Does NSAID use modify cognitive trajectories in the elderly?

The Cache County Study

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ABSTRACT Background: Epidemiologic studies have suggested that nonsteroidal anti-inflammatory drugs (NSAIDs) may be useful for the prevention of Alzheimer disease (AD). By contrast, clinical trials have not supported NSAID use to delay or treat AD. Few studies have evaluated cognitive trajectories of NSAID users over time. **Methods:** Residents of Cache County, UT, aged 65 or older on January 1, 1995, were invited to participate in the study. At baseline, participants provided a detailed inventory of their medications and completed a revised Modified Mini-Mental State Examination (3MS). Participants (n = 3,383) who were cognitively normal at baseline were re-examined after 3 and 8 years. The association between NSAID use and 3MS scores over time was estimated using random effects modeling. **Results:** Associations depended upon when NSAIDs were started and *APOE* genotype. In participants who started NSAID use prior to age 65, those with no *APOE* ε4 alleles performed similarly to nonusers (a difference of 0.10 points per year; $p = 0.19$), while those with one or more ε4 allele(s) showed more protection (0.40 points per year; $p = 0.0005$). Among participants who first used NSAIDs at or after age 65, those with one or more ε4 alleles had higher baseline scores (0.95 points; $p = 0.03$) but did not show subsequent difference in change in score over time (0.06 points per year; $p = 0.56$). Those without an ε4 allele who started NSAID use after age 65 showed greater decline than nonusers (−0.16 points per year; $p = 0.02$). **Conclusions:** Nonsteroidal anti-inflammatory drug use may help to prevent cognitive decline in older adults if started in midlife rather than late life. This effect may be more notable in those who have one or more *APOE* ε4 alleles. **NEUROLOGY 2007;69:275-282**

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A number of epidemiologic studies have suggested that nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce the risk of Alzheimer disease (AD).[1] However, randomized trials of NSAIDs for the treatment of AD have not been successful,[2-6] and a trial for the prevention of AD was recently stopped early due to clinical safety issues.[7] Thus, many questions remain about the neuroprotective effects of these drugs. Because NSAIDs are so commonly used by the elderly for other indications,[8] it is important to continue to study their neuroprotective effects in order to better understand the benefits vs the risks of taking them.

To date, only a few epidemiologic studies have evaluated the effects of NSAIDs on cognitive trajectories over time in a sample of individuals who were cognitively normal at baseline. Reports using data from the Established Populations for Epidemiologic Studies of the Elderly (EPESE) cohorts offered mixed results.[9-11] An evaluation of data from the Longitudinal Aging Study Amsterdam (LASA) cohort indicated that aspirin, but not other NSAIDs, offered protection against cognitive decline.[12] These studies evaluated the effects of NSAIDs over 3 years or less using two time points, but some researchers have suggested that NSAIDs are protective only if taken for an extended period of time[13,14] or earlier in life, before underlying neuropathologic changes have become advanced.[13] A previous report from the Cache County Study showed that the incidence of AD is reduced only if NSAIDs were taken several years

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prior to the onset of dementia.[15] Here, we extend these findings by examining the effects of NSAID use on a broader range of cognitive abilities over as much as 8 years of observations encompassing three assessments. We hypothesized that NSAID use earlier (but not later) in life would have a beneficial effect on cognitive trajectories. We also examined whether the benefits would differ by *APOE* genotype, because a recent report suggested stronger effects in those who carry the *APOE* ε4 allele.[16]

METHODS

The Cache County Study is a longitudinal study of adults aged 65 and older living in Cache County, UT. Details of the study design have been published elsewhere.[17,18] Briefly, all persons aged 65 or older on January 1, 1995, were invited to participate, and 90% of the sample (n = 5,092) completed the baseline screening and interviews in 1995 to 1996. A revised version[19] of the Modified Mini-Mental State Examination (3MS)[20] was administered as part of a dementia screen at baseline and subsequent follow-up interviews in 1998 to 1999 and 2002 to 2003. In the current analyses, we excluded 356 participants who were diagnosed with dementia at baseline. We further excluded those who provided a 3MS score at only one time point (n = 1,324), thereby limiting the sample to individuals who contributed multiple time points for longitudinal analysis. Another 29 participants did not provide complete information on NSAID use and were also excluded. Thus, the final sample included 3,383 participants, of whom 3,294 completed the first follow-up examination in 1998 to 1999, and 2,235 who completed the second follow-up examination in 2002 to 2003. Over 99% of this sample (n = 3,361) provided buccal swab DNA for genotyping at the *APOE* locus. Detailed interviews were used to gather information on participants' age, educational attainment, health issues including cardiovascular history, and use of medications and supplements.

NSAID use. At the baseline visit, participants were queried about their current and prior use of over-the-counter and prescription medications including NSAIDs. They were asked to present all their current medications for review, and were then asked a series of detailed probe questions to identify any use of medicines not disclosed or those used in the past. In addition to the probe questions, drug cards were presented with trade and generic names of common medications in large print. The names of the drugs were recorded along with information about when they were started, how long they were taken, and dose. By attempting multiple methods of ascertainment, i.e., visual inspection, verbal and visual cues, we were likely to obtain more complete information than would have been gained from using only one method. These methods allow the interviewer to capture both prescription and nonprescription drug information. Per our previous work, we considered participants as (ever) NSAID users if they reported any regular use of NSAIDs at baseline, defined as ≥4 doses per week for a month or more.[15] Further, we classified participants based on accumulated duration of use at baseline dichotomized at 2 years per our previous study of NSAIDs[15] and the age at which they began taking NSAIDs dichotomized at age 65 years. We selected the cutpoint of 65 years because it is a common milestone and very close to the mean age at which participants in this sample started to use NSAIDs (mean age = 65.5, SD = 10.2). The reasoning for the latter classification was based on earlier findings suggesting that the effects of NSAIDs may differ depending on when they are taken. In the current analysis with continuous cognitive trajectories, we sought to examine specifically whether the effects differed depending upon when in the course of aging they are taken.[13] Following from this second point, we did not consider new NSAID use during the course of follow-up as we reasoned that more recent use of NSAIDs would have little impact on cognitive function over the short term.

Statistical analysis. Differences in baseline characteristics between NSAID users and nonusers were examined with *t* tests for continuous variables and χ^2 tests for categorical variables. Mixed effects models were then used to assess the relationship between NSAID use at baseline and subsequent performance on the 3MS. Mixed models accommodate both fixed and random effects that account for individual differences in performance on the 3MS at baseline and the subsequent correlated 3MS scores. All models controlled for factors significantly associated with baseline 3MS including baseline age (centered at the population mean of 74.1 year), sex, education (centered at population mean of 13.4 years), *APOE* status (one or more *APOE* ε4 alleles vs no ε4 alleles), history of diabetes, and history of stroke. Time was captured as a nominal variable (0 years at baseline, 3 years for the first follow-up, and 8 years for the second follow-up). A quadratic term for time (time^2) was included to allow for nonlinear change over time. NSAID use was modeled separately in three different ways: 1) as ever/never use, 2) by duration of use (dichotomized at 2 years),[15] and 3) by the age at which NSAID use began (dichotomized at age 65). In order to assess the effects of NSAIDs on 3MS over time, interaction terms between the NSAID and time variables were included in the models and then compared to models without these terms using likelihood ratio tests. The interaction terms between the NSAID variables and quadratic time were not significant and thus only the interactions with linear time were considered in the final models. Parameterized in this way, the main effect terms for NSAIDs provided estimates of mean differences in 3MS scores at baseline between NSAID users and nonusers, while the interaction terms provided estimates of the difference in the annual rates of change on the 3MS among users and nonusers. To evaluate whether the effects of NSAID use over time differed by *APOE* ε4 status, we tested a three-way interaction term for NSAID use × time × *APOE* status; analyses were then stratified by *APOE* ε4 status. Finally, because of recent interest in the potential effects of selective amyloid beta$_{42}$ (Aβ_{42}) lowering NSAIDs, we classified NSAIDs based on recent reports from in vivo and in vitro models showing differences in Aβ_{42} lowering capabilities[21,22] and performed an analysis with NSAID users grouped as 1) users of any Aβ_{42} lowering NSAIDs, 2) users of non Aβ_{42} lowering NSAIDs, and 3) nonusers.

We repeated the above main analyses after excluding subjects with incident dementia. Furthermore, because of the potential adverse effects associated with NSAID use or the conditions for which the NSAIDs may be taken, we undertook another analysis to evaluate whether the observed effects of NSAID use on cognitive trajectories were due to differential survival. To accomplish this, we created a set of three variables to indicate the main reason for censoring, including death, dementia, or missing due to other reasons (i.e., refused or moved out of area). We then included the three indicator variables and

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Table 1 Demographic characteristics of 3,383 participants in this Cache County Study at baseline visit

Characteristic*	NSAID user (n = 998)	Nonuser (n = 2,385)
Age, mean (SD), y	73.7 (6.2)	74.2 (6.5)
Women†	690 (69.1)	1288 (54.0)
Education, mean (SD), y	13.4 (2.7)	13.4 (2.9)
Cardiovascular factors		
Hypertension†	464 (46.5)	887 (37.2)
Myocardial infarction	114 (11.5)	264 (11.1)
Stroke	32 (3.2)	77 (3.3)
Diabetes	117 (11.7)	232 (9.7)
Hypercholesterolemia‡	233 (23.5)	411 (17.4)
CABG	61 (6.1)	152 (6.4)
Number of *APOE* ε4 alleles		
0	689 (69.3)	1637 (69.2)
1 or more	305 (30.7)	730 (30.8)
Age at start of NSAID use, mean (SD), y†		
<65	56.3 (7.2)	—
≥65	72.0 (6.1)	—

*Data are expressed as number (%) unless otherwise specified.
†$p < 0.0001$.
‡$p < 0.01$.
NSAID = nonsteroidal anti-inflammatory drug; CABG = coronary artery bypass graft surgery; *APOE* = apolipoprotein E.

interaction terms for each by time in our mixed models to control for the potential effects of these different mechanisms of loss to follow-up on the observed relationship between NSAID use and 3MS performance over time. SAS version 9.1 was used for all analyses. The SAS PROC MIXED procedure was used to estimate the mixed models, and Wald *p* values are reported.

RESULTS We compared the characteristics of participants eligible for inclusion in the current analysis (n = 3,412) with those who were not included because they did not provide longitudinal data at two or more time points (n = 1,324) and there were no differences between the two groups regarding *APOE* status or the use of NSAIDs at baseline. Among the participants available for the current analysis, 29 did not provide sufficient information about their NSAID use at baseline, thus leaving 3,386 participants with complete information. Of these, approximately 30% reported a history of regular NSAID use at baseline. Compared to nonusers, the NSAID users were more likely to be women and have a history of hypertension and high cholesterol. There was no significant difference between groups' mean age at baseline (table 1). Ninety-three percent of the regular NSAID users reported a starting age for NSAID use (range 25 to 96, mean age = 65.5, SD = 10.2). Those who reportedly began NSAID use prior to age 65 (mean age 56.3; SD = 7.2) also reported using NSAIDs for an average of 6.5 years (SD = 7.2) while those who reported beginning NSAID use after age 65 (mean age 72.0; SD = 6.1) used NSAIDs for an average of 2.5 years (SD = 3.7).

Unadjusted mean 3MS scores and 95% CIs for baseline NSAID users and nonusers for each time point are shown in table 2. Compared with nonusers, NSAID users tended to score slightly higher on the 3MS at each assessment. A planned stratification of the groups by *APOE* status showed that the differences in scores is greater in the group with one or more *APOE* ε4 alleles.

Mixed models were used to explore the relationship between NSAID use and 3MS score trajectory while controlling for baseline age, sex, education, *APOE* status, and self- or proxy-reported history of diabetes or stroke (table 3). After controlling for these factors, baseline NSAID users appeared to perform similarly to nonusers, both at baseline and over time. This was true for both putative selective $A\beta_{42}$ lowering NSAIDs (85.6% of all NSAID use in the sample) as well as non $A\beta_{42}$ lowering NSAIDs (model 2); thus, there were no differences between the two types of NSAIDs. As in prior analyses, we also examined the effect of duration of NSAID use (model 3), noting that those who reported 2 or more years of use scored about half of a point higher than nonusers at baseline ($p = 0.04$), but extended use (≥2 years) was not associated with better performance over time. We then examined the effect of when participants started NSAID use (model 4).

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Table 2 Mean 3MS scores and 95% CIs for 3,383 Cache County residents over 8 years of observation by NSAID use

	Baseline		First follow-up		Second follow-up	
Group	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)
Nonuser	2,384	91.08 (90.86–91.30)	2,327	90.51 (90.18–90.84)	1,553	89.09 (88.63–89.55)
NSAID user	998	91.66 (91.35–91.98)	967	91.46 (91.01–91.90)	682	89.40 (88.74–90.06)
0 *APOE* ε4 alleles						
Nonuser	1,636	91.22 (90.96–91.49)	1,603	90.76 (90.38–91.15)	1,064	89.65 (89.11–90.19)
NSAID user	689	91.55 (91.15–91.94)	669	91.39 (90.86–91.92)	461	89.23 (88.41–90.04)
1+ *APOE* ε4 allele(s)						
Nonuser	730	90.75 (90.34–91.16)	706	89.95 (89.32–90.59)	484	87.85 (86.99–88.70)
NSAID user	305	91.94 (91.41–92.46)	296	91.69 (90.88–92.50)	218	89.98 (88.87–91.08)

3MS = revised Modified Mini-Mental State Examination; NSAID = nonsteroidal anti-inflammatory drug.

Participants who started taking NSAIDs at or after age 65 scored an average one-half point (0.51) higher on the baseline 3MS compared to nonusers ($p = 0.03$). By contrast, participants who started taking NSAIDs prior to age 65 did no better than nonusers on the baseline 3MS, but they declined by 0.20 points per year less than nonusers ($p = 0.003$).

In order to determine whether the relationship between NSAID use and cognitive performance over time differed by *APOE* genotype, we tested the three way interaction term for NSAID use × *APOE* status × time and found a significant interaction. Next, we re-evaluated the above after stratifying the sample by the presence of one or more *APOE* ε4 alleles vs no ε4 allele (table 4). We found that among participants with one or more *APOE* ε4 alleles, NSAID use (model 1) was associated with a higher baseline 3MS score (0.70 points, $p = 0.04$) and less decline over time (0.22 points per year; $p = 0.009$). By contrast, among participants with no ε4

Table 3 Mixed models of trajectories of 3MS scores of 3,383 study participants over 8 years

	Model 1		Model 2		Model 3		Model 4	
	β_i	(95% CI)	β_i	(95% CI)	β_i	(95% CI)	β_i	(95% CI)
Intercept	90.72	(90.41–91.02)	90.73	(90.43–91.03)	90.75	(90.44–91.05)	90.73	(90.43–91.04)
NSAID use	0.29	(−0.08–0.66)						
NSAID use × time	0.04	(−0.05–0.13)						
Aβ_{42} lowering NSAID use			0.30	(−0.09–0.69)				
Aβ_{42} lowering NSAID use × time			0.04	(−0.06–0.13)				
Non Aβ_{42} lowering NSAID use			0.60	(−0.27–1.47)				
Non Aβ_{42} lowering NSAID use × time			0.02	(−0.20–0.23)				
Duration of use <2					0.12	(−0.39–0.64)		
Duration of use <2 × time					0.03	(−0.09–0.15)		
Duration of use ≥2					0.51	(0.02–1.00)*		
Duration of use ≥2 × time					0.04	(−0.08–0.16)		
NSAID use < age 65							0.09	(−0.45–0.64)
NSAID use < age 65 × time							0.20	(0.07–0.32)*
NSAID use ≥ age 65							0.51	(0.05–0.98)*
NSAID use ≥ age 65 × time							−0.10	(−0.21–0.02)

Model 1: nonsteroidal anti-inflammatory drug (NSAID) users compared to nonusers. Model 2: Selective Aβ_{42} lowering NSAID users compared to nonusers and non Aβ_{42} lowering NSAID users compared to nonusers. Model 3: NSAID users with a duration of use <2 years at baseline compared to nonusers and NSAID users with a duration ≥2 years at baseline compared to nonusers. Model 4: NSAID users who began use < age 65 compared to nonusers and NSAID users who began NSAID use ≥ age 65 compared to nonusers. Models are adjusted for baseline age, sex, years of education, *APOE* status (1 or more *APOE* ε4 alleles vs no ε4 allele), and history of diabetes or stroke.
*$p < 0.05$.
3MS = revised Modified Mini-Mental State Examination.

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Table 4 Mixed models of trajectories of 3MS scores of 3,383 study participants over 8 years stratified by number of *APOE* ε4 alleles

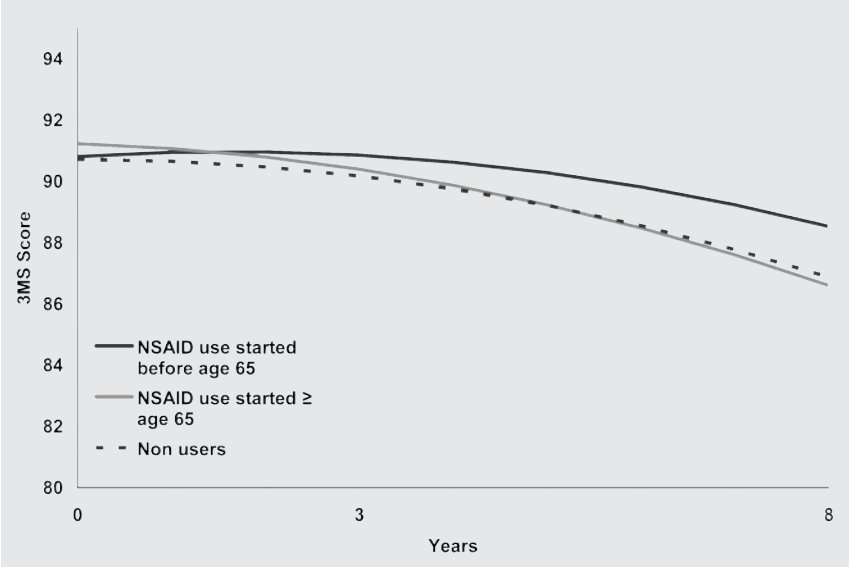
	Model 1				Model 2			
	APOE = 0		*APOE* = 1+		*APOE* = 0		*APOE* = 1+	
	β_i	(95% CI)	β_i	(95% CI)	β_i	(95% CI)	β_i	(95% CI)
Intercept	90.77	(90.43–91.11)	89.91	(89.39–90.43)	90.78	(90.45–91.12)	89.90	(89.37–90.42)
NSAID use	0.12	(−0.33–0.56)	0.70	(0.03–1.37)*				
NSAID use × time	−0.04	(−0.15–0.07)	0.22	(0.05–0.38)*				
NSAID use < age 65					−0.02	(−0.67–0.64)	0.40	(−0.59–1.39)
NSAID use < age 65 × time					0.10	(−0.05–0.25)	0.40	(0.18–0.63)*
NSAID use age ≥ 65					0.34	(−0.22–0.89)	0.95	(0.08–1.82)*
NSAID use age ≥ 65 × time					−0.16	(−0.30 to −0.03)*	0.06	(−0.15–0.27)

Model 1: nonsteroidal anti-inflammatory drug (NSAID) users compared to nonusers stratified by *APOE* ε4 status. Model 2: NSAID users who began use prior to age 65 compared to nonusers and NSAID users who began using NSAIDS ≥ age 65 compared to nonusers stratified by *APOE* ε4 status. Models are adjusted for baseline age, sex, years of education, and history of diabetes or stroke.
*$p < 0.05$.
3MS = revised Modified Mini-Mental State Examination.

allele(s), there was no association between NSAID use and better performance on the 3MS at baseline or over time. An evaluation based on the age at which participants started NSAID use (model 2) provided even more striking results. While participants with no ε4 alleles who started NSAID use prior to age 65 showed no change on the 3MS compared to nonusers over time (0.10 points per year, $p = 0.19$), those with one or more ε4 alleles showed greater protection over time (0.40 points per year; $p = 0.0005$). Participants with one or more ε4 alleles who started NSAID use after age 65 had higher baseline scores (0.95 points, $p = 0.033$) but did not maintain any advantage over time ($p = 0.56$). Interestingly, participants with no ε4 alleles who started to use NSAIDs at or after age 65 showed greater decline over time compared to nonusers (−0.16 points per year, $p = 0.02$). Figures 1 through 3 show the estimated trajectories on the 3MS over the 8 years of follow-up as a function of the age at which regular NSAID use was started for the whole sample (figure 1) and stratified by *APOE* status (figures 2 and 3).

We repeated the analyses after excluding incident dementia cases and noted that the above associations were slightly mitigated but still significant and in the same directions (data not shown). Additionally, we carried out another evaluation to examine whether the observed associations may be due to a bias resulting from differential loss to follow-up among NSAID users. Here, we included in the mixed models a series of indicator variables to capture censoring due to dementia, death, or loss to follow-up for other reasons. Not surprisingly, these terms were significantly associated with lower baseline scores and greater decline over time compared to the noncensored reference group. Their inclusion did not meaningfully alter the estimated associations between NSAID use initiated prior to age 65 and cognitive performance over time. In NSAID users who began use after age 65 and had no ε4 alleles, inclusion of the censoring terms did not substantively change the findings of greater decline although the p value shifted from $p = 0.018$ to $p = 0.054$.

Figure 1 Trajectories of revised Modified Mini-Mental State Examination scores over 8 years of follow-up by nonsteroidal anti-inflammatory drug use categories



Adjusted for baseline age, sex, education, *APOE* ε4 status (0, 1), diabetes, and stroke.

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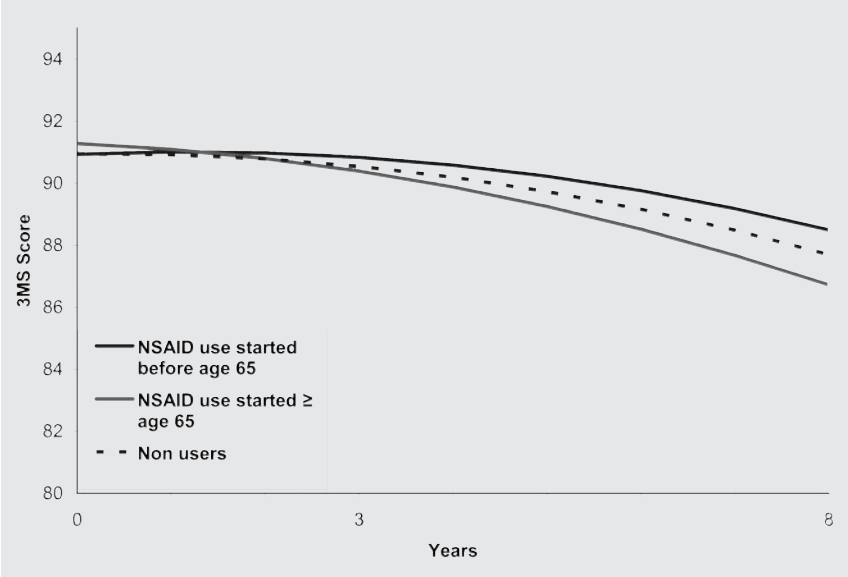
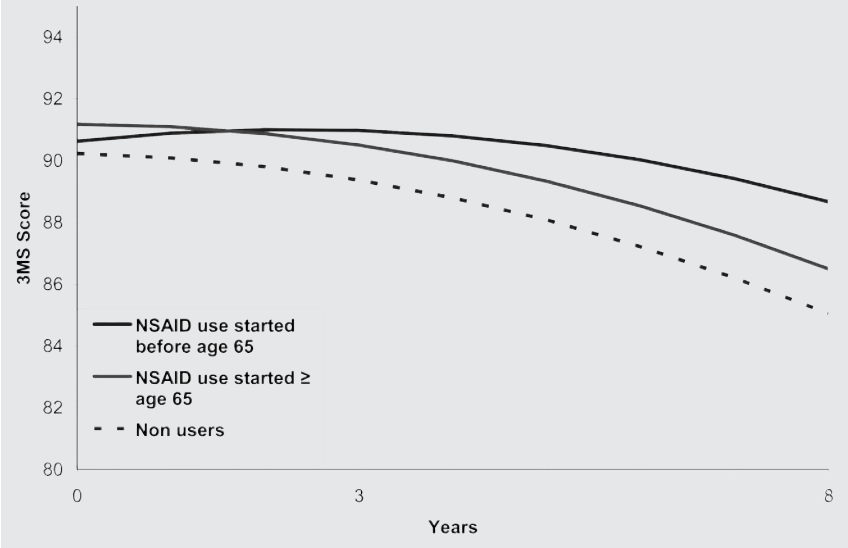
Figure 2 Trajectories of revised Modified Mini-Mental State Examination scores over 8 years of follow-up by nonsteroidal anti-inflammatory drug use categories among those with no *APOE* ε4 alleles



Adjusted for baseline age, sex, education, diabetes, and stroke.

DISCUSSION These findings add to a growing body of evidence that points to the potential long-term beneficial effects of NSAID use on cognitive function in the elderly. Although this is an observational study and no clinical recommendations can be made from these results, our results suggest that beneficial effects occurred mainly in those who started using NSAIDs in mid-life (i.e., prior to age 65), and were stronger among those who are *APOE* ε4 positive. We note that in this study, those who started to use NSAIDs earlier in life also tended to take NSAIDs for a longer duration of time. While the findings are incrementally small, one might speculate that they could be significant within the context of delaying onset of AD or loss of independence by a few months on a population level. These findings indicate a need for further study of the utility of NSAIDs for delaying the onset of AD.

Figure 3 Trajectories of revised Modified Mini-Mental State Examination scores over 8 years of follow-up by nonsteroidal anti-inflammatory drug use categories among those with one or more *APOE* ε4 alleles



Adjusted for baseline age, sex, education, diabetes, and stroke.

There are compelling, biologically plausible reasons to believe NSAIDs have neuroprotective effects. By inhibiting cyclo-oxygenase-2 (COX-2), an enzyme that converts arachidonic acid to prostaglandin E-2 and subsequent prostanoids,[23] NSAIDs may reduce inflammation that is thought to play an important role in neurodegenerative conditions such as AD.[24] In addition, some NSAIDs may also modulate γ-secretase activity and thereby reduce the production of neurotoxic $A\beta_{42}$ peptide fragments[21,22] that accumulate during the pathogenesis of AD. We performed subanalyses to investigate this hypothesis and did not find any evidence to support it. However, our power to detect differences was limited by small numbers especially in the non $A\beta_{42}$ lowering NSAID group.

Discrepancies between observational and randomized studies may be due to potential differences in the efficacy of NSAIDs depending upon when they are taken in the course of cognitive decline or disease. Indeed, we have shown in previous analyses of data from the Cache County Study that NSAIDs are associated with reduced risk of AD, but only if they are taken several years prior to the onset of disease.[15] Thus, NSAIDs may be effective if taken when an individual is still cognitively intact, but they may no longer be effective if taken after cognitive symptoms have emerged and the progression of the underlying disease processes has become too far advanced. The current study extends these findings and suggests that NSAIDs may preserve overall cognitive functioning if they are started in mid-life (before the age of 65), especially among those with one or more *APOE* ε4 alleles. It is important to note that in this study, those who started to use NSAIDs before age 65 also had a longer duration of NSAID use. Taking NSAIDs earlier in life might be equivalent to taking them prior to onset of cognitive problems. Our results further suggest that NSAIDs may potentially worsen cognitive function if they are started after age 65, among those with no *APOE* ε4 alleles; however, this finding needs to be investigated further as a correction for censoring slightly mitigated the result.

While the current findings suggest an intriguing resolution to the discrepancies seen between previ-

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ous studies, caution is warranted because the validity of the findings may be threatened by limitations inherent in observational studies. For example, the observed associations between NSAID use and cognitive performance may be due to uncontrolled confounding or biases which have not been addressed in the analyses. Of particular concern is the fact that NSAIDs are often taken for chronic pain associated with underlying conditions that may lead to poor health outcomes. Furthermore, the regular use of NSAIDs themselves may be associated with increased risk for negative sequelae, including gastrointestinal, nephritic, and cardiovascular-related adverse events. As a result, the use of NSAIDs may be associated with increased rates of loss to follow-up. If this loss to follow-up is differential with respect to cognitive performance, then it is possible that NSAID use may be spuriously associated with better cognitive performance over time among those who remain on study. However, the rates of NSAID use among those lost to follow-up and those included in the current analysis were not different. We attempted to account for this possibility in our analyses and found that our conclusions were not substantially altered after controlling for loss to follow-up. Patterns of NSAID use after the initial baseline report were not considered in this analysis because we reasoned that more recent use of NSAIDs would have little impact on cognitive function over the short term. This assumption may have led to some misclassification bias in the NSAID user groups we identified for analysis. However, there is no reason to believe such misclassification would be differential with respect to *APOE* status or the outcome, and therefore our estimates of the effect of NSAIDs may be biased toward the null. Finally, we note that while there is always the possibility that multiple comparisons can lead to spurious results, we have made no correction here for the multiple comparisons that were planned a priori. As with all observational studies, these findings should be investigated further and replicated by others.

The current study has several strengths that merit consideration. We studied a cohort of elderly people which was population-based and thus not subject to the same selection bias encountered by other clinical or volunteer samples. The cohort was sufficiently large with over 3,000 participants who were followed for up to 8 years allowing us to more fully characterize the longitudinal trajectories in cognitive performance over time. Additionally, the participants were evaluated at multiple time points using the same rigorous procedures that have become standard for population-based studies of AD. The participants were assessed for cognitive performance with a widely used neurocognitive instrument[19,20] and information about NSAID use was gathered from the participants when they were cognitively intact, using methods that are well documented and have yielded useful information in past research.[15,25-28] Finally, the cohort was relatively homogeneous with respect to sociodemographic factors. While this may raise concerns about generalizability, it helps to minimize the possibility that unmeasured confounds explain the findings.

Despite these strengths, the only way to conclusively demonstrate the neuroprotective effects of NSAIDs is with randomized clinical trials. If the current findings are valid, such a trial should be designed to draw on a pool of younger subjects (aged < 65 years) and follow them for a sufficient amount of time, taking into account *APOE* genotype in order to note an effect. A trial of this sort would be cost prohibitive, and there are legitimate concerns about the safety of using NSAIDs for an extended period. Thus, it is unlikely that an appropriately designed randomized clinical trial to test the neuroprotective effects of NSAIDs will be carried out. Nevertheless, some vitally important questions remain. Because a significant proportion of the elderly continue to take NSAIDs regularly for a variety of other indications, it is crucial to understand the potential neurocognitive benefits of NSAIDs so that these can be properly weighed against their known risks. Furthermore, if these agents can offer protection against debilitating neurodegenerative diseases, it would be helpful to determine exactly how and why so that we might be able to develop modified treatments that can provide the benefits without the concomitant risks. In the absence of randomized clinical trials, we will have to rely on utilizing either laboratory studies or the information gathered from observational studies like the current one in strategic ways in order to address the many questions that remain.

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ical assessment procedures were developed by Dr. Welsh-Bohmer and Dr. Breitner. Dr. Tschanz provided training and oversight of all field staff and reviewed all individual neuropsychological test results to render professional diagnoses. The board-certified or board-eligible geriatric psychiatrists or neurologists who examined the study members included Drs. Steinberg, Breitner, Steffens, Lyketsos, and Green. Dr. Williams also examined several subjects and provided expert neurologic consultation. Autopsy examinations were conducted by Dr. Townsend. Ms. Leslie coordinated the autopsy enrollment program. Diagnosticians at the expert consensus conferences included Drs. Breitner, Burke, Lyketsos, Plassman, Steffens, Steinberg, Tschanz, and Welsh-Bohmer.d Drs. Breitner, Burke, Lyketsos, Plassman, Steffens, Steinberg, Tschanz, and Welsh-Bohmer.

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