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NSAID Use and Dementia Risk in the Cardiovascular Health Study: Role of *APOE* and NSAID Type

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Abstract

Background: Epidemiologic and laboratory studies suggest that non-steroidal anti-inflammatory drugs (NSAIDs) reduce risk of Alzheimer dementia (AD). We therefore investigated the association between use of NSAIDs, aspirin, and the non-NSAID analgesic acetaminophen with incidence of dementia and AD.

Methods: Participants in the Cardiovascular Health Cognition Study included 3,229 individuals aged 65 or older, free of dementia at baseline, with information on medication use. We used Cox proportional hazards regression to estimate the association of medication use with incident all-cause dementia, AD, and vascular dementia (VaD). Additional analyses considered the NSAID-AD relationship as a function of age, presence of at least one ε4 allele at *APOE*, race, and individual NSAIDs' reported ability to reduce production of the amyloid-beta peptide variant $A\beta_{42}$.

Results: Use of NSAIDs was associated with a lower risk of dementia (adjusted hazard ratio or aHR 0.76, 95% confidence interval or CI 0.60–0.96), and, in particular, AD (aHR 0.63, CI 0.45–0.88), but not VaD (aHR 0.92, CI 0.65–1.28). No similar trends were observed with acetaminophen (aHR 0.99, CI 0.79 - 1.24). Closer examination suggested AD risk reduction with NSAIDs only in participants having an *APOE* ε4 allele (aHR 0.34, CI 0.18–0.65; aHR for others 0.88, CI 0.59–1.32). There was no advantage in AD risk reduction with NSAIDs reported to selectively reduce $A\beta_{42}$.

Conclusions: Results were consistent with previous cohort studies showing reduced risk of AD in NSAID users, but this association was found only in those with an *APOE* ε4 allele, and there was no advantage for $A\beta_{42}$ lowering NSAIDs.

INTRODUCTION

Epidemiologic studies suggest that non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) commonly used by the elderly for relief of pain or inflammatory conditions may protect against the development of Alzheimer's dementia (AD).[1-4] These studies are supported by cell culture and animal experiments showing that NSAIDs reduce brain

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inflammatory markers such as activated microglia[5-7] and may reduce brain deposits of amyloid-beta peptide (Aβ).[8,9] Specifically, certain NSAIDs have been shown in laboratory experiments to selectively lower the more pathogenic $A\beta_{42}$ species, as compared with the reportedly more benign $A\beta_{40}$.[8,9]

At least five prospective studies have investigated the relationship between NSAID use and AD with results that generally support the notion that NSAIDs reduce the risk of incident AD.[4, 10-13] Three of these studies suggest that longer duration of use confers greater risk reduction.[4,10,13] By contrast, randomized clinical trials in patients with AD or other high-risk populations have failed to indicate that NSAIDs are effective treatments for patients with established AD[14-16] or mild cognitive impairment.[17] A more recent study also suggests potential effect modification by *APOE* genotype in the NSAID-AD association.[18]

Using data from the population-based Cardiovascular Health Study (CHS), we investigated the relationship between self-reported NSAID use and incident all-cause dementia, AD, and vascular dementia (VaD). The relatively large size of this cohort and its availability of *APOE* genotype information enabled us to assess whether the association between NSAIDs and AD differed by age, *APOE* genotype, or race. Availability of detailed agent-specific NSAID exposure data further enabled us to assess whether such association was dependent upon the reported $A\beta_{42}$-lowering capability of individual agents. The current investigation may help clarify whether certain groups of people might selectively benefit from NSAID use and whether specific NSAIDs may confer greater benefit than others.

METHODS

Study Overview

The CHS is a prospective study designed to investigate factors related to coronary heart disease and stroke in adults aged 65 years and older.[19] The study began enrolling participants in 1989 from four communities in the United States: Sacramento County, California; Washington County, Maryland; Forsyth County, North Carolina; and Allegheny County, Pennsylvania. In 1992, an added cohort of African Americans were recruited into the study from three of these communities. Participants were subsequently evaluated in person annually for up to ten years. A subset of participants who completed brain MRI and the Modified Mini Mental State Examination (3MSE)[20] at visits between 1992 and 1994 were enrolled in the CHS Cognition Study.21

Demographic information from these participants included age, race, sex, and education level.[19] Additionally, at each of the annual visits, participants underwent extensive assessment that included measurement of cognitive status, physical ability, routine laboratory tests, and psychosocial and behavioral domains. Data regarding prescription medication use were obtained from 1992 onward, and over-the-counter (OTC) medication use was recorded from 1993 or 1994 onward.

The primary analyses here are based on the 3,229 participants in the CHS Cognition Study who were free of dementia at the time of their 1992 - 1994 MRI. Their baseline visit was the first visit either at or after the MRI in which information was available on both prescription and OTC medication use.

Exposures

At annual visits, participants were asked to report and to bring all vials for medications taken within fourteen days of the visit, for visual inspection by interviewers.[22,23] Here, the main exposures of interest were use of prescription and OTC NSAIDs, aspirin, or acetaminophen. We classified participants as NSAID users if they were taking any of the

following medications: diclofenac, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, nabumetone, naproxen, oxaprozin, piroxicam, sulindac, or tolmetin. No other NSAIDs were used by this cohort. We further classified NSAIDs into two groups based on their reported ability to selectively lower $A\beta_{42}$ production in *in vitro* or *in vivo* animal studies.[8,9] The $A\beta_{42}$-lowering NSAIDs were diclofenac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, meclofenamate, piroxicam, and sulindac. Non-$A\beta_{42}$-lowering NSAIDs included etodolac, ketoprofen, ketorolac, mefanamic acid, nabumetone, naproxen, and phenylbutazone. We classified participants as aspirin users if they were taking acetylsalicylic acid or other salicylic acid derivates such as diflunisal, salsalate, trilisate, salicylate, or salicylamide. We classified participants as acetaminophen users if they were taking medications that contained acetaminophen.

Outcome Measures

Procedures for screening and assessment of dementia have been detailed elsewhere.[21, 24] The main outcome measures here included time to diagnosis of incident all-cause dementia, Alzheimer's dementia (AD), and vascular dementia (VaD). Participants assigned a diagnosis of AD met criteria for Probable or Possible AD using the National Institute of Neurological and Communicative Diseases and Strokes – Alzheimer's Disease and Related Disorders Association criteria,[25] and did not meet criteria for Probable or Possible vascular dementia using the State of California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) criteria.26 Participants were diagnosed with VaD if they met ADDTC criteria for Probable or Possible vascular dementia, yielding a group that included VaD alone and mixed VaD plus AD.

Statistical analyses

Baseline demographic characteristics of NSAID users were compared with non-users using χ^2 or t-tests as appropriate. For the primary analyses, Cox proportional hazards regression was used to obtain crude and adjusted hazard ratios (HR) and 95% confidence intervals (CI) for the association of medication use with incident all-cause dementia, AD, and VaD. Chronological age was used as the time axis, and follow-up began after the baseline visit. Follow-up ended at the midpoint in the year of dementia onset for cases, or the date of death or last follow-up visit for non-cases. Reports of medication use (NSAIDs, aspirin, and acetaminophen) were categorized as ever- versus never- and modeled as time-dependent variables. Covariates that differed between NSAID users and non-users or between AD and non-AD cases were included in adjusted models. Other covariates were considered including baseline stroke, heart disease (myocardial infarction, angina, coronary artery bypass graft, or angioplasty), total number of prescription medications taken, alcohol consumption, and general health ratings, but these did not change the observed association between medication use and AD and were not retained in the final models.

Subsequent analyses focused on the NSAID medication class and AD outcome only. To help control for changes in drug reporting immediately prior to diagnosis and to investigate potential lag effects of NSAID exposure on AD risk, models with “lagged” exposure of one and two years were examined. In these models the exposure status (NSAID use or no NSAID use) for each visit was assigned the value from the prior visit (either one or two years prior) to help account for the lag or delay of effect of drug exposure.10 Duration of NSAID use was examined by calculating a cumulative time-varying variable that was then operationalized in different models as a continuous variable or dichotomized into less than or equal to two years of use and greater than two years of use, as has been done in previous studies of NSAIDs and AD.13 We calculated dose equivalencies between different NSAIDs by converting the daily dose of each NSAID to a proportion of the maximum daily dose reported on product monographs. Using this standardized dose we were able to add NSAIDs

if more than one type (e.g., ibuprofen and naproxen) were taken at one visit, and we were able to calculate the maximum dose each participant took over the course of observation. Cumulative dose was then captured in separate models as a continuous variable or a categorical variable with cut-points guided by typical dosing of NSAIDs and the distribution of use in the sample. We also investigated use of prescription NSAIDs only, because usage by prescription may be more regular or in higher dosage. For the latter analysis, the baseline was taken as the MRI visit because only information on prescription medications was available at that visit.

Subgroup analyses investigated potential differences in the relationship between NSAIDs and AD by age (at baseline visit), race (African-American and white), and presence of ε4 allele(s) at the *APOE* locus. We tested for such differences by including a cross-product term between the covariate of interest and the NSAID variable and comparing this model to the model without the product term using a likelihood ratio test (LRT). Then, we stratified the sample by these covariates and re-ran the models (without the product terms) in the sub-groups. Finally, we investigated possible differences in AD risk reduction based on type of NSAID by classifying users into those who used any $A\beta_{42}$-lowering NSAIDs or any non-$A\beta_{42}$-lowering NSAIDs and examining a model that simultaneously included terms for both. Data management was done using SPSS version 13[27] and statistical analyses were done using SAS version 8.[28]

RESULTS

Of the 3,229 participants, 1,180 (36.5%) reported use of NSAIDs at some point in the course of observation, while 1,933 (59.9%) reported aspirin use, and 1,228 (38.0%) reported acetaminophen use. Among the NSAID users, 577 (48.9%) used prescription NSAIDs only, 404 (34.2%) used OTC NSAIDs only, and 199 (16.9%) used both prescription and OTC NSAIDs. To assess differences in NSAID users and non-users at baseline we compared baseline characteristics by NSAID use (Table 1). NSAID users tended to be women, to be younger, and to report arthritis more commonly (all p-values <0.05). African Americans were somewhat more likely to be NSAID users than whites (p=0.06). Compared with non-demented participants, AD cases tended to be older, to carry at least one ε4 allele, to be less educated, and to have lower baseline 3MSE scores (all p-values <0.05; data not shown).

A total of 452 individuals developed all-cause dementia over 13,885 person-years of follow-up. Of these, 231 were classified as having AD and 199 as VaD. Use of NSAIDs was associated with a lower risk of all-cause dementia (adjusted HR, or aHR 0.76; 95% confidence interval or CI 0.60 – 0.96) (Table 2). Risk of dementia was not associated with use of aspirin (aHR 1.07, CI 0.88 – 1.32) or with use of acetaminophen (aHR 0.99, CI 0.79 – 1.24). Similarly, risk of AD was lower in NSAID users (aHR 0.63, CI 0.45 – 0.88) but evidently not in participants who used aspirin (aHR 0.87, CI 0.65 – 1.16) or acetaminophen (aHR 0.89;,CI 0.65 – 1.22). Use of aspirin was associated with an increased risk of VaD (aHR 1.42, CI 1.05 – 1.94) but this result was no longer apparent when cardiovascular risk factors such as prior stroke and myocardial infarction were added to the model (data not shown). The results for all-cause dementia, AD, and VaD were unchanged in models that included all three medication groups at the same time (data not shown).

Secondary analyses investigated the relationship between NSAIDs and AD. A model that controlled for arthritis suggested that the relationship between NSAIDs and AD was not confounded by this indication; the HR for NSAID use was 0.62 (CI 0.44 – 0.88) while the HR for arthritis was 1.02 (CI 0.73 – 1.41). There was no consistent evidence of greater reduction in risk of AD with lagging of exposure, longer duration of use, or higher doses of NSAIDs. The above analyses were repeated considering prescription NSAID use only, and

the results were similar. Similar results were also obtained when NSAID use was defined as use at more than one annual visit, excluding those participants who only reported one-time NSAID use.

When the data were stratified by age, the point estimate for NSAID use among younger participants was lower compared with older participants but the 95% confidence intervals overlapped widely (LRT for test of interaction: $\chi^2_{(1)}$=1.18, p=0.27) (Table 3). Similarly, when we stratified by race, the point estimate for AD risk with NSAID use in whites was lower compared with African Americans but the 95% confidence intervals again overlapped (LRT for test of interaction: $\chi^2_{(1)}$=0.85, p=0.36). By contrast, the interaction between NSAID use and *APOE* status (presence or absence of ε4 allele) was significant (LRT for test of interaction $\chi^2_{(1)}$=5.69, p=0.02), suggesting that the reduction in risk of AD associated with NSAID use was greater among those who were ε4-positive.

To help clarify whether sub-group variation was related to age or *APOE* status (given that ε4 carriers tend to develop AD at a younger age), we stratified the sample into four mutually exclusive groups: ≤75 years of age at baseline and ε4 negative, ≤75 years of age at baseline and ε4 positive, >75 years of age at baseline and ε4 negative, >75 years of age at baseline and ε4 positive. We found a reduction in AD incidence in NSAID users with an ε4 allele regardless of age, but no such effect in those without ε4 in either age group. (Table 4).

Finally, we examined whether the apparent reduction in AD risk differed according to NSAIDs classified by $A\beta_{42}$-lowering capability. In the full sample, after controlling for age, sex, education level, presence of *APOE* ε4, race, and baseline 3MSE, the risk reduction was similar for ever-use of any $A\beta_{42}$-lowering NSAIDs (42 AD / 2,815 person-years; aHR 0.67, CI 0.46 - 0.98) versus any non-$A\beta_{42}$-lowering NSAIDs (18 AD / 2,061 person-years; aHR, 0.69; 0.41 - 1.15),. Given the significant interaction between NSAID use and *APOE* status, we re-examined the association of type of NSAID and AD by *APOE* status. Among ε4 positive participants, use of $A\beta_{42}$-lowering NSAIDs (aHR 0.33, CI 0.15 – 0.73) and use of non-$A\beta_{42}$-lowering NSAIDs (aHR 0.34, CI 0.01 – 1.08) showed nearly identical risk reductions. Among ε4-negative participants, neither use of $A\beta_{42}$-lowering NSAIDs (aHR 0.97, CI 0.63 – 1.51) nor use of non-$A\beta_{42}$-lowering NSAIDs (aHR 0.97, CI 0.54 – 1.74) showed any significant relation to AD risk.

DISCUSSION

In the subset of Cardiovascular Health Study participants enrolled in the CHS Cognition Study, NSAID use was associated with a reduced risk of incident all-cause dementia and, in particular, AD. This apparent benefit of NSAID use appeared to depend strongly on *APOE* status, being evident only in people with one or more ε4 alleles. There was no apparent advantage of NSAIDs that have been reported to selectively lower $A\beta_{42}$ production. Use of acetaminophen, which is often taken for similar indications but has a different mechanism of action, was not associated with risk of all-cause dementia or AD. Similarly, aspirin showed little or no association with AD.

A reduced risk of AD with NSAID use has been reported in previous case-control and cross-sectional studies.[1,2] Consistent with the current findings, results from five other prospective studies have shown either significant[10] or suggestive reductions in AD risk[4,11-13] with NSAID use. The strongest apparent effects have been reported with NSAID use of longer duration. Thus, the Baltimore Longitudinal Study on Aging[10], the Rotterdam study[13], and the Cache County Memory Study[4], showed strongest risk reductions in people who had used NSAIDs for longer than two years. It is unclear why we did not see a duration effect here, but we note that we did not have information on NSAID use prior to entry into the study,

which may have been common, and this fact may have led to misclassification of usage duration for many participants. A similar phenomenon may also explain the absence here of a significant “lag” effect. We also failed to observe a dosage effect with NSAIDs, but this finding is consistent with the two previous studies that have examined this issue.[13,29]

Our results are consistent with two other prospective studies that found no association between aspirin use and AD.[11,13] However, other prospective studies have reported that aspirin is associated with reduced AD risk, if to a lesser degree than other NSAIDs, [4,10,12,30] and one study reported a significant risk reduction with aspirin but not with other NSAIDs.31 Aspirin is typically taken by the elderly for cardioprophylaxis at doses that may be too low to provide the same neuro-protection as other NSAIDs. An increased risk of VaD in aspirin users was also reported from the Rotterdam cohort[13] and might be explained through “confounding by indication” (see below) as people with known risk factors for VaD may be more likely to use aspirin. Here, when prior cardiovascular disease was considered, the increased risk of VaD in aspirin users was no longer evident.

Several studies have reported that the NSAID-AD association varies with age. Specifically, two reports[4,32] but not all have suggested that the risk reduction with NSAIDs decreases with age. The current results seemed consistent with the notion that the potential protective effect of NSAID use decreases with age, but this finding appeared primarily to reflect the known tendency of those with *APOE* ε4 to develop AD at younger ages. A potential effect modification by *APOE* genotype has been suggested by several previous studies. Although not significant, estimates from the MIRAGE multi-center family study[18], the Kungsholmen cohort[11], and the Rotterdam cohort[13] were similar to the current findings in that the greatest risk reduction occurred in ε4 carriers. It may be that the ε4-positive group of participants receive greater benefit than others from the anti-inflammatory effects of NSAIDs. Animal studies have also shown that transgenic mice expressing the human ε4 allele have more pronounced brain inflammatory responses than mice expressing the ε3 allele.[33,34]

Finally, several studies *in vitro* and *in vivo* have suggested that certain NSAIDs selectively lower $A\beta_{42}$. Because $A\beta_{42}$ may play a central role in AD pathogenesis, these findings have suggested the hypothesis that only the selective $A\beta_{42}$-lowering agents (SALAs) should lower the risk of AD in humans. We found no evidence to support this hypothesis, a finding that is consistent with data from a meta-analysis of three other cohort studies[35] but is in apparent contradistinction with recently presented data from the Rotterdam Study36. We note, however, that the 95% confidence intervals of the two NSAID groups in the Rotterdam work overlapped considerably, and the reported HR's were not inconsistent with the confidence intervals presented here. Further investigation of this important question in human populations is needed in order to confirm whether there are differences in effects on AD risk between SALAs and other types of NSAIDs. Until this question is addressed in studies with sufficient sample size, we regard the claim of differential human benefit with SALAs as speculative.

As with all observational studies, our analyses are subject to certain limitations. The CHS pharmacological data were collected by self-report, and are therefore vulnerable to misclassification error. However, these data were collected prospectively with simultaneous viewing of pill bottles, probably reducing recall error. Recall error that does not differ between AD cases and non-cases should add only “noise” to the data, thus moving the results toward the null. Unfortunately, our participants who were destined to develop AD within a few years may plausibly have had reduced memory abilities, thus under-reported their use of NSAIDs. To some extent this explanation is inconsistent, however, with the lack of an inverse association of AD with acetaminophen. We know of no obvious reason why forgetful people should have difficulty remembering NSAID use but not acetaminophen use.

We attempted to control for other known potential confounders including age, sex, and education. However, there can always be other unsuspected sources of confounding that explain the observed relationship between NSAID use and AD. A particular problem for studies such as this is confounding by indication in which a drug under investigation is used to treat a disease, which is itself associated with the outcome of interest.[37,38] For example, the apparent risk reduction associated with NSAID use could actually be due to arthritic conditions for which NSAIDs are routinely used. We therefore controlled for arthritis but observed no change in the association between NSAIDs use and AD risk. Furthermore, it is unlikely that other indications for NSAID use can fully explain their reduction in AD risk because most of these would be similarly associated with the use of acetaminophen, which showed little or no association with AD risk. Despite these findings, it is still possible that the results of the current analysis are due to confounding-by-indication or other unknown sources of confounding.

Another source of bias in prospective studies is differential mortality associated with an agent under investigation. This may occur if participants exposed to NSAIDs have increased mortality due to NSAID-related complications compared with those unexposed to NSAIDs. Such differential mortality could again result in an apparent inverse relationship between NSAID use and AD because the NSAID users are removed from the risk set before they have a chance to develop dementia. However, we investigated whether NSAID use was associated with a higher risk of mortality in the CHS cohort and found no evidence of this effect. This issue was also addressed with similar results in both the Rotterdam[39] and Cache County cohorts (unpublished data), in which NSAID use was associated with a reduced risk of AD but not with all-cause mortality.

The relatively large sample size of the CHS cohort and its high number of cases (attributable presumably to its age structure) enabled us to investigate the effects of both *APOE* genotype and differences in NSAIDs' reported ability to reduce production of $A\beta_{42}$. While the reported findings can be further investigated in other epidemiologic studies of sufficient size, or in pooled datasets from existing studies, properly conducted randomized prevention trials will be needed to confirm whether NSAIDs protect against AD. The current results may help inform the design of such trials.

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Table 1

NSAID use by baseline characteristics

Baseline* characteristic	No NSAID use n=2,049 (%)	Yes NSAID use† n=1,180 (%)
Sex ‡		
Women	1,137 (55.5)	794 (67.3)
Men	912 (44.5)	386 (32.7)
Age ‡		
≤ 75 years	992 (48.4)	639 (54.2)
>75 years	1,057 (51.6)	541 (45.8)
Education		
< High school	480 (23.4)	283 (24.0)
High school or vocational school	766 (37.4)	438 (37.1)
College or graduate school	800 (39.0)	457 (38.7)
Missing	3 (0.1)	2 (0.2)
Race		
African American	281 (13.7)	190 (16.1)
White	1,760 (85.9)	983 (83.3)
Other	8 (0.4)	7 (0.7)
APOE ε4 alleles		
None	1,408 (68.7)	824 (69.8)
One or two	446 (21.8)	259 (21.9)
Missing	195 (9.5)	97 (8.2)
3MSE (out of 100)		
< 95	1,152 (56.2)	631 (53.5)
≥ 95	897 (43.8)	548 (46.4)
Missing	0 (0)	1 (0.1)
History of arthritis ‡		
Yes	1,184 (57.8)	933 (79.1)
No	854 (41.7)	243 (20.6)
Missing	11 (0.5)	4 (0.3)

NSAID = non-aspirin non-steroidal anti-inflammatory drugs; APOE = apolipoprotein E; 3MSE = Modified Mini-Mental State Examination

*Baseline was considered the first year where information was available on both prescription and over-the-counter medication use

†For this table, a participant was considered an NSAID user if they had reported exposure at any time over the course of follow-up

‡χ^2 p-values < 0.05

Table 2

Risk of incident dementia by medication use (HR and 95% CI)

	All-cause Dementia			
	#DEM / PY*	Model 1	Model 2	Model 3
NSAID				
no	337 / 8,514	1.0	1.0	1.0
yes	115 / 5,371	0.83 (0.67 - 1.02)	0.84 (0.68 - 1.05)	0.76 (0.60 - 0.96)
ASPIRIN				
no	216 / 5,274	1.0	1.0	1.0
yes	236 / 8,611	0.98 (0.81 - 1.18)	1.02 (0.84 - 1.23)	1.07 (0.88 - 1.32)
ACETAMINOPHEN				
no	312 / 8,346	1.0	1.0	1.0
yes	140 / 5,539	0.99 (0.81 - 1.21)	1.00 (0.81 - 1.23)	0.99 (0.79 - 1.24)
	Alzheimer's Disease			
	#AD / PY*	Model 1	Model 2	Model 3
NSAID				
no	175 / 8,162	1.0	1.0	1.0
yes	56 / 5,204	0.76 (0.56 - 1.02)	0.75 (0.55 - 1.01)	0.63 (0.45 - 0.88)
ASPIRIN				
no	122 / 5,093	1.0	1.0	1.0
yes	109/ 8,273	0.82 (0.63 - 1.06)	0.85 (0.65 - 1.11)	0.87 (0.65 - 1.16)
ACETAMINOPHEN				
no	161 / 8,011	1.0	1.0	1.0
yes	70 / 5,355	0.95 (0.72 - 1.26)	0.91 (0.68 - 1.22)	0.89 (0.65 - 1.22)
	Vascular Dementia			
	#VaD / PY*	Model 1	Model 2	Model 3
NSAID				
no	142 / 8,043	1.0	1.0	1.0
yes	57 / 5,210	0.97 (0.71 - 1.31)	1.06 (0.77 - 1.45)	0.92 (0.65 - 1.28)
ASPIRIN				
no	86 / 4,990	1.0	1.0	1.0
yes	113/ 8,263	1.13 (0.85 - 1.50)	1.23 (0.92 - 1.63)	1.42 (1.05 - 1.94)
ACETAMINOPHEN				
no	135 / 7,929	1.0	1.0	1.0
yes	64 / 5,324	1.04 (0.77 - 1.40)	1.14 (0.84 - 1.55)	1.11 (0.80 - 1.53)

DEM = incident dementia cases; PY = cumulative person-years (risks cannot be calculated based on these PY as time-varying Cox regression was used for analysis); NSAID = non-aspirin non-steroidal anti-inflammatory drugs; AD = incident Alzheimer's disease cases (without VaD); VaD = incident vascular dementia cases (VaD alone and mixed VaD plus AD)

Model 1 – crude; Model 2 – adjusted by age, sex, education level; Model 3 – adjusted by age, sex, education level, presence of APOEε4, race (white or African American), baseline 3MSE

* numbers shown for crude model only

Table 3

NSAIDs and incident AD stratified by baseline age, apolipoprotein E status, and race (HR and 95% CI)

	#AD/PY*	Model 1 (crude)	Model 2 (age, sex, education)	Model 3 (Model 2 + race†, 3MSE‡, APOEε4)
≤75 years				
NSAID no	49/4,386	1.0	1.0	1.0
NSAID yes	11/2,956	0.47 (0.24-0.91)	0.45 (0.23-0.87)	0.44 (0.22-0.89)
>75 years				
NSAID no	126/3,776	1.0	1.0	1.0
NSAID yes	45/2,249	0.89 (0.63-1.25)	0.88 (0.62-1.25)	0.71 (0.48-1.04)

	#AD/PY*	Model 1 (crude)	Model 2 (age, sex, education)	Model 3 (Model 2 + race†, 3MSE‡)
No ε4 alleles				
NSAID no	86/5,739	1.0	1.0	1.0
NSAID yes	35/3,667	0.97 (0.65-1.44)	0.96 (0.64-1.44)	0.88 (0.59-1.32)
Any ε4 allele				
NSAID no	64/1,678	1.0	1.0	1.0
NSAID yes	11/1,120	0.37 (0.20-0.71)	0.37 (0.19-0.70)	0.34 (0.18-0.65)

	#AD/PY*	Model 1 (crude)	Model 2 (age, sex, education)	Model 3 (Model 2 + APOEε4, 3MSE‡)
African American				
NSAID no	25/1,115	1.0	1.0	1.0
NSAID yes	13/812	0.90 (0.45-1.77)	0.90 (0.45-1.80)	0.91 (0.42-1.98)
White				
NSAID no	148/7,020	1.0	1.0	1.0
NSAID yes	42/4,362	0.70 (0.50-0.98)	0.68 (0.48-0.97)	0.57 (0.40-0.83)

NSAID = non-aspirin non-steroidal anti-inflammatory drugs; AD = incident Alzheimer's disease cases; PY = cumulative person-years (risks cannot be calculated based on these PY as time-varying Cox regression was used for analysis)

*numbers shown for crude model only, differences in #AD/PY due to missing APOE genotype or exclusion of non-White non-African American participants

†white or African American

‡baseline Modified Mini Mental State Examination

Table 4

NSAID use and incident AD - Joint effects of baseline age and apolipoprotein E status

	Presence of ε4 allele			
	No		Yes	
	#AD / PY	HR (95% CI)*	#AD / PY	HR (95% CI)*
≤75 years				
NSAID no	18 / 2,964	1.0	22/ 1,002	1.0
NSAID yes	7 / 1,953	0.79 (0.32 - 1.93)	3 / 810	0.22 (0.06 - 0.73)
>75 years				
NSAID no	68 / 2,775	1.0	42 / 676	1.0
NSAID yes	28 / 1,714	0.92 (0.59 - 1.45)	8 / 310	0.45 (0.20 - 0.97)

NSAID = non-aspirin non-steroidal anti-inflammatory drugs; AD = incident Alzheimer's disease cases; PY = cumulative person-years (risks cannot be calculated based on these PY as time-varying Cox regression was used for analysis)

*adjusted by age, sex, education level, race (white or African American), and baseline 3MSE