

Protective effects of NSAIDs on the development of Alzheimer disease

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ABSTRACT

Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) may protect against Alzheimer disease (AD), but observational studies and trials have offered contradictory results. Prior studies have also been relatively short and small. We examined the effects on AD risk of NSAID use for >5 years and of NSAIDs that suppress formation of $A\beta_{1-42}$ amyloid in a large health care database.

Methods: Cases were veterans aged 55 years and older with incident AD using the US Veterans Affairs Health Care system. Matched controls were drawn from the same population. NSAID exposure was categorized into seven time periods: no use, ≤ 1 year, >1 but ≤ 2 years, and so on. Using conditional logistic regression, adjusted for race and comorbidities, we tested the association between AD development and the use of 1) any NSAID, 2) any NSAID excluding nonacetylated salicylates, 3) each NSAID class, 4) each individual NSAID, and 5) $A\beta_{1-42}$ -suppressing NSAIDs.

Results: We identified 49,349 cases and 196,850 controls. Compared with no NSAID use, the adjusted odds ratios for AD among NSAID users decreased from 0.98 for ≤ 1 year of use (95% CI 0.95–1.00) to 0.76 for >5 years of use (0.68–0.85). For users of ibuprofen, it decreased from 1.03 (1.00–1.06) to 0.56 (0.42–0.75). Effects of other NSAID classes and individual NSAIDs were inconsistent. There was no difference between a group of $A\beta_{1-42}$ -suppressing NSAIDs and others.

Discussion: Long-term nonsteroidal anti-inflammatory drug (NSAID) use was protective against Alzheimer disease. Findings were clearest for ibuprofen. $A\beta_{1-42}$ -suppressing NSAIDs did not differ from others. *Neurology*® 2008;70:1672–1677

GLOSSARY

AD = Alzheimer disease; **ADAPT** = Alzheimer's Disease Anti-inflammatory Prevention Trial; **COX-2** = cyclooxygenase-2; **DEpiC** = Disease Epidemiology Cohorts; **NSAID** = nonsteroidal anti-inflammatory drug; **VA** = Veterans Affairs.

There is contradictory evidence as to whether nonsteroidal anti-inflammatory drugs (NSAIDs) play a role in preventing or slowing the onset of Alzheimer disease (AD).^{1,2} A number of epidemiologic studies have reported that NSAIDs delay AD onset.³ However, no study has had sufficient size, duration, or medication record details to provide estimates for periods of NSAID use longer than 2 years or to provide estimates for the effect of specific NSAIDs on AD risk

In contrast to observational studies, randomized clinical trials in persons with established AD have not shown benefit from NSAID use. In studies lasting 6 to 12 months,^{4,7} naproxen, rofecoxib, diclofenac/misoprostol, and nimesulide showed no improvement in or slowing of cognitive function. Only a small, 6-month trial of indomethacin suggested an improvement in cognitive function in patients with AD.⁸ The recently published Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) found no significant

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decrease in the risk of AD from either naproxen or celecoxib, though follow-up was curtailed at 3 years and a trend toward efficacy of both drugs was evident.⁹

Results of observational studies and trials might differ because different NSAIDs have different effects on AD.¹⁰ Animal and laboratory studies have documented drug-specific, cyclooxygenase-independent effects of NSAIDs.¹⁰ In particular, ibuprofen, flurbiprofen, and diclofenac reduce serum levels of $A\beta_{1-42}$, a major component of senile plaques in AD amyloid.¹¹⁻¹⁴ Indeed, though both are members of the same NSAID class, ibuprofen decreased $A\beta_{1-42}$ levels in transgenic mice given the drug for 3 days, whereas naproxen did not.¹⁴ Though there are no data on $A\beta_{1-42}$ in humans, it is interesting to note that none of the NSAIDs used in human trials have had anti-amyloid effects in animal models of AD except for indomethacin.⁸

Our goal was to explore the effects of long-term use of specific NSAIDs on the risk for incident AD. We also tested the hypothesis that NSAIDs that suppress $A\beta_{1-42}$ levels would be more likely to have a protective effect on AD.

METHODS Data sources. We studied veterans aged 50 years and older who received medical care and prescriptions through the US national Veterans Affairs (VA) Health Care system. Several VA data sets were combined to form the Disease Epidemiology Cohorts (DEpiC),¹⁵ which includes VA pharmacy, laboratory, diagnosis, and survey data as well as linked Medicare data. We used these to provide information on drug usage, diagnosis of AD, and other variables of interest. DEpiC currently contains complete pharmacy records for all veterans with diabetes, and for all NSAID users from October 1, 1998, through September 30, 2005. Partial pharmacy records are present for the remaining veterans.

Eligible population. The base population consisted of veterans who had at least one outpatient visit from October 1, 1998, through September 30, 2005. To eliminate preexisting cases of AD, we excluded any veteran who had a diagnosis code (*International Classification of Diseases*, Ninth Revision, Clinical Modification) indicating AD (331.0) or any other form of dementia (codes 290.0–290.3, 290.4–290.9, 331.1–331.2, 331.9, and 797; table e-1 on the *Neurology*[®] Web site at www.neurology.org), or who had used a drug for dementia (donepezil, galantamine, rivastigmine, memantine, or tacrine) within 6 months of their initial visit. Those remaining were eligible to be cases or controls.

Case definition. Cases were all veterans, free of AD at baseline, in whose record a new diagnosis code for AD

(331.0) appeared during the study period. The date of “onset” for each case was defined by the earliest appearance of any of the following: 1) the first specific code for AD, 2) the first appearance of any dementia-indicating code (as listed above), or 3) a first prescription for any dementia drug (as listed above).

Control definition. Potential controls for a case were subjects who could be matched by age within 5-year strata (50–54 years, 55–59 years, and so on), sex, and the VA facility in which they received care. They were also required to have a first VA outpatient visit in the same year as that of the case and to have an inpatient stay or outpatient visit in the same year as the case’s “onset” date. The latter two criteria ensured that a control was followed in the VA system over the same period as his matched case and had equal exposure opportunity. Four controls were then selected using a computer-generated algorithm. Where four controls could not be matched to a case (e.g., in higher age strata), as many controls as possible were used.

Exposure definitions. We investigated exposure to NSAIDs over the study period and before disease onset, using several definitions of exposure: 1) use of any NSAID; 2) use of any NSAID but excluding nonacetylated salicylates, which may differ in their anti-inflammatory mechanism from other NSAIDs¹⁶; 3) NSAID use stratified by specific NSAID classes; 4) use of each individual NSAID; and 5) use of NSAIDs that decrease $A\beta_{1-42}$ levels in animal and experimental models (called $A\beta_{1-42}$ suppressors).

NSAID classes (and individual drugs) included the arylpropionic acids (ibuprofen, naproxen, ketoprofen, oxaprozin), the indolic acids (etodolac, sulindac, indomethacin), the heteroarylacetic acids (diclofenac, ketorolac, tolmetin), the enolic acids (meloxicam, piroxicam, nabumetone), the cyclooxygenase-2 (COX-2) inhibitors (rofecoxib, celecoxib, valdecoxib), nonacetylated salicylates (salsalate, diflunisal, magnesium and choline salicylates), and high-dose aspirin (defined as average use > 325 mg per day). Of these, $A\beta_{1-42}$ suppressors used in the VA system included ibuprofen, sulindac, indomethacin, and diclofenac.¹⁰

We defined the cumulative duration of use in each of these groups as the sum of the durations of all relevant prescriptions received by a veteran. Duration of use was then divided into seven categories: no use, ≤ 1 year of use, >1 but ≤ 2 years of use, >2 but ≤ 3 years of use, >3 but ≤ 4 years of use, >4 but ≤ 5 years of use, and >5 years of use.

Covariates. Besides the matching variables, we controlled for age, race (white, black, Hispanic, native American/Asian/Pacific Islander, or other), low-dose aspirin use (defined as average use ≤ 325 mg per day), and VA priority. The priority status of a veteran is determined on entry into the VA system and determines the veteran’s level of services. It consists of seven mutually exclusive categories, which we collapsed into four: severely disabled, moderately disabled, requiring financial assistance, and able to make copayments.

We controlled for comorbid diseases and conditions that had the potential to confound the relationship between NSAIDs and AD. These were defined by the presence of one or more diagnosis codes in the 2 years before disease onset for the following conditions: rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, psoriatic arthritis, vasculitis, inflammatory bowel disease, acute or chronic renal insufficiency, other renal disease, gastrointesti-

nal bleeding or ulcer, gastroesophageal reflux, cardiac ischemia, angina, myocardial infarction, congestive heart failure, hyperlipidemia, diabetes mellitus, osteoarthritis, gout, other crystal diseases, chronic obstructive pulmonary disease, stroke, TIA, major depression, major anxiety, bipolar disorder, and schizophrenia (table e-1).

We chose to differentiate between “cardioprotective” aspirin use and “therapeutic” use by treating the former (≤ 325 mg per day) as a binary variable and dealing with the latter (> 325 mg per day) like other exposures. We thought this would minimize the risk of confounding when aspirin use was considered as binary (use vs no use) without affecting our ability to detect a dose–response relationship when it was treated as a categorical exposure.

Main analyses. We used conditional logistic regression in SAS version 9.1 (SAS Institute Inc., Cary, NC) to calculate the odds of AD for each category of duration of use for each exposure definition. An unadjusted model was first constructed. This generated odds ratios (ORs) for each category of duration of use (≤ 1 year, > 1 to ≤ 2 years, and so on) compared with the no-use group. We then fit a model adjusted for race, priority, and residual age. Finally, we constructed a model including all the defined covariates and comorbidities. In models where NSAIDs were divided into classes or individual drugs, we controlled for duration of use of other NSAIDs.

We tested for a significant difference in trend between AB_{1-42} suppressors and non- AB_{1-42} suppressors by treating duration of use in each case as a linear variable and fitting a model that included the multiplicative interaction between these two groups. A significant interaction would indicate that the slopes of the two trends were different and therefore that the two groups showed different effects over time.

Because there were no major differences between the unadjusted, partially adjusted, and fully adjusted ORs, indicating the absence of significant confounding, the fully adjusted results are presented here.

Sensitivity analyses. We repeated our analyses restricting the case definition to a subject with at least two separate diagnosis codes for AD. We also liberalized the definition of a case by including as cases those with codes for “senile dementias” (290.09–290.3); for these cases, we selected additional controls from the eligible population. Finally, we excluded patients who had used any NSAID within the first year of their VA enrolment or within the first year of the study period if they had been enrolled before the study onset date. Thus, persons who were likely to take NSAIDs before our study period began were excluded.

RESULTS Study sample. We identified 49,349 cases of incident AD during the study period and matched these to 196,850 controls (case:control ratio 1:3.99). Because the source of our sample was veterans, 97.4% of subjects were male; the mean age at AD onset was 74.1 years (SD 6.9 years). The majority of subjects were white (65.8% of cases and 64.8% of controls) and needed financial assistance (57.6% of cases and 59.4% of controls; table 1). 20.9% of the cases were veterans who were not diabetic and did not use NSAIDs. Because these cases may not have

	Cases	Controls
No. of subjects	49,349	196,850
Male, no. (%)	47,969 (97.2)	191,701 (97.4)
Age, mean, y	74.3	74.0
Race, no. (%)		
White	32,484 (65.8)	127,475 (64.8)
Black	5,007 (10.2)	15,340 (7.8)
Hispanic	2,412 (4.9)	9,083 (4.6)
Asian/Pacific Islander/ Native American	291 (0.6)	1,531 (0.8)
Unknown	9,155 (18.6)	43,421 (22.1)
VA priority, no. (%)		
Disabled	7,757 (15.7)	23,424 (11.9)
Moderately disabled	9,928 (19.9)	40,083 (20.4)
Poor	28,408 (57.6)	117,006 (59.4)
Making copayments	3,256 (6.6)	16,337 (8.3)

VA = Veterans Affairs.

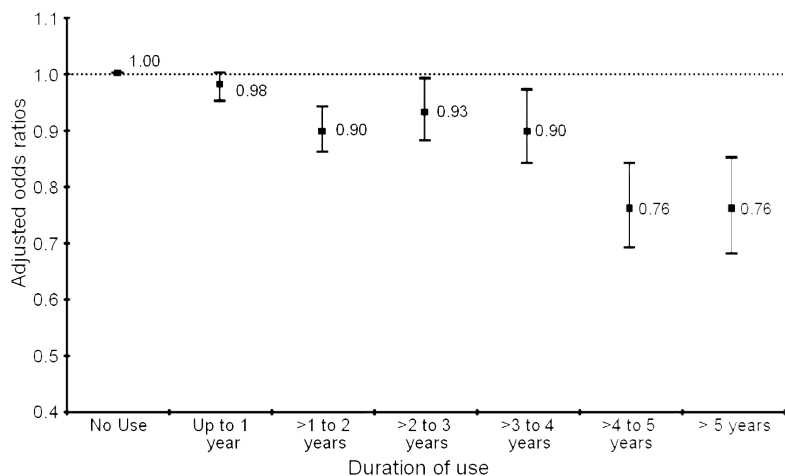
had complete pharmacy records, their use of anti-dementia drugs was unknowable, and some subjects’ “true” disease onset dates may have been somewhat earlier than that assigned.

Comorbid diseases. We characterized any difference in comorbidity prevalence between cases and controls as important if greater than 2%. We found such differences for low-dose aspirin use (48.7% of cases, 39.3% of controls), gastrointestinal bleeding (12.0% of cases, 9.6% of controls), acute renal failure (6.5% of cases, 3.9% of controls), hearing loss (37.3% of cases, 34.3% of controls), and osteoarthritis (48.0% of cases, 46.0% of controls). Rates of all mental illness were higher in cases than in controls (table e-2).

NSAID use. 42.2% of cases and 40.2% of controls received at least one prescription for an NSAID during the study period (table e-3). The arylpropionic acids were the most frequently prescribed class (31.3% of cases and 29.1% of controls). This class included the two most frequently prescribed NSAIDs, ibuprofen (20.9% of cases, 18.7% of controls) and naproxen (15.2% of cases, 14.6% of controls). Roughly 15% of cases and controls used NSAIDs for > 1 year, with almost half of these using either ibuprofen or naproxen. Four hundred cases (0.81%) and 1,952 controls (0.99%) used NSAIDs for longer than 5 years.

Main analyses. The odds of AD decreased with longer NSAID use (figure 1). Compared with persons not using NSAIDs, the odds of AD decreased from 0.98 (95% CI 0.95–1.00) among those with

Figure 1 Adjusted odds of Alzheimer disease for any nonsteroidal anti-inflammatory drug use



use for ≤ 1 year to 0.76 (0.68–0.85) for those who used NSAIDs for >5 years. Results did not change with exclusion of nonacetylated NSAIDs.

Among NSAID classes, a similar but more pronounced trend was seen for use of the arylpropionic acids. Compared with persons not using NSAIDs, those using for ≤ 1 year had an OR of 1.00 (1.98–1.03), whereas among those using for >5 years, the OR decreased to 0.63 (0.51–0.77). For other NSAID classes, there was a similar decrease in risk with long-term use, but the CIs for most time periods did not consistently exclude 1 (data not shown). There was no protective effect observed for users of COX-2 inhibitors or nonacetylated NSAIDs.

Among individual NSAIDs, ibuprofen showed the most marked protective effect (table 2 and fig-

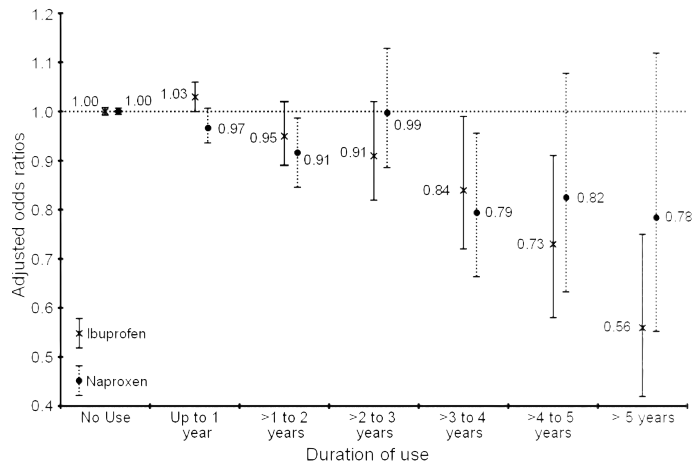
Table 2 Odds ratios of Alzheimer disease for selected nonsteroidal anti-inflammatory drugs

	Adjusted odds ratio* (95% CI)						
	No use (reference)	≤ 1 y of use	>1 to ≤ 2 y of use	>2 to ≤ 3 y of use	>3 to ≤ 4 y of use	>4 to ≤ 5 y of use	>5 y of use
All NSAIDs	1	0.98 (0.95–1.00)	0.90 (0.86–0.94)	0.93 (0.88–0.99)	0.90 (0.84–0.97)	0.76 (0.69–0.84)	0.76 (0.68–0.85)
Ibuprofen [†]	1	1.03 (1.00–1.06)	0.95 (0.89–1.02)	0.91 (0.82–1.02)	0.84 (0.72–0.99)	0.73 (0.58–0.91)	0.56 (0.42–0.75)
Naproxen	1	0.96 (0.93–1.00)	0.91 (0.84–0.98)	0.99 (0.88–1.12)	0.79 (0.66–0.95)	0.82 (0.63–1.07)	0.78 (0.55–1.11)
Etodolac	1	0.86 (0.81–0.91)	1.04 (0.92–1.19)	0.84 (0.67–1.06)	0.96 (0.69–1.33)	0.62 (0.32–1.20)	1.87 (0.17–20.81)
Indomethacin [†]	1	0.97 (0.91–1.03)	0.92 (0.75–1.13)	0.79 (0.54–1.16)	0.64 (0.37–1.12)	0.34 (0.10–1.12)	0.45 (0.13–1.55)
Sulindac [†]	1	1.00 (0.93–1.07)	1.00 (0.84–1.19)	1.18 (0.90–1.55)	1.24 (0.86–1.78)	0.60 (0.31–1.18)	0.84 (0.45–1.57)
Celecoxib	1	0.94 (0.87–1.02)	0.85 (0.73–0.98)	1.06 (0.86–1.30)	1.01 (0.77–1.34)	0.57 (0.34–0.96)	1.27 (0.55–2.93)
Rofecoxib	1	0.90 (0.82–0.97)	0.84 (0.71–0.99)	0.86 (0.65–1.12)	0.96 (0.68–1.35)	0.71 (0.31–1.63)	5.89 (0.33–105.82)
Piroxicam	1	0.92 (0.85–1.00)	1.03 (0.85–1.24)	0.85 (0.64–1.13)	0.91 (0.61–1.36)	0.87 (0.52–1.45)	0.54 (0.28–1.03)
Diclofenac [†]	1	0.86 (0.80–0.93)	0.78 (0.65–0.94)	0.81 (0.60–1.09)	0.80 (0.49–1.30)	0.56 (0.26–1.21)	0.64 (0.29–1.39)
Salsalate	1	1.03 (0.98–1.08)	1.37 (1.21–1.55)	1.20 (0.99–1.46)	1.15 (0.87–1.54)	1.06 (0.68–1.67)	0.74 (0.47–1.19)
$A\beta_{1-42}$ -suppressing NSAIDs	1	1.00 (0.97–1.02)	0.94 (0.89–1.00)	0.90 (0.82–0.99)	0.84 (0.73–0.96)	0.74 (0.62–0.90)	0.62 (0.49–0.78)
Non- $A\beta_{1-42}$ -suppressing NSAIDs	1	0.88 (0.84–0.91)	0.89 (0.83–0.96)	0.89 (0.79–0.99)	0.86 (0.74–1.00)	0.75 (0.60–0.94)	0.71 (0.50–1.01)

* Adjusted for age, race, Veterans Affairs priority, comorbidities, and low-dose aspirin use.

[†] $A\beta_{1-42}$ -suppressing nonsteroidal anti-inflammatory drugs (NSAIDs).

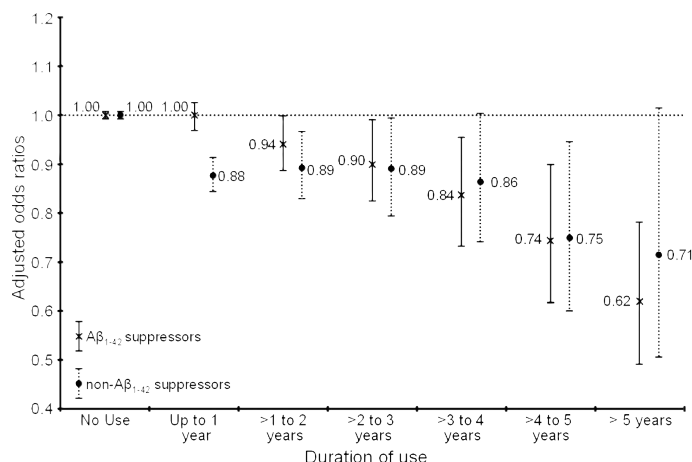
Figure 2 Adjusted odds ratios of Alzheimer disease for ibuprofen and naproxen



ure 2). Compared with no use, the OR of AD decreased from 1.03 (1.0–1.06) for ≤ 1 year of use to 0.56 (0.42–0.75) with > 5 years of use. For naproxen, the next most frequently used NSAID, the OR decreased from 0.96 with ≤ 1 year of use to 0.78 with > 5 years of use, but CIs often crossed the null. The only other NSAID for which there was a possible protective effect was indomethacin (OR 0.97 [0.91–1.03] with ≤ 1 year of use and OR 0.45 [0.13–1.55] with > 5 years of use; table 2).

Among NSAIDs in the $A\beta_{1-42}$ -suppressor group, long-term use also protected against AD, but the effect of these drugs differed little from the nonsuppressor group (figure 3). For > 5 years of use, persons using $A\beta_{1-42}$ suppressors had an OR for AD of 0.62 (0.49–0.78) compared with 0.71 (0.50–1.01) for users of non- $A\beta_{1-42}$ suppressors. There was no difference between effects of $A\beta_{1-42}$ suppressors and nonsuppressors on AD risk ($p = 0.41$ for the interaction term).

Figure 3 Adjusted odds ratios of Alzheimer disease for $A\beta_{1-42}$ suppressors and non- $A\beta_{1-42}$ suppressors



Sensitivity analyses. When our case definition required two separate 331.0 diagnosis codes, we identified 26,927 cases and 107,415 matched controls. For any NSAID use, the ORs were similar to those shown above. Results for NSAID classes and individual NSAIDs were also largely unchanged, although CIs widened.

Using an expanded case definition that incorporated any dementia diagnosis code, we identified 84,501 cases and 336,796 matched controls. Again, the results for any NSAID, each NSAID class, and individual NSAIDs were largely unchanged, but CIs were generally narrower. When those with NSAID use in the year before VA enrollment were excluded, we identified 40,179 cases and 159,843 controls. ORs were again largely unchanged (data not shown).

DISCUSSION We found that long-term users of NSAIDs were at lower-than-expected risk of AD. Our results generally agree with and extend those of prior epidemiologic studies. We found that the protective effect did not seem to be identical for each NSAID: some showed clear protective effects, others did not, and in yet others the effect on AD risk was unclear.

Ibuprofen showed a strong protective effect that increased with duration of use, consistent with nonclinical studies of this $A\beta_{1-42}$ -suppressing NSAID. We were probably able to observe this effect because of the large numbers of users of this medication in the VA system. At least one other $A\beta_{1-42}$ -suppressing NSAID seemed to show a similar effect (indomethacin). However, a number of non- $A\beta_{1-42}$ suppressors did not show any protective effect (celecoxib, the salicylates). This was also consistent with prior nonclinical studies. Unfortunately, the effect of many NSAIDs was not clear. In particular, small numbers of users made it difficult to ascertain whether other $A\beta_{1-42}$ -suppressing NSAIDs (sulindac, flurbiprofen) showed the same protective effect as ibuprofen. Likewise, it was difficult to confirm that other non- $A\beta_{1-42}$ -suppressing NSAIDs showed no effect.

Attempting to clarify the specific effect of $A\beta_{1-42}$ suppression, we grouped these drugs together and compared them with non- $A\beta_{1-42}$ -suppressing NSAIDs. There was a duration-dependent protective effect in the former group with CIs that consistently excluded the null with use over 1 year. The curve was similar to that for ibuprofen alone, suggesting that this NSAID may have been responsible for most of the protective effect observed. However, the non- $A\beta_{1-42}$ -suppressing group also showed a decrease in ORs over time, though CIs were wider

and often crossed the null. The difference in linear slope between the two groups was not significantly different, implying no difference between the two groups. It may be that $A\beta_{1-42}$ suppression does not fully account for differences between individual NSAIDs and that some other mechanism of action, mediated through drugs present in both groups, accounted for similar protective effects over time.

We recognize a number of limitations in our study. Our outcomes were derived from clinical visits and hospitalizations and were therefore liable to errors in coding. We attempted to account for this by using a variety of outcome definitions. Even if we missed a significant number of cases, we would have expected our results to underestimate the effect rather than showing the strong effects we observed for some NSAIDs. Drug exposure could also have been misclassified if subjects did not take medications as prescribed or used over-the-counter NSAIDs, which we could not capture. We think this is unlikely to be a significant problem with long-term prescriptions of NSAIDs. Information on confounders that could have been of relevance, such as actual socioeconomic status, education, or tobacco use, was unavailable. Some of these may have important associations with AD.¹⁷

Confounding by indication could have occurred in this study if persons developing, but not yet diagnosed with, AD were more likely to discontinue NSAIDs than others who remained healthy. We believe there are arguments against confounding by indication as an explanation of our results. First, our data set was large enough that we could evaluate long-term use of several different NSAIDs. Some, but not all, had protective associations for AD. If confounding by indication explained our results, we should have seen similar protective effects with all NSAIDs. Second, significant bias in our results would have required that practitioners systematically recognized patients at risk of AD before they were diagnosed and avoided prescribing NSAIDs before making a diagnosis. This seems unlikely.

Our study has implications for future trials of NSAIDs in AD. Randomized trials have almost exclusively used NSAIDs whose long-term use may not be protective (e.g., rofecoxib, naproxen). It is interesting that in ADAPT, which randomly assigned patients at risk for AD to either naproxen or celecoxib, neither drug showed a definite effect, though naproxen showed a somewhat stronger trend compared with celecoxib, a finding that is consistent with the results of our study.⁹ Other drugs that we found to be protective, such as ibuprofen, might be good candidates for future trials.

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