 (31–62)	65.1 (51–83)	<.001
Red and yellow	21.9 (14–32)	35.2 (24–49)	<.001
Other vegetables	91.6 (64–123)	148.0 (127–179)	<.001
Fruit	209.6 (134–292)	311.6 (263–401)	<.001
Fish	6.6 (0–20)	42.7 (36–57)	<.001
Butter and margarine	25.1 (18–36)	22.5 (12–31)	<.001
Meat	92.6 (67–123)	85.2 (57–122)	.005
Total grains	140.0 (107–182)	137.7 (110–188)	.47
Whole grains	120.0 (81–162)	123.1 (84–180)	.56
Refined grains	10.0 (0–30)	5.0 (0–20)	.02
Poultry	8.9 (2–18)	17.9 (11–26)	<.001
Eggs	14.3 (7–14)	14.3 (7–14)	.75
Potatoes	121.8 (85–171)	106.9 (75–148)	.01
Legumes	38.2 (25–54)	43.8 (31–60)	.05
Dairy	352.9 (215–516)	374.7 (241–534)	.30

BMI = body mass index; FVF = recommended minimum intake values of fish, vegetables, and fruit (food pattern 9); IQR = interquartile range; Kcal = kilocalorie; SD = standard deviation.

[a]Calculated using analysis of covariance for continuous variables and logistic regression for discrete variables and adjusted for age and sex. P values for foods were beside adjustment for age and sex and were also adjusted for total energy intake.

[b]Defined as low (≤35,999 Dutch guilders), average (36,000–48,999 Dutch guilders), and high (≥49,000 Dutch guilders).

present in photoreceptor outer segments, which improves fluidity of the photoreceptor membranes that results in a faster response to stimulation.[29] There is now ample evidence that these fatty acids may protect against ischemia, as well as against light, oxygen, and inflammatory damage contributing to AMD.[29,30]

Vegetables and fruit contain carotenoids, which have antioxidant properties. In the published literature, many different types of carotenoids have been analyzed in association with AMD. The most frequently studied carotenoids are lutein and zeaxanthin. These carotenoids form the major components of macular pigment and are involved in maintenance of the morphologic and functional integrity of the retina.[31] Lutein and zeaxanthin concentrate in the macula and have the capacity to filter blue light and quench reactive oxygen species, thereby reducing light-induced oxidative damage,[30,31] reducing inflammation, and protecting neural membranes.[32] For the single food categories vegetables and fruit, no significant association with incident AMD was found. Although intake was reasonable, the type of vegetables and fruit consumed in western countries may not contain enough beneficial

nutrients for AMD. Abundantly eaten vegetables in western countries are lettuce, tomatoes, cucumber, red bell pepper, and leek.[17,26] Vegetables containing the highest concentrations of lutein and zeaxanthin, such as kale, endive, spinach, and orange bell pepper, are not consumed in great amounts.[24] Similarly, the most commonly eaten fruits are apples, pears, oranges, and bananas, while the less often consumed blackberries, kakis (persimmons), and raspberries contain the highest concentration of lutein and zeaxanthin.[17,24,26] Other carotenoids, like α-carotene, β-carotene, β-cryptoxanthin, and lycopene, have been studied less thoroughly than lutein and zeaxanthin in association with AMD. Unfortunately, there is no clear evidence that the dietary intake of these carotenoids lowers the risk of AMD,[33] except for dietary intake of β-carotene, which reduces the risk of AMD in particular in those who are at high genetic risk.[34] β-carotene can be found in dark leafy vegetables like spinach and kale, and in yellow and orange vegetables like carrots and bell peppers.[24]

Other potential nutrients that could explain the associated lower risk of AMD with the intake of fish, vegetables, and fruit are folate and vitamin B_{12}. Two studies have reported a beneficial effect of the dietary intake of these vitamins against AMD.[35,36] Vitamin B_{12} and folate are important for DNA methylation, and dysregulation could lead to increased serum levels of homocysteine, which are associated with an increased risk of AMD.[35–37] Natural sources of vitamin B_{12} are fish, meat, especially liver, and eggs; legumes, grains, and green leafy vegetables are natural sources of folate.[24] We did not find an association of AMD with the intake of meat, eggs, legumes, or grains, and therefore these sources of vitamin B_{12} and folate do not appear to help protect against AMD.

Our findings are consistent with recent studies on dietary patterns and AMD. The Melbourne collaborative cohort study showed that higher intake of grains and fish considerably reduced the risk of late AMD.[14] Intake of vegetables and fruit alone was not associated with late AMD; unfortunately, the combined intake of these foods was not studied. Merle and associates investigated the Mediterranean diet, which is characterized by the high intake of vegetables, fruit, whole grains, legumes, nuts, and fish and the limited intake of red and processed meat. This diet significantly reduced the risk of progression to late AMD by 25%.[16] Chiu and associates studied an "Oriental" food pattern, typified by a high intake of vegetables and fish, and also found protection against AMD. By contrast, the "western" diet, which was characterized by a high intake of processed food and red meat, increased the risk ≤50% for late AMD.[15] Although similar conclusions can be drawn from these studies, the novelty of our research was to explore minimal levels for intake, which helps to translate findings into clinical recommendations.

It is well established that combined intake of foods influences bioavailability and nutritional value of individuals nutrients. In our study, we observed that the combined intake of vegetables, fruit, and fish performed better than each item by itself. Carotenoids, nutrients in vegetables and fruits, are fat-soluble nutrients, and their uptake by the intestine is better and more consistent when they are delivered via a lipid matrix, for instance from fish intake.[38–40] In addition, combined intake of foods can lead to competitive processing. For instance, meats and egg yolks are the major source of the omega-6 fatty acid arachidonic acid,[38,41] and excessive intake of arachidonic acid interferes with omega-3 processing through competition via enzymes in the eicosanoid pathway.[29,42] A high omega-6 to omega-3 ratio has been associated with cardiovascular disease and a variety of inflammation-related diseases.[29] This exemplifies the complexity of dietary effects, and indicates that single nutrient studies tend to overlook the entire context.

The type of persons consuming the recommended daily intake of fish, vegetables, and fruit (ie, food pattern 9) were younger and were less likely to smoke. Their TEI was higher, which seemed to come from a higher intake of vegetable proteins. Net household income was higher in the group that was adherent to food pattern 9. However, this did not explain the relationship with diet, because income was not significantly associated with AMD.[43] Nevertheless, individuals with higher standards of living and education generally have healthier dietary eating patterns, and we cannot exclude that residual confounding may have played a role.[44,45]

Strengths of our study were the prospective design and large study population, the extensive 170-item Food Frequency Questionnaire ascertained before disease onset, the detailed and consistent diagnosis of AMD features throughout the study, and the availability of a large set of covariates for analysis. Potential weaknesses were selective nonresponse of the more diseased eligible persons, the imprecision of dietary data, missing data on physical exercise, and the lack of power to assess risks in small subgroups, especially for the late AMD cases. Almost two thirds of the study population had available and reliable data on eye examinations, diet, and ≥1 follow-up; therefore, one third did not enter the analysis because of the lack of complete data. Participants with missing data tended to be older, included more women, had <12 years of education, and had higher incomes. They did not differ in their TEI. During the extensive follow-up, we lost a considerable proportion of participants, primarily because of death. Those not fully participating in the analysis tended to be older, and together with the possible differential mortality in AMD patients may have led to an underestimation of the true effect. The baseline phase of this study was performed almost 3 decades ago; therefore, the studied intakes may not reflect current eating habits. Nevertheless, as knowledge of beneficial AMD foods and supplements was limited at the time, we expect associations to be genuine and not biased by preventative recommendations.

What are the clinical implications of our findings? Notwithstanding all limitations, there is good advice that ophthalmologists and other eye care providers can give to patients who are at risk of AMD: consume a diet consisting of a large variety of vegetables, fruit, and fish. The amount advised is a minimum, but this consumption will still be a challenge to the average elderly person. A recommendation of a lifestyle including a healthy diet, refrainment from smoking, and regular exercise should be part of any counseling session for those who are at risk of AMD progression.[42] Given the low adherence to healthy food patterns, the current evidence for a beneficial effect may help alter lifestyles in individual patients as well as in the population at large.

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