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NSAID use and incident cognitive impairment in a population-based cohort

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) may prevent dementia, but previous studies have yielded conflicting results. This study estimated the association of prior NSAID use with incident cognitive impairment in the population-based Epidemiology of Hearing Loss Study (n=2422 without cognitive impairment in 1998-2000). Prospectively collected medication data from 1988-1990, 1993-1995, and 1998-2000 were used to categorize NSAID use history at the cognitive baseline (1998-2000). Aspirin use and non-aspirin NSAID use were separately examined. Cox regression models were used to estimate the associations between NSAID use history at baseline and incident cognitive impairment in 2003-2005 or 2009-2010. Logistic regression analyses were used to estimate associations with a second outcome, mild cognitive impairment (MCI)/dementia, available in 2009-2010. Participants using aspirin at baseline but not 5 years prior were more likely to develop cognitive impairment (adjusted hazard ratio (HR) = 1.77; 95% confidence interval (CI) = 1.11, 2.82; Model 2), with non-significant associations for longer term use. Non-aspirin NSAID use was not associated with incident cognitive impairment or MCI/

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dementia odds. These results provided no evidence to support a potential protective effect of NSAIDs against dementia.

Keywords

cognition; dementia; population-based; non-steroidal anti-inflammatory drug; aspirin

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most widely used classes of medications. A recent study in the United States estimated that there were 43 million regular aspirin users (19.0% of the U.S. adult population) and 29 million regular users of other NSAIDs (12.1%) in 2010.¹ Compared to 2005, this was an overall increase of 57% in regular aspirin use and 41% in regular use of other NSAIDs.¹ Although these medications have a variety of well-known benefits and risks, controversy remains regarding the neuroprotective potential of NSAIDs, particularly non-aspirin NSAIDs.²

An early study observed lower than expected Alzheimer's disease (AD) prevalence among rheumatoid arthritis clinic patients and the authors suggested this could reflect a protective effect of anti-inflammatory therapy against AD.³ Many subsequent reports from large prospective observational studies at least partially supported the possibility that non-aspirin NSAIDs may protect against AD,⁴⁻⁹ although other well-designed studies clearly did not support that hypothesis,^{10, 11} including one report that pharmacy-defined heavy NSAID users were at significantly increased risk of AD or all-cause dementia.¹¹ Randomized trials of non-aspirin NSAIDs have also failed to support the hypothesis that non-aspirin NSAIDs reduce AD risk, showing no benefit in either preventing or treating AD.¹²⁻¹⁴

In contrast to non-aspirin NSAIDs, there is less support for a protective effect of aspirin use against dementia,⁹ with most observational and trial data suggesting no benefit. Several previous prospective observational studies have reported null associations for aspirin use with AD,^{4, 5, 8, 10} although the Rotterdam Study reported a marginally significantly increased AD risk among participants using aspirin for more than 1 month but less than 2 years.⁷ Additional positive associations have been reported for aspirin use with the outcomes vascular dementia (VaD)^{7, 8} and all-cause dementia.¹⁵ Importantly, given the cardiovascular indications for aspirin use, positive associations from these observational studies could reflect indication bias. Randomized trials of aspirin use for the prevention of cardiovascular disease have reported no overall cognitive benefits of aspirin use in women only¹⁶ or both sexes.¹⁷

Given that NSAIDs are so commonly used, it is critical to determine their potential neuroprotective or neurotoxic effects in order to better assess their risks and benefits. Thus, the divergent results from observational studies and randomized trials regarding non-aspirin NSAID use and AD risk are problematic. Results from a randomized trial are generally considered better evidence than results from an observational study; however, in this case the results from the primary prevention trial, the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT), are limited because the trial was stopped early due to concerns

about adverse cardiovascular effects of NSAIDs.¹² Due to concerns about the safety of NSAIDs, additional randomized trials for dementia prevention may not be conducted. Therefore, acquisition of vital information about the complex NSAID-dementia relationship may be limited to careful consideration of previous studies' potential biases, together with continued surveillance in well-designed prospective, population-based studies.

The prior observational studies have various potential limitations, including use of exposure and outcome data that were concurrently measured or analyzed with only 1-2 year lag periods, inclusion of prevalent cases, and failure to separate former users (who may have substantially different risk) from never users. Previous investigators have concluded that recall, prescription, and publication bias may underlie reported beneficial effects of NSAIDs on dementia, based on a systematic review and meta-analysis.¹⁸

Using 20 years of prospectively collected data from a population-based cohort, the current study estimated the relationship between NSAID use and incident cognitive impairment. Aspirin use and non-aspirin NSAID use were separately examined, due to differences in their indications for use, mechanisms of action (reviewed in ²), and previously reported associations with dementia. With exposure data from multiple time points, including from 5 and 10 years prior to baseline, former users could be identified and separately examined. This study also provided up to 10 years of follow-up for the incidence of the main cognitive impairment outcome, allowing for a more biologically plausible lag time between exposure and outcome.

Methods

Study population

The Epidemiology of Hearing Loss Study (EHLS) is a longitudinal, population-based study of sensory aging in Beaver Dam, WI. A private census was conducted in 1987-1988 to identify all 43- to 84-year-old residents of Beaver Dam, WI. In 1988-1990, 4926 (83%) of the 5924 eligible residents participated in the Beaver Dam Eye Study (BDES).¹⁹ These original BDES participants were eligible for the EHLS and during 1993-1995, 3753 participated in the first phase of the EHLS (82.6% of the 4541 BDES participants alive on March 1, 1993).²⁰ Additional data collection took place approximately every 5 years thereafter, in 1998-2000 (n= 2800),²¹ 2003-2005 (n= 2395),²² and 2009-2010 (n= 1812), with each phase achieving greater than 80% participation rates. BDES examinations took place concurrently with EHLS examinations, and provided some data used in this study, including medication data. Cognition was first measured in all participants in 1998-2000, and this phase will be considered the baseline for these analyses. Participants without cognitive impairment at baseline (n=2422) were included in these analyses. This study was approved by the Health Sciences Institutional Review Board of the University of Wisconsin and informed consent was obtained from each participant.

Outcomes

The Mini-Mental State Examination (MMSE) is a brief test of general cognitive function, commonly used as a screening device for cognitive impairment.²³ It was administered in

1998-2000, 2003-2005 and 2009-2010.²⁴ Cognitive impairment was defined as a self- or proxy-reported diagnosis of AD or dementia, or a MMSE score less than 24 out of 30.

Additional cognitive tests were added at the examination in 2009-2010: Trail Making Test, Digit Symbol Substitution Test, Verbal Fluency Test, and the Rey Auditory Verbal Learning Test. Two questionnaire items on memory problems were also included: "Have you, your family, or your physician ever expressed concerns about your memory?" and "Do (your) memory loss symptoms interfere with your ability to do your own day-to-day activities?" As previously described in more detail,²⁵ these additional cognitive test and questionnaire data were used to define mild cognitive impairment (MCI) and dementia based on the recently revised criteria for MCI²⁶ and all-cause dementia²⁷ from the National Institute on Aging-Alzheimer's Association workgroups. Briefly, cognitive test performance was used to classify impairment in 3 cognitive domains (executive function, memory, and language). Dementia was defined as impairment in 2-3 cognitive domains and a positive response to the latter question (memory affects daily activities), or a self- or proxy-report of physician-diagnosed AD or dementia. MCI was defined as impairment in at least one cognitive domain, a positive response to the first question (concerns about memory), and not meeting the criteria for dementia.²⁵

NSAID medication use

Participants were asked to bring to examinations all medications used in the past month, both prescription and over-the-counter, and examiners recorded medication names directly from containers. Additionally, participants were asked whether they regularly use aspirin (at least twice/week for more than 3 months). Duration of use was not directly ascertained. Non-aspirin NSAID use was defined as the presence of any medication containing non-aspirin NSAIDs in the list of past month medications. Aspirin use was defined as the presence of any aspirin-containing medication in the list of past month medications, or an affirmative response to the regular aspirin use question.

Covariates

Covariate data were ascertained from the baseline examination phase (1998-2000) except as otherwise noted. Participants self-reported education (<12, 12, 13-15, or 16 years), smoking status (never, former, or current), exercise (times per week engaged in regular activity long enough to work up a sweat), and overall health (excellent, good, fair, or poor). Ever heavy drinking was defined as ever regularly consuming 4 alcohol-containing drinks per day, self-reported at baseline or prior phases. The mental component score (MCS) of the Short Form Health Survey (SF-36) was used as a proxy measure of general mental health (higher scores indicate better mental health).²⁸

Body mass index (BMI) was calculated by dividing measured weight (in kilograms) by measured height (in meters) squared. Histories of stroke, angina, myocardial infarction (MI), and arthritis were based on self-reported physician diagnoses. Diabetes was defined as a self-reported physician diagnosis, hemoglobin A1C $\geq 6.5\%$, or diabetes treatment. Blood pressure was measured based on the Hypertension Detection and Follow-Up Program protocol.²⁹ Hypertension was defined as systolic blood pressure ≥ 140 mmHg, or diastolic

pressure 90 mmHg, or self-reported physician-diagnosed hypertension and current use of hypertension medications. For those who participated in 2003-2005, Apolipoprotein E (*APOE*) genotype was measured (Children's Hospital of Philadelphia, Center for Applied Genomics), and was available for 1773 (73%) of the 2422 participants at risk of cognitive impairment in 1998-2000.

Statistical analyses

Categorical variables (aspirin status, aspirin duration, non-aspirin NSAID status, and non-aspirin NSAID duration) were created to group participants based on their NSAID use history at baseline, using data from baseline (1998-2000) and two prior examinations (1988-1990 and 1993-1995). For aspirin and non-aspirin NSAIDs, respectively, status was categorized as current, former, or never. Never use was defined as non-use at all three time points. Former use was defined as non-use in 1998-2000 with prior use in 1988-1990 or 1993-1995. Current use was defined as use in 1998-2000. For aspirin and non-aspirin NSAID duration variables, current users were further subdivided according to the first examination since which they had persistently reported use. Never users were the reference group for all analyses. For aspirin use, the reference group of never users included non-aspirin NSAID users and similarly, for non-aspirin NSAID use, the reference group included aspirin users.

All analyses excluded participants with prevalent cognitive impairment at baseline. To assess the characteristics associated with aspirin use and, separately, non-aspirin NSAID use, baseline ever users (current or former users in 1998-2000) were compared to baseline never users. These comparisons used the Cochran-Mantel-Haenszel statistic for general association (for categorical variables) or analysis of covariance (for continuous variables), and were adjusted for age and sex.

Discrete-time Cox regression models with time on study as the time scale were used to estimate the longitudinal associations of aspirin status, aspirin duration, non-aspirin NSAID status, and non-aspirin NSAID duration, respectively, with incident cognitive impairment in 2003-2005 or 2009-2010. The proportional hazards assumption was tested using interaction terms for exposure by time, with no significant violations observed. Logistic regression models were used to estimate the associations of the same four NSAID exposure variables with the odds of MCI/dementia in 2009-2010.

All models were minimally adjusted for age, age², sex, and education (Model 1). Fully-adjusted models included all the covariates described above (Model 2). Reduced models (Model 3) retained covariates that were statistically significant or moderately changed estimates for the exposure status variable (see Tables 2 and 3 for Model 3 covariate lists). These reduced models (Model 3) were built separately for 4 exposure-outcome dyads: aspirin status – cognitive impairment, aspirin status – MCI/dementia, non-aspirin NSAID status – cognitive impairment, and non-aspirin NSAID status – MCI/dementia. For the analyses with the duration variables (aspirin duration and non-aspirin NSAID duration), covariates selected for the corresponding status variable were applied. Interaction terms for exposure status variables by *APOE* ε4 carrier status were tested.

Results

Aspirin ever users at baseline were older and more likely to be male, compared to aspirin never users, and greater proportions reported more frequent exercise, statin use, and histories of angina, MI, or diabetes, adjusted for age and sex (Table 1). Ever users of non-aspirin NSAIDs were more likely to be female, compared to never users of non-aspirin NSAIDs, and greater proportions reported arthritis, diabetes, and fair or poor self-rated health (Table 1).

Compared to aspirin never use, neither former nor current aspirin use was significantly associated with incident cognitive impairment, although both had positive hazard ratios (Table 2). In the duration analyses, current aspirin users in 1998-2000 but not 5 years prior were more likely to develop cognitive impairment over the subsequent 10 years (compared to aspirin never users); longer term use was not associated with cognitive impairment (Table 2). Non-aspirin NSAID use was not associated with incident cognitive impairment (Table 2). There were no statistically significant associations with the MCI/dementia outcome (Table 3). No significant interactions with *APOE* ϵ 4 carrier status were observed.

To investigate whether cardiovascular disease might explain the increased risk of cognitive impairment among those using aspirin at baseline but not 5 years prior, sensitivity analyses examined the association among those without a history of MI, angina, or stroke at baseline. The association was similar and remained statistically significant (HR = 1.90; 95% CI = 1.16-3.11, Model 2, adjusted for all covariates).

To investigate the potential impact of selective attrition, we conducted a sensitivity analysis that assumed that those taking aspirin at baseline but not followed-up would have a 20% higher (age, sex, and education-adjusted) hazard ratio for risk of cognitive impairment than was observed among those who were followed-up. Then we repeated the calculations, this time assuming a 20% lower hazard ratio. Under these assumptions, no hazard ratio shown in Table 2 would have been altered by more than 0.05 in either direction, and no odds ratio shown in Table 3 would have been altered by more than 0.10.

Discussion

The results from this study do not support a potential protective effect of NSAID use on cognitive impairment. Non-aspirin NSAID use was not significantly associated with cognitive outcomes, and there was some evidence that aspirin use may be associated with increased risk of cognitive impairment, potentially reflecting indication bias. Those using aspirin at baseline but not 5 years prior were more likely to develop cognitive impairment over the subsequent 10 years, compared to never users of aspirin. No significant increased risk was observed for those with other patterns of aspirin use, although some point estimates suggested possible increased risk associated with current and former use.

Non-aspirin NSAID use may not protect against dementia. Consistent with the current study, other well-designed observational studies and randomized trials have reported no protective effect of non-aspirin NSAID use. The Religious Orders Study found no association with incident AD or AD pathology,¹⁰ and the Adult Changes in Thought study reported increased

AD and all-cause dementia risk in heavy NSAID users.¹¹ Randomized trials of non-aspirin NSAID use compared to placebo have reported no reduction in AD risk among those at high risk due to a family history of AD (ADAPT),¹² no benefit on disease progression among patients with AD dementia,¹³ and increased rate of progression from MCI to AD dementia.¹⁴ Yet it is important to note that the primary prevention trial in particular had several important limitations that must be considered along with the study's reported conclusions, including that duration of treatment was substantially shorter than planned, there was unexpectedly low statistical power due to lower than anticipated incidence of AD, and after the treatment study ended and before the follow-up study was conducted, NSAIDs were used by (similar) portions of both treatment groups.¹² Impacting the potential for future trials (and perhaps the likelihood of cognitive benefits), studies have shown that non-aspirin NSAIDs are associated with increased risk of adverse cardiovascular effects,³⁰ and the FDA now requires all prescription and non-prescription NSAID labels (except aspirin) to include information about cardiovascular risks.³¹ Additionally, one of the original rationales for hypothesizing that NSAIDs reduced AD risk may have been misguided, as observations of decreased AD prevalence in rheumatoid arthritis clinic patients could be explained by their increased and earlier CVD mortality,³² which would theoretically decrease the probability of surviving to dementia onset and diagnosis. Finally, although chronic inflammation is likely to contribute to dementia development, physiological inflammatory responses are often beneficial, arguing against a simple paradigm in which suppressing inflammation should necessarily prevent dementia.³³ Together these factors suggest diminished rationale to support a protective effect of non-aspirin NSAIDs against dementia.

Although several large observational studies with longitudinal data have previously reported inverse associations for non-aspirin NSAIDs,⁴⁻⁹ most studies had at least one limitation that might explain their observed inverse association (e.g., analyses with concurrent exposure and outcome measures, inclusion of participants with prevalent cognitive impairment, failure to separate former users, or retrospective collection of self-reported NSAID use). In particular, if the period between exposure and outcome measurement is short, it is difficult to distinguish between cause and effect, thus such associations could reflect the impact of pre-dementia cognitive decline on NSAID use³⁴ or reporting of NSAID use. Although some studies stated that they addressed this issue by incorporating 1-2 year lag periods, Alzheimer's disease is thought to develop over several decades and decreased cognitive function could affect behavior for several years prior to dementia onset. In fact, a meta-analysis concluded that much of the observed beneficial effect of NSAIDs is likely due to recall, prescription, and publication bias based on their pooled estimates of a 50% risk reduction from studies of prevalent dementia, 20% reduction for incident dementia studies, and no association overall among studies of cognitive decline.¹⁸

In the current study, aspirin users appeared to have increased cognitive impairment risk, although the association was only significant among current users at baseline but not 5 years prior. These results are generally consistent with prior studies, most of which have reported null or positive associations of aspirin use with various cognitive impairment outcomes. Positive associations for aspirin use with vascular dementia (VaD)^{7, 8} and all-cause dementia have been reported.¹⁵ Several studies have reported no significant overall association with incident AD,^{4, 5, 7-10, 15} although one reported marginally significant increased AD risk for

shorter-term (1 month – 2 years) aspirin users.⁷ Randomized trials of aspirin use for the prevention of cardiovascular disease have reported no overall cognitive effects of aspirin use.^{16, 17}

Aspirin and non-aspirin NSAIDs have some differences in both biological effects and indications for use, either of which could explain why positive associations with cognitive impairment are more often observed for aspirin use. Although all NSAIDs inhibit cyclooxygenase (COX) by blocking access to its active site, aspirin does so in an irreversible manner. In platelets, which have no nuclei and cannot synthesize new COX, this prevents the synthesis of thromboxanes and results in an anti-clotting effect that makes aspirin useful for cardiovascular disease prevention (reviewed in ²). This aspirin anti-clotting effect could contribute to increased risk of cognitive impairment through increased risk of hemorrhagic stroke,³⁵ although in general any such increased risk would likely be offset by simultaneous decreased risk of ischemic stroke.³⁶ Additionally, adjustment for baseline stroke history did not substantially attenuate the significant increased risk for those using aspirin at baseline but not 5 years prior. Although other potential biological explanations for a positive aspirin-dementia association exist (e.g., cerebral microbleeds^{37, 38}), they were not addressed by this population-based study. However, a more likely explanation is indication bias, as CVD and CVD risk factors have been associated with both aspirin use and dementia incidence. In the current study, aspirin ever users were more likely to have a history of MI and angina. Although these and other CVD indicators and risk factors were tested as potential covariates and retained in models as needed, and results were similar in a sensitivity analysis restricted to participants with no history of angina, MI or stroke at baseline, residual confounding by indication could explain the observed positive association of aspirin use and cognitive impairment. This possibility is supported by the pattern in prior studies of more consistent positive associations for VaD, compared to AD, and also by the aspirin randomized trials, which reported no adverse cognitive effects.^{16, 17}

The current study has both limitations and strengths. This study did not address dose, frequency, or specific NSAID medications (other than aspirin). NSAID exposure may need to occur at higher doses or greater frequency in order to protect against dementia, although a large cohort study reported that pharmacy-defined heavy NSAID users actually had increased risk of AD and all-cause dementia.¹¹ Potential benefits could also be limited to specific NSAIDs or types of NSAIDs which were not examined separately here. However, prior studies have investigated the most promising subclass, selective beta-amyloid ($A\beta_{42}$) lowering NSAIDs, and found no advantage over other NSAIDs.^{6, 39} In this study, past month medication use was ascertained approximately every 5 years, and used to approximate duration of use, but direct duration data were not available, and duration may have been misclassified. It is possible that an association with long-term use was undetected. However, with multiple time points it was possible to identify consistent users, and separate former users from the reference group of never users. The cognitive impairment outcome for which longitudinal data was available was based on a single cognitive test (MMSE) and reported physician-diagnosed AD or dementia, and may have misclassified some participants' cognitive status, potentially biasing results towards the null. In order to address this limitation, a second outcome (MCI/dementia), based on a more detailed cognitive battery administered only at the most recent examination phase (2009-2010), was also

examined, but was not significantly associated with NSAID use. The MCI/dementia estimates are generally similar to the cognitive impairment results, and could be closer to null and not statistically significant partly because of the loss of sample size with additional follow-up. Both results are presented because they have different strengths and limitations. The cognitive impairment outcome was measured in a simple manner, but was ascertained longitudinally, and allowed for inclusion of participants that were subsequently lost to follow-up due to death or other reasons. In contrast, the MCI/dementia outcome was ascertained at only the most recent time point, but was strengthened by the more extensive cognitive assessment. Yet both sets of results fail to indicate an inverse association between non-aspirin NSAID or aspirin use and either cognitive outcome. Residual confounding, particularly by indication, may have been present, although these analyses were adjusted for many possible confounders, including factors associated with NSAID use. The positive association observed for aspirin use was significant only for one analysis with the cognitive impairment outcome, and could be due to indication bias, as discussed above. Finally, as in all large longitudinal studies, there were losses to follow-up over the twenty year period, but a sensitivity analysis provided some evidence that selective attrition is unlikely to have substantially biased the reported results. This study was conducted in a large, prospective, population-based cohort with consistently high participation rates. Home visits and nursing home visits were provided in order to minimize losses to follow-up. Those with cognitive impairment at baseline were excluded, NSAID exposure data were prospectively collected over 10 years, and outcomes were ascertained 5 and 10 years after exposure, reducing the likelihood that underlying early cognitive decline affected exposure ascertainment.

In conclusion, with data collected over a 20-year period, this study examined NSAID use and incident cognitive impairment and found no evidence to support a protective effect. Instead, the results suggested aspirin users may have greater risk of cognitive impairment, potentially reflecting underlying relationships between indications for aspirin use and cognitive impairment risk. The discrepant results between most observational studies and the randomized trials regarding non-aspirin NSAID use and dementia risk have led to debate.² Randomized trials are able to address some of the major concerns in observational studies, including indication bias and reverse causality. However, the primary prevention trial was ultimately limited by several important factors that could have left it underpowered to detect an effect (e.g., substantially shorter duration of treatment, contamination across treatment arms during the follow-up study).¹² Although evidence suggests that chronic inflammation is involved in the development of dementia, some inflammatory responses are beneficial,⁴⁰ thus suppression with anti-inflammatory interventions may be less useful than interventions designed to promote or preserve a dynamic, balanced inflammatory response.

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Table 1
Baseline Characteristics by NSAID Use Status, among Those without Cognitive Impairment at Baseline (1998-2000)

Characteristic	Aspirin			Non-aspirin NSAIDs		
	Never users (N=753)		p-value	Never users (N=1212)		p-value
	N (%)	N (%)		N (%)	N (%)	
Male sex	257 (34.1)	704 (44.5)	<0.01	571 (47.1)	387 (34.8)	<0.01
Education, years			0.05			0.84
<12	105 (14.0)	255 (16.1)		189 (15.6)	167 (15.0)	
12	404 (53.7)	751 (47.4)		592 (48.9)	555 (50.0)	
13-15	115 (15.3)	284 (17.9)		199 (16.4)	199 (17.9)	
16	128 (17.0)	293 (18.5)		231 (19.1)	190 (17.1)	
Smoking status			0.21			<0.01
Never	374 (49.7)	726 (45.9)		588 (48.5)	505 (45.5)	
Past	290 (38.5)	710 (44.9)		486 (40.1)	509 (45.8)	
Current	89 (11.8)	147 (9.3)		138 (11.4)	97 (8.7)	
Ever heavy drinking	166 (22.1)	383 (24.2)	0.61	298 (24.6)	245 (22.1)	0.36
Exercise			0.03			0.96
0 times/week	461 (61.2)	905 (57.2)		697 (57.5)	658 (59.2)	
1-2 times/week	99 (13.2)	219 (13.8)		167 (13.8)	151 (13.6)	
3 times/week	193 (25.6)	459 (29.0)		348 (28.7)	302 (27.2)	
Hypertension	413 (55.0)	962 (60.9)	0.17	715 (59.0)	650 (58.7)	0.88
Diabetes	76 (10.1)	222 (14.0)	0.04	143 (11.8)	154 (13.9)	0.04
Myocardial infarction	22 (2.9)	184 (11.6)	<0.01	123 (10.2)	81 (7.3)	0.12
Angina	22 (2.9)	215 (13.6)	<0.01	133 (11.0)	102 (9.2)	0.59
Stroke	10 (1.3)	43 (2.7)	0.13	33 (2.7)	18 (1.6)	0.07
Statin use	102 (13.6)	363 (22.9)	<0.01	231 (19.1)	226 (20.3)	0.16
Arthritis	332 (44.2)	737 (46.6)	0.75	403 (33.3)	668 (60.2)	<0.01
Self-reported Health			0.22			<0.01
Excellent	143 (19.0)	305 (19.3)		268 (22.2)	180 (16.2)	
Good	512 (68.0)	1019 (64.5)		780 (64.5)	743 (66.9)	

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Characteristic	Aspirin				Non-aspirin NSAIDs			
	Never users (N=753)		Ever users (N=1583)		Never users (N=1212)		Ever users (N=1111)	
	N (%)		N (%)		N (%)		N (%)	
	p-value		p-value		Mean (SD)		Mean (SD)	
Fair/Poor	98 (13.0)		256 (16.2)		162 (13.4)		187 (16.9)	
Age, years	66.6 (9.0)		69.0 (9.4)		68.5 (9.2)		68.0 (9.4)	
Body mass index, kg/m ²	30.2 (6.3)		29.8 (5.7)		29.2 (5.6)		30.9 (6.1)	
SF-36 Mental Score	55.2 (7.8)		55.4 (7.4)		55.5 (7.2)		55.2 (7.8)	

Abbreviations: NSAID=non-steroidal anti-inflammatory drug; SF-36 Mental Score = Short Form Health Survey Mental Component Score; SD = standard deviation

Notes: P-values are adjusted for age and sex, except p-values for sex and age, which are adjusted for age only and sex only, respectively. Percentages are of the number with data for a given covariate and counts may not sum to the total N for the column because of missing data.

Table 2
Cox Regression Models for the Associations of NSAID Use History in 1998-2000 with Incident Cognitive Impairment in 2003-2005 or 2009-2010, among Those without Cognitive Impairment in 1998-2000

	At risk* (n)	Follow-up (%)	Incident Cases (n)	Cumulative incidence (%)	Model 1 [†]		Model 2 [‡] (Full)		Model 3 [§] (Reduced)	
					HR (95% CI)	N=1995	HR (95% CI)	N=1964	HR (95% CI)	N=1982
					Aspirin status					
Never user	753	86.5	42	7.1	Reference	Reference	Reference	Reference		
Former user	333	82.3	30	12.7	1.46 (0.88, 2.43)		1.36 (0.80, 2.31)		1.46 (0.87, 2.44)	
Current user	1250	85.7	109	11.7	1.36 (0.93, 1.99)		1.40 (0.94, 2.10)		1.43 (0.96, 2.12)	
Aspirin duration										
Never user	753	86.5	42	7.1	Reference	Reference	Reference	Reference		N=1960
Former user	333	82.3	30	12.7	1.46 (0.88, 2.43)		1.34 (0.79, 2.28)		1.45 (0.86, 2.43)	
Current, not 5y prior	486	87.2	48	12.6	1.67 (1.07, 2.60)		1.77 (1.11, 2.82)		1.79 (1.13, 2.83)	
Current and 5y prior	440	85.2	33	10.4	1.17 (0.72, 1.90)		1.25 (0.75, 2.08)		1.29 (0.78, 2.12)	
Current, 5 and 10y prior	294	85.0	26	11.9	1.23 (0.72, 2.08)		1.11 (0.62, 1.98)		1.16 (0.66, 2.03)	
Non-aspirin NSAID status										
Never user	1212	84.6	97	10.8	Reference	Reference	Reference	Reference		
Former user	337	83.1	27	10.8	1.09 (0.69, 1.72)		0.97 (0.59, 1.61)		1.01 (0.62, 1.64)	
Current user	774	88.2	56	9.2	0.97 (0.68, 1.38)		0.91 (0.62, 1.34)		0.92 (0.63, 1.36)	
Non-aspirin NSAID duration										
Never user	1212	84.6	97	10.8	Reference	Reference	Reference	Reference		N=1962
Former user	337	83.1	27	10.8	1.09 (0.69, 1.73)		0.98 (0.59, 1.61)		1.01 (0.62, 1.64)	
Current, not 5y prior	407	88.5	30	9.2	0.93 (0.60, 1.45)		0.93 (0.58, 1.48)		0.95 (0.60, 1.50)	
Current and 5y prior	223	88.3	16	9.2	1.11 (0.63, 1.98)		0.95 (0.51, 1.77)		0.98 (0.53, 1.81)	
Current, 5 and 10y prior	131	87.8	10	10.0	0.98 (0.49, 1.97)		0.95 (0.45, 2.00)		0.91 (0.44, 1.89)	

Abbreviations: HR = hazard ratio; CI = confidence interval; SF-36 MCS = Short Form Health Survey Mental Component Score

* Participants without cognitive impairment at baseline (1998-2000).

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[†]Model 1 adjusted for baseline age, age2, sex, and education.

[‡]Model 2 (FULL) adjusted for all covariates: baseline age, age2, sex, education, smoking, ever heavy drinking, exercise, hypertension, diabetes, myocardial infarction, stroke, angina, statin use, arthritis, self-rated health, body mass index, SF-36 MCS.

[§]Model 3 (REDUCED) covariates differed for aspirin and non-aspirin NSAIDs. For aspirin, Model 3 adjusted for baseline age, age2, sex, education, smoking, ever heavy drinking, SF-36 MCS, self-rated health, stroke, and myocardial infarction. For non-aspirin NSAIDs, Model 3 adjusted for baseline age, age2, sex, education, smoking, ever heavy drinking, SF-36 MCS, self-rated health, stroke, and arthritis.

Table 3
Logistic Regression Models for the Associations of NSAID Use History in 1998-2000 with MCI/dementia in 2009-2010, among Those without Cognitive Impairment in 1998-2000

	At risk* (n)	Follow-up (%)	Cases (n)	MCI/Dementia (%) [†]	Model 1 [‡]		Model 2 [§] (Full)		Model 3 ^{***} (Reduced)	
					OR (95% CI)	N=1522	OR (95% CI)	N=1499	OR (95% CI)	N=1513
Aspirin status										
Never user	753	68.7	48	9.3	Reference		Reference		Reference	
Former user	333	59.8	24	12.1	1.14 (0.66, 1.95)		1.01 (0.57, 1.80)		1.08 (0.62, 1.89)	
Current user	1250	64.6	102	12.6	1.14 (0.78, 1.67)		1.15 (0.76, 1.74)		1.18 (0.79, 1.76)	
Aspirin duration										
Never user	753	68.7	48	9.3	Reference		Reference		Reference	
Former user	333	59.8	24	12.1	1.14 (0.66, 1.95)		1.00 (0.56, 1.78)		1.07 (0.61, 1.88)	
Current, not 5y prior	486	70.0	46	13.5	1.25 (0.80, 1.97)		1.33 (0.82, 2.17)		1.37 (0.85, 2.19)	
Current and 5y prior	440	64.3	32	11.3	1.04 (0.63, 1.70)		1.09 (0.64, 1.85)		1.09 (0.65, 1.83)	
Current, 5 and 10y prior	294	57.5	23	13.6	1.12 (0.64, 1.97)		0.94 (0.51, 1.75)		1.05 (0.58, 1.90)	
Non-aspirin NSAID status										
Never user	1212	64.8	85	10.8	Reference		Reference		Reference	
Former user	337	62.9	29	13.7	1.35 (0.84, 2.18)		0.98 (0.58, 1.66)		0.99 (0.59, 1.65)	
Current user	774	67.6	59	11.3	1.13 (0.78, 1.64)		0.93 (0.61, 1.40)		0.87 (0.58, 1.30)	
Non-aspirin NSAID duration										
Never user	1212	64.8	85	10.8	Reference		Reference		Reference	
Former user	337	62.9	29	13.7	1.36 (0.84, 2.18)		0.97 (0.57, 1.65)		0.98 (0.58, 1.63)	
Current, not 5y prior	407	67.8	33	12.0	1.15 (0.73, 1.80)		1.02 (0.63, 1.65)		0.96 (0.60, 1.54)	
Current and 5y prior	223	68.6	19	12.4	1.50 (0.85, 2.63)		1.10 (0.59, 2.06)		1.09 (0.59, 2.00)	
Current, 5 and 10y prior	131	65.6	7	8.1	0.71 (0.31, 1.64)		0.57 (0.24, 1.37)		0.48 (0.20, 1.14)	

Abbreviations: OR = odds ratio; CI = confidence interval; SF-36 MCS = Short Form Health Survey Mental Component Score

*. Participants without cognitive impairment at baseline (1998-2000).

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[†]Percentage with MCI/Dementia used those with follow-up as the denominator (n not shown).

[‡]Model 1 adjusted for baseline age, age2, sex, and education.

[§]Model 2 (FULL) adjusted for all covariates: baseline age, age2, sex, education, smoking, ever heavy drinking, exercise, hypertension, diabetes, myocardial infarction, stroke, angina, statin use, arthritis, self-rated health, body mass index, SF-36 MCS.

^{**}Model 3 (REDUCED) adjusted for baseline age, age2, sex, education, smoking, SF-36 MCS, self-rated health, and arthritis.