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Non-steroidal Anti-inflammatory Drug Use and Risk of Age-Related Macular Degeneration in California

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Abstract

Purpose

To examine whether use of regular aspirin and/or other non-steroidal anti-inflammatory drugs (NSAIDs) is associated with the development of age-related macular degeneration (AMD).

Methods

In the California Teachers Study (CTS) cohort (N = 88, 481) we identified diagnoses of AMD up to Dec.31, 2012 by linkage to statewide hospital discharge records. Aspirin, ibuprofen, other NSAIDs, and acetaminophen use and comprehensive risk factor information were collected via self-administered questionnaires at baseline in 1995-1996 and a follow-up questionnaire in 2005-2006. We employed Cox proportional hazard regression to model AMD risk.

Results

We did not find any associations between AMD and frequency and duration of aspirin or ibuprofen use reported at baseline. In the subsample with more specific information on medication use, we observed a 20% decrease in risk of AMD among low-dose aspirin users (HR = 0.81, 95% CI: 0.70, 0.95) and a 55% decrease among COX-2 inhibitors users (HR = 0.45, 95% CI: 0.26, 0.78) during 6.3 years of average follow-up.

Conclusion

The decrease in risk of intermediate- or late-stage AMD among women who reported regular use of low-dose aspirin or specific COX-2 inhibitors suggests a possible protective role for medications with COX-2 inhibitory properties or aspirin at doses used for cardiovascular disease prevention.

Key points:

- AMD was not related to duration or use of (full dose) aspirin or ibuprofen at the start of the study.

- Participants who took COX-2 inhibitors had a 55% decrease in AMD risk, and low-dose aspirin users had a 20% decreased risk of AMD, across 6 years of followup.

1. Introduction

Following cataract and glaucoma, age-related macular degeneration (AMD) is the third leading cause of blindness worldwide, and is associated with decreased quality of life and increased dependence on caregivers [1, 2]. Early-stage AMD is usually asymptomatic and can develop into one of two forms considered late-stage AMD: 1) geographic atrophy (dry form) and 2) neovascular AMD (wet-AMD) [2,3]. In the US, 6.5% of the population over age 40 is suffering from AMD at any stage. For late-stage disease, the prevalence is 1.5% and this is projected to increase dramatically as the nation's 65-and-older population grows [3].

Inflammation is proven to be a key component of drusen biogenesis, a significant pathogenic factor for both forms of AMD [4]. Cyclooxygenase-2 (COX-2), an inducible enzyme involved in the process of inflammation, is highly expressed in choroidal neovascular membranes in wet-AMD patients [5]. These findings warrant research on a putative beneficial effect that anti-COX-2 medications may have for AMD. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit COX enzymes and may also have the potential to prevent the development of AMD. Moreover, low-dose (baby) aspirin is widely used for its antithrombotic properties in the primary and secondary prevention of cardiovascular diseases, such as heart attack and stroke, both of which are clinical risk factors for AMD [6-10].

Except for aspirin, few previous studies examined associations between specific types of NSAIDs and AMD and conflicting results have been reported on aspirin [11-16]. Though inverse associations between long-term low-dose aspirin use and AMD were reported in clinical trials [14, 15], large cohort studies concluded that long-term aspirin users had a 2 to 2.5 times increased risk for developing wet-AMD, and this raised concern about the side effects of aspirin's anti-platlet property [11,12]. Long-term aspirin use may affect AMD through three mechanisms: 1) reduced neovascularization through COX-2 inhibition; 2) reduced development of AMD through its cardioprotective effects; or 3) neovascularization stimulation at the retina as a result of aspirin's inhibition of platelet-mediated release of vascular endothelial growth factor (VEGF) and subsequently induced hypoxia. Non-aspirin NSAIDs are thought to affect AMD through the first mechanism only.

The primary aim of our study is to assess associations between long-term use of NSAIDs and AMD in a cohort of California teachers who were followed for up to 17 years, accounting for frequency, duration, and co-medication use. Since acetaminophen is the most common pain medication used for similar indications as aspirin and other NSAIDs such as managing musculoskeletal pain and chronic headaches, but does not have anti-inflammatory or cardioprotective properties, here we used acetaminophen as a negative control to assess bias by indication.

2. Materials and Methods

A detailed description of the California Teachers Study (CTS) and its data has been published [17, 18]. Briefly, a prospective cohort of 133,477 female California teachers who completed a baseline self-administered questionnaire in 1995-1996 were followed both actively and passively with annual linkage to the California Office of Statewide Health Planning and Development (OSHPD) hospital discharge records and to state-wide death records (Note: two participants who withdrew their consent to participate in CTS have been excluded from analyses).

With institutional review board (IRB) approval, we generated a linked hospital, vital status, and baseline questionnaire dataset for each CTS participant [19]. Eligibility was limited to women who were California residents at baseline and had at least one OSHPD record available through 12/31/2012 (N = 89,877). Participants who suffered from AMD prior to completing the baseline questionnaire (N = 22) and those who did not report their regular analgesic medication use (n = 1,347) were excluded, leaving 88,481 participants for basline analysis. After excluding women who developed AMD before 2005 or did not return this questionnaire, 50,202 subjects were eligible for the subsample analyses.

The first AMD event was identified from OSHPD hospital discharge data, which captured up to 25 diagnoses and the date of service at the visit. According to the guideline for secondary diagnoses in hospitals [20], only co-existing conditions that affect current treatments should be recorded. Thus, we assumed that the majority of AMD cases identified in this manner were intermediate to advanced and had impaired central vision, because these patients are more likely to require additional therapeutic procedures, and increased nursing care and have an extended length of stay [21]. In contrast, patients with early stage AMD do not meet the criteria for a comorbid disorder relevant to

current treatment and care during hospitalization; thus, we most likely did not capture as many of these with our passive linkage to hospital discharge records.

Follow-up started the day the baseline questionnaire was completed and ended at the earliest occurrence of one of the four events: 1) AMD diagnosis; 2) moving out of California; 3) death; 4) date of the administrative censoring for this analysis (Dec. 31st, 2012).

At baseline, participants reported regular medication use (at least once per week), average frequency of use, and total years of use. Regular aspirin, acetaminophen, and ibuprofen consumption were asked separately. More detailed NSAIDs use was recorded in a subsequent questionnaire mailed to cohort members in 2005: 'baby' or low-dose aspirin, aspirin, acetaminophen, ibuprofen, COX-2 inhibitors, and other NSAIDs. To better evaluate any possible role of confounding by indication, we examined acetaminophen as a negative control.

Potential confounder information was identified from questionnaire data or OSHPD hospital discharge records and selected based on the literature on AMD [3,22]. We included in our models sociodemographic factors, life-style risk factors, indications and contraindications for aspirin and other NSAIDs which may also affect AMD risk (Appendix 1).

Statistical Analysis

Multivariable Cox proportional hazards regression was used to assess the association between NSAIDS use and AMD. We examined the baseline analgesics in categories of frequency and duration of use, and tested for trend using category midpoints. To account for potential effects from use of other classes of analgesics, we calculated the approximate intensity of each of the three medications by multiplying the average frequency and total years of use and mutually adjusting in our models for these variables. The proportional hazards assumption was checked using Kaplan-Meier survival curves and graphs of the log(-log(survival)) versus log of survival time; parallel lines indicated proportionality of hazards [23]. Cox proportional hazard regression with inverse probability weighting methods [24] was applied in subsample analyses that relied on the 2005 questionnaire information.

We performed sensitivity analyses by excluding women who had the first AMD diagnosis within the first two or five years of follow-up in the primary cohort and two years only in the subsample from 2005 onward to exclude prevalent AMD cases and the exlusion did not change our results more than minimally, thus we report results for the entire cohort without any exclusion.

To account for possible selection bias due to only including women with at least one OSHPD record available through December 31, 2012 (72% of eligible CTS subjects), we also conducted additional sensitivity analyses weighing the data in the Cox models by the inverse probability of selection (Appendix1). All analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC).

3. Results

Among 88,481 CTS participants, we identified 1,762 subjects with AMD. During an average of 14.8 years follow-up, 6598 (7.5%) women moved out of California for a period of more than one year and 16,444 (18.6%) died, leaving 63,677 (72%) subjects who were right censored at end of follow-up (Dec.31, 2012). The median time to first AMD diagnosis was 13.5 years (interquartile range: 10.2, 15.5). The distribution of demographic and life-style factors for the study population and AMD cases are presented in Table 1. AMD frequency increased sharply with increasing age and was higher among Whites, overweight women, women who exercised little, and women with a self-reported history of medical conditions at baseline that are known to contribute to AMD. The current smoking rates were low in the cohort and comparable between AMD cases and controls, but total pack-years of smoking was higher among AMD cases. A similar proportion of women drank alcohol, but heavier drinkers were more common among AMD cases. Analgesic consumption in relation to demographic characteristics and health-related factors in the CTS has been previously described [23,25].

Regular aspirin users were more likely to take these medications for more days per week and a higher proportion were long-term ($\geq$ 5 years) compared with ibuprofen and acetaminophen users (Table 2). The hazard ratio for AMD was above one for most of the use categories of aspirin and acetaminophen (between 1.00 and 1.29) but no trend was apparent for frequency or duration, while regular ibuprofen use was not associated with AMD. When we

jointly examined frequency and duration of use, the highest intensity use (more than 3 days per week and longer than 5 years) for the three baseline analgesics did not increase the risk of AMD (Table 3).

For women in the 2005 subsample, the median time to diagnosis of AMD was 4.3 years (interquartile range: 2.9, 7.1). We estimated inverse hazard ratios for use of low-dose aspirin (HR = 0.81, 95% CI: 0.70, 0.95) and Cox-2 inhibitors (HR = 0.45, 95% CI: 0.26, 0.78) (Table 4). The inverse associations between low-dose aspirin or Cox-2 inhibitors and AMD were with stronger magnitude in older adult patients (age>50) in our data. Regular acetaminophen use was positively associated with AMD risk (HR = 1.24, 95% CI: 1.06, 1.45) after accounting for the intensity of previous analgesic use and concurrent use of other classes of anti-inflammatory drugs or acetaminophen.

4. Discussion

In a prospective cohort of CTS participants followed on average for 14.8 years, regular consumption of aspirin or ibuprofen was not associated with increased risk of intermediate- or late-stage AMD. For the subsample of CTS participants who answered to the 2005 questionnaire, low-dose aspirin was assessed separately from standard-dose, and we observed a 20% decrease in the risk of AMD among women who regularly used low-dose aspirin. A potential beneficial effect was also seen in women who used selective COX-2 inhibitors, in fact, their risk of developing AMD was 55% lower.

Previous studies of aspirin use and AMD risk reported negative, null, as well as positive associations possibly due to the lack of a uniform definition of AMD, heterogeneous patterns of anti-inflammatory medication use, different lengths of follow-up, different degrees of residual confounding, and possibly confounding by indication. Positive associations between aspirin use and wet AMD and a null association for geographic atrophy were seen in cross-sectional studies and prospective cohorts [11,12,13]. Long-term aspirin use reduces synthesis of prostacyclin and leads to hypoxia with subsequent stimulation of neovascularization in the retina [13], however, these positive associations observed in prospective cohorts might also be due to selection bias from differential censoring by AMD status and aspirin use since these cohorts had high follow-up loss rates [11,12]. The CTS follow-up we employed – OSHPD linkage - was passive in nature thus making a selective loss to follow-up among users less likely.

In contrast to these prospective cohort and cross-sectional studies, a clinical trial of female health professionals suggested a 20% decreased risk of AMD over ten years following 100 mg regular aspirin use (on alternate days i.e. ~3 days per week) to prevent cardiovascular diseases [15], which is consistent with our findings of a 20% risk reduction for ‘baby’ aspirin use. Another randomized clinical trial of physicians followed for five years reported a comparable size risk reduction [14]. The proposed mechanism for aspirin are its beneficial effects on cardiovascular disease and atherosclerosis, which are risk factors for AMD development [3, 26]. Moreover, low dose aspirin can up-regulate the production of a local endogenous anti-inflammatory mediator [15, 27]. The inhibitive effects of aspirin on isoforms of the COX enzymes is irreversible and non-selective. Aspirin exerts its anti-thrombotic function through the acetylation of COX-1, a constitutive enzyme that is responsible for platelet aggregation. Long-term suppression of platelet aggregation is thought to decrease the progression to atherosclerosis, a common etiologic

factor for cardiovascular disease and AMD [28, 29]. Deactivation of COX-2 by aspirin, on the other hand, reduces the production of proinflammatory prostaglandins. Aspirin-triggered anti-inflammatory mediators have the potential to suppress drusen formation [30]. Another plausible biologic explanation is that the inhibition of COX-2 expression can regulate VEGF levels and prevent the development of neovascular AMD [5].

Previous observational studies of aspirin use and AMD risk did not distinguish between low- and standard-dose treatments [31]. In our study, dose information was not ascertained in the baseline questionnaire, but in 1995, regular aspirin users would have been taking a standard dose (325mg) rather than the cardioprotective low-dose aspirin (81mg) recommended in the early 2000s by the American Heart Association guidelines [32]. For baseline analgesic use, the hazard ratio greater than one for AMD among regular acetaminophen users (the negative control group) implies that the underlying indications for analgesic use may contribute to increased AMD risk and it may explain the estimated hazard ratios above one for aspirin and ibuprofen use at baseline as well. The discrepancy between our study's estimates for aspirin use in 1995 and in 2005 in addition to dose changes, may also be due to residual confounding, shorter lengths of follow-up, or the shift in the age structure of the cohort. As discussed earlier, certain underlying conditions that necessitate analgesic use may have confounded the association between baseline aspirin use and AMD [22,26, 33]. Moreover, a small group of women who were aspirin users in 1995 but had discontinued use in 2005 - probably due to side effects [7] –were also at a higher risk of developing AMD compared with never users (Appendix 2).

Previous studies reported inconclusive findings for non-aspirin NSAID use and AMD but few had information about the types of NSAIDs participants used. No association was observed between self-reported regular non-aspirin NSAIDs use and the five-year incidence of early- or late-stage AMD in two prospective cohort studies [34, 35]. In our 2005 subcohort analysis, a 55% decreased risk of AMD was detected specifically for COX-2 inhibitors but not for ibuprofen or other NSAIDs. This finding is further supported by an animal study in which oral administration of selective COX-2 inhibitors suppressed retinal VEGF expression and vascular leakage [36]. Although we cannot preclude the possibility of existing early-stage AMD at the time of completing the 2005 questionnaire, it was unlikely that women would stop taking COX-2 inhibitors after developing early-stage disease since a previous large

multicenter study of AMD indicated a potentially protective effect of non-aspirin NSAIDs use on the risk of progression to geographic atrophy though not neovascular AMD [37]. The biologic explanations of potentially beneficial effects for COX-2 inhibitors are similar to aspirin, except that non-aspirin NSAIDs do not have anti-thrombotic or cardioprotective effects.

Our study has several strengths. This prospective study with routine passive follow-up via administrative hospital records provides us with a long average follow-up time and precludes self-selection out of this cohort. The large number of AMD cases observed enabled us to investigate effects for individual medications by duration and frequency and account for concurrent use of other types of medication. Furthermore, the mixed approach of data collection--self-reported medication use covered prescription and non-prescription anti-inflammatory medications and the use of OSHPD records allowed us to examine a comprehensive set of potential confounding factors, including indications and contraindications for aspirin and other NSAIDs use. However, there are also several limitations most notably, the onset of early AMD could not be captured using the hospitalization records and the AMD cases identified using this data source cannot be used to estimate the incidence rate of the disease. On the other hand, we did not have to rely on self-reported diagnoses and any outcome misclassification would be expected to be non-differential. Moreover, we were not able to disentangle effects of medications on incident AMD from their effect on progression from early- to late-stage AMD. However, in sensitivity analyses that excluded AMD cases within the first two or even five years of follow-up effect estimates did not change more than minimally. A randomized clinical trial is in progress to examine the potential protective effects of aspirin on the incidence and progression of AMD and results are expected by 2021 [38]. Also, we were not able to separate geographic atrophy and neovascular AMD, which may have different pathophysiologies [39]. Third, our study may suffer from bias due to non-differential misclassification of frequency and duration of medication use. Also, we had limited information to evaluate cumulative dose-response patterns since participants may have changed the frequency of their medication use over time. Lastly, we cannot rule out the possibility that the inverse association between low-dose aspirin use was due to ophthalmologists' suggestion to avoid or discontinue regular use of aspirin to reduce AMD progression [40].

Conclusions

The risk of intermediate- or late-stage AMD among women who reported regularly taking low-dose aspirin or COX-2 inhibitors was reduced in the California Teachers Study. However, standard-dose aspirin use and ibuprofen or other NSAIDs use was not protective,. The elevated risk we also estimated for acetaminophen use, our negative control medication, suggests that these increased risk estimates might be due to confounding by indication. Future prospective studies of AMD and pain medications should evaluate the dosage, type, and timing of analgesic use [41]

Declarations

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Authors have no conflicts of interest to report.

This study was approved by Institutional Review Boards at the University of Southern California and the University of California, Los Angeles. Informed consent was collected prior to subjects' participation. The California Teachers Study may be contacted regarding data sharing.

Author Contributions All authors contributed to the study conception and design. Data Extraction and Analysis was performed by Xiaoiqng Xu, Rich Pinder, and Sarah Marshall. Interpretation of Results, Writing and Revising the Manuscript: ALL authors.

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357 Table 1 Demographic characteristics and lifestyle factors of study population at baseline in the
358 California Teachers Cohort, 1995-2012 (N=88,481).

Characteristics	All Participants	AMD Cases
Total	88481 (100%)	1762 (100%)
Age		
<50	35500 (40.1%)	53 (3.0%)
51-60	19916 (22.5%)	143 (8.0%)
61-70	16571 (18.7%)	498 (28.3%)
71-80	11825 (13.4%)	743 (42.2%)
>80	4669 (5.3%)	325 (18.4%)
Race/Ethnicity		
Non-Latina white	77079 (87.9%)	1662 (95.1%)
African American	2260 (2.6%)	24 (1.4%)
Native American	3709 (4.2%)	20 (1.1%)
Latina	829 (0.9%)	21 (1.2%)
Asian/Pacific Islander	2796 (3.2%)	12 (0.7%)
Other	1048 (1.2%)	8 (0.5%)
Missing	760	15
BMI		
Underweight	2276 (2.7%)	40 (2.5%)
Normal	47374 (56.1%)	495 (49.7%)
Overweight	21831 (25.8%)	525 (32.9%)
Obese	13012 (15.4%)	238 (14.9%)
Unknown	3988	164
History of High blood pressure		
No	70874 (80.1%)	1140 (64.7%)
Yes	17607 (19.9%)	622 (35.3%)
History of Heart attack/MI		
No	87035 (98.4%)	1707 (96.9%)
Yes	1446 (1.6%)	55 (3.1%)

History of Stroke		
No	87189 (98.5%)	1725 (97.9%)
Yes	1292 (1.5%)	37 (2.1%)
History of Diabetes		
No	85492 (96.6%)	1659 (94.2%)
Yes	2989 (3.4%)	103 (5.8%)
Smoking		
Never	16782 (19.2%)	270 (15.5%)
Passive	40368 (46.1%)	735 (42.2%)
Former	25751 (29.4%)	642 (36.8%)
Current	4590 (5.2%)	96 (5.5%)
Missing	990	19
No. of smoking pack-years		
Never or passive smoker	57150 (67.4%)	1005 (59.9%)
≤ 10	14052 (16.6%)	246 (14.7%)
11-20	5187 (6.1%)	126 (7.5%)
≥ 20	8464 (10.0%)	301 (17.9%)
Missing	3628	84
Daily alcohol intake (g)		
None	29086 (34.9%)	578 (35.1%)
<20	47340 (56.7%)	898 (54.5%)
≥ 20	7015 (8.4%)	173 (10.5%)
Unknown	5040	113
Lifetime moderate and strenuous physical activity (h/week)		
<2	29272 (33.3%)	804 (46%)
2 to 4	21822 (24.8%)	386 (22.1%)
4 to <6	14426 (16.4%)	240 (13.7%)
≥ 6	22319 (25.4%)	317 (18.1%)
Unknown	642	15

359

360

Table 2 Self-reported NSAIDs and acetaminophen use at baseline and age-related macular degeneration by frequency and duration of use in California Teachers Cohort, 1995-2012 (N=88,481).

Frequency and duration of analgesics use	Aspirin			Ibuprofen			Acetaminophen		
	No. of participants	No. of AMD	Adjusted-HR (95% CI) [a]	No. of participants	No. of AMD	Adjusted-HR (95% CI) [a]	No. of participants	No. of AMD	Adjusted-HR (95% CI) [a]
Frequency of regular use (days/week)									
None	67269 (76.6%)	1194 (68.5%)	1.00 (Ref.)	70146 (80.3%)	1428 (82.5%)	1.00 (Ref.)	76082 (86.7%)	1532 (87.7%)	1.00 (Ref.)
1 to 3	9539 (10.9%)	171 (9.8%)	1.20 (0.93, 1.55)	9241 (10.6%)	93 (5.4%)	0.97 (0.72, 1.31)	8130 (9.3%)	111 (6.3%)	1.21 (0.85, 1.73)
More then 3	11011 (12.5%)	378 (21.7%)	1.16 (0.95, 1.41)	7945 (9.1%)	209 (12.1%)	1.17 (0.94, 1.45)	3513 (4.0%)	104 (5.9%)	1.29 (0.94, 1.78)
P trend			0.48			0.22			0.69
Duration of regular use (yrs)									
Never	67269 (76.6%)	1194 (68.4%)	1.00 (Ref.)	70146 (79.5%)	1428 (81.3%)	1.00 (Ref.)	76082 (86.7%)	1532 (87.5%)	1.00 (Ref.)
<1 to 2	5270 (6.0%)	149 (8.5%)	1.28 (0.94, 1.73)	7932 (9.0%)	172 (9.8%)	1.03 (0.71, 1.48)	2908 (3.3%)	65 (3.7%)	1.22 (0.80, 1.86)
3 to 4	2796 (3.2%)	90 (5.2%)	1.26 (0.90, 1.76)	3920 (4.4%)	61 (3.5%)	0.86 (0.57, 1.31)	1672 (1.9%)	32 (1.8%)	1.00 (0.61, 1.66)
≥ 5	12650 (14.4%)	312 (17.9%)	1.22 (0.96, 1.55)	6178 (7.0%)	95 (5.4%)	1.01 (0.69, 1.48)	7556 (8.6%)	121 (6.9%)	1.08 (0.77, 1.51)
P trend			0.77			0.97			0.58

363 [a] Multivariable-adjusted model adjusted for age, smoking, diabetes, race/ethnicity, BMI, physical activities, alcohol use, hospitalization due to musculoskeletal
364 system and connective tissue disease, hospitalization due to circulatory disease, asthma, coagulation/hemorrhagic conditions, antihypertensive medications use,
365 frequency/duration of the index medication, and mutually adjusted for frequency/duration of other classes of medication

366

Table 3 Joint analysis of dose and duration of regular NSAIDs and acetaminophen use at baseline and risk of age-related macular degeneration in California Teachers Cohort, 1995-2012 (N=88,481).

No. of AMD HR (95% CI)	Frequency (times/wk)	Year of Use		
		Never	<5 [a]	≥ 5 [a]
Aspirin	None	1194		
		1.00 (ref.)		
	1 to 3		49	119
			1.23 (0.90, 1.67)	1.14 (0.93, 1,40)
	4 or more		182	182
			1.14 (0.96, 1.35)	1.12 (0.95, 1.33)
Ibuprofen	None	1428		
		1.00 (ref.)		
	1 to 3		63	26
			1.12 (0.85, 1.47)	0.93 (0.61, 1.40)
	4 or more		141	66
			1.16 (0.96, 1.39)	1.23 (0.95, 1.60)
Acetaminophen	None	1532		
		1.00 (ref.)		
	1 to 3		42	63
			1.23 (0.87, 1.74)	1.07 (0.81, 1.42)
	4 or more		46	52
			1.19 (0.88, 1.62)	1.24 (0.91, 1.69)

[a] Multivariable-adjusted model adjusted for age, smoking, diabetes, race/ethnicity, BMI, physical activities, alcohol use, hospitalization due to musculoskeletal system and connective tissue disease, hospitalization due to circulatory disease, asthma, coagulation/hemorrhagic conditions, antihypertensive medications use, and mutually adjusted for intensity of other classes of medication.

374 Table 4 Self-reported NSAIDs and acetaminophen use in subsequent (2005) questionnaire and age-related macular
375 degeneration in California Teachers Cohort, 2005-2012 (N=50,202).

Regular Medication use at 2005	No. of participants	Multivariable adjusted-HR [a]
Baby' or low-dose aspirin		
No	35834 (71.4%)	1.00 (ref.)
Yes	14368 (28.6%)	0.81 (0.70, 0.95)
Aspirin		
No	43594 (86.9%)	1.00 (ref.)
Yes	6596 (13.1%)	0.90 (0.73, 1.12)
Unknown	12	
Naproxen, ketoprofen or other NSAIDs		
No	45265 (90.2%)	1.00 (ref.)
Yes	4933 (9.8%)	1.00 (0.79, 1.27)
Unknown	4	
Ibuprofen		
No	40012 (79.7%)	1.00 (ref.)
Yes	10184 (20.3%)	0.90 (0.75, 1.07)
Unknown	6	
COX-2 Inhibitors		
No	48302 (96.2%)	1.00 (ref.)
Yes	1897 (3.8%)	0.45 (0.26, 0.78)
Unknown	3	
Steroid		
No	42859 (87.7%)	1.00 (ref.)
Yes	5993 (12.3%)	0.91 (0.73, 1.13)
Unknown		
Acetaminophen		
No	38697 (77.1%)	1.00 (ref.)
Yes	11504 (22.9%)	1.24 (1.06, 1.45)
Unknown	1	

376 [a] Multivariable-adjusted model adjusted for updated age, smoking, diabetes, race/ethnicity, BMI, physical activities,
377 alcohol use, hospitalization due to musculoskeletal system and connective tissue disease, hospitalization due to

circulatory disease, asthma, coagulation/hemorrhagic conditions, antihypertensive medications use, previous analgesics use and mutually adjusted for other classes of medicatio

Appendix 1. Demographic characteristics and lifestyle factors of participants at baseline in the California Teachers Cohort, 1995-2012 (N=122,629).

Characteristics	Participants with No hospitalization data (All CA residents)	Study population (CA resident with at least 1 OSHPD record)	Age-adjusted HR	Multivariable adjusted-HR [a]	Multivariable adjusted-HR weighted by 1/P(selection) [b]
Total	34148 (100%)	88481 (100%)	NA	NA	NA
Age					
<50	17615 (51.6%)	35500 (40.1%)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
51-60	10038 (29.4%)	19916 (22.5%)	5.11 (3.73, 7.00)	4.30 (3.07, 6.01)	4.30 (3.11, 5.94)
61-70	3868 (11.3%)	16571 (18.7%)	23.70 (17.86, 31.46)	19.60 (14.50, 26.55)	20.05 (14.92, 26.93)
71-80	1654 (4.8%)	11825 (13.4%)	71.80 (54.33, 94.90)	57.22 (42.39, 77.24)	58.46 (43.60, 78.39)
>80	973 (2.8%)	4669 (5.3%)	200.03 (149.28, 268.02)	160 (116.12, 220.81)	164 (119.68, 226.16)
Race/Ethnicity					

Non-Latina white	29157 (86.2%)	77079 (87.9%)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
African American	991 (2.9%)	2260 (2.6%)	0.56 (0.37, 0.84)	0.63 (0.41, 0.96)	0.68 (0.45, 1.04)
Native American	1446 (4.3%)	3709 (4.2%)	0.66 (0.42, 1.03)	0.61 (0.36, 1.01)	0.58 (0.34, 1.00)
Latina	283 (0.8%)	829 (0.9%)	0.99 (0.64, 1.52)	0.99 (0.58, 1.68)	0.98 (0.55, 1.74)
Asian/Pacific Islander	1488 (4.4%)	2796 (3.2%)	0.31 (0.18, 0.55)	0.24 (0.12, 0.49)	0.27 (0.13, 0.53)
Other	468 (1.4%)	1048 (1.2%)	0.80 (0.40, 1.61)	0.69 (0.28, 1.65)	0.69 (0.28, 1.71)
Missing	315	760			
BMI					
Underweight	921 (2.8%)	2276 (2.7%)	1.25 (0.91, 1.71)	1.12 (0.78, 1.61)	1.12 (0.77, 1.65)
Normal	21056 (63.9%)	47374 (56.1%)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Overweight	7499 (22.8%)	21831 (25.8%)	1.18 (1.05, 1.31)	1.14 (1.01, 1.28)	1.16 (1.02, 1.31)
Obese	3484 (10.6%)	13012 (15.4%)	1.21 (1.04, 1.39)	1.06 (0.90, 1.24)	1.08 (0.91, 1.29)
Unknown	1188	3988			

History of High blood pressure					
No	30239 (88.6%)	70874 (80.1%)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes	3909 (11.4%)	17607 (19.9%)	1.25 (1.13, 1.38)	1.17 (0.97, 1.40)	1.16 (0.96, 1.42)
History of Heart attack/MI					
No	33961 (99.5%)	87035 (98.4%)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes	187 (0.5%)	1446 (1.6%)	1.14 (0.87, 1.50)	1.05 (0.77, 1.42)	1.05 (0.75, 1.49)
History of Stroke					
No	33874 (99.2%)	87189 (98.5%)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes	274 (0.8%)	1292 (1.5%)	1.02 (0,74, 1.42)	0.95 (0.66, 1.36)	0.95 (0.63, 1.41)
History of Diabetes					
No	33615 (98.4%)	85492 (96.6%)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes	533 (1.6%)	2989 (3.4%)	1.75 (1.43, 2.13)	1.72 (1.37, 2.15)	1.73 (1.35, 2.22)

Smoking					
Never	6555 (19.4%)	16782 (19.2 %)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Passive	16314 (48.4%)	40368 (46.1 %)	0.95 (0.82, 1.09)	0.98 (0.84, 1.15)	0.99 (0.84, 1.17)
Former	9253 (27.4%)	25751 (29.4 %)	1.16 (1.01, 1.34)	1.16 (0.99, 1.37)	1.16 (0.97, 1.38)
Current	1594 (4.7%)	4590 (5.2%)	1.41 (1.12, 1.78)	1.31 (1.00, 1.71)	1.33 (0.99, 1.79)
Missing	432	990			
No. of smoking pack-years					
Never or passive smoker	22869 (69.9%)	57150 (67.4 %)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
≤ 10	5881 (18%)	14052 (16.6 %)	1.00 (0.87, 1.15)	0.99 (0.86, 1.23)	1.00 (0.85, 1.18)
11-20	1901 (5.8%)	5187 (6.1%)	1.14 (0.95, 1.37)	1.09 (0.88, 1.33)	1.10 (0.88, 1.37)
≥ 20	2077 (6.3%)	8464 (10%)	1.62 (1.42, 1.84)	1.50 (1.30, 1.73)	1.50 (1.28, 1.76)
Missing	1420	3628			
Daily alcohol intake (g)					
None	10188 (31.3%	29086 (34.9	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)

	)	%)			
<20	19700 (60.5%)	47340 (56.7%)	0.97 (0.87, 1.08)	0.93 (0.83, 1.05)	0.93 (0.82, 1.05)
≥20	2651 (8.1%)	7015 (8.4%)	1.06 (0.90, 1.26)	0.95 (0.79, 1.15)	0.98 (0.80, 1.20)
Unknown	1609	5040			
Lifetime moderate and strenuous physical activity (h/week)					
<2	10390 (30.6%)	29272 (33.3%)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
2 to 4	9019 (26.6%)	21822 (24.8%)	0.93 (0.82, 1.05)	0.91 (0.79, 1.04)	0.91 (0.78, 1.04)
4 to <6	5853 (17.3%)	14426 (16.4%)	0.95 (0.82, 1.10)	0.89 (0.76, 1.05)	0.87 (0.73, 1.04)
≥ 6	8667 (25.5%)	22319 (25.4%)	0.83 (0.73, 0.94)	0.81 (0.70, 0.93)	0.80 (0.69, 0.94)
Unknown		642			
Aspirin use					
No	27464 (80.4%)	67269 (76.0%)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes	6684 (19.6%)	21212 (24.0%)	1.14 (1.03, 1.26)	1.10 (0.99, 1.24)	1.10 (0.97, 1.24)

Ibuprofen use					
No	27991 (82%)	70146 (79.3%)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes	6157 (18%)	18335 (20.7%)	1.22 (1.08, 1.37)	1.10 (0.95, 1.25)	1.07 (0.92, 1.24)
NSAIDs					
No	23617 (69.2%)	55967 (63.2%)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes	10530 (30.8%)	32514 (36.7%)	1.19 (1.09, 1.31)	1.13 (1.01, 1.39)	1.12 (1.00, 1.26)
Acetaminophen use					
No	30253 (88.6%)	76082 (86.0%)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes	3895 (11.4%)	12399 (14.0%)	1.28 (1.12, 1.48)	1.19 (1.01, 1.39)	1.18 (1.00, 1.40)
Antihypertensives					
No	30156 (88.3%)	77706 (87.8%)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes	3992 (11.7%)	10775 (12.2%)	1.25 (1.14, 1.38)	1.03 (0.86, 1.23)	1.02 (0.84, 1.25)

[a] Multivariable model adjusted for all variables listed in the table.

383 [b] Weighted multivariable model is weighted by the inverse probability of having at least one OSHPD records
384 throughout the study period.

385

Appendix 2. Self-reported NSAIDs and acetaminophen use and age-related macular degeneration stratified by time of initiation in California Teachers Cohort, 2005-2012 (N=50,202).

	No. of participants	Adjusted-OR[a] (95% CI)
Aspirin		
No use at baseline or in 2005	22635 (51.9%)	1.00 (ref.)
Use at baseline, no use in 2005	4446 (10.2%)	1.24 (0.98, 1.56)
No use at baseline, use in 2005	10713 (24.6%)	0.98 (0.83, 1.17)
Use at baseline and in 2005	5817 (13.3%)	0.86 (0.70, 1.07)
Non-aspirin NSAIDs		
No use at baseline or in 2005	2558 (58.6%)	1.00 (ref.)
Use at baseline, no use in 2005	4363 (10.0%)	1.14 (0.91, 1.43)
No use at baseline, use in 2005	8702 (19.9%)	0.84 (0.69, 1.03)
Use at baseline and in 2005	4993 (11.4%)	0.87 (0.66, 1.15)
Acetaminophen		
No use at baseline or in 2005	30781 (70.6%)	1.00 (ref.)
Use at baseline, no use in 2005	3174 (7.3%)	1.15 (0.83, 1.60)
No use at baseline, use in 2005	6891 (15.8%)	1.15 (0.96, 1.37)
Use at baseline and in 2005	2772 (6.4%)	1.50 (1.13, 1.96)

[a] Multivariable-adjusted model adjusted for age, smoking, diabetes, race/ethnicity, BMI, physical activities, alcohol use, hospitalization due to musculoskeletal system and connective tissue disease, hospitalization due to circulatory disease, asthma, coagulation/hemorrhagic conditions, antihypertensive medications use, frequency/duration of the index medication, and mutually adjusted for intensity of other classes of medication