

Dietary ω -3 Fatty Acid and Fish Intake in the Primary Prevention of Age-Related Macular Degeneration

A Systematic Review and Meta-analysis

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Objective: To systematically review the evidence on dietary ω -3 fatty acid and fish intake in the primary prevention of age-related macular degeneration (AMD).

Methods: Seven databases were systematically searched with no limits on publication year or language using standardized criteria. Randomized controlled trials and prospective cohort, case-control, and cross-sectional studies were included. Of 2754 abstracts identified, 3 prospective cohort, 3 case-control, and 3 cross-sectional studies met the criteria. Measures of associations were pooled quantitatively using meta-analytic methods.

Results: Nine studies provided data on a total sample of 88 974 people, including 3203 AMD cases. A high dietary

intake of ω -3 fatty acids was associated with a 38% reduction in the risk of late AMD (pooled odds ratio [OR], 0.62; 95% confidence interval [CI], 0.48-0.82). Fish intake at least twice a week was associated with a reduced risk of both early AMD (pooled OR, 0.76; 95% CI, 0.64-0.90) and late AMD (pooled OR, 0.67; 95% CI, 0.53-0.85).

Conclusions: Although this meta-analysis suggests that consumption of fish and foods rich in ω -3 fatty acids may be associated with a lower risk of AMD, there is insufficient evidence from the current literature, with few prospective studies and no randomized clinical trials, to support their routine consumption for AMD prevention.


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AGE-RELATED MACULAR DEGENERATION (AMD) is the leading cause of severe vision loss among elderly people.¹⁻⁷ New treatments for AMD are limited to patients with exudative AMD⁸⁻¹¹ and are not without risks.¹² Thus, primary prevention of AMD by modifying risk factors (eg, cigarette smoking)¹³⁻¹⁵ remains an important public health strategy.

pentaenoic acid (EPA) (both long-chain ω -3 fatty acids). Alpha-linolenic acid is the dietary precursor to both DHA and EPA and can be converted to a long-chain ω -3 fatty acid.^{16,17} Importantly, DHA is present in high concentrations in the retinal outer segments, and its deficiency may initiate the onset of AMD.¹⁸ Long-chain ω -3 fatty acids may also protect against oxygenic, inflammatory, and age-related retinal damage,¹⁶ which are key pathogenic processes in AMD development.¹⁹⁻²¹

Epidemiological studies have shown inverse associations, albeit not consistently, between dietary long-chain ω -3 fatty acid and fish intake and AMD risk.²²⁻²⁴ To evaluate these associations further, we performed a systematic review and meta-analysis on dietary ω -3 fatty acid and fish intake in the primary prevention of AMD.

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Intake of dietary ω -3 fatty acids and/or fish, the main dietary source of long-chain ω -3 fatty acids, have been suggested to prevent AMD. ω -3 Fatty acids are essential fatty acids because humans cannot synthesize these essential components de novo and rely on diet as their sole source. ω -3 Fatty acids include alpha-linolenic acid (a short-chain ω -3 fatty acid), docosahexaenoic acid (DHA), and eicosa-

METHODS

DATA SOURCES

We conducted a systematic review of 7 databases (up to May 2007), including PubMed,

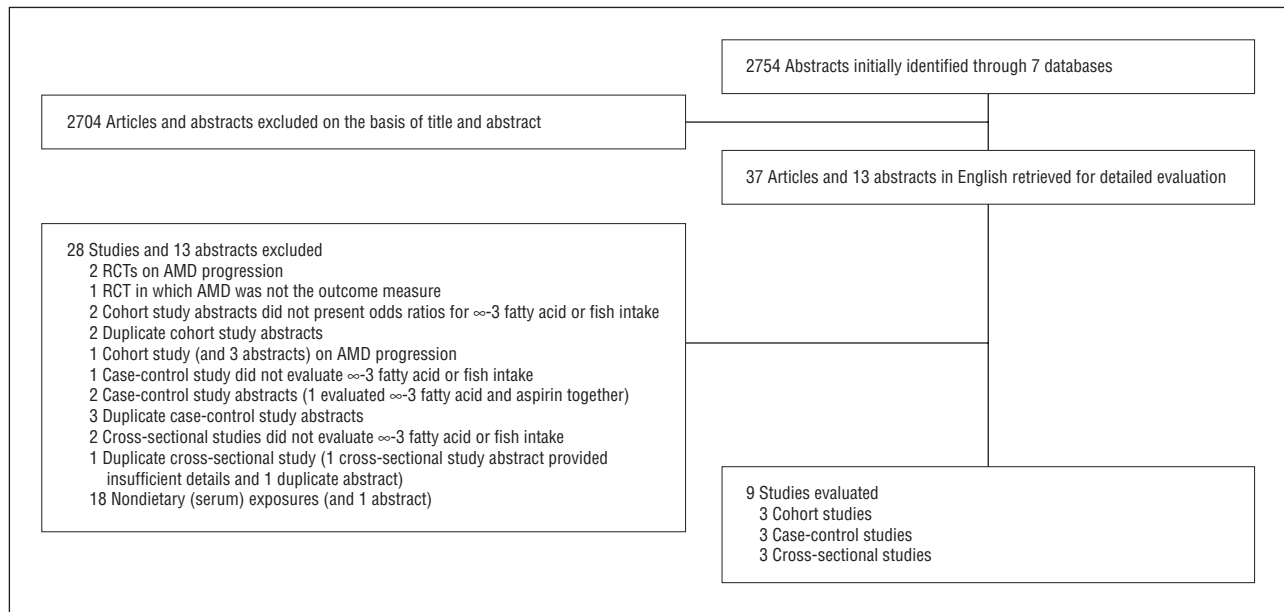


Figure 1. Flowchart of study selection process. AMD indicates age-related macular degeneration; RCT, randomized controlled trial.

Web of Science, EMBASE, MEDLINE, Cochrane Library (including the Cochrane Central Register of Controlled Trials), abstracts from the Association for Research in Vision and Ophthalmology, and the National Institutes of Health Clinical Trial Databases (<http://clinicaltrials.gov>). These databases were systematically searched using the terms *diet, nutrition, supplement, fats, fatty acids, polyunsaturated, omega 3, docosahexaenoic, eicosapentaenoic, linolenic, linoleic, and fish and age-related macular degeneration, age-related maculopathy, drusen, choroidal neovascularisation, and geographic atrophy*. There were no limits on year or language of publication. References identified from bibliographies of pertinent articles or books were also retrieved.

STUDIES AND PARTICIPANTS

For inclusion in the study, we considered randomized controlled trials (RCTs) and prospective cohort, case-control, and cross-sectional studies evaluating ω -3 fatty acid or fish intake from food or ω -3 fatty acid supplements in the primary prevention of AMD (ie, from no disease to early or late AMD). We excluded studies in which participants already had early AMD, as these studies evaluated the role of ω -3 fatty acid and fish intake for secondary prevention (ie, progression of early to late AMD). Studies were prespecified for inclusion if they met the following criteria: (1) clear definition of exposure (dietary or supplemental ω -3 fatty acid and fish intake), (2) clear definition of AMD, (3) appropriate statistical techniques adjusting for key confounders (eg, age and cigarette smoking), and (4) estimates of odds ratios (ORs), relative risks, or the primary data to calculate these ratios. In studies without ORs or relative risks comparing the highest with the lowest tertiles, quartiles, or quintiles of intake, we contacted authors for this information. We evaluated 2 primary outcomes: early AMD (defined as soft drusen and/or retinal pigmentary changes) and late AMD (exudative AMD or geographic atrophy).

STUDY SELECTION

Two reviewers (E.W-T.C. and A.J.K.) independently searched the 7 databases, including gray literature databases (unpublished work, such as conference abstracts). We initially iden-

tified 2754 abstracts. Studies were then systematically excluded if the title and abstract were not relevant. Full manuscripts were obtained for all studies that were potentially relevant.

DATA EXTRACTION AND STUDY QUALITY EVALUATION

Data extraction and study quality evaluation were independently performed by 2 reviewers (E.W-T.C. and A.J.K.) using a standardized extraction form. Assessment of the studies' methodological quality was based on the Downs and Black instrument for observational studies^{25,26} and the QUOROM statement checklist for RCTs.²⁷ The scores were categorized as A (high quality), B (moderate), and C (low). Any disagreement was resolved through discussion with senior investigators (T.Y.W. and R.H.G.).

DATA SYNTHESIS

We used RevMan 4.2.8 software (The Cochrane Collaboration, Oxford, England) for the meta-analyses. Fully adjusted ORs or relative risks from each study was used. The standard error of the natural logarithm (ln) of the OR was calculated from the 95% confidence intervals (CIs) using the following formula: $(\ln[\text{upper limit of CI}] - \ln[\text{lower limit of CI}])/3.92$. Heterogeneity between studies was tested using the I^2 statistic.²⁸ Studies were pooled using the fixed-effects model if the I^2 statistic was less than or equal to 30%; otherwise, the random-effects model was used.²⁸ We visually evaluated publication bias by using a funnel plot.^{29,30}

RESULTS

DESCRIPTION OF STUDIES

Of 2754 abstracts screened, 50 were considered potentially relevant. Of these, 41 did not meet the inclusion criteria, leaving 9 studies in this analysis (**Figure 1**). No RCTs met the inclusion criteria. Final studies included

Table 1. Prospective Cohort Studies Evaluating ω -3 Fatty Acid and Fish Intake for the Primary Prevention of Early AMD

Source (Study, Country)	Follow-up	Population (Sample Size)	Mean Age, y	AMD Definition (No. of Cases)	Exposures Investigated (Categories)	Confounders Adjusted for	Study Quality ^a
Chua et al ³² (Blue Mountain Eye Study, Australia)	5-Year incidence	Population based (N=2258)	≥ 49	WARMGS (158 early, 26 late)	Validated FFQ: ω -3 fatty acids (quintile) and fish (tertile)	Age, smoking, sex, energy intake, and vitamin C intake	A
Cho et al ²⁴ (Nurses' Health Study and the Health Professional Follow-up Study, United States)	10- to 12-year incidence	Volunteer health professionals (N=72 489)	≥ 50	Drusen or pigment change and VA ≤20/30 (567)	Validated FFQ: alpha-linolenic acid, EPA, and DHA, (quintile) and tuna and dark-meat and white-meat fish (quartile)	Age, smoking, energy intake, body mass index, exercise, lutein and zeaxanthin intake, 2-year period, hormone replacement therapy, alcohol intake, and occupation (male)	A
Arnarsson et al ³¹ (Reykjavik Eye Study, Iceland)	5-Year incidence	Population based (N=846)	≥ 50	International classification (126 early, 8 late)	FFQ: herring (tertile)	Age, smoking, and sex	B

Abbreviations: AMD, age-related macular degeneration; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FFQ, food frequency questionnaire; VA, visual acuity; WARMGS, Wisconsin Age-Related Maculopathy Grading System.

^aCategorized as A (high quality), B (moderate), and C (low).

Table 2. Case-Control Studies Evaluating ω -3 Fatty Acid and Fish Intake for the Primary Prevention of Late AMD

Source (Study, Country)	Population	Mean Age, y	AMD Case Definition (No. of Cases)	Control Definition (No. of Controls)	Exposures Investigated (Categories)	Confounders Adjusted for	Study Quality ^a
Seddon et al ³³ (Eye Disease Case Control Study, United States)	Hospital-based case-control study	55-80	Late neovascular AMD diagnosed within 1 year of enrolment (349)	Frequency matched to residential areas, age, sex, and clinic; diagnosed with other ocular disease within 1 year of enrolment (504)	Validated FFQ: ω -3 fatty acids (quintile) and fish (quintile)	Age, smoking, sex, energy intake, alcohol, carotenoid intake, body mass index, hypertension, exercise, education, clinic, and other fats	A
Seddon et al ³⁴ (US Twin Study of AMD, United States)	Population-based US veterans twin registry (men only)	≥ 60	CARMGS extensive intermediate drusen or large soft drusen, or geographic atrophy or neovascular disease (222)	No AMD or ≥ 15 drusen that are < 63 μ m or < 20 drusen that are ≥ 63 μ m to < 125 μ m or pigmentary abnormalities associated with these changes (459)	Validated FFQ: ω -3 fatty acids (quartile) and fish (tertile)	Age, smoking, energy intake, body mass index, systolic blood pressure, exercise, cardiovascular disease, education, alcohol, β -carotene, zinc, and vitamins E and C	B
SanGiovanni et al ³⁵ (AREDS, United States)	Hospital-based study	60-80	Late neovascular AMD (658)	No AMD (1115)	Validated FFQ: ω -3 fatty acids, DHA, (quintile) and fish and cooking methods (quintile)	Age, smoking, sex, energy intake, body mass index, education, refractive error, race, hypertension, lens opacity (additional adjustment for lutein and zeaxanthin; alcohol and supplements had negligible effects on the odds ratio)	A

Abbreviations: AMD, age-related macular degeneration; AREDS, Age-Related Eye Disease Study; CARMGS, Clinical Age-Related Maculopathy Grading System; DHA, docosahexaenoic acid; FFQ, food frequency questionnaire.

^aCategorized as A (high quality), B (moderate), and C (low).

3 prospective cohort,^{24,31,32} 3 case-control,³³⁻³⁵ and 3 cross-sectional^{22,23,36} studies, with complete agreement between the reviewers for eligibility. **Tables 1, 2, and 3** provide summaries of the study designs and participant characteristics. The 9 studies provided a total sample size of 88 974 people, which included 3203 AMD cases (1847 early and 1356 late AMD cases), though not all studies reported both ω -3 fatty acid and fish intake.

Prospective Cohort Studies

The 3 prospective cohort studies recruited participants between 1984 and 1996; dietary data were also recorded during this period. All studies were published within the last 7 years and were conducted in Australia, Iceland, and the United States. Participants were aged 49 years or older with a mean follow-up ranging from 5 to

Table 3. Cross-Sectional Studies Evaluating Fish Intake for the Primary Prevention of Early AMD

Source (Study, Country)	Population (Sample Size)	Mean Age, y	AMD Definition (No. of Cases)	Exposures Investigated (Categories)	Confounders Adjusted for	Study Quality ^a
Mares-Perlman et al ²² (Beaver Dam Eye Study, United States)	Population based (N=1968)	43-84	WARMGS (314 early, 30 late)	Validated FFQ: seafood (quintile)	Age, alcohol, smoking, and other covariates not adjusted for ^b	B
Heuberger et al ²³ (National Health and Nutrition Examination Survey 3, United States)	Population based (N=7405)	40-79	Modified WARMGS based on 1 random eye (644 early, 53 late)	Validated FFQ: fish (tertile)	Age, race, smoking, and other covariates not adjusted for ^b	C
Delcourt et al ³⁶ (POLANUT, France)	Population based (N=701)	≥ 70	International classification (38 early, 10 late)	Validated FFQ: white fish and fatty fish, eg, tuna, sardines, and anchovies (tertile)	Age, smoking, sex, energy intake, body mass index, and self-reported cardiovascular disease	C

Abbreviations: AMD, age-related macular degeneration; FFQ, food frequency questionnaire; POLANUT, Pathologies Oculaires Liées à l'Age Nutrition; WARMGS, Wisconsin Age-Related Maculopathy Grading System.

^aCategorized as A (high quality), B (moderate), and C (low).

^bOdds ratio did not change by more than 10%.

12 years. Two of the studies were population based (Blue Mountains Eye Study³² and Reykjavik Eye Study³¹), while the third included volunteer health professionals (Nurses' Health Study and Health Professional Follow-up Study²⁴). Initial participation rates varied among studies; 1 had a participation rate of 82%,³² another reported a rate of 61%,³¹ and the last study did not report a participation rate.²⁴ However, all studies reported follow-up rates of 75% or better. Two studies evaluated ω -3 fatty acid and fish intake using validated food frequency questionnaires; the Reykjavik Eye Study did not report questionnaire validity.³¹ Because 2 of 3 cohort studies did not evaluate late AMD as an outcome^{24,31} (because late AMD was uncommon), we pooled estimates for only early AMD from these studies.

Age-related macular degeneration assessments and definitions varied among the studies (Table 1). Importantly, all studies adjusted for age and smoking in their analyses. These studies analyzed the risk of AMD, comparing the highest with the lowest category of ω -3 fatty acid or fish intake, except 1 study,³² which evaluated the risk of AMD using the middle 3 quintiles of ω -3 fatty acid intake as the reference group. The authors were contacted and they provided us with the ORs for AMD, comparing the highest with the lowest quintile of ω -3 fatty acid intake.³² There was independent agreement in 2 of 3 cohort studies for study quality between the 2 reviewers (Table 1); disagreements were resolved by discussion.

Case-Control Studies

Three case-control studies recruited participants from 1986 to 1998, 1 of which did not report the dates of participant recruitment.³⁴ All studies were published in the last 7 years and were only conducted in the United States. Participants included in the studies were aged 49 years or older. One study was population based (US Twin Study of Age-Related Macular Degeneration³⁴), while the other 2 studies were hospital based (Age-Related Eye Disease Study³⁵ and Eye Disease Case-Control Study³³). The twin study was composed predominantly of male partici-

pants. All study participants had late AMD, while the controls either did not have AMD^{33,35} or had nonextensive intermediate drusen.³⁴ Because case-control studies mainly evaluated late AMD, pooled ORs for late AMD were calculated from these studies. The Eye Disease Case-Control Study reported 82% and 78% participation rates for patients and controls, respectively.³³ However, participation rates were not reported in the other studies.^{34,35} All studies evaluated ω -3 fatty acid and fish intake using validated food frequency questionnaires (Table 2).

Age-related macular degeneration assessment and definition varied among studies (Table 2). All studies adjusted for age, smoking, and energy intake in their analyses. Most studies analyzed AMD risk, comparing the highest with the lowest category of ω -3 fatty acid or fish intake. There was complete agreement between the 2 independent reviewers for study quality (Table 2).

Cross-Sectional Studies

Three cross-sectional studies recruited participants between 1984 and 1997, and dietary data were recorded during recruitment or after eye examinations. Initial participation rates varied: 1 study had a participation rate of 90%,²² another reported a rate of 60%,³⁶ and the last study did not report participation rates.²³ Validated food frequency questionnaires were used to ascertain fish intake, but ω -3 fatty acid intake was not analyzed in all 3 studies (Table 3). Two studies did not include smoking in their models but reported that smoking did not change the OR by more than 10%.^{22,23} The 2 independent reviewers agreed on study quality (Table 3).

DIETARY ω -3 FATTY ACID INTAKE AND EARLY AMD

We did not pool results to evaluate the associations of ω -3 fatty acid and fish intake with early AMD, as only 2 prospective cohort studies evaluated this. In the Blue Mountains Eye Study, comparing the highest with the

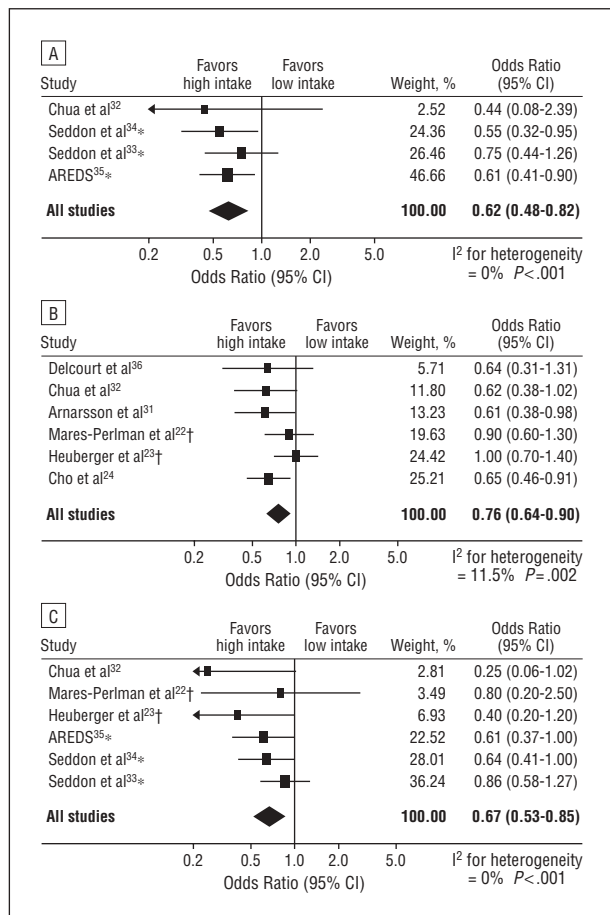


Figure 2. Pooled odds ratios for age-related macular degeneration (AMD), comparing the highest with the lowest dietary intake categories. A, ω -3 Fatty acid intake and late AMD (meta-analysis of 1 cohort study and 3 case-control studies [fixed-effects model]). B, Fish intake and early AMD (meta-analysis of 3 cohort studies and 3 cross-sectional studies [fixed-effects model]). C, Fish intake and late AMD (meta-analysis of 1 cohort study, 3 case-control studies, and 2 cross-sectional studies [fixed-effects model]). The diamond's vertical axis indicates the pooled odds ratios, while its horizontal axis spans the 95% confidence intervals (CIs) from pooled analyses. * Indicates a case-control study; †, cross-sectional study; error bar, 95% CIs; squares, point estimates of each study.

lowest ω -3 fatty acid intake quintiles, the OR for early AMD was 0.41 (95% CI, 0.22-0.75).³² In the Nurses' Health Study and the Health Professional Follow-up Study, ω -3 fatty acid intake was evaluated individually as alpha-linolenic acid, EPA, and DHA. The ORs for early AMD, comparing the highest with the lowest fatty acid intake quintile, were 1.49 (95% CI, 1.15-1.94) for alpha-linolenic acid, 0.77 (95% CI, 0.59-1.01) for EPA, and 0.70 (95% CI, 0.52-0.93) for DHA.²⁴ The early AMD definition in this study included vision loss and hence may be more indicative of an intermediate stage of AMD.

DIETARY ω -3 FATTY ACID INTAKE AND LATE AMD

The point estimates for ω -3 fatty acid intake comparing the highest with the lowest quartile or quintile of intake for late AMD are shown in **Figure 2A**. One prospective cohort study and 3 case-control studies contributed to the pooled analysis. All 4 studies reported an inverse as-

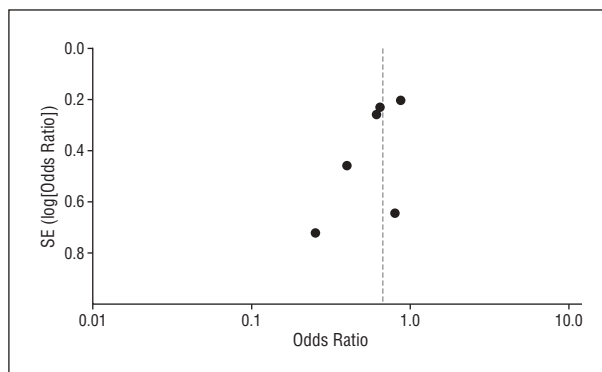


Figure 3. Funnel plot of the odds ratio (for the highest vs the lowest intake categories) vs the standard error (SE) of the log of the odds ratio for studies evaluating fish intake.²⁹ The dotted line crosses the x-axis at the estimate of the pooled odds ratio for late age-related macular degeneration.

sociation, with 2 case-control studies reporting a statistically significant association between ω -3 fatty acid intake and late AMD. The findings were homogeneous across the studies ($I^2=0\%$, $P=.84$). The pooled OR for late AMD comparing the highest with the lowest ω -3 fatty acid intake category was 0.62 (95% CI, 0.48-0.82).

FISH INTAKE AND EARLY AMD

The point estimate for fish comparing the highest with the lowest category of intake for early AMD is shown in **Figure 2B**. Three prospective cohort studies and 3 cross-sectional studies contributed to the pooled analysis, with all studies reporting an inverse association; only 1 cohort study²⁴ reported a statistically significant association between fish intake and early AMD. Findings across the studies were homogeneous ($I^2=11.5\%$, $P=.34$). The pooled OR for early AMD comparing the highest with the lowest fish intake category was 0.76 (95% CI, 0.64-0.90). Pooling results from only prospective studies, the OR increased to 0.63 (95% CI, 0.50-0.80).

FISH INTAKE AND LATE AMD

The point estimate for fish comparing the highest with the lowest category of intake for late AMD is shown in **Figure 2C**. One prospective cohort study, 3 case-control studies, and 2 cross-sectional studies contributed to the pooled analysis. All studies reported an inverse association with little heterogeneity across studies ($I^2=0\%$, $P=.42$). The pooled OR for late AMD comparing participants in the highest with those in the lowest fish-intake category was 0.67 (95% CI, 0.53-0.85). The funnel plot for these 6 studies suggested an asymmetrical inverted V-shape, indicating that publication bias is possible (**Figure 3**).

COMMENT

The primary prevention of AMD by modifying risk factors remains a key public health strategy to tackle this common condition. Long-chain ω -3 fatty acids, DHA in particular, form an integral part of the neural retina.³⁷ A diet rich in ω -3 fatty acids and fish, as a proxy for long-

chain ω -3 fatty acid intake, has therefore been hypothesized as a means to prevent AMD. Results from our meta-analysis showed that consumption of fish twice or more per week and foods rich in ω -3 fatty acids was associated with a reduced risk of both early and late AMD. We should emphasize that our results, particularly for late AMD, should be interpreted cautiously, as the available evidence is based on observational studies, including 3 case-control and 3 cross-sectional studies, with known limitations of possible recall bias and inability to infer temporal associations.

Our study showed that ω -3 fatty acid intake, comparing the highest with the lowest intake category, was associated with a 38% reduction in the likelihood of late AMD. Although we did not pool results to evaluate the association of ω -3 fatty acids and early AMD, data from 2 prospective cohort studies, the Blue Mountains Eye Study (OR, 0.41; 95% CI, 0.22-0.75)³² and the Nurses' Health Study and the Health Professional Follow-up Study (OR for DHA, 0.70; 95% CI, 0.52-0.93)²⁴ were consistent with a protective effect of ω -3 fatty acids for early AMD. Fish intake of twice or more per week compared with an intake less than once per month was similarly associated with a 37% reduction in risk of early AMD (derived only from prospective cohort studies). Fish intake was also associated with a protective effect on the risk of late AMD (pooled OR, 0.67, derived mostly from case-control and cross-sectional studies). Of note, as studies mostly analyzed ω -3 fatty acid intake as a whole, presented pooled estimates did not differentiate between long-chain and short-chain ω -3 fatty acid intake. Additional studies evaluating ω -3 fatty acid and AMD should include both collective and specific ω -3 fatty acid analyses.

Our findings are supported by a strong underlying biological rationale. The major ω -3 fatty acids of interest, DHA and EPA, are marine-based, long-chain ω -3 fatty acids found mainly in oily fish, such as tuna, sardines, salmon, and trout.³⁸ These marine, long-chain ω -3 fatty acids often form a minor part of an individual's diet (<0.1%-0.2% of energy intake).³⁹ Docosahexaenoic acid in particular is an essential structural component of the retinal membranes³⁷ and is found in the highest concentration per unit area in the retina.⁴⁰ The outer photoreceptor-cell segments of the retina are constantly shed in the normal visual cycle and deficiency of this ω -3 fatty acid may initiate AMD.¹⁸ There is also evidence that such long-chain ω -3 fatty acids protect against oxygenic, inflammatory, and age-associated pathology of the vascular and neural retina,^{16,41,42} which are possible pathogenic factors for AMD development.^{19,43,44}

Our study should be compared with a recent systematic review by Hodge et al,⁴⁵ in which the authors critically reviewed 6 observational studies for evidence that ω -3 fatty acids prevent AMD. The authors concluded that some evidence of a protective effect for ω -3 fatty acids exists, but they cautioned that there was not sufficient evidence to draw definitive conclusions.⁴⁵ Results from our current analysis are consistent with this. We found highly statistically significant pooled estimates, but owing to inherent biases from some of the studies, we concur with Hodge and colleagues that additional prospective data, especially from RCTs, are warranted. A recent

meta-analysis, from 48 RCTs and 41 cohort studies, evaluating ω -3 fatty acids (both short-chain and long-chain) for mortality, cardiovascular disease, and cancer found no clear benefit of ω -3 fatty acids on general health; clinically important harm could not be excluded, as there were insufficient events for stroke and cancer for them to exclude these as potential risks.⁴⁶

Our systematic review has several strengths. In accordance with meta-analytical guidelines,^{47,48} we were comprehensive and searched 7 databases, including gray literature databases, without limiting searches by language or time.^{49,50} Included studies had sound methodological qualities (Tables 1-3) and risk estimates adjusted for age and cigarette smoking (except 2 cross-sectional studies). There was little heterogeneity in the results between studies, enabling pooling of data. Although pooled results for ω -3 fatty acid and fish intake were derived from different studies, the consistency between these findings suggests that the associations are robust and combining studies with different study designs did not bias our results.

We identified important limitations in the current literature. First, we did not find any RCTs evaluating ω -3 fatty acid and fish intake in the primary prevention of AMD. Although a large RCT, the Age-Related Eye Disease Study 2, evaluating ω -3 fatty acid (EPA and DHA) and/or carotenoid (lutein and zeaxanthin) supplement intake compared with placebo has started recruitment in the United States,⁵¹ it will evaluate their roles in the secondary prevention of AMD (ie, progression from early to late AMD). Hence currently, observational studies, particularly prospective cohort studies, provide the best available evidence regarding these dietary factors for the primary prevention of AMD. With only 9 studies, the funnel plot indicated possible publication bias, likely reflecting the absence of small studies reporting a null association with AMD.^{29,30} Second, meta-analyses of observational data are known to have more biases than meta-analyses of RCTs,⁵² particularly because case-control and cross-sectional studies may be more prone to recall bias, and temporal relationships between diet and disease cannot be inferred. Nonetheless, the similarity of the direction of associations of ω -3 fatty acid and fish intakes with both early and late AMD supports the possibility of the associations. Third, associations between AMD prevention and ω -3 fatty acid or fish intakes may reflect other broader aspects of diet or lifestyle. For example, people who consume high levels of ω -3 fatty acids may also have higher antioxidant intakes^{53,54} and may consume more foods with lower glycemic indices,⁵⁵ both of which are associated with lower risks of AMD. Such aspects of diet may not have been adequately controlled for in observational studies. Therefore, additional analyses of associations between dietary patterns and AMD are warranted. Fourth, the evaluated studies were derived from populations in which participants are well nourished. Consequently, our findings may not be representative of communities outside of these areas. Fifth, the assessment of AMD varied between studies (Tables 1-3). It is possible that studies using visual acuity criteria for their definition of AMD may underestimate early AMD cases compared with studies using photographic definitions evaluating AMD signs. Finally, although most stud-

ies used validated food frequency questionnaires, these questionnaires were administered only once at baseline, and misclassification of dietary factors could have occurred. This nondifferential error would have biased the results towards the null.

In conclusion, these results suggest that high dietary intakes of ω -3 fatty acids and fish are associated with a reduced risk of both early and late AMD. As there are currently no published RCTs on the subject, we could not evaluate the wider role of ω -3 fatty acid supplementation in preventing AMD. While our review suggests that consumption of foods rich in ω -3 fatty acids and fish intake twice or more per week may play important roles in the primary prevention of AMD, in the context of the limited literature available, particularly for late AMD and conclusions from other reviews,^{45,46} routine recommendation of ω -3 fatty acid and fish intake for AMD prevention is not warranted until additional information from prospective studies and RCTs emerges.

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Ophthalmological Numismatics

Born in Assisi, Cesare Paoli (1813-1901) received his medical degree in Pisa, where he practiced for a short time before moving to Florence in 1839. There, 10 years later, he became professor of ophthalmology, a position he held for the next 50 years.

In Italy in 1899, a commemorative medal for the 50th anniversary of his professorship was struck in bronze, 41 mm in diameter.

The obverse depicts a tied laurel wreath within which an inscription appears in 6 parallel lines: A/CESARE PAOLI/NEL/CINQUANTESIMO ANNO/DEL SUO/INSEGNAMENTO.

The reverse depicts an inscription in 4 parallel lines: STUDENTI E DOTTORI/RIVERENTI DISCEPOLI/OFFRONO/MDCCCIC.



Courtesy of: Jay M. Galst, MD, Clinical Associate Professor, New York Medical College, and Peter van Alfen, PhD, Associate Curator, American Numismatic Society.

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