Associations between Aspirin Use and Aging Macula Disorder

The European Eye Study

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Objective: To study associations between aspirin use and early and late aging macula disorder (AMD).

Design: Population-based cross-sectional European Eye Study in 7 centers from northern to southern Europe.

Participants: In total, 4691 participants 65 years of age and older, collected by random sampling.

Methods: Aspirin intake and possible confounders for AMD were ascertained by a structured questionnaire. Ophthalmic and basic systemic measurements were performed in a standardized way. The study classified AMD according to the modified International Classification System on digitized fundus images at 1 grading center. Nonfasting blood samples were analyzed in a single laboratory. Associations were analyzed by logistic regression.

Main Outcome Measures: Odds ratios (ORs) for AMD in aspirin users.

Results: Early AMD was present in 36.4% of the participants and late AMD was present in 3.3% of participants. Monthly aspirin use was reported by 1931 (41.2%), at least once weekly by 7%, and daily use by 17.3%. For daily aspirin users, the ORs, adjusted for potential confounders, showed a steady increase with increasing severity of AMD grades. These were: grade 1, 1.26 (95% confidence interval [CI], 1.08–1.46; P=0.001); grade 2, 1.42 (95% CI, 1.18–1.70), and wet late AMD, 2.22 (95% CI, 1.61–3.05).

Conclusions: Frequent aspirin use was associated with early AMD and wet late AMD, and the ORs rose with increasing frequency of consumption. This interesting observation warrants further evaluation of the associations between aspirin use and AMD.

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Aging macula disorder (AMD) is considered by us to be exactly the same disorder as age-related macular degeneration, with the identical acronym AMD, but we prefer the former name for reasons cited previously. Associations between aspirin use and AMD have been addressed in various settings with inconsistent results. In a retrospective clinical survey, aspirin use was found in 49% of 109 patients with macular hemorrhages. Several publications reporting moderate to severe retinal hemorrhages in late AMD cases found that aspirin played a minor role, contrary to anticoagulants. This is in contrast with 2 recent studies of AMD clinic patients that reported an increased incidence of severe subretinal hemorrhages in AMD patients using aspirin or anticoagulants or aspirin only. A case-control study mentioned an association between aspirin and early but not late AMD, whereas another small case-control study found no association, consistent with studies that could not find more hemorrhages or increased recurrence of wet AMD in aspirin users. A cross-sectional, population-based study found no increased prevalence of AMD in aspirin users, a finding consistent with a longitudinal study and with an analysis of the United Kingdom general practitioner database, which found no association between prescribed aspirin and any AMD.

However, a randomized trial found a nonsignificant inverse association between any reported AMD and aspirin use in the subgroup randomized to aspirin plus β-carotene. A trial using aspirin and vitamin E reported a similar result. Thus, although several studies suggested a deleterious effect of aspirin on AMD, others found no evidence of this or possibly a nonsignificant beneficial action.

Estimates of the yearly worldwide aspirin production vary between 20 and 120 billion tablets, averaging 300 mg, often freely available over the counter. Because of possible implications of aspirin intake on AMD, associations between reported aspirin use and the prevalence of AMD were studied in a cross-sectional, population-based setting across Europe. The primary aims of this European Eye Study were to estimate the prevalence of AMD across Europe and to investigate its risk factors, with a focus on solar radiation and antioxidant vitamins.

Patients and Methods

Participants were recruited between 2000 and 2003 by random sampling of population registers of inhabitants older than 65 years...
of age across various latitudes in 7 European countries: Bergen (Norway), Tallinn (Estonia), Belfast (United Kingdom), Paris-Creteil (France), Verona (Italy), Thessaloniki (Greece), and Alicante (Spain). Participants were interviewed by field workers. Self-reported data included sociodemographic details, educational level, current and past smoking status, alcohol consumption habits, medical history including history of stroke or heart attack, and a doctor’s diagnosis of angina or diabetes mellitus. Use of aspirin was determined with a precoded response category of 7 options ranging from never to daily. A similar question was asked for use of other painkillers. Aspirin use was recategorized according to the reported frequency into the following groups: never, monthly or less, at least once weekly (but not daily), and daily. A single variable for cardiovascular disease (CVD) was created based on a positive history of either a heart attack or stroke. Demiquest index was measured, and for comparison with other studies, body mass index was calculated as weight (kg)/height² (m). Brachial systolic and diastolic blood pressures were measured in seated position after 3 to 5 minutes of rest. Two readings were taken with 5-minute intervals, and the average of the 2 values recorded was used. Fieldworkers in all centers followed the same protocol and used the same type of sphygmomanometer (Omron Hem 705 CP Omron Healthcare, Kyoto, Japan).

Nonfasting blood samples packed in dry ice were shipped to the study’s central laboratory (Queen’s University, Belfast) on a monthly basis and were stored at ~70°C until analysis. Cholesterol was measured using an enzymatic assay (Randox, Crumlin, United Kingdom) on a Cobas FARA centrifugal analyser (Roche Diagnostics, Bath, United Kingdom).

After pupillary dilation with tropicamide 0.5% and phenylephrine 5%, 2.35° nonsimultaneous stereoscopic digitized color fundus images were obtained of each eye, centered on the fovea. Images from participants were saved without manipulation as raw TIFF files to compact discs and were sent to the grader center in Rotterdam. Two staff graders in the Rotterdam fundus photography reading center with 12 years of experience graded the fundus images according to the International Classification and Grading System for Age-Related Maculopathy and AMD. In this system, all AMD fundus signs within a standard circle (diameter of 6 mm) around the fovea are recorded. The classification was modified by categorizing the features observed into 1 of 5 mutually exclusive severity stages from grades 0 to 4. This staging system was validated in the Rotterdam Eye Study. In addition, to reflect modern nomenclature, the terms early and late age-related maculopathy in the original International Classification were changed to early and late AMD. Graders assigned each of the 2 eyes of each participant into the grades, as described below. Grade 0 was defined as a macula free of drusen or pigmentary irregularities or with hard drusen (<63 μm) only. Early AMD was subdivided in grade 1, defined as soft distinct drusen (≥63 μμm) or pigmentary abnormalities; grade 2 was defined as soft indistinct drusen (≥125 μm) or reticular drusen only or soft distinct drusen (≥63 μm) with pigmentary abnormalities; and grade 3 was defined as soft indistinct drusen (≥125 μm) or reticular drusen with pigmentary abnormalities. Reticular drusen were identified on the color images, not by autofluorescence. Late AMD was similar to grade 4, subdivided into dry AMD (dAMD), equal to geographic atrophy, or wAMD. Dry AMD was defined as any sharply demarcated round or oval area of apparent absence of the retinal pigment epithelium (RPE), largest diameter more than 175 μm, with visible choroidal vessels, and no wAMD. Wet AMD was defined as the presence of a serous or hemorrhagic detachment of the RPE, a subretinal neovascular membrane, subretinal hemorrhage, periretinal fibrous scarring, or a combination thereof, even with patches of dAMD.

Written informed consent was obtained from all study participants. Ethical approval for all procedures was obtained for each country from the relevant ethics committees.

Statistical Analyses
Statistical analysis was carried out using Stata software version 10.1 (Stata Corp., College Station, TX). Account of the study design (7 centers) was made by estimating robust standard errors and corresponding P values and 95% confidence intervals (CIs). Logistic regression was used to examine the association of aspirin frequency with each stage of early AMD and with dAMD or wAMD. Possible confounding variables were identified initially from univariate analysis of frequency of aspirin use and were identified further in stepwise regression with a P value of 0.2 to be retained in the model. Characteristics according to aspirin use were compared using design-based chi-square tests and t tests for comparison of means, using robust standard errors. Variables entered in final models were age; gender; body mass index; systolic blood pressure; cholesterol; and history of education, smoking, CVD or angina, and diabetes.

The most parsimonious model was estimated by excluding all covariates that did not change the odds ratios (ORs) for aspirin frequency and grade of AMD by 10% or more when added to the model. Whether the association between aspirin use and AMD was different according to history of CVD or angina (interactions) was investigated. Tests for interactions were design-adjusted Wald tests.

Results
In 62 of 4753 participants graded for AMD, information on aspirin use was missing (29 control persons, 28 with grade 1 AMD, 3 with grade 2 AMD, 1 with grade 3 AMD, and 1 with grade 4 AMD), leaving 4691 participants. The characteristics according to reported frequency of aspirin use are given in Table 1. Those who reported daily aspirin use were older, were less likely to be smokers, and had lower blood pressure and cholesterol levels. They reported significantly more CVD and angina. Early AMD was graded in 1706 (36.4%) participants and late AMD was graded in 157 (3.3%) participants, of whom 108 had wAMD and 49 had dAMD. The distribution of AMD by aspirin frequency is shown in Table 2. One third of the participants with wAMD were in the daily aspirin consumption category, compared with 16% of control persons.

In analyses adjusted only for age and gender, aspirin use was associated significantly with wAMD; there was an increasing trend with increasing frequency of aspirin use (P = 0.001). The OR of wAMD for daily users was 2.61 (95% CI, 1.67–4.07; Table 3). The ORs were attenuated slightly after adjustment for all potential confounders, but there remained 2-fold higher odds for wAMD. The most parsimonious model for aspirin use and wAMD was that adjusted for age, gender, and CVD with an OR for daily aspirin use of 2.22 (95% CI, 1.61–3.05). There were no significant interactions between aspirin use and either CVD or angina. The OR for daily aspirin use in those who reported a CVD history was 2.55 (95% CI, 1.57–4.15; P = 0.001), whereas for those with no CVD history it was 2.02 (95% CI, 1.21–3.73; P < 0.01; value interaction, 0.6).

Similarly, the association of aspirin with wAMD was the same for those with and without angina. For those who did not report angina, the OR for wAMD in daily aspirin users was 2.37 (95% CI, 1.43–3.92; P = 0.001), and for those with angina it was 2.39 (95% CI, 0.75–6.66; P = 0.15). The P value for interaction was 0.9. Using a combined variable of either angina or CVD, the adverse association with daily aspirin use was seen both in those with no report of CVD or angina (OR, 2.58; 95% CI, 1.48–4.50; P < 0.001) and those who reported either CVD or angina (OR, 2.09; 95% CI,
1.25–3.51; P = 0.005; test for interaction, P = 0.6). Associations between CVD or angina and wAMD also were examined. In analyses adjusted only for age and gender, there was a significant association of CVD with wAMD (OR, 2.22; 95% CI, 1.10–4.47; P = 0.03). The OR was attenuated and nonsignificant after adjustment for a range of confounders, including aspirin use (OR for CVD, 1.46; 95% CI, 0.82–2.59; P = 0.2). For angina, the attenuation with confounder adjustment was more marked: from an age- and gender-adjusted OR of 1.80 (95% CI, 0.90–3.59; P = 0.09) to an OR of 1.18 (95% CI, 0.71–1.96; P = 0.5).

There were 49 cases of dAMD, of which 42 had information on aspirin use and potential confounders. In age- and gender-adjusted analyses, there was no association between aspirin use and dAMD. The ORs for dAMD by category of aspirin consumption compared with never use of aspirin were 0.92 (95% CI, 0.38–2.26) for monthly or less, 1.14 (95% CI, 0.48–2.68) for at least once weekly.

### Table 1. Characteristics of Participants by History of Aspirin Use (N = 4691)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Never (n = 2760)</th>
<th>Monthly or Less (n = 766)</th>
<th>At Least Once Weekly (n = 326)</th>
<th>Daily (n = 839)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD), yrs</td>
<td>73.2 (5.6)</td>
<td>72.4 (5.6)</td>
<td>72.8 (5.4)</td>
<td>74.2 (5.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Missing data (n = 0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (% men)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing data (n = 0)</td>
<td>1170 (43.0)</td>
<td>374 (49.3)</td>
<td>122 (37.9)</td>
<td>412 (49.6)</td>
<td>0.1</td>
</tr>
<tr>
<td>Lowest tertile of education (%)</td>
<td>1067 (38.8)</td>
<td>248 (32.6)</td>
<td>119 (36.7)</td>
<td>352 (42.2)</td>
<td>0.1</td>
</tr>
<tr>
<td>Missing (n = 27; 0.6%)</td>
<td>16 (0.6%)</td>
<td>5 (0.7%)</td>
<td>2 (0.6%)</td>
<td>4 (0.5%)</td>
<td></td>
</tr>
<tr>
<td>Smoking (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1502 (54.4)</td>
<td>401 (52.4)</td>
<td>176 (54.0)</td>
<td>395 (47.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Former</td>
<td>879 (31.9)</td>
<td>235 (30.7)</td>
<td>97 (29.8)</td>
<td>337 (40.2)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>379 (13.7)</td>
<td>130 (17.0)</td>
<td>53 (16.3)</td>
<td>100 (11.9)</td>
<td></td>
</tr>
<tr>
<td>Missing (n = 1; 0.02%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (0.1%)</td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>480 (17.4)</td>
<td>91 (11.9)</td>
<td>40 (12.3)</td>
<td>163 (19.4)</td>
<td>0.2</td>
</tr>
<tr>
<td>Infrequent</td>
<td>1182 (42.9)</td>
<td>309 (40.3)</td>
<td>152 (46.6)</td>
<td>367 (43.7)</td>
<td></td>
</tr>
<tr>
<td>Weekly or more</td>
<td>1094 (39.7)</td>
<td>366 (47.8)</td>
<td>134 (41.1)</td>
<td>309 (36.8)</td>
<td></td>
</tr>
<tr>
<td>Missing (n = 4; 0.1%)</td>
<td>4 (0.1%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease*</td>
<td>241 (8.7)</td>
<td>61 (8.0)</td>
<td>35 (10.8)</td>
<td>318 (37.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Missing (n = 8; 0.2%)</td>
<td>4 (0.1%)</td>
<td>1 (0.1%)</td>
<td>1 (0.3%)</td>
<td>2 (0.2%)</td>
<td></td>
</tr>
<tr>
<td>Angina (%)</td>
<td>221 (8.0)</td>
<td>50 (6.5)</td>
<td>40 (12.4)</td>
<td>317 (38.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Missing (n = 16; 0.3%)</td>
<td>10 (0.4%)</td>
<td>1 (0.1%)</td>
<td>2 (0.6%)</td>
<td>3 (0.4%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>328 (11.9)</td>
<td>100 (13.1)</td>
<td>36 (11.1)</td>
<td>147 (17.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Missing (n = 12; 0.3%)</td>
<td>8 (0.3%)</td>
<td>1 (0.1%)</td>
<td>1 (0.3%)</td>
<td>2 (0.2%)</td>
<td></td>
</tr>
<tr>
<td>Daily use of other pain killers</td>
<td>330 (12.0%)</td>
<td>49 (6.4%)</td>
<td>20 (6.1%)</td>
<td>113 (13.5%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Missing (n = 99)</td>
<td>12 (0.4%)</td>
<td>16 (2.1%)</td>
<td>18 (5.5%)</td>
<td>53 (6.3%)</td>
<td></td>
</tr>
<tr>
<td>BMI ≥30 kg/m² (%)</td>
<td>890 (33.4)</td>
<td>268 (36.0)</td>
<td>149 (46.6)</td>
<td>302 (37.2)</td>
<td>0.1</td>
</tr>
<tr>
<td>Missing (n = 151; 3.2%)</td>
<td>95 (3.4%)</td>
<td>22 (2.9%)</td>
<td>6 (1.9%)</td>
<td>28 (3.3%)</td>
<td></td>
</tr>
<tr>
<td>Mean SBP (SD), mmHg</td>
<td>150.3 (23.0)</td>
<td>150.8 (21.1)</td>
<td>152.6 (22.6)</td>
<td>150.6 (22.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Missing (n = 135; 2.9%)</td>
<td>8 (3.2%)</td>
<td>25 (3.3%)</td>
<td>6 (1.8%)</td>
<td>17 (2.0%)</td>
<td></td>
</tr>
<tr>
<td>Mean total cholesterol (SD), μmol/l</td>
<td>5.8 (1.12)</td>
<td>5.7 (1.1)</td>
<td>5.9 (1.0)</td>
<td>5.4 (1.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Missing (n = 147; 3.1%)</td>
<td>83 (3.0%)</td>
<td>22 (2.9%)</td>
<td>5 (1.5%)</td>
<td>37 (4.4%)</td>
<td></td>
</tr>
</tbody>
</table>

BMI = body mass index; SBP = systolic blood pressure; SD = standard deviation.

*History of heart attack or stroke.

### Table 2. Aspirin Use by Grade of Aging Macula Disorder

<table>
<thead>
<tr>
<th>Grade of AMD</th>
<th>Never</th>
<th>Monthly or Less</th>
<th>At Least Once Weekly</th>
<th>Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls, grade 0 AMD</td>
<td>1376 (61.6)</td>
<td>356 (15.9)</td>
<td>145 (6.5)</td>
<td>356 (15.9)</td>
</tr>
<tr>
<td>Early AMD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>969 (56.8)</td>
<td>299 (17.5)</td>
<td>121 (7.1)</td>
<td>317 (18.6)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>265 (55.3)</td>
<td>73 (15.2)</td>
<td>39 (8.1)</td>
<td>102 (21.3)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>71 (61.2)</td>
<td>17 (14.7)</td>
<td>9 (7.8)</td>
<td>19 (16.4)</td>
</tr>
<tr>
<td>Late AMD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>79 (50.3)</td>
<td>21 (13.4)</td>
<td>12 (7.6)</td>
<td>45 (28.7)</td>
</tr>
<tr>
<td>Dry</td>
<td>28 (57.1)</td>
<td>8 (16.3)</td>
<td>4 (8.2)</td>
<td>9 (18.4)</td>
</tr>
<tr>
<td>Wet</td>
<td>51 (47.2)</td>
<td>13 (12.0)</td>
<td>8 (7.4)</td>
<td>36 (33.3)</td>
</tr>
</tbody>
</table>

AMD = aging macular disorder.

Data are presented as no. (%).
Early AMD grades 1 and 2, but not grade 3, also were associ-
ated with aspirin use (Table 4). In these analyses, there was no
attenuation of the ORs with potential confounder adjustment,
including CVD. There was no association between CVD and any
type of early AMD; the grade 1 age- and gender-adjusted OR was
0.93 (P = 0.5), the grade 2 age- and gender-adjusted OR was 0.99
(P = 0.9), and the grade 3 age- and gender-adjusted OR was 0.96
(P = 0.8).

**Discussion**

The main findings in this study were that frequent aspirin
use was associated with wAMD and that intake frequency
exhibited a consistent relationship across the severity grades
of the AMD spectrum with the exception of grade 3. When
adjustment was made for all known confounders including
CVD or angina, the associations did not change. However,
there may be other confounders that were not measured. No
association or trend was found between aspirin intake and
dAMD, but the number of cases was small.

Interestingly, the univariate analysis in the case-
controlled Age-Related Eye Disease Study (AREDS) re-
ported similar associations between aspirin intake and only
early but not late prevalent AMD, and these reached only
nominal significance (P < 0.15). This AREDS report pro-
vided no details about the ORs and 95% CIs for the final
model with regard to aspirin. Although the lack of an
association between aspirin use and dAMD may be ex-
plained by the smaller number of cases in this category, in
the present study, there was no indication from the ORs of
an increasing association. Moreover, it is worth noting that
the AREDS study, with a substantially larger number of
dAMD cases, also did not find an association between
aspirin use and dAMD.

Only 1 earlier population-based study examined aspi-
rin use and late AMD. In this study of people 70 years
of age or older, approximately 40% of the participants
used aspirin. No association was found between aspirin
use and pooled early or late AMD, nor with late AMD in
those older than 85 years. In the Beaver Dam study, no
association was found between aspirin use and incident
early AMD; no analysis on late AMD was reported. The
pooled Beaver Dam, Blue Mountain, and Rotterdam
studies did not examine associations between aspirin and
AMD because less than 1% of the study population
reported aspirin intake. In 2 recent studies of clinic
patients with AMD, the ORs for severe subretinal hem-
orrhages were 8.0 (95% CI, 2.5–25.7) for aspirin or

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**Table 3. Associations between Aspirin Use and Wet Late Aging Macula Disorder**

<table>
<thead>
<tr>
<th>Aspirin Use</th>
<th>Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted for Age and Gender</td>
</tr>
<tr>
<td></td>
<td>Adjusted for Age, Gender, and Cardiovascular Disease</td>
</tr>
<tr>
<td>Never</td>
<td>1</td>
</tr>
<tr>
<td>Monthly or less</td>
<td>0.84 (0.42–1.69)</td>
</tr>
<tr>
<td>At least once a week but less than daily</td>
<td>1.45 (0.65–3.19)</td>
</tr>
<tr>
<td>Daily</td>
<td>2.61 (1.67–4.07)</td>
</tr>
<tr>
<td>P trend</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, education, smoking, body mass index, diabetes, cardiovascular disease, angina, cholesterol, and systolic blood pressure.

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**Table 4. Association between Aspirin Use and Early Age-Related Macular Degeneration**

<table>
<thead>
<tr>
<th>Aspirin Use</th>
<th>Aging Macula Disorder Grade 1 (n = 1652): Odds Ratio (95% Confidence Interval)</th>
<th>Aging Macula Disorder Grade 2 (n = 463): Odds Ratio (95% Confidence Interval)</th>
<th>Aging Macula Disorder Grade 3 (n = 114): Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted for Age and Gender</td>
<td>Adjusted for All Potential Confounders*</td>
<td>Adjusted for Age and Gender</td>
</tr>
<tr>
<td>Never</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Monthly or less</td>
<td>1.20 (0.96–1.49)</td>
<td>1.19 (0.96–1.47)</td>
<td>1.10 (0.85–1.41)</td>
</tr>
<tr>
<td>At least once weekly but less than daily</td>
<td>1.18 (0.96–1.45)</td>
<td>1.19 (0.98–1.45)</td>
<td>1.40 (0.76–2.60)</td>
</tr>
<tr>
<td>Daily</td>
<td>1.24 (1.07–1.44)</td>
<td>1.27 (1.09–1.48)</td>
<td>1.34 (1.12–1.61)</td>
</tr>
<tr>
<td>P trend</td>
<td>0.002</td>
<td>0.001</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, cardiovascular disease, smoking, and cholesterol.
anticoagulant intake and 3.8 (95% CI, 1.9–7.5) for aspirin use only. There were 3.75 more subretinal hemorrhages in AMD patients taking daily aspirin versus no aspirin, and these hemorrhages on average were 3 times larger than in nonaspirin users.

Two trials reported a possible nonsignificant, protective effect of aspirin use on AMD. The Physicians’ Health Study (PHS) was a randomized trial comparing 325 mg aspirin and 50 mg β-carotene on alternative days with placebo; 20% of both groups used multivitamins. The PHS was based on self-reported use and used a category of AMD with vision loss of 20/30 or worse. Most AMD (72%) was early AMD (drusen, RPE changes or both), 8% had dAMD, and 20% were described as having exudative changes. The prevalences of AMD on average were 10 times lower than in population-based studies, and the authors stated that the PHS was a highly selected, healthier-than-normal cohort, with a 6-fold lower mortality rate compared with the general population. The relative risk for aspirin (n = 25) compared with placebo (n = 32) was 0.78 (95% CI, 0.46–1.32). In the Women’s Health Study (WHS), 100 mg aspirin was combined with vitamin E, while β-carotene was given for a median duration of 2.5 years. Of all participants, 37% took multivitamin supplements. Also in the WHS, the 10-year incidences of early and late AMD were 10 and 25 times lower than in the previously mentioned population-based studies. The number of cases of visually significant AMD (n = 245) was considerably larger than in the PHS; 80% were early AMD (drusen, RPE changes, or both). The hazard ratio for aspirin (n = 111) compared with placebo (n = 134) was 0.82 (95% CI, 0.64–1.06). For advanced AMD, the hazard ratio based on 26 cases in the aspirin group and 29 cases in the placebo group was 0.90 (95% CI, 0.53–1.52). For all AMD cases, regardless of vision loss, the hazard ratio for aspirin (n = 302) compared with placebo (n = 291) was 1.03 (95% CI, 0.88–1.21). The combined hazard ratio from the PHS and WHS trials based on visually significant AMD (mostly early AMD) was 0.82 (95% CI, 0.65–1.03). Thus, neither these trials individually, nor in combination, provide convincing evidence for the benefit or adverse effect of aspirin on AMD.

Whether confounding by indication in part could explain the association between aspirin consumption and AMD was considered in our study. For example, one might expect that persons with arthritis would take more aspirin. Arthritis was mentioned to be associated with AMD in 1 study without further details, and the AREDS found an association (P < 0.15) between arthritis and prevalent AMD. However, in their incidence study, arthritis was not associated with early or late AMD. Daily aspirin use also may be observed by those with a history of CVD. Cardiovascular disease was associated with aspirin use (Table 1), and CVD was an independent risk factor for wAMD, thus fulfilling the necessary requirements for a potential confounder. However, the ORs for aspirin use and wAMD were virtually unchanged when CVD was included in the analysis, indicating that the association of aspirin with AMD was independent of any association with CVD and was not confounded by CVD. There was also no evidence that the effect of aspirin on AMD in those with CVD was different from those without CVD (P = 0.6 for interaction with CVD and aspirin use), nor was there an interaction between angina and aspirin use. Neither CVD nor angina was associated with any stage of early AMD, and these disorders were not confounders of the observed association with aspirin. Although an association with CVD and wAMD was found in the data, the evidence from other studies on the association with CVD is inconsistent. A meta-analysis of 5 prospective studies and 7 cross-sectional studies found no association of CVD with wAMD. A significant association was observed only in the meta-analysis of 4 case-control studies.

Aspirin may act in several ways. Its most common effect is by irreversibly inhibiting prostaglandin-endoperoxide synthetase 1, similar to cyclooxygenase-1, and partly inhibiting prostaglandin-endoperoxide synthetase 2. Prostaglandin-endoperoxide synthetase 2 is expressed in human RPE and in surgically excised choroidal neovascular membranes. Aspirin inhibits thromboxane A2, and it uncouples oxidative phosphorylation in cartilage and liver mitochondria, thus buffering and transporting protons. Finally, aspirin induces the formation of nitric oxygen radicals in the body, which have been shown in mice to have an independent mechanism of reducing inflammation. This reduces leukocyte adhesion, which is an important step in immune response to infection. In the authors’ view, these mechanisms do not provide sufficient explanation for the association between aspirin and AMD. The inhibition of cyclooxygenase 1 and prostaglandin-endoperoxide synthetase 2 by aspirin, however, may reduce the synthesis of prostacyclin, an endothelium-derived vasodilator in blood vessels. This may lead to hypoxia and thus to neovascularization. Another hypothetical mechanism may be that aspirin disturbs the fine balance between lipid oxidation, in particular low-density lipoprotein, by its direct action and its own metabolites that protect against lipid oxidation.

There are several points in this study that warrant caution in interpreting the results. This was a cross-sectional study, and the possibility that people with AMD took aspirin after experiencing visual problems cannot be excluded. This is unlikely to explain the associations observed for early AMD because this in general does not create visual problems. There are no data regarding the amount of aspirin the participants used. In a meta-analysis of 31 trials including nearly 200,000 patients, however, daily aspirin intake of less than 100 mg was associated with bleeding, without mention of ocular hemorrhages, but with a lower risk than aspirin intake of 100 mg or more. In a study of AMD patients whose average aspirin intake was 100 mg/day, the OR for severe subretinal hemorrhage was 7.99; so, one could extrapolate that our findings may even be explained by these low doses. Confounding by indication cannot be ruled out completely, despite efforts to eliminate the potential influence of CVD or angina in the analyses. There are no data on other morbidities, such as arthritis, for which aspirin may be indicated. However, for these diseases to be confounders of the association with aspirin, they themselves would have to be associated strongly with AMD. As discussed previously, the evidence for an association between arthritis and AMD is extremely weak. Recall error may have
occurred when respondents switched other pain killers with aspirin, but because there is no reason to assume that the opposite would not have occurred to the same extent, this probably would not have had a strong impact on the analyses. It is possible that participants incorrectly reported their CVD history, leading to residual confounding and measurement error. The protocol attempted to minimize misreporting by asking about serious events such as heart attack and stroke and also recorded the date of the event. Expected relationships for CVD were found, such as being more common in men (19% of men reported a history of heart attack or stroke compared with 10% of women, \(P<0.001\)), in older people (10% of people aged 65–69 compared with 17% of people aged 70 years and older, \(P<0.01\)), in those with diabetes (23% of those with diabetes compared with 12% of those without diabetes, \(P<0.0001\)), and in those with angina (41% of those with angina compared with 10% of those without, \(P<0.00001\)). Former smokers were more likely to report CVD (20% of former smokers and 13% of current smokers compared with 10% of never smokers, \(P<0.0001\)). Strengths of the present study include the random sampling of the study population, the standardized documentation of AMD by photography and robust validated grading procedures to assign severity status, the use of standardized protocols for determining medication use, and the recording of important confounders in all centers. Possible underreporting of reticular drusen by grading on color images and not, for example, by autofluorescence, fluorescein angiography, or optical coherence tomography does not seem to alter the conclusions, because this would have occurred nondifferentially in both aspirin users and nonusers.

There are increasing reports of both nonocular and ocular hemorrhages with aspirin use. A recent meta-analysis of the major trials of aspirin reported that there was an increase in hemorrhagic stroke, gastrointestinal bleeds, and extracranial bleeds in those randomized to aspirin. The authors concluded that for primary prevention of coronary heart disease, there was little net benefit of aspirin because of its adverse effects. The studies reviewed above highlight the risk of intraocular hemorrhages in patients with wAMD taking aspirin. In view of these concerns, the authors considered it important to present their results to the scientific and clinical community to draw attention to the possible adverse effect of aspirin on AMD and to stimulate other studies with data on aspirin use and AMD to investigate these effects.

### References

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Footnotes and Financial Disclosures

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