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Long Term Use of Aspirin and Age-Related Macular Degeneration

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Abstract

Context—Aspirin is widely used for relief of pain and for cardio-protective effects. Its use is of concern to ophthalmologists when ocular surgery is being considered and also in the presence of age-related macular degeneration (AMD).

Objective—To examine the association of regular aspirin use with incidence of AMD.

Design, Setting, and Participants—A longitudinal population-based study of age-related eye diseases in Beaver Dam, Wisconsin. Examinations were performed every 5 years over a 20-year period (1988–1990 through 2008–2010). Participants were aged 43–86 years at the baseline examination. At subsequent examinations, study participants were asked if they had regularly used aspirin at least twice a week for more than 3 months.

Main Outcome Measure—The incidence of early AMD, late AMD, and 2 subtypes of late AMD (neovascular AMD and pure geographic atrophy) were assessed in retinal photographs according to the Wisconsin Age-Related Maculopathy Grading System.

Results—The mean duration of follow-up was 14.8 years. There were 512 incident cases of early (of 6243 person-visits at risk) and 117 incident cases of late AMD (of 8675 person-visits at risk) over the course of the study. Regular aspirin use 10 years prior to retinal examination was associated with late AMD (hazard ratio 1.63; 95% CI 1.01–2.63; P=0.05) with estimated incidence of 1.76% (1.17–2.64) in regular users and 1.03% (0.70–1.51) in non-users. For subtypes of late AMD, regular aspirin use 10 years prior to retinal examination was significantly associated with neovascular AMD (reported as hazard ratio 2.20; 95% CI 1.20–4.15; P=0.01) but not pure geographic atrophy (0.66; 0.25–1.95; P=0.45). Aspirin use 5 (0.86; 0.71–1.05; P=0.13) or 10 years prior (0.86; 0.65–1.13; P=0.28) to retinal examination was not associated with incident early AMD.

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Access to Data Statement: Dr. B. E. K. Klein had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conclusions—Among persons aged 43 years and older followed for 20 years, aspirin use 5 years prior to observed incidence was not associated with incident early or late AMD. However, regular aspirin use 10 years prior was associated with a small but statistically significant increase in the risk of incident late and neovascular AMD.

Keywords

aspirin; age-related macular degeneration; epidemiology

Aspirin use in the United States is widespread, with an estimated 19.3% of adults reporting regular consumption, and reported use increases with age.[1] Aspirin is used for temporary relief of pain and for arthritic or rheumatologic diseases[2] and for its anti-pyretic effects. It is considered a non-steroidal anti-inflammatory drug (NSAID) but it also suppresses thromboxanes by inactivation of cyclooxygenase, thus impairing the clot-enhancing action of platelets. This has made it attractive as a medical intervention for acute myocardial infarction; about half of persons who were told that they have heart disease reported taking aspirin every day or every other day.[1]

The results of cross-sectional studies of aspirin use and its relation to age-related macular degeneration (AMD) have been inconsistent.[3–5] AMD is a potentially blinding condition whose prevalence and incidence is increasing with the increased survival of the population, and regular use of aspirin is common and becoming more widespread in persons in the age range at highest risk for this disease. Therefore, it is imperative to further examine this potential association. The Beaver Dam Eye Study, a longitudinal study of age-related eye diseases, has followed an adult population aged 43–86 years at baseline at 5-year intervals over a 20-year period. This study provided the unique opportunity to investigate the link between AMD and aspirin use in a population which, by virtue of its age distribution and low attrition, permitted examination of the associations of aspirin use 5 and 10 years before observed incidence.

Methods

Participants

A private census of Beaver Dam, Wisconsin, was performed in 1987–1988 to identify all residents eligible for the study.[6] Participants were examined at the baseline examination (1988–1990) and every five years thereafter (1993–1995, 1998–2000, 2003–2005, 2008–2010) over a 20-year period. All data were collected with Institutional Review Board approval from the University of Wisconsin-Madison in conformity with all federal and state laws, the work was HIPAA compliant, and the study adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from every participant at each examination.

Participants were examined at the study site, a nursing home, or their home. By design, participants were requested to be seen on or near the anniversary date of their first examination. In this way, examinations occurred at regular 5-year intervals. For all person-visits included in analyses, 86% of visits occurred within 6 months of the target visit date. The same protocols for measurements relevant to this investigation were used at each examination.[7] Participants were asked if they regularly used aspirin at least twice per week for more than 3 months. This self-report of regular aspirin use was the main exposure measure of interest in our primary analysis because it was asked at every examination. Additional information concerning frequency of aspirin use (<1 every other day, 1 every other day, 1/day, 2/day, 3–7/day or ≥8/day) and dosage were obtained at the third, fourth, and fifth examinations. These data were used to calculate an estimated dose (in milligrams)

per day and were used for auxiliary analyses to examine the potential dosing effect of aspirin on incidence of AMD.

Participants were asked to bring all currently used medications to the examinations. All medications, including NSAIDs and anticoagulants (eg, warfarin), were recorded. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, and/or history of blood pressure medication use. Blood samples were obtained and analyzed for glycosylated hemoglobin A1c and inflammatory factors, eg, leukocyte count and C-reactive protein (CRP). CRP was measured only at the baseline examination, and leukocyte count was measured at the baseline and second examinations. Diabetes was defined as self-report confirmed by use of insulin or diet to control diabetes, self-report with glycosylated hemoglobin A1c level above 6.5%, or no self-report with glycosylated hemoglobin A1c above 7%.[8]

Photographs of the retina[7] were taken after pupillary dilation according to protocol[9] and graded in masked fashion by experienced graders using the Wisconsin Age-Related Maculopathy Grading System to assess the presence and severity of lesions associated with AMD.[9–11] Grading procedures, lesion descriptions, and detailed definitions of presence and severity appear elsewhere (see eMethods).[9]

The natural progression of this disease is described by the increase in level of severity. It is generally understood that an eye will have transitioned through each previous level (lower number in the scoring system) when it presents at a given severity level.

Statistical Analysis

We examined the relationship between self-reported regular aspirin use and incidence of early and late AMD in the presence of other known risk variables over 20 years of follow-up. Presence of early or late AMD was analyzed by person, combining the data from both eyes. Person-level variables were calculated at each visit for presence of early, late, neovascular AMD and pure GA. At a given visit, a person was considered free from a given type of AMD if both eyes were gradable and determined to be free of that type of AMD. A person was considered to have a specific type of AMD at a given examination if at least one eye had gradable photos and was determined to be prevalent of the given type of AMD. If information from one eye was missing and the other eye was free from the given type of AMD, the person-level data was considered missing at that examination.

To be eligible for incidence of a specified type of AMD (early, late, neovascular, pure GA), a participant must have been free of the given AMD outcome at the baseline examination and have complete AMD data from consecutive follow-up examinations, until incidence or censoring occurred. Further, to be included in analyses, a participant must have had complete data for self-reported aspirin use, age, sex, education, history of arthritis, and history of CVD.

The two types of late AMD are not mutually exclusive, and both types may appear in the same eye sequentially or simultaneously. Incidence of late AMD was calculated as the first incidence of pure GA or neovascular AMD. We followed the commonly accepted paradigm that once a person develops neovascular AMD they cannot be further classified as having developed pure GA (despite a change in the appearance of the fundus lesion); therefore, while a person who has prevalent or incident pure GA is still at risk of developing neovascular AMD, the converse is not true. In this way, there were more persons at risk of developing neovascular AMD than any late AMD or pure GA. Similarly, participants with early AMD were still at risk for developing late AMD; therefore, there were more participants in the risk set for late AMD than for early AMD.

For preliminary analyses, we calculated the overall percentage of persons incident for each combination of aspirin use 5 and 10 years prior to observed incidence (none at 5 and none at 10, 5 years only, 10 years only, 5 and 10 years). We then calculated the age- and sex-adjusted percentages for incidence for each combination. To explore the potential longitudinal association between aspirin use and AMD, we computed hazard ratios (HRs) for incidence of early and late AMD over 20 years with time-varying covariates updated at each examination. As the first incident cases were observed at the second examination and the main risk factor of interest was aspirin use at baseline, we refer to this as aspirin use "5 years prior". We also considered the hypothesis that the association between aspirin and development of AMD may not be apparent with exposure at only 5 years prior to incidence. Therefore, for this analysis we accounted for aspirin use at the examination 5 years prior to incidence as well as aspirin use reported at the previous examination, 10 years prior to observed incidence. When examining data which included aspirin use 10 years prior to incidence, those cases incident at the first interval were not included because aspirin use 5 years prior to the baseline examination was unknown. Because of this, the total interval for the longitudinal analysis of 10-year aspirin use is 15 years.

To establish the maximally adjusted statistical models, variables potentially associated with risk of AMD were first analyzed individually in age- and sex-adjusted models. These variables included body mass index, annual income, education, diabetes, systolic and diastolic blood pressure, hypertension, history of cancer, smoking (never, past, current), ever drinking, ever heavy drinking, history of arthritis, and history of CVD. All significant factors in the age- and sex-adjusted models were then included in a maximally adjusted model. The maximally adjusted model for early AMD included age, sex, education level, ever heavy drinking, smoking, and history of arthritis. The maximally adjusted model for late AMD and its subtypes included age, age^2, sex, education, heavy drinking history, and smoking. Lastly, non-significant predictors from the maximally adjusted model were removed to establish the most parsimonious model; only these data are presented. This resulted in adjustment for age, arthritis history, and education level in models for early AMD and age, age^2, and education level in models for late AMD. Interactions for potential reasons for aspirin use (arthritis and CVD history) with aspirin were tested.

To assess whether the timing of visits was driven by confounding factors, visits were divided into 3 groups: early (at least 6 months before the targeted visit date [the anniversary of the baseline visit]), late (more than 6 months after the targeted visit date), and on time (within 6 months of the targeted visit date). For the sensitivity analysis, observations from early or late visits were censored. The point estimates and confidence intervals (CIs) in the two models were very consistent; therefore the full models are presented.

To explore whether frequency and amount of aspirin used was associated with AMD, we examined the association between self-reported daily dose of aspirin (in milligrams) on the incidence of early and late AMD with available data from the third, fourth, and fifth examinations. We also modeled the effect of inflammatory factors (leukocyte count, interleukin-6, and CRP) on the association between aspirin and incidence of AMD. We then examined the relationship between any NSAID and incidence of AMD, and the relationship between warfarin and incidence of AMD.

All models presented were fitted using the discrete-time hazard model using the complementary log-log link function with time-varying predictors, with P values representing a 2-tailed test of significance with alpha level 0.05.[12] In this way, risk variables (eg, use of aspirin 5 and 10 years previously) were updated throughout the course of the study and the model thus captures the change in risk for incidence of AMD, and censoring is

accounted for appropriately. SAS software version 9.3 (SAS Institute, Cary, NC) was used for all analyses.

We also conducted a secondary, exploratory analysis to examine whether the data supported the notion that time since first report of regular aspirin use was associated with incidence of late AMD. For these models, the outcome of interest was incidence of AMD between the fourth and fifth examinations. Our exposure variable was first self-reported aspirin use 5, 10, 15, or 20 years prior to observed incidence, which was examined in two ways. First, we included only participants who reported using aspirin consistently at each examination following their first self-reported use, or never reported using aspirin regularly. Next, we included participants who were inconsistent in reporting regular aspirin use following their first self-report of regular aspirin use. Participants with missing aspirin data were excluded from both of these analyses. For these models, logistic regression was used with a two-tailed test of significance at alpha level 0.05.

Results

Of the 5924 eligible, 4926 (83%) persons aged 43–86 years participated in the baseline examination in 1988–1990. Ninety-nine percent of the population was white and 56% was female. The cohort was re-examined at 5- (n=3722), 10- (n=2962), 15- (n=2375) and 20-year (n=1913) follow-up examinations. There was greater than 80% participation among survivors at each examination.[13–15] The mean duration of follow-up time was 14.8 years, with a median duration of 15.9 years. Participants included in these analyses tended to be younger and have fewer comorbidities at baseline than those excluded (Table 1). For incident early AMD, 2547 persons of the 4926 seen at baseline were excluded from analysis (1008 had prevalent early or late AMD at baseline, 84 persons were missing a covariate, 448 were missing AMD data at baseline, and 1007 did not have data at the first follow-up examination). Overall, there were 2379 participants at risk for early AMD, of which 512 were incident, with a total of 6243 person-visits contributing to the analysis (Figure 1). For incidence of late AMD, 1794 persons of the 4926 seen at baseline were excluded from analysis (74 persons had prevalent late AMD at baseline, 104 were missing a covariate, 407 had missing AMD data at baseline, and 1209 had missing data at the first follow-up examination). There were 3132 participants at risk for developing late AMD, of which 117 were incident, with a total of 8621 person-visits included in analyses (Figure 2). The unadjusted incidence rate per 10 person-years was 0.164 for early AMD and 0.027 for late AMD.

There was no significant association of self-reported aspirin use 5 years prior to observed incidence of early AMD accumulated over 20 years (HR 0.86; 95% CI 0.71–1.05; P=0.13; age-sex adjusted incidence for users 9.55% [95% CI 8.27–11.01] vs. non-users 10.46% [95% CI 9.46–11.56], Table 2). The incidence of late AMD was greater in persons using aspirin 5 years previously than in non-users (age-sex adjusted incidence 1.4% [95% CI 0.97–1.87] vs. 1.0% [95% CI 0.74–1.39]), although the association was not significant (HR 1.21; 95% CI 0.84–1.74; P=0.31), and there was no significant association for either late AMD subtype (neovascular AMD: HR 1.07, 95% CI 0.68–1.67, P= 0.77; pure GA: HR 1.65, 95% CI 0.91–2.99, P=0.10) for those who reported aspirin use 5 years prior (age-sex adjusted incidence for neovascular AMD: 0.84% [95% CI 0.54–1.29]; pure GA: 0.59% [95% CI 0.36–0.95]) versus those who did not (age-sex adjusted incidence for neovascular AMD: 0.69% [0.48–0.99], pure GA: 0.35% [0.20–0.61], Table 2).

Because of the possibility of a lag in effect of first reported regular use of aspirin and AMD, we examined use at both 5 and 10 years prior to observed incidence. These data were combined and modeled as a 4-level non-ordinal categorical variable (Table 3). Only

incidence analysis over 15 years can be performed because of the lack of information regarding regular aspirin use prior to the baseline examination. The overall test for association was not significant for any category of aspirin use and incident early AMD (P=0.43), late AMD (P=0.20), neovascular AMD (P=0.07) and pure GA (P=0.20, Table 3). We then tested the main effects of aspirin use 5 and 10 years prior to observed incidence in this model. The main effect of aspirin use 5 years prior showed no significant association with incident early AMD (HR 0.93; 95% CI 0.70–1.23; P=0.60; age-sex adjusted incidence for users 9.0% [95% CI 7.6–10.7] vs. non-users 9.0% [95% CI 7.6–10.6]), late AMD (HR 0.91; 95% CI 0.57–1.46; P=0.69; age-sex adjusted incidence for users 1.3% [95% CI 0.9–1.9] vs. non-users 1.4% [95% CI 1.9–2.1]), neovascular AMD (HR 0.66, 95% CI 0.37–1.19; P=0.17; age-sex adjusted incidence for users 0.8% [95% CI 0.5–1.3] vs. non-users 1.1% [95% CI 0.7–1.6]), or pure GA (HR 2.25; 95% CI 0.75–6.72; P=0.15; age-sex adjusted incidence for users 0.6% [95% CI 0.4–1.1] vs. non-users 0.4% [95% CI 0.2–0.8]). The main effect of aspirin use 10 years prior was significant for predicting the incidence of late AMD (HR 1.63; 95% CI 1.01–2.63; P=0.045; age-sex adjusted incidence for users 1.8% [95% CI 1.2–2.6] vs. non-users 1.0% [95% CI 0.7–1.5]). When examining the relationships by late AMD subtype, neovascular AMD was significantly associated with such use (HR 2.20; 95% CI 1.20–4.15; P=0.01; age-sex adjusted incidence for users 1.4% [95% CI 0.9–2.1] vs. non-users 0.6% [95% CI 0.4–1.0]) but pure GA was not (HR 0.66; 95% CI 0.25–1.95; P=0.46; age-sex adjusted incidence for users 0.5% [95% CI 0.3–1.0] vs. non-users 0.5% [95% CI 0.3–0.9]). Similar analyses for the incidence of early AMD showed no significant associations with use of aspirin 10 years prior (HR 0.86; 95% CI 0.65–1.13; P=0.28; age-sex adjusted incidence for users 8.5% [95% CI 6.9–10.5] vs. non-users 9.5% [95% CI 8.3–10.9]).

History of arthritis and CVD, two common reasons for aspirin use, were analyzed to investigate the possibility of confounding by indication. No significant interactions were found in predicting early AMD between arthritis or CVD and aspirin use 5 years prior to incidence (arthritis P=0.16, CVD P=0.45) or 5 and 10 years prior (arthritis P=0.64, CVD P=0.33). Similarly, no significant interactions were found in predicting incidence of any form of late AMD between aspirin use 5 years prior and history of arthritis (P=0.28) or CVD (P=0.62), or with aspirin use 5 and 10 years prior with arthritis (P=0.16) or CVD (P=0.43).

Milligrams of aspirin per day were calculated for the third, fourth and fifth examination phases. No significant relationship was found between milligrams of aspirin per day taken 5 years prior to observed early AMD (P=0.53) or late AMD (P=0.22). Similarly, no significant relationship was found between milligrams of aspirin reported 5 and 10 years prior to observed incidence of early AMD (P=0.27) or late AMD (P=0.37).

We examined whether the association of aspirin to neovascular AMD was related to use of any NSAID and found no relationship between the use of any NSAID 10 years prior to incidence of neovascular AMD (P=0.33). We also investigated whether warfarin was associated with incidence of late AMD or its subtypes, and found no associations between AMD and warfarin use 5 years prior (late AMD P=0.56; neovascular AMD P=0.88; pure GA P=0.52) or 10 years prior (late AMD P=0.15; neovascular AMD non-estimable; pure GA P=0.89) to observed incidence.

To examine possible effects of systemic inflammation and the possible protective role of aspirin in the presence of evidence of systemic inflammation, we examined the associations of leukocyte count and CRP with incidence of AMD and their effects on the relationship between aspirin use reported 5 years prior and incident AMD. Neither were associated with incidence of early (leukocyte count P=0.13; CRP P=0.21) or late AMD (leukocyte count P=0.56; CRP P=0.29), and neither showed a significant interaction with aspirin use (early

AMD: leukocyte count P=0.87, CRP P=0.29; late AMD: leukocyte count P=0.25, CRP P=0.07). Adjusting for leukocyte count and CRP did not alter the associations seen between aspirin use and incident late AMD.

To further explore the finding that time of first reported regular aspirin use was associated with AMD, we examined the data on aspirin use only in participants with complete information on self-reported aspirin use at all study visits from the baseline visit through the fourth visit, who were free from AMD at the fourth visit, and had complete outcome information from the most recent visit (Table 4). There was no apparent relationship between the visit since first regular use of aspirin and incidence of early AMD. Results are similar for those with consistent and inconsistent use.

For any late AMD, participants with no aspirin use and those only with aspirin use at the visit prior to the incidence of late AMD (use at the fourth visit) had a similar incidence (1.75% and 1.40%, respectively). Those who had reported regular aspirin use 10, 15, or 20 years prior to observed incidence showed a higher incidence than those with no aspirin use or only recent aspirin use (5 years prior to observed incidence). Incidence was similar for 10, 15, and 20 years (4.67%, 4.21%, and 5.10%, respectively) since aspirin use was first consistently reported. The results are similar for those with inconsistent use. It should be noted that for late AMD, there are several cells with very low counts for incident cases.

For pure geographic atrophy, there was no discernible pattern between incidence and years since first self-reported aspirin use. For neovascular AMD, the pattern was similar to what was seen for incidence of any late AMD.

Comment

In our study, aspirin use 10 years prior to observed AMD incidence was associated with the 15-year incidence of neovascular AMD. Our exploratory analyses tend to support the findings of our primary analysis. Our hazard ratio estimate, given in Table 3, for neovascular AMD in those whose first regular use of aspirin was at least 10 years prior to observed AMD is 2.20 (95% CI 1.20–4.15). This is based on our modeling of specific potential risk factors in a Midwestern, primarily white population. While it is possible to estimate an attributable risk, the number of incident cases that our estimate is based on is small and requires corroboration before developing risk algorithms for clinical use. Adjusting for age, age^2, education level and aspirin use 5 years prior to observed incidence, the attributable risk of late AMD for aspirin use 10 years prior to observed incidence was 0.77%, with adjusted attributable risk fraction of 53.2%.[16] This is in keeping with the finding of a small but significant cross-sectional association between aspirin use and AMD in the EUREYE study and the inference that for a patient, aspirin use for cardio-prevention does not imply a great increase in risk of AMD.[17,18] If our finding is borne out in other studies, it suggests that the effect of aspirin on mechanisms leading to AMD may be different, at least partially, from aspirin's immediate effects on clotting that seem to be responsible for cardio-protection.[19] Not all retinal lesions characterizing neovascular AMD involve bleeding that is detectable in photography. Aspirin, aside from its effects on clotting, may enhance choroidal neovascularization.[20] Aspirin has been shown to increase vascular density in a laboratory model.[21] Thus, it is possible that in the presence of injury, aspirin encourages the growth of aberrant new vessels.

Two studies by Christen and colleagues[22,23] describing the experience in 2 large randomized controlled trials for prevention of CVD, one with a 7-year follow-up and the other with 10-year follow-up, found no evidence of a direct association of low-dose aspirin use and late lesions of AMD. Those studies were performed in health professionals who are likely to be

more health conscious than general populations. The number of AMD cases was small in both studies, and the definition and method of classification of the endpoint differed from the current study and the European Eye Study,[17] which both used photographic documentation and systematic grading of lesions as opposed to self-reported AMD with decreased vision confirmed by medical record. Thus, there are likely to be important differences in exposures and outcomes and ascertainment between studies that may have caused the disparate findings.

Several limitations may have affected our findings. First, there was a lack of detailed information on aspirin exposure at some visits. When the study began, questions on frequency of use and dosage were not initially included, but were added into subsequent examinations to accommodate important clinical therapeutic trends in the community, especially the increasing use of aspirin for CVD. Second, leukocyte count was only measured at the baseline and second examinations; therefore, we could not evaluate potential associations for every study interval. Similar limitations apply to CRP measures, which might have informed our analysis regarding possible effects of systemic inflammation and its potentially modifying effect on the association of AMD with aspirin. Third, the study population is almost entirely white of European ancestry, so the extent to which our results may generalize to other races/ethnicities, particularly groups at elevated risk for CVD, is unknown.

Our findings are consistent with an association between regular aspirin use and incidence of neovascular AMD. Additional replication is required to confirm our observation. If confirmed, defining the causal mechanisms will be important in developing methods to block this effect to prevent or retard the development of neovascular AMD in persons who use aspirin especially to prevent CVD.

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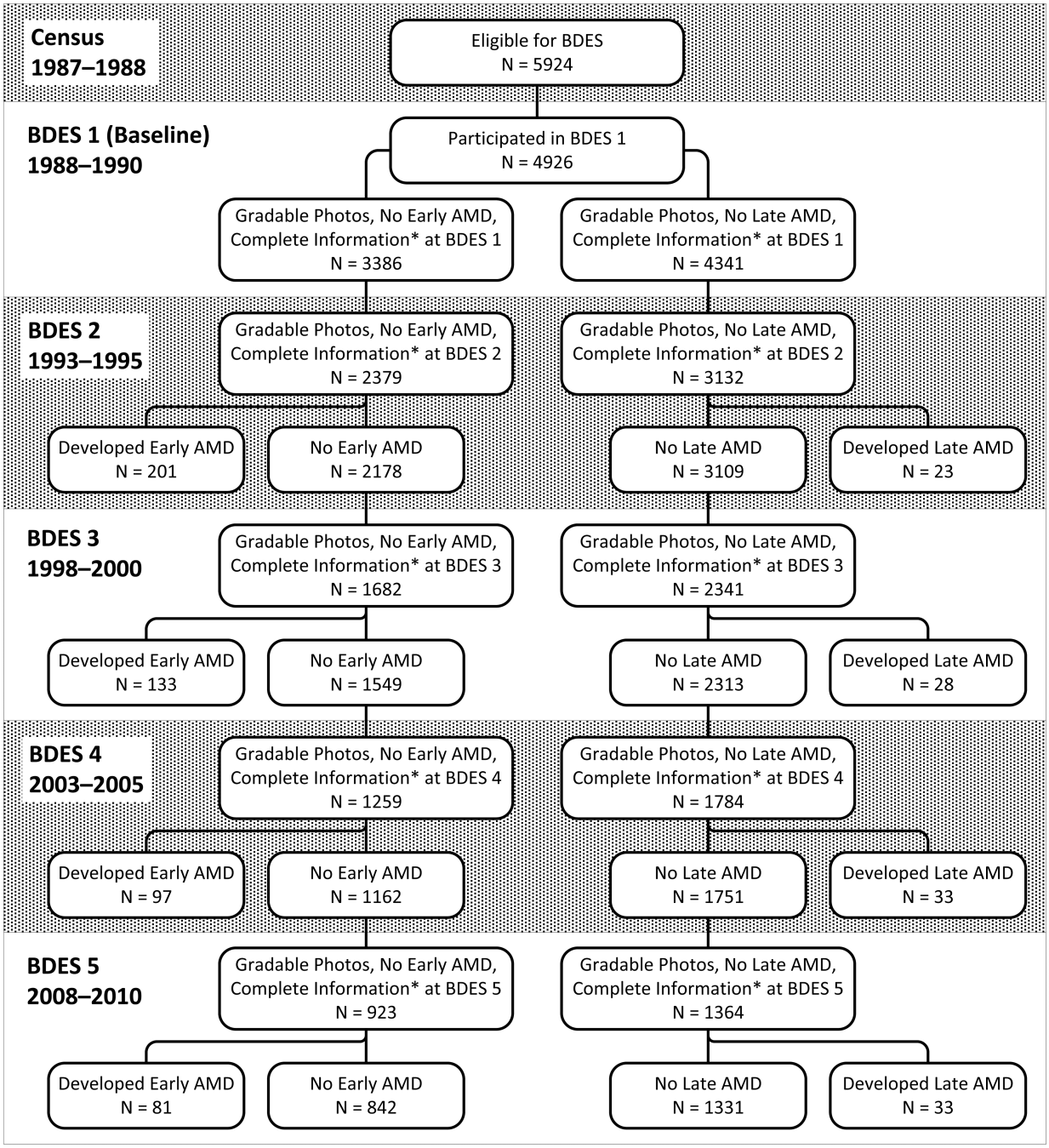

Figure.

Numbers of participants at each phase of the Beaver Dam Eye Study included in analyses of incidence of early and late age-related macular degeneration. *Complete information includes complete data on self-reported use of aspirin, age, education, and (for early AMD) history of arthritis.

Table 1

Baseline Characteristics of the Beaver Dam Eye Study Population and Those Included and Excluded from Analyses.

	Whole Population (N=4926)		Included* (N=3206)		Excluded* (N=1720)	
Characteristic	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age (years)	62.0	11.2	59.3	10.0	67.2	11.6
Body mass index (kg/m^2)	28.8	5.4	28.8	5.3	28.7	5.5
Systolic BP (mmHg)	132.1	20.5	130.1	19.2	135.9	22.2
	N	**%**	**N**	**%**	**N**	**%**
Sex						
Women	2762	56.1	1790	55.8	972	56.5
Men	2164	43.9	1416	44.2	748	43.5
Annual income (USD)						
≤$9,000	760	16.3	354	11.4	406	25.7
$10–19,000	1301	27.8	768	24.8	533	33.8
$20–29,000	946	20.2	677	21.9	269	17.1
$30–44,000	956	20.5	723	23.4	233	14.8
≥ $45,000	709	15.2	573	18.5	136	8.6
Education						
Less than high school	1440	29.3	719	22.4	721	42.1
High school	2134	43.4	1480	46.2	654	38.2
College	701	14.2	498	15.5	203	11.8
More than college	645	13.1	509	15.9	136	7.9
Smoking status						
Never	2204	44.8	1433	44.7	771	44.9
Past	1747	35.5	1148	35.8	599	34.9
Current	970	19.7	624	19.5	346	20.2
Diabetes present						
No	4460	91.0	2984	93.4	1476	86.5
Yes	441	9.0	211	6.6	230	13.5

	Whole Population (N=4926)		Included* (N=3206)		Excluded* (N=1720)	
Characteristic	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Hypertension† present						
No	2428	49.4	1723	53.8	705	41.2
Yes	2489	50.6	1482	46.2	1007	58.8
History of CVD						
No	4124	84.9	2843	89.3	1281	76.6
Yes	731	15.1	339	10.7	392	23.4
History of heavy drinking						
No	4068	82.8	2677	83.6	1391	81.4
Yes	844	17.2	526	16.4	318	18.6
Using aspirin						
No	3816	77.6	2513	78.4	1303	76.2
Yes	1101	22.4	693	21.6	408	23.8

AMD, age-related macular degeneration; BP, blood pressure; CVD, cardiovascular disease; GA, geographic atrophy; SD, standard deviation; USD, United States dollars.

*Included = participant data included in ≥1 analysis (incidence of early AMD, late AMD, neovascular AMD and/or pure GA); Excluded = Participant data excluded from all analyses

†Defined as systolic BP ≥ 140 mmHg and/or diastolic BP ≥90 mmHg and/or use of antihypertensive medication(s).

Table 2

Relationships of Incidence of Age-related Macular Degeneration Outcomes with Self-Reported Regular Aspirin Use 5 Years Prior Over 20 Years in the Beaver Dam Eye Study.

Incident AMD Outcome	Using Aspirin 5 Years Prior to Incidence	Person-visits: N at Risk	Person-visits: N Incident Cases	Age-Sex Adjusted % Incidence (95% CI)	HR (95% CI)	P value
Early AMD*	No	4398	348	10.5 (9.5, 11.6)	Referent	0.13
	Yes	1845	164	9.6 (8.3, 11.0)	0.86 (0.71, 1.05)	
Any Late AMD†	No	5957	62	1.0 (0.7, 1.4)	Referent	0.31
	Yes	2664	55	1.4 (1.0, 1.9)	1.21 (0.84, 1.74)	
Neovascular AMD†	No	5994	44	0.7 (0.5, 1.0)	Referent	0.77
	Yes	2681	34	0.8 (0.5, 1.3)	1.07 (0.68, 1.67)	
Pure GA†	No	5915	20	0.4 (0.2, 0.6)	Referent	0.10
	Yes	2633	24	0.6 (0.4, 1.0)	1.65 (0.91, 2.99)	

AMD, age-related macular degeneration; CI, confidence interval; GA, geographic atrophy; HR, hazard ratio.

*Adjusted for age, arthritis history, and education level.

†Adjusted for age, age^2, and education level.

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Table 3

Relationships of Incidence of Age-Related Macular Degeneration Outcomes with Self-Reported Regular Use of Aspirin 5 and 10 Years Prior to Observed Incidence Over 15 Years in the Beaver Dam Eye Study.

	Person-visits					
	N at Risk for Outcome	N Incident Cases	Age-Sex Adjusted % Incidence (95% CI)	HR (95% CI)	P value	Overall P value
Early AMD						
Aspirin Use						
No Use 5 or 10 Years Prior	2254	170	9.3 (8.1, 10.7)	Referent		0.43
Use 5 Years Prior, No Use 10 Years Prior	644	60	10.0 (7.9, 12.6)	1.03 (0.77, 1.38)	0.85	
No Use 5 Years Prior, Use 10 Years Prior	277	24	9.6 (6.7, 13.7)	0.95 (0.63, 1.45)	0.83	
Use 5 and 10 Years Prior	686	57	8.1 (6.3, 10.4)	0.79 (0.58, 1.09)	0.15	
Test of Main Effects						
Use vs. No Use 5 Years Prior						
No Use 5 Years Prior	2531	194	9.0 (7.6, 10.6)	Referent		
Use 5 Years Prior	1330	117	9.0 (7.6, 10.7)	0.93 (0.70, 1.23)	0.60	
Use vs. No Use 10 Years Prior						
No Use 10 Years Prior	2898	230	9.5 (8.3, 10.9)	Referent		
Use 10 Years Prior	963	81	8.5 (6.9, 10.5)	0.86 (0.65, 1.13)	0.28	
Any Late AMD						
Aspirin Use						
No Use 5 or 10 Years Prior	3091	38	1.1 (0.7, 1.7)	Referent		0.20
Use 5 Years Prior, No Use 10 Years Prior	948	13	0.9 (0.5, 1.6)	0.81 (0.44, 1.52)	0.52	
No Use 5 Years Prior, Use 10 Years Prior	401	10	1.7 (0.9, 3.1)	1.46 (0.73, 2.91)	0.29	
Use 5 and 10 Years Prior	1045	33	1.8 (1.1, 2.7)	1.48 (0.93, 2.37)	0.10	
Test of Main Effects						
Use vs. No Use 5 Years Prior						
No Use 5 Years Prior	3492	48	1.4 (0.9, 2.1)	Referent		
Use 5 Years Prior	1993	46	1.3 (0.9, 1.9)	0.91 (0.57, 1.46)	0.69	
Use vs. No Use 10 Years Prior						
No Use 10 Years Prior	4039	51	1.0 (0.7, 1.5)	Referent		

	Person-visits					
	N at Risk for Outcome	N Incident Cases	Age-Sex Adjusted % Incidence (95% CI)	HR (95% CI)	P value	Overall P value
Use 10 Years Prior	1446	43	1.8 (1.2, 2.6)	1.63 (1.01, 2.63)	0.05	
Neovascular AMD						
Aspirin Use						
No Use 5 or 10 Years Prior	3111	25	0.7 (0.5, 1.2)	Referent		0.07
Use 5 Years Prior, No Use 10 Years Prior	954	6	0.4 (0.2, 1.1)	0.58 (0.24, 1.40)	0.23	
No Use 5 Years Prior, Use 10 Years Prior	408	9	1.5 (0.7, 2.9)	1.92 (0.89, 4.13)	0.10	
Use 5 and 10 Years Prior	1054	21	1.2 (0.7, 2.0)	1.46 (0.81, 2.60)	0.21	
Test of Main Effects						
Use vs. No Use 5 Years Prior						
No Use 5 Years Prior	3519	34	1.1 (0.7, 1.6)	Referent		
Use 5 Years Prior	2008	27	0.8 (0.5, 1.3)	0.66 (0.37, 1.19)	0.17	
Use vs. No Use 10 Years Prior						
No Use 10 Years Prior	4065	31	0.6 (0.4, 1.0)	Referent		
Use 10 Years Prior	1462	30	1.4 (0.9, 2.1)	2.20 (1.20, 4.15)	0.01	
Pure Geographic Atrophy						
Aspirin Use						
No Use 5 or 10 Years Prior	3068	15	0.5 (0.2, 0.9)	Referent		0.20
Use 5 Years Prior, No Use 10 Years Prior	943	8	0.6 (0.3, 1.2)	1.26 (0.54, 2.94)	0.60	
No Use 5 Years Prior, Use 10 Years Prior	392	1	0.2 (0.0, 1.3)	0.37 (0.05, 2.66)	0.32	
Use 5 and 10 Years Prior	1025	13	0.7 (0.3, 1.3)	1.49 (0.71, 3.12)	0.29	
Test of Main Effects						
Use vs. No Use 5 Years Prior						
No Use 5 Years Prior	3460	16	0.4 (0.2, 0.8)	Referent		
Use 5 Years Prior	1968	21	0.6 (0.4, 1.1)	2.25 (0.75, 6.72)	0.15	
Use vs. No Use 10 Years Prior						
No Use 10 Years Prior	4011	23	0.5 (0.3, 0.9)	Referent		
Use 10 Years Prior	1417	14	0.5 (0.3, 1.0)	0.66 (0.25, 1.95)	0.45	

AMD, age-related macular degeneration; CI, confidence interval; HR, hazard ratio.

[*] Adjusted for age, arthritis history, and education level.

[†] Adjusted for age, age^2, and education level.

Table 4

Relationship of Age-related Macular Degeneration Outcomes to Aspirin Exposure Patterns Prior to the Incidence of Age-related Macular Degeneration.

	Unadjusted			Age-Sex Adjusted		
AMD Outcome and Aspirin Exposure Pattern	**N at risk**	**N Incident**	**% Incidence (95% CI)**	**OR (95% CI)**	**P value**	**Overall P value**
Early AMD						
First consistent exposure						
None	403	40	9.4 (6.8, 12.8)	Referent		0.52
5 years prior	169	21	11.7 (7.6, 17.5)	1.28 (0.72, 2.26)	0.41	
10 years prior	164	12	6.3 (3.5, 11.0)	0.65 (0.33, 1.29)	0.22	
15 years prior	61	8	9.5 (4.6, 18.6)	1.01 (0.44, 2.33)	0.98	
20 years prior	64	7	8.9 (4.1, 18.0)	0.94 (0.39, 2.26)	0.89	
None or at visit 4 only	572	61	10.1 (7.8, 13.0)	Referent		
10, 15, or 20 years prior	289	27	7.6 (5.1, 11.2)	0.73 (0.45, 1.20)	0.22	
First exposure *						
None	403	40	9.6 (6.8, 12.7)	Referent		0.48
5 years prior	169	21	11.7 (7.7, 17.5)	1.29 (0.73, 2.29)	0.39	
10 years prior	199	15	6.6 (4.0, 10.9)	0.69 (0.37, 1.30)	0.25	
15 years prior	115	14	9.3 (5.4, 15.6)	1.00 (0.51, 1.94)	0.99	
20 years prior	175	22	10.6 (6.9, 15.9)	1.15 (0.65, 2.04)	0.63	
None or at visit 4 only	572	61	10.1 (7.8, 12.9)	Referent		
10, 15, or 20 years prior	489	51	8.7 (6.5, 11.6)	0.85 (0.57, 1.28)	0.44	
Any Late AMD						
First consistent exposure						
None	514	9	1.1 (0.5, 2.3)	Referent		0.53
5 years prior	215	3	0.9 (0.3, 2.8)	0.81 (0.21, 3.09)	0.76	
10 years prior	214	10	2.1 (1.0, 4.7)	2.02 (0.77, 5.30)	0.15	
15 years prior	95	4	1.5 (0.5, 4.5)	1.38 (0.40, 4.79)	0.62	
20 years prior	98	5	2.0 (0.7, 5.6)	1.85 (0.56, 6.08)	0.31	
None or at visit 4 only	729	12	1.0 (0.5, 2.0)	Referent		
10, 15, or 20 years prior	407	19	1.9 (1.0, 3.8)	1.91 (0.88, 4.14)	0.10	

AMD Outcome and Aspirin Exposure Pattern	Unadjusted N at risk	Unadjusted N Incident	Unadjusted % Incidence (95% CI)	Age-Sex Adjusted OR (95% CI)	Age-Sex Adjusted P value	Age-Sex Adjusted Overall P value
First exposure *						
None	514	9	1.1 (0.5, 2.3)	Referent		0.64
5 years prior	215	3	0.9 (0.3, 2.9)	0.81 (0.21, 3.09)	0.76	
10 years prior	268	10	1.6 (0.8, 3.8)	1.62 (0.63, 4.20)	0.32	
15 years prior	170	9	1.9 (0.8, 4.4)	1.79 (0.67, 4.80)	0.25	
20 years prior	249	7	1.2 (0.5, 2.9)	1.11 (0.40, 3.12)	0.84	
None or at visit 4 only	729	12	1.0 (0.5, 2.0)	Referent		
10, 15, or 20 years prior	687	26	1.6 (0.9, 2.9)	1.57 (0.76, 3.23)	0.22	
Pure Geographic Atrophy						
First consistent exposure						
None	508	3	0.3 (0.1, 1.2)	†		
5 years prior	214	2	0.5 (0.1, 2.4)	†		
10 years prior	206	2	0.3 (0.1, 2.0)	†		
15 years prior	92	1	0.3 (0.0, 2.8)	†		
20 years prior	93	0		†		
None or at visit 4 only	722	5	0.3 (0.1, 1.2)	†		
10, 15, or 20 years prior	391	3	0.2 (0.1, 1.2)	†		
First exposure *						
None	508	3	0.3 (0.1, 1.3)	†		
5 years prior	214	2	0.5 (0.1, 2.5)	†		
10 years prior	260	2	0.3 (0.1, 1.6)	†		
15 years prior	163	2	0.6 (0.1, 2.0)	†		
20 years prior	243	1	0.2 (0.0, 1.3)	†		
None or at visit 4 only	722	5	0.4 (0.1, 1.2)	Referent		
10, 15, or 20 years prior	666	5	0.3 (0.1, 1.0)	0.69 (0.19, 2.50)	0.57	
Neovascular AMD						
First consistent exposure						
None	518	6	0.8 (0.3, 1.8)	Referent		0.14

AMD Outcome and Aspirin Exposure Pattern	Unadjusted		Age-Sex Adjusted			
	N at risk	N Incident	% Incidence (95% CI)	OR (95% CI)	P value	Overall P value
5 years prior	217	1	0.3 (0.0, 2.2)	0.41 (0.05, 3.45)	0.41	
10 years prior	214	8	1.9 (0.8, 4.4)	2.52 (0.83, 7.63)	0.10	
15 years prior	98	4	1.6 (0.5, 4.9)	2.09 (0.56, 7.88)	0.28	
20 years prior	100	5	2.1 (0.7, 6.1)	2.87 (0.80, 10.37)	0.11	
None or at visit 4 only	735	7	0.6 (0.3, 1.4)	Referent		
10, 15, or 20 years prior	412	17	1.8 (0.9, 3.8)	2.99 (1.18, 7.57)	0.02	
First exposure *						
None	518	6	0.8 (0.3, 1.9)	Referent		0.23
5 years prior	217	1	0.3 (0.0, 2.3)	0.41 (0.05, 3.44)	0.41	
10 years prior	269	8	1.5 (0.7, 3.5)	1.99 (0.66, 5.97)	0.22	
15 years prior	175	8	1.8 (0.8, 4.4)	2.41 (0.79, 7.32)	0.12	
20 years prior	254	7	1.3 (0.5, 3.1)	1.69 (0.55, 5.24)	0.36	
None or at visit 4 only	735	7	0.6 (0.3, 1.4)	Referent		
10, 15, or 20 years prior	698	23	1.5 (0.8, 2.8)	2.41 (1.00, 5.81)	0.05	

AMD, age-related macular degeneration.

* Includes participants with inconsistent aspirin exposure (a participant reported aspirin use, followed by reporting no aspirin use at a later examination). This category does not include participants with reported aspirin use followed by missing aspirin use data.

† Cannot estimate.