The Association of Aspirin Use With Age-Related Macular Degeneration

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Objective: To determine whether regular aspirin use is associated with a higher risk for developing age-related macular degeneration (AMD) by using analyzed data from a 15-year prospective cohort.

Methods: A prospective analysis was conducted of data from an Australian population-based cohort with 4 examinations during a 15-year period (1992-1994 to 2007-2009). Participants completed a detailed questionnaire at baseline assessing aspirin use, cardiovascular disease status, and AMD risk factors. Age-related macular degeneration was graded side-by-side from retinal photographs taken at each study visit to assess the incidence of neovascular (wet) AMD and geographic atrophy (dry AMD) according to the international AMD classification.

Results: Of 2389 baseline participants with follow-up data available, 257 individuals (10.8%) were regular aspirin users and 63 of the 2389 developed neovascular AMD. Persons who were regular aspirin users were more likely to have incident neovascular AMD: the 15-year cumulative incidence was 9.3% in users and 3.7% in nonusers. After adjustment for age, sex, smoking, history of cardiovascular disease, systolic blood pressure, and body mass index, persons who were regular aspirin users had a higher risk of developing neovascular AMD (odds ratio [OR], 2.46; 95% CI, 1.25-4.83). The association showed a dose-response effect (multivariate-adjusted $P = .01$ for trend). Aspirin use was not associated with the incidence of geographic atrophy (multivariate-adjusted OR, 0.99; 95% CI, 0.59-1.65).

Conclusion: Regular aspirin use is associated with increased risk of incident neovascular AMD, independent of a history of cardiovascular disease and smoking.

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ASPIRIN IS ONE OF THE MOST widely used medications worldwide, with more than 100 billion tablets consumed each year.[1] The benefits of aspirin in secondary prevention of recurrent cardiovascular disease (CVD), such as myocardial infarction and ischemic stroke, are well established and outweigh the increased risk for gastrointestinal and intracranial bleeding.[2] Aspirin is also widely used for primary prevention of CVD, although its value in low-risk individuals is less certain[3] and has been questioned.[2,4] Recently, evidence has accumulated that aspirin may also reduce the incidence of cancer and cancer-related mortality.[5]

Age-related macular degeneration (AMD) is a leading cause of blindness in older persons.[6] Until very recently, vision loss from AMD was largely irreversible. Despite extensive studies, cigarette smoking remains the only consistently reported preventable risk factor for AMD.[7]

Recently, a cross-sectional study[8] of 4691 older individuals found that, controlling for age and cardiovascular risk factors, regular aspirin use was associated with AMD, particularly the more visually devastating neovascular (wet) form. This observation is of significant concern and has generated substantial publicity in the lay media.[9-11] If these results reflect a true causal relationship, there are serious implications for the millions of people using aspirin therapy. Notably, other studies[12-18] that have examined this relationship have reported inconsistent findings, ranging from no association to slightly increased risk and even to possibly beneficial effects with aspirin use. Few studies have investigated whether aspirin use is prospectively associated with incident AMD beyond 5 years' follow-up.

See Invited Commentary and Editor's Note at end of article

In this study, we prospectively examined the relationship of regular aspirin use to 15-year incidence of AMD, particularly neovascular AMD, in the Blue Moun-

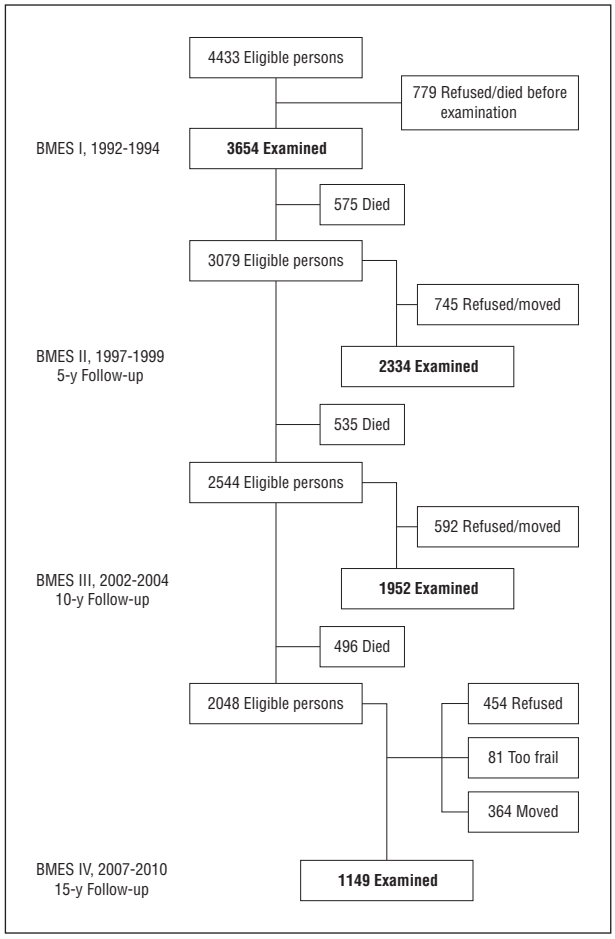

Figure 1. Flowchart of the Blue Mountains Eye Study (BMES) participants during 15 years of follow-up.

tains Eye Study (BMES), a population-based cohort of older participants designed to study the prevalence, incidence, and risk factors of eye disease.

METHODS

STUDY POPULATION

The BMES is a population-based cohort study of eye disease in an urban Australian population aged 49 years or older, details of which have been reported.[19-23] **Figure 1** shows the number of participants examined at each follow-up visit during the next 15 years. For the purposes of the present study, we included data from 2389 participants. The Human Research Ethics Committees of the Western Sydney Area Health Service and University of Sydney approved all examinations. Signed informed consent was obtained from participants at each examination.

ASSESSMENT OF AMD

At each visit, 30° stereoscopic retinal photographs of the macula and other retinal fields of both eyes were taken as described previously[21] (Zeiss FF3 fundus camera; Carl Zeiss). Details of photographic grading for AMD lesions performed in this study have been reported.[21,22] Assessments of intergrader and intragrader reliability showed good agreement for grading of specific AMD lesions, with quadratic weighted κ values ranging from 0.64 to 0.93 and 0.54 to 0.94, respectively.[21]

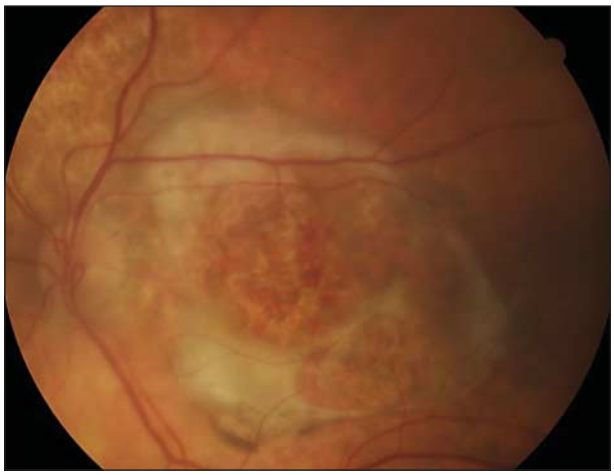

Figure 2. Left eye retinal photograph of a participant with regular aspirin use who developed neovascular age-related macular degeneration with an extensive subretinal fibrous scar.

Neovascular (wet) AMD was defined as serous or hemorrhagic detachment of the sensory retina or retinal pigment epithelium, presence of subretinal or subretinal pigment epithelium hemorrhage, or subretinal fibrous scarring[24] (**Figure 2**). Geographic atrophy (dry AMD) was defined as a discrete area, at least 175 μm in diameter, characterized by a sharp border and presence of visible choroidal vessels, using the definitions of the international AMD classification.[24] Incident early AMD was defined as the absence of neovascular or atrophic AMD and the presence of either (1) large (>125 μm diameter), indistinct soft or reticular drusen or (2) large, distinct soft drusen and retinal pigmentary abnormalities (hyperpigmentation or hypopigmentation)[21,24] in either eye. Further details of AMD grading are reported elsewhere.[21,22]

ASSESSMENT OF ASPIRIN USE

We determined the use of aspirin and other medications during a structured interview using a standard questionnaire.[16,19,25] We defined regular use of aspirin as frequency of once or more per week in the past year and confirmed this with a current medication list where participants listed all the medications they had taken for at least 1 month before the study examination. This list was then checked against the medication bottles that participants were asked to bring to the examination. Occasional use was defined as a frequency of less than once per week in the past year. Nonregular aspirin users included nonusers and occasional users. Although we did not collect information on aspirin dosage, most aspirin use in Australia is prescribed at 150 mg daily.

ASSESSMENT OF OTHER RISK FACTORS

At baseline, blood pressure was measured after participants had been comfortably seated for at least 5 minutes, using the same mercury sphygmomanometer with appropriate cuff size. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared, and smoking status was defined from history as never smoked, ex-smoker, and current smoker (which included individuals who had ceased smoking within the past 12 months). A history of CVD was defined as participant-reported previous diagnosis of angina, myocardial infarction, or stroke. We measured fasting blood glucose and fasting total cholesterol levels and defined diabetes mellitus as a physician diagnosis of diabetes or a fasting blood glucose level

Table 1. Baseline Characteristics of Regular and Nonregular Aspirin Users[a]

Characteristic[b]	Regular Aspirin Users (n = 257)	Nonregular Aspirin Users (n = 2132)	*P* Value
Age, mean (95% CI), y	67.7 (66.7-68.7)	63.7 (63.4-64.1)	<.001
Age group, y			
<60	16.3	34.0	<.001
60-69	40.5	41.0	
70-79	34.6	21.2	
≥80	8.6	3.8	
Female sex	52.1	58.2	.045
History of stroke	10.7	2.3	<.001
History of heart disease	39.5	11.2	<.001
History of diabetes mellitus	10.8	5.8	.03
Presence of hypertension	51.6	41.5	.009
Systolic blood pressure, mean (95% CI), mm Hg	146.6 (144.5-148.6)	146.1 (145.4-146.8)	.67
BMI, mean (95% CI)	26.4 (26.0-26.9)	26.1 (25.9-26.3)	.22
Fish consumption	63.6	58.8	.18
White blood cell count, mean (95% CI), /μL	5920 (5800-6030)	6030 (5990-6070)	.07
Total serum cholesterol level, mean (95% CI), mg/dL	257.9 (251.0-266.0)	257.9 (248.2-253.3)	.06
Smoking status			
Never	48.7	53.6	.37
Past	37.2	34.1	
Current	14.1	12.3	

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).
SI conversion factors: to convert white blood cell count to $\times 10^9$/L, multiply by 0.001; to convert total serum cholesterol to millimoles per liter, multiply by 0.0259.
[a] Data are given as percentage of participants unless otherwise indicated.
[b] Age-adjusted except for age.

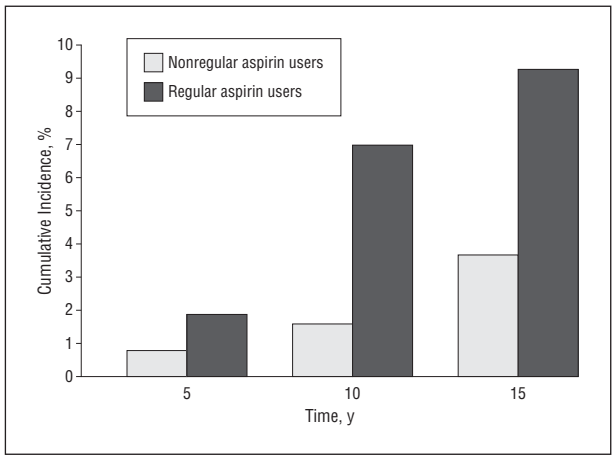

Figure 3. Cumulative incidence of neovascular age-related macular degeneration by time intervals. Cumulative incidence was estimated using the Kaplan-Meier (product limit) method.

of 126 mg/dL or more (to convert to millimoles per liter, multiply by 0.0555). Data on DNA were available from 2027 participants; in 2009, we genotyped the complement factor H (*CFH*) single-nucleotide polymorphism rs1061170 (*Y402H*) in exon 9 in these individuals, using polymerase chain reaction amplification in a volume of 5 μL (including 1 × TaqMan Universal PCR Master Mix; Applied Biosystems).[26]

STATISTICAL ANALYSES

We used commercial software (SAS, version 9.2; SAS Institute Inc) for statistical analyses. Discrete logistic models[20,27] were used to assess the association between regular use of aspirin and incident neovascular as well as atrophic and early AMD at any of the 3 follow-up time points (5, 10, and 15 years). This time-dependent analytical approach allows data on persons who were right censored (not seen after the 5- or 10-year examination because of death or nonparticipation) to be included in the estimates. Cumulative incidence was estimated using the Kaplan-Meier (product limit) survival approach. The models adjusted for potential confounders, including age, sex, smoking, BMI, history of CVD, and systolic blood pressure. Odds ratios (ORs) and 95% CIs are presented. Supplementary analyses using propensity scores are also presented.

RESULTS

Of 2389 participants at baseline, 257 individuals (10.8%) were regular aspirin users as confirmed by their medication lists and/or bottles. Regular users were older and more likely to have hypertension, CVD, and diabetes mellitus than were those who were not regular aspirin users (**Table 1**).

After the 15-year follow-up, 63 individuals developed incident neovascular AMD. The cumulative incidence of neovascular AMD among nonregular aspirin users was 0.8% at 5 years, 1.6% at 10 years, and 3.7% at 15 years; among regular aspirin users, the cumulative incidence was 1.9% at 5 years, 7.0% at 10 years, and 9.3% at 15 years, respectively (**Figure 3**). Regular aspirin use was significantly associated with an increased incidence of neovascular AMD (age-, sex-, and smoking-adjusted OR, 2.37; 95% CI, 1.25-4.49) (**Table 2**). The association remained unchanged after further adjustment for history of CVD, BMI, and systolic blood pressure (multivariate-adjusted OR, 2.46; 95% CI, 1.25-4.83). Regular aspirin use was not associated with an increased risk of geographic atrophy (multivariate-adjusted OR, 0.99; 95% CI, 0.59-1.65).

Table 2. Frequency of Aspirin Use and 15-Year Incident Neovascular Age-Related Macular Degeneration

Aspirin Use	No. at Risk[a]	% With Neovascular AMD	Odds Ratio (95% CI)	
			Age-, Sex-, Smoking-Adjusted	Multivariate-Adjusted[b]
Nonusers	1524	2.2	1 [Reference]	1 [Reference]
Occasional users	375	2.9	1.26 (0.63-2.55)	1.26 (0.62-2.55)
Regular users	257	5.8	2.37 (1.25-4.49)	2.46 (1.25-4.83)
P value for trend		.004	.01	.01

Abbreviation: AMD, age-related macular degeneration.
[a] Two hundred forty-two participants denied taking aspirin regularly but did not provide sufficient information to enable classification as nonusers or occasional users. Their data were not used in the analyses for this table.
[b] Multivariate models are adjusted for age, body mass index, systolic blood pressure (all continuous variables), sex (male or female), smoking (never, past, or current), and history of cardiovascular disease (angina, myocardial infarction, or stroke) (present or absent).

Table 3. Regular Aspirin Use and 15-Year Incident Neovascular AMD by CVD Status

Aspirin Use	History of CVD[a]				No History of CVD			
	No. at Risk	No. (%) With Neovascular AMD	OR (95% CI)		No. at Risk	No. (%) With Neovascular AMD	OR (95% CI)	
			Age-, Sex-, Smoking-Adjusted	Multivariate-Adjusted[b]			Age-, Sex-, Smoking-Adjusted	Multivariate-Adjusted[b]
Nonregular	265	4 (1.5)	1 [Reference]	1 [Reference]	1867	44 (2.4)	1 [Reference]	1 [Reference]
Regular	123	8 (6.5)	4.39 (1.25-15.43)	4.36 (1.24-15.32)	134	7 (5.2)	1.93 (0.85-4.38)	1.90 (0.84-4.34)

Abbreviations: AMD, age-related macular degeneration; CVD, cardiovascular disease (angina, myocardial infarction, or stroke); OR, odds ratio.
[a] Interaction for history of CVD, $P = .31$.
[b] Multivariate models were adjusted for age, sex, smoking, and systolic blood pressure.

Table 4. Regular Aspirin Use and 15-Year Incident Neovascular AMD by *CFHY402H* Polymorphism Status

Aspirin Use	Any *CFHY402H* Allele[a]				No *CFHY402H* Allele			
	No. at Risk	No. (%) With Neovascular AMD	OR (95% CI)		No. at Risk	No. (%) With Neovascular AMD	OR (95% CI)	
			Age-, Sex-, Smoking-Adjusted	Multivariate-Adjusted[b]			Age-, Sex-, Smoking-Adjusted	Multivariate-Adjusted[b]
Nonregular	1076	38 (3.5)	1 [Reference]	1 [Reference]	723	7 (1.0)	1 [Reference]	1 [Reference]
Regular	139	8 (5.8)	1.58 (0.71-3.52)	1.74 (0.76-4.01)	76	4 (5.3)	4.16 (1.17-14.79)	4.17 (1.05-16.49)

Abbreviations: AMD, age-related macular degeneration; *CFH*, complement factor H; OR, odds ratio.
[a] Interaction for any *CFGY402H* allele, $P = .24$.
[b] Multivariate models were adjusted for age, sex, smoking, and systolic blood pressure.

Incidence rates for neovascular AMD increased with increasing aspirin use, from 2.2% (nonusers) to 2.9% (occasional users) to 5.8% (regular users) (Table 2). Increasing frequency of aspirin use was associated with an increasing risk of neovascular AMD (multivariate-adjusted $P = .01$ for trend).

Baseline participants without follow-up data (n = 1082) were older (70.7 vs 64.3 years, $P < .001$) and were more likely to be female (57.9% vs 53.4%, $P = .03$), smokers (17.8% vs 12.9%, $P < .001$), and have a history of CVD (27.3% vs 16.2%, $P < .001$). The groups had similar rates of aspirin use (11.6 vs 10.7, $P = .47$).

We also performed the secondary analyses (**Table 3** and **Table 4**). First, in persons with a history of CVD, regular aspirin use was associated with a 4-fold increased risk of incident neovascular AMD after adjustment for AMD risk factors (OR, 4.36; 95% CI, 1.24-15.32) (Table 3). The association was weaker and not statistically significant in persons without a history of CVD (OR, 1.90; 95% CI, 0.84-4.34). Next, we stratified by *CFHY402H* polymorphism status (Table 4). The association of regular aspirin use with incident neovascular AMD was stronger in persons without the polymorphism (OR, 4.17; 95% CI, 1.05-16.49) and weaker in those with either homozygous or heterozygous genotypes of *CFHY402H* (OR, 1.74; 95% CI, 0.76-4.01). Geographic atrophy was not associated with aspirin use in persons with or without the *CFHY402H* polymorphism (OR, 0.80; 95% CI, 0.20-3.21 and OR, 1.89; 95% CI, 0.21-17.40, respectively). There was no significant interaction between a history of CVD or the *CFHY402H* polymorphism and aspirin use on the risk of neovascular AMD ($P = .31$ and $P = .24$, respectively). Finally, additional adjustment for other risk and protective factors, including regular fish consumption, white blood cell count, total cholesterol level, and presence of diabetes mellitus did not materially alter the association between regular aspirin use and incident neovascular AMD (OR, 2.05; 95% CI, 0.96-4.40; $P = .06$).

Aspirin use was not associated with incident early AMD in our study. During the follow-up period, 37 regular aspirin users (17.8%) developed incident early AMD compared with 285 nonusers (15.6%) (age-, sex-, and smoking-

adjusted OR, 0.94; 95% CI, 0.65-1.37; data not shown). The association of aspirin use and incident neovascular AMD was similar in persons with (OR, 1.87; 95% CI, 0.51-6.77) and without (OR, 2.38; 95% CI, 1.13-5.03) early AMD at baseline but was significant only in the latter group. There was no evidence that the existence of early AMD modified the association between aspirin use and incident neovascular AMD ($P = .79$ for interaction).

Because aspirin use is strongly associated with painful conditions and CVD, we examined whether other medications associated with these conditions had a similar association with neovascular AMD. At baseline, acetaminophen was used by 5.8% of participants and β-blockers were used by 15.2%. None of these medications was significantly associated with neovascular AMD, and including them in our multivariate model with age, sex, smoking, history of CVD, systolic blood pressure, and BMI did not change our findings. We also performed analyses using age, sex, smoking, history of CVD, systolic blood pressure, BMI, diabetes mellitus, regular fish consumption, total cholesterol level, and white blood cell count to calculate a propensity score. When used in the model instead of the same set of covariates, these factors resulted in slightly stronger findings when adjusted for propensity score (OR, 2.31; 95% CI, 1.11-4.82; $P = .03$) and when multivariate adjusted (OR, 2.05; 95% CI, 0.96-4.40; $P = .06$).

COMMENT

Age-related macular degeneration is responsible for blindness in up to 500 000 Americans,[6] with a prevalence of approximately 1.5% in Americans older than 55 years, 1.8% in Australians, and 1.6% in Europeans of similar age.[28] Surveys suggest that people fear blindness from AMD more than they do stroke and myocardial infarction.[29] In this study we found that regular aspirin use was associated with risk of neovascular AMD during a 15-year follow-up period, independent of history of CVD, smoking, and other potential AMD risk factors.

Our results therefore confirm the findings from the European cross-sectional survey that reported a 2-fold increased prevalence of neovascular AMD (OR, 2.22; 95% CI, 1.61-3.05) among regular aspirin users.[8] Other studies have provided conflicting results, with a small number of case-control studies[13] reporting increased frequency of subretinal and vitreous hemorrhage with aspirin use in persons with AMD and 2 large randomized clinical trials, the Physicians' Health Study[14] and the Women's Health Study,[15] reporting no increased AMD risk during 7 to 10 years among aspirin users. However, these studies relied mainly on self-reported AMD diagnosis or used AMD definitions that have been criticized[30] and, importantly, did not examine neovascular AMD and geographic atrophy separately. In contrast, the case-controlled Age-Related Eye Disease Study[18] (AREDS) reported that the use of anti-inflammatory medications, including aspirin, had a protective effect on geographic atrophy. An earlier report from the BMES,[16] the Beaver Dam Eye Study,[17] and pooled findings from the BMES and Beaver Dam Eye Study plus the Rotterdam Study[12] reported no association of aspirin use at baseline with the 5-year incidence of any AMD, although there was a suggestion of increased risk for late AMD (ie, combined neovascular AMD and geographic atrophy) in the earlier report.[16]

Several findings from our study warrant further discussion. The increased risk of neovascular AMD was detected only after 10 or 15 years, suggesting that cumulative dosage is important in pathogenesis. This long lead time may explain why previous studies, including the earlier report,[16] failed to detect this association. The *CFHY402H* polymorphism is a strong risk factor for all forms of AMD and codes for a CFH regulatory protein with impaired ability to inhibit complement pathway activation.[31] We speculate that aspirin, which is known to increase complement activation in vitro and in vivo, partly through inhibition of the C1 inactivator,[32] may also be associated with incident AMD via complement pathways. Other proposed mechanisms include disruption of prostacyclin synthesis and increased lipid metabolism.[8]

Given the widespread use of aspirin, any increased risk of disabling conditions and morbidity will be significant and affect many people. Although aspirin is one of the most effective CVD treatments and reduces recurrent CVD events by one-fifth,[2] some meta-analyses[2] have called into question the efficacy of aspirin use in CVD primary prevention and highlighted the significant adverse effects, such as increased gastrointestinal, intracerebral, and extracranial hemorrhage. Our present study now raises the possibility that the risk of neovascular AMD may also need to be considered. This potential risk appears small (9.3% after 15 years) and should be balanced with the significant morbidity and mortality of suboptimally treated CVD. Another factor to consider is that there are now effective but costly treatments for neovascular AMD comprising regular injections of anti–vascular endothelial growth factor, which may need to be accounted for in cost-benefit studies of aspirin efficacy. Any decision concerning whether to stop aspirin therapy is thus complex and needs to be individualized. Currently, there is insufficient evidence to recommend changing clinical practice, except perhaps in patients with strong risk factors for neovascular AMD (eg, existing late AMD in the fellow eye) in whom it may be appropriate to raise the potentially small risk of incident neovascular AMD with long-term aspirin therapy.

Strengths of our study include its population-based, prospective design with long-term follow-up and careful ascertainment of aspirin use, AMD subtypes, and major confounders. Major limitations include, first, the possibility of residual confounding, such as by indication, whereby CVD rather than aspirin use contributes to the increased AMD risk. We note that, after adjustment for additional CVD risk factors (BMI, blood pressure, blood total cholesterol level, diabetes mellitus, fish consumption, inflammatory markers), our findings became marginally nonsignificant (OR, 2.05; 95% CI, 0.96-4.40; $P = .06$), likely because of reduced power from additional covariates in the model. To address this, we performed propensity score analysis. This incorporates the same variables as an indicator variable represented by the propensity score, and adjusting for this score in the model

to replace several covariables resulted in slightly stronger findings, supporting a persistent association. Furthermore, other medications associated with painful conditions and CVD (acetaminophen and β-blockers) were not associated with incident wet AMD, and adjusting for them in the multivariate model did not change our findings. Second, aspirin use was determined only at baseline and was not updated. If participants started taking aspirin after the baseline assessment, they would have been classified as nonregular users. This would bias our findings toward the null, that is, reduce the magnitude of any associations of aspirin use with incident AMD, if any association existed. Including aspirin users with less than 10 years' duration in our analyses could dilute our findings to a large extent, since our a priori hypothesis was that long-term (>10 years) aspirin use is associated with incident AMD. Our findings appear to bear this out, as shown in Figure 3, where the association became evident only after 10 to 15 years of follow-up. Cessation of aspirin use during follow-up would tend to bias toward the null as well, but since most persons with regular aspirin use continue it for life, we believe that this is unlikely to cause a large bias. Third, we have no data on the indications for aspirin use in our cohort and are unable to adjust for all possible indications (eg, rheumatologic conditions). Nonetheless, acetaminophen was not significantly associated with neovascular AMD, with a multivariate-adjusted OR of 1.04 (95% CI, 0.61-1.79). Fourth, our ascertainment of aspirin use was through questionnaire (with confirmation using medication bottles brought to examinations by participants), the assessment of geographic atrophy did not use fundus autofluorescence, the study design was observational, and the participants were mostly a homogeneous white population. Our results should thus be viewed as potentially influenced by ascertainment bias (ie, underreporting of regular aspirin use and underdetection of geographic atrophy) and nonrandom allocation of aspirin use and may not be applicable to nonwhite populations with different risk profiles for CVD and AMD. However, we anticipate the ascertainment bias from aspirin use to be nondifferential and occur equally in the groups who developed and did not develop incident AMD and thus to dilute the observed association toward the null. Our results may be influenced by the low proportion of participants who attended 15-year follow-up examinations. Participants with CVD were less likely to be followed up because of higher mortality and were more likely be regular aspirin users and develop incident AMD.[7] We could have missed persons who were using aspirin and would have gone on to develop incident AMD had they lived longer. This would, however, tend to attenuate the association and bias our findings toward the null.

In summary, we report from this prospective population-based cohort that regular aspirin use is associated with a 2-fold increase in risk of neovascular AMD during a 15-year period. These findings appear to be independent of CVD, smoking, and other risk factors.

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Author Contributions: Dr Wang had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Liew, Mitchell, Wong, and Wang. *Acquisition of data:* Mitchell, Wong, and Wang. *Analysis and interpretation of data:* Liew, Wong, Rochtchina, and Wang. *Drafting of the manuscript:* Liew and Wong. *Critical revision of the manuscript for important intellectual content:* Liew, Mitchell, Wong, Rochtchina, and Wang. *Statistical analysis:* Liew and Rochtchina. *Obtained funding:* Mitchell and Wang. *Administrative, technical, and material support:* Mitchell and Wong. *Study supervision:* Liew, Mitchell, Wong, and Wang.
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INVITED COMMENTARY

Relationship of Aspirin Use With Age-Related Macular Degeneration

Association or Causation?

In their prospective population-based cohort study of 2389 patients in the Blue Mountains region in Australia, Liew and colleagues[1] report on the association of long-term use of low-dose aspirin and age-related macular degeneration (AMD), the leading cause of blindness in Western countries. The principal finding is that regular aspirin use is associated with an approximately 2.5-fold greater risk of incident AMD. This relationship is specific for late neovascular (wet) AMD but not geographic atrophy (dry AMD) and is independent of potential confounders, such as cardiovascular disease, smoking, age, sex, systolic blood pressure, and body mass index.

STRENGTH OF EVIDENCE

This study has important strengths and limitations. It provides evidence from the largest prospective cohort with more than 5 years of longitudinal evaluation reported to date using objective and standardized ascertainment of AMD. Additional strengths include the use of standardized protocols for determining medication use, the recording of detailed demographic and clinical information for risk adjustment, and appropriate methodologic approaches, such as multivariate logistic regression and propensity score adjustment, to minimize the impact of confounding.

The key limitation is the nonrandomized design of the study with its potential for residual (unmeasured or unobserved) confounding that cannot be mitigated by multivariate logistic regression or propensity score analysis. Limitations, such as the potential of recall and ascertainment bias, are addressed transparently, and reasonable arguments are offered to counter the effect of these biases on study results. Additional limitations that deserve attention include the modest strength of association (odds ratio, 2.0-2.5); incomplete data on other morbidities, such as arthritis, for which aspirin may be indicated; the potential for "overfitting" resulting in biased estimates because of the limited number of incident cases of AMD (n=63) and 10 or more candidate predictor variables; and the issue of missing data (only 56% of the cohort eligible for follow-up at >15 years were assessed). All of these limitations can potentially undermine the interpretation and threaten the validity of trial results.