The New England Journal of Medicine

VOLUME 345 NOVEMBER 22, 2001 NUMBER 21

NONSTEROIDAL ANTIINFLAMMATORY DRUGS AND THE RISK OF ALZHEIMER'S DISEASE

BAS A. IN 'T VELD, M.D., PH.D., ANNEMIEKE RUITENBERG, M.D., PH.D., ALBERT HOFMAN, M.D., PH.D., LENORE J. LAUNER, PH.D., CORNELIA M. VAN DUIJN, PH.D., THEO STIJNEN, PH.D., MONIQUE M.B. BRETELER, M.D., PH.D., AND BRUNO H.C. STRICKER, M.B., PH.D.

ABSTRACT

Background Previous studies have suggested that the use of nonsteroidal antiinflammatory drugs (NSAIDs) may help to prevent Alzheimer's disease. The results, however, have been inconsistent.

Methods We studied the association between the use of NSAIDs and Alzheimer's disease and vascular dementia in a prospective, population-based cohort study of 6989 subjects 55 years of age or older who were free of dementia at base line. The risk of Alzheimer's disease was estimated in relation to the use of NSAIDs as documented in pharmacy records. We defined four mutually exclusive categories of use: nonuse, short-term use (1 month or less of cumulative use), intermediate-term use (more than 1 but less than 24 months of cumulative use), and long-term use (24 months or more of cumulative use). Adjustments were made by Cox regression analysis for age, sex, education, smoking status, and the use or nonuse of salicylates, histamine H_2-receptor antagonists, antihypertensive agents, and hypoglycemic agents.

Results During an average follow-up period of 6.8 years, dementia developed in 394 subjects, of whom 293 had Alzheimer's disease, 56 vascular dementia, and 45 other types of dementia. The relative risk of Alzheimer's disease was 0.95 (95 percent confidence interval, 0.70 to 1.29) in subjects with short-term use of NSAIDs, 0.83 (95 percent confidence interval, 0.62 to 1.11) in those with intermediate-term use, and 0.20 (95 percent confidence interval, 0.05 to 0.83) in those with long-term use. The risk did not vary according to age. The use of NSAIDs was not associated with a reduction in the risk of vascular dementia.

Conclusions The long-term use of NSAIDs may protect against Alzheimer's disease but not against vascular dementia. (N Engl J Med 2001;345:1515-21.)

THE neuropathologic features of Alzheimer's disease include the accumulation of microglia around plaques, a local cytokine-mediated acute-phase response, and activation of the complement cascade.[1,2] This inflammatory response may damage neurons and exacerbate the pathologic processes underlying the disease.[3] Nonsteroidal antiinflammatory drugs (NSAIDs) may influence this inflammatory response by inhibiting cyclooxygenase-1 and cyclooxygenase-2 and by activating the peroxisome proliferator γ (PPARγ) nuclear transcription factor.[4-6] In addition, cyclooxygenase-mediated oxidation is important in the calcium-dependent glutamate-signaling pathway that involves *N*-methyl-D-aspartate. In this way, NSAIDs may be able to protect neurons directly by reducing cellular responses to glutamate.[7]

The results of observational studies have been inconsistent with regard to the association between NSAIDs and Alzheimer's disease.[8-30] Some have suggested a protective effect, whereas others have not. In almost all the studies, information on NSAIDs was obtained retrospectively from patients or relatives or from medical records. These methods are vulnerable to misclassification of drug exposure. In the Netherlands, computerized pharmacy records are virtually complete sources of information on the delivery of drugs. We conducted a prospective, population-based cohort study to determine whether the use of NSAIDs other than aspirin was associated with a decreased risk of Alzheimer's disease or vascular dementia.

From the Department of Epidemiology and Biostatistics, Erasmus Medical Center, Rotterdam, the Netherlands (B.A.V., A.R., A.H., C.M.D., T.S., M.M.B.B., B.H.C.S.); the Epidemiology, Demography, and Biometry Program, National Institute on Aging, National Institutes of Health, Bethesda, Md. (L.J.L.); and the Inspectorate for Health Care, The Hague, the Netherlands (B.A.V., B.H.C.S.). Address reprint requests to Dr. Stricker at the Department of Epidemiology and Biostatistics, Erasmus Medical Center, P.O. Box 1738, 3000 DR Rotterdam, the Netherlands.

METHODS

Study Population

The Rotterdam Study is a prospective, population-based cohort study of neurologic, cardiovascular, locomotor, and ophthalmologic diseases in elderly persons.[31] In brief, all persons 55 years of age or older who were living in Ommoord, a suburb of Rotterdam, the Netherlands, were invited to participate in the study between 1990 and 1993. Of the 10,275 eligible subjects, 7983 (78 percent) gave written informed consent to participate. They were interviewed at home by trained interviewers on a wide range of topics, including socioeconomic background, medical history, and medication use. During subsequent visits to the research center, the subjects underwent additional interviews and examinations, including screening and clinical workup for dementia. In addition, apolipoprotein E genotyping was performed on coded DNA samples by investigators who were unaware of whether the subjects had dementia.[32] Nearly all the participants (99.7 percent) were registered at one or more of the seven pharmacies serving the Ommoord area. These pharmacies are fully automated, and all recorded data on drug use during the period from January 1, 1991, through December 31, 1998.

The potential study period consisted of the eight-year period from January 1, 1991, through December 31, 1998. Of the 7983 subjects who had agreed to participate, 7528 (94.3 percent) were screened and examined for dementia,[33,34] and 7046 were found to be free of dementia at base line. From this group, we excluded the 57 subjects for whom follow-up ended before July 1, 1991, because there was less than six months of data on their history of medication use. Participants were then screened again for dementia at a second examination (during 1993 or 1994) and at a third examination (during 1997, 1998, or 1999), as described below. Every member of the final study population of 6989 subjects was followed until the occurrence of death, a diagnosis of dementia, or the end of the study period, which was the date of the last examination unless this examination was performed in 1999, in which case the end of the study period was defined as December 31, 1998.

Information on the Use of NSAIDs and Other Drugs

Complete information on prescriptions was available in automated form and included the product name; the international nonproprietary name of the drug; the number of tablets, capsules, or other vehicle in the filled prescription; the date of delivery of the product; the prescribed daily number of tablets to be taken; the drug dosage; and the duration of the prescription period. For comparisons of dosages, we used the "defined daily dose," which is the average dosage of a drug taken by adults for the main indication, according to the World Health Organization.[35] All prescriptions for oral NSAIDs filled during follow-up were used to create time-dependent covariates, as described below. Because oral salicylate-based analgesics, including the platelet-inhibiting salicylates acetylsalicylic acid (aspirin) and carbaspirin calcium, are pharmacologically related to NSAIDs, separate time-dependent covariates were also created for these drugs so that we could study their association with Alzheimer's disease.

Ascertainment of Dementia

Both at the base-line examination and at follow-up examinations, the subjects were examined for dementia according to a three-step protocol.[33,34] First, subjects were screened with the use of the Mini–Mental State Examination (on which possible scores range from 0 to 30, with lower scores indicating worse cognitive function)[36] and the Geriatric Mental State Schedule (organic level [a subquestionnaire used to screen for an organic syndrome]) (where possible scores range from 0 to 5, with higher scores indicating a higher probability of dementia).[37] Second, those scoring 25 or below on the Mini–Mental State Examination or scoring 1 or more on the Geriatric Mental State Schedule were selected for further diagnostic evaluation and were subsequently examined by a physician using the Cambridge Mental Disorders of the Elderly Examination diagnostic interview.[38] Third, subjects who were believed to have dementia were examined by a neurologist and a neuropsychologist and underwent magnetic resonance imaging of the brain.

In addition to undergoing screening for dementia, the subjects were continuously monitored for cases of dementia during follow-up.[33] A clinical diagnosis of dementia was made according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders,* third edition, revised, by a panel that reviewed all existing information. A subdiagnosis of Alzheimer's disease was made according to the criteria of the National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer's Disease and Related Disorders Association.[39] A subdiagnosis of vascular dementia was made according to the criteria of the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences.[40] The date of onset of dementia was defined as the date midway between the date of the last examination at which the subject was deemed to be free of dementia and the date of the examination at which he or she was given a diagnosis of dementia.

Statistical Analysis

For every subject in the cohort, we calculated the person-time between January 1, 1991, and death, a diagnosis of dementia, or the end of the study period, whichever came first. We calculated the relative risks of dementia (and 95 percent confidence intervals) with the use of a Cox proportional-hazards model[41]; the cumulative use of each drug was represented by a time-dependent covariate. In the Cox model, age in days was used as the time axis to ensure optimal adjustment for age.[42] We used SAS software (PHREG procedure, version 6.12, SAS Institute, Cary, N.C.) to estimate the age-specific incidence of Alzheimer's disease and vascular dementia in relation to the use of NSAIDs.

Apart from a time-dependent comparison in which any use was compared with no use, we created time-dependent categorical variables by dividing the cumulative use of NSAIDs during the study period into four mutually exclusive categories: nonuse, short-term use (1 month or less of cumulative use), intermediate-term use (more than 1 but less than 24 months of cumulative use), and long-term use (24 months or more of cumulative use). These cutoff points were chosen to ensure an adequate number of subjects in each group and are similar to those used in a previous, long-term prospective study.[26] The four time-dependent categorical variables with respect to cumulative exposure times were represented in the models by three dummy variables, with nonuse as the reference category. In this model, a cohort member could contribute person-time to more than one category of cumulative exposure. To adjust for the loss of information by the categorization of duration, we also modeled the relation between cumulative duration and effect by using quadratic spline regression.[43] In addition, in this analysis, we examined the effect on the relative risks of a lag time[26,44-46] by excluding either the last year or the last two years before diagnosis. In this way, we dealt with potential protopathic bias that might be caused by changes in the use of NSAIDs during the prodromal phase of dementia. In addition, we performed a test for trend for each of the three splines. In a similar manner, time-dependent categorical variables were constructed with respect to the cumulative duration of use of aspirin and of related oral salicylates.

Potential confounding variables included sex, age (as defined above), level of education, smoking status, duration of use of hypoglycemic agents (as a proxy for the duration of diabetes mellitus), and treatment with histamine H_2-receptor antagonists and antihypertensive agents, which have been reported to be associated with dementia in previous studies. We also investigated whether there was an association between the use of corticosteroids or nonnarcotic analgesic agents and dementia. To study a possible dose–effect relation with respect to NSAIDs, we dichotomized dosage around the median ($\leq$1 vs. $>$1 defined daily dose per day). In additional analyses, we examined whether age and the presence of the apolipoprotein E ϵ4 allele modified the effect of NSAIDs on the risk of

Alzheimer's disease. Finally, in a subanalysis, we examined whether prior use of estrogen influenced this risk among the female subjects.

RESULTS

During a total of 47,498 person-years of follow-up, with a mean follow-up time of 6.8 years per subject, 394 subjects received a diagnosis of dementia. Of these patients, 293 had Alzheimer's disease, 56 vascular dementia, and 45 other types of dementia. Characteristics of the study population are given in Table 1. Diclofenac, ibuprofen, and naproxen together accounted for approximately 83 percent of the total number of prescriptions for NSAIDs (Table 2). A greater proportion of the subjects with less than six years of education than of those with six or more years of education took NSAIDs during follow-up (66 percent vs. 60 percent). The yearly rate of use was remarkably constant over time, with 37 to 40 days of use per 1000 person-days during the 8 years of follow-up; the mean duration of a prescription varied between 26.3 and 31.4 days. The total number of NSAID prescriptions during the follow-up period was 23,685. The average daily number of medicines used by subjects with dementia was 2.7, as compared with 1.9 in those without dementia ($P<0.001$). In total, 2314 subjects (33.1 percent) had used aspirin or related oral salicylates, almost invariably in doses that inhibit platelets but do not have antiinflammatory activity (<300 mg per day).

Use of an NSAID at any time, defined as a binary, time-dependent variable and compared with no use at any time, was associated with a lower risk of Alzheimer's disease (relative risk, 0.86; 95 percent confidence interval, 0.66 to 1.09). Relative to the risk in those who did not use NSAIDs, the risk of Alzheimer's disease was 0.95 (95 percent confidence interval, 0.70 to 1.29) in those whose cumulative NSAID use was categorized as short-term use, 0.83 (95 percent confidence interval, 0.62 to 1.11) in those with intermediate-term use, and 0.20 (95 percent confidence interval, 0.05 to 0.83) in those with long-term use. These risk reductions could not be attributed to the use of a particular NSAID. No association was found between the use of NSAIDs and the risk of

TABLE 1. BASE-LINE CHARACTERISTICS OF THE STUDY COHORT AND RELATIVE RISK OF DEMENTIA.*

VARIABLE	ENTIRE COHORT (N=6989)	PERSON-YR (N=47,498)	SUBJECTS WITH DEMENTIA (N=394)	CRUDE RELATIVE RISK (95% CI)
		number (percent)		
Sex				
Male†	2795 (40.0)	19,014 (40.0)	125 (31.7)	1.00
Female	4194 (60.0)	28,484 (60.0)	269 (68.3)	1.43 (1.16–1.77)
Educational level‡				
Low†	4407 (63.1)	29,635 (62.4)	271 (68.8)	1.00
High	2379 (34.0)	16,834 (35.4)	82 (20.8)	0.53 (0.42–0.68)
No data	203 (2.9)	1,029 (2.2)	41 (10.4)	—
Age				
≤65 yr†	3162 (45.2)	23,485 (49.4)	25 (6.3)	1.00
66–75 yr	2323 (33.2)	15,776 (33.2)	127 (32.2)	6.62 (4.15–10.56)
>75 yr	1504 (21.5)	8,237 (17.3)	242 (61.4)	29.59 (19.0–46.2)
Reason for NSAID use				
Rheumatoid arthritis	236 (3.4)	1,518 (3.2)	17 (4.3)	1.37 (0.84–2.22)
Osteoarthritis	1647 (23.6)	11,449 (24.1)	89 (22.6)	0.92 (0.73–1.16)
Joint symptoms§	3487 (49.9)	23,999 (50.5)	179 (45.4)	0.97 (0.79–1.20)
Apolipoprotein E genotype				
$\epsilon2/\epsilon2$ or $\epsilon2/\epsilon3$†	880 (12.6)	6,146 (12.9)	27 (6.9)	1.00
$\epsilon3/\epsilon3$	3780 (54.1)	26,027 (54.8)	166 (42.1)	1.46 (0.97–2.19)
$\epsilon2/\epsilon4$, $\epsilon3/\epsilon4$, or $\epsilon4/\epsilon4$	1793 (25.7)	12,240 (25.8)	152 (38.6)	2.84 (1.89–4.27)
No data	536 (7.7)	3,085 (6.5)	49 (12.4)	—
Smoking				
Current†	1558 (22.3)	10,617 (22.4)	66 (16.8)	1.00
Previous	2834 (40.5)	19,582 (41.2)	126 (32.0)	1.04 (0.77–1.40)
Never	2430 (34.8)	16,422 (34.6)	174 (44.2)	1.72 (1.29–2.28)
No data	167 (2.4)	877 (1.8)	28 (7.1)	—

*Because of rounding, not all percentages total 100. CI denotes confidence interval.

†Patients with this characteristic served as the reference group.

‡A low level of education was defined as a primary education only or low-level vocational training; a high level was defined as intermediate-level vocational training or a university education.

§Joint symptoms were defined as those that had occurred within one month before the base-line interview.

TABLE 2. USE OF NSAIDS BY THE STUDY COHORT DURING THE EIGHT-YEAR STUDY PERIOD (1991 TO 1998).*

NSAID	PRESCRIPTIONS (N=23,685)	CUMULATIVE DURATION (N=666,903)	DEFINED DAILY DOSE
	no. (% of total)	days (% of total)	mg
Diclofenac	10,235 (43.21)	239,410 (35.90)	100
Ibuprofen	5,114 (21.59)	140,608 (21.08)	1200
Naproxen	4,177 (17.64)	109,760 (16.46)	500
Piroxicam	1,579 (6.67)	65,564 (9.83)	20
Indomethacin	1,099 (4.64)	47,409 (7.11)	100
Ketoprofen	592 (2.50)	27,385 (4.11)	150
Nabumetone	309 (1.30)	12,736 (1.91)	1000
Apazone	222 (0.94)	6,060 (0.91)	750
Sulindac	127 (0.54)	5,896 (0.88)	400
Meloxicam	75 (0.32)	2,420 (0.36)	15
Tiaprofenic acid	64 (0.27)	3,299 (0.49)	600
Flurbiprofen	55 (0.23)	4,711 (0.71)	200
Tolfenamic acid	16 (0.07)	1,039 (0.16)	300
Phenylbutazone	11 (0.05)	353 (0.05)	300
Tenoxicam	8 (0.03)	225 (0.03)	20
Benzydamine	2 (0.01)	28 (0.004)	150

*Because of rounding, not all percentages total 100.

vascular dementia (Table 3). In subjects who took oral salicylates, we found no association between these drugs and the risk of Alzheimer's disease, but this group did have an increased risk of vascular dementia, which increased with the duration of use (Table 3). As Figure 1 shows, there was a gradual decline in the relative risk of Alzheimer's disease with increasing duration of NSAID use. This trend became more prominent when lag times of one and two years were taken into account in the analyses.

To investigate whether subjects who had normal cognitive function at base line (1991) but in whom Alzheimer's disease developed five or more years later (in 1995 through 1998) were already taking fewer NSAIDs than other subjects in 1991, we stratified the new cases of Alzheimer's disease into those diagnosed during the period from 1991 through 1994 and those diagnosed during the period from 1995 through 1998. For the period from 1991 through 1994, the crude relative risk of Alzheimer's disease in aspirin users was 1.17 (95 percent confidence interval, 0.85 to 1.62), and for the period from 1995 through 1998, the crude relative risk was 0.72 (95 percent confidence interval, 0.51 to 1.02). Of those with long-term cumulative use of NSAIDs, 86 percent were already taking these drugs at base line. Of those with intermediate-term use, 51 percent were taking NSAIDs at base line, and of those with short-term use, 20 percent were doing so at base line.

TABLE 3. RELATIVE RISK OF ALZHEIMER'S DISEASE AND VASCULAR DEMENTIA ASSOCIATED WITH THE USE OF NSAIDS AND ORAL SALICYLATES.

DRUG AND CUMULATIVE EXPOSURE TIME	SUBJECTS WITH DEMENTIA (N=394)	ENTIRE COHORT (N=6989)	NO. OF PERSON-YR	RELATIVE RISK (95% CI)*	
				ALZHEIMER'S DISEASE (N=293)	VASCULAR DEMENTIA (N=56)
	number				
NSAIDs					
No exposure†	210	2553	16,715	1.00	1.00
≤1 mo	88	2001	13,970	0.95 (0.70–1.29)	1.25 (0.63–2.53)
>1 to 23 mo	93	2202	15,156	0.83 (0.62–1.11)	1.36 (0.70–2.64)
≥24 mo	3	233	1,654	0.20 (0.05–0.83)	0.99 (0.13–7.58)
Oral salicylates					
No exposure†	252	4675	31,881	1.00	1.00
≤1 mo	7	285	1,972	0.76 (0.31–1.84)	—
>1 to 23 mo	93	1017	6,498	1.30 (0.97–1.74)	2.99 (1.57–5.71)
≥24 mo	42	1012	7,147	0.76 (0.49–1.19)	4.88 (2.38–10.0)

*The relative risks were adjusted for age (as a continuous variable), sex (as a categorical variable), level of education (low or high), smoking status (current, previous, or never), and use or nonuse of histamine H_2-receptor antagonists, hypoglycemic medications, antihypertensive agents, and either oral salicylates or NSAIDs. CI denotes confidence interval.

†We used a time-dependent Cox regression analysis in which nonuse served as the reference category. Relative risks cannot be calculated on the basis of the numbers given in this table.

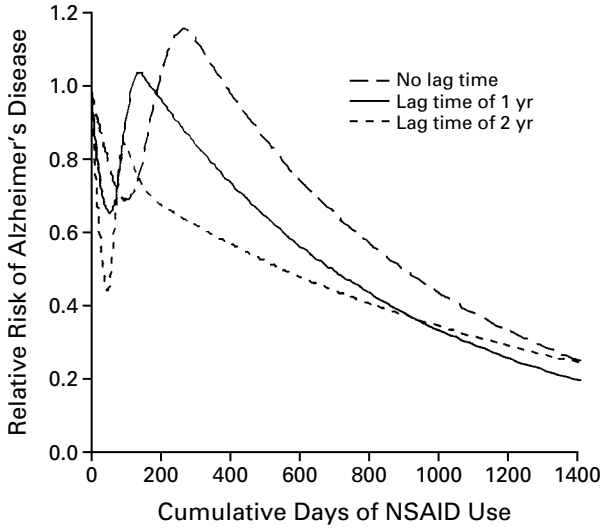

Figure 1. The Relative Risk of Alzheimer's Disease in Relation to the Cumulative Duration of NSAID Use after Base Line.

The curves were generated with the use of three quadratic spline regressions, one without lag time, one with a lag time of one year (meaning the exclusion from the analysis of the year before diagnosis), and one with a lag time of two years. They reveal a consistently decreasing risk of Alzheimer's disease with increasing cumulative duration of NSAID use (P for trend=0.06 for the analysis with no lag time, P for trend=0.05 for the analysis with a lag time of one year, and P for trend=0.04 for the analysis with a lag time of two years). The course of the curve at cumulative durations of use of less than 400 days can probably be explained by misclassification of drug use, since there were both subjects who were already using NSAIDs on a long-term basis at base line (and for whom the precise cumulative duration of NSAID exposure could not be calculated, because data on drug use before base line were not available) and new users with less than 400 days of cumulative exposure after base line. The apparent increase in risk seen in the curve without lag time may be explained in part by an increased use of NSAIDs in the prodromal phase of Alzheimer's disease. The increase in risk disappears when a lag time is included.

Among the subjects with two or more years of cumulative use of NSAIDs, there was no significant difference in the reduction in the risk of Alzheimer's disease between those taking less than one or one defined daily dose per day (relative risk as compared with no use, 0.17; 95 percent confidence interval, 0.02 to 1.22) and those taking more than one defined daily dose per day (relative risk, 0.25; 95 percent confidence interval, 0.03 to 1.78). There was no significant difference in the reduction in the risk of Alzheimer's disease with any use between persons less than 80 years of age (relative risk as compared with no use, 0.23; 95 percent confidence interval, 0.03 to 1.71) and persons 80 years of age or older (relative risk, 0.18; 95 percent confidence interval, 0.03 to 1.31). We used this cutoff point because there were only 11 subjects who already had Alzheimer's disease before 75 years of age. This fact relates to the high mean age at base line of this cohort and the selection of subjects who were free of cognitive dysfunction at the start of the study. Because there were no subjects with at least one apolipoprotein E ϵ4 allele among those with long-term cumulative use of NSAIDs, the relative risk among such users could not be estimated. However, among the subjects with less than 24 months but more than 1 month of cumulative exposure to NSAIDs, there was no significant difference in the reduction in the risk between those with at least one apolipoprotein E ϵ4 allele (relative risk as compared with no use, 0.73; 95 percent confidence interval, 0.45 to 1.19) and those with two apolipoprotein E ϵ3 alleles (relative risk, 0.94; 95 percent confidence interval, 0.63 to 1.40). No association was found between the risk of Alzheimer's disease and the use of nonnarcotic analgesics or corticosteroids. Furthermore, adjustment for the use of estrogen did not substantially alter the estimates of risk in women.

DISCUSSION

In this prospective, population-based study, we found a significantly reduced risk of Alzheimer's disease in subjects who had taken NSAIDs for a cumulative period of 24 months or more. This reduction was not modified by age or apolipoprotein E genotype. The use of NSAIDs was not associated with a reduction in the risk of vascular dementia. Our results are compatible with the hypothesis that inflammatory mechanisms may play a part in Alzheimer's disease. The results are also in line with those of some longitudinal studies[26,28] but not all.[22,24,25,29,30] In the Baltimore Longitudinal Study of Aging,[26] the risk of Alzheimer's disease was significantly lower among subjects who took NSAIDs for two or more years than among nonusers. Although the results of the latter study are in accordance with our findings, assessment of drug exposure was based on extrapolated, cross-sectional data acquired during interviews at biennial examinations. Drug-exposure data gathered this way are probably more vulnerable to misclassification than data from pharmacy records, especially with respect to the duration of use and the doses taken.

In the current study, a cohort of subjects who were screened and found to be free of dementia at base line was followed for up to eight years. Since follow-up information was almost complete, selection bias was eliminated. The main concern regarding most previous studies of the association between NSAIDs and the risk of Alzheimer's disease has been the potential for misclassification of the use of drugs. For example, persons with preclinical dementia might more easily forget and not report their medication history than persons with normal cognitive function. To overcome this potential source of information bias, we drew data on the use of NSAIDs from pharmacy records. The information in these pharmacy records was independ-

ent of characteristics such as age, sex, and cognitive status, and thus we avoided the limitations of similar studies in which information on the use of NSAIDs was obtained from interviews or medical records. Until 1995, NSAIDs could be obtained in the Netherlands only by prescription, and most over-the-counter analgesics consist of acetaminophen, which has no appreciable antiinflammatory properties. Moreover, in our study, nonnarcotic analgesics other than NSAIDs did not protect against Alzheimer's disease. Since 1995, some NSAIDs have become available in low doses on an over-the-counter basis. Even if the use of over-the-counter medications led to misclassification of NSAID exposure in our study cohort, however, this source of bias would underestimate, rather than overestimate, a true risk reduction.

A limitation of our study is that we had no data on the use of NSAIDs before 1991. However, since 86 percent of subjects with 24 months or more of cumulative use were already taking NSAIDs in 1991, it is likely that they took these drugs on a long-term basis. Confounding by indication may explain the increased risk of vascular dementia among subjects who took platelet-inhibiting salicylates, because patients who take these drugs for this indication may have a higher base-line risk of vascular dementia. However, it does not explain the reduced risk of Alzheimer's disease among those who took NSAIDs, since there was no association between the presence of rheumatoid arthritis or osteoarthritis at base line and the risk of Alzheimer's disease. Another potential source of confounding that we investigated is related to the possibility that persons with preclinical dementia may experience less pain or may communicate their pain less clearly than unaffected persons. If they take fewer NSAIDs, a spurious protective effect would be found. This assumes, however, that before dementia occurs, there is no difference in the use of NSAIDs and that in those in whom dementia develops, the use of NSAIDs will insidiously decrease. In our study, however, the use of NSAIDs was already lower five years before the diagnosis of dementia, when cognitive function was still normal. Another argument against this potential source of confounding is the fact that NSAIDs had no protective effect against vascular dementia, whereas one might then expect that the same direction and magnitude of confounding would have occurred. Moreover, less use of medical care would probably also mean that, overall, patients with dementia would take fewer drugs. On the contrary, we found a higher prevalence of overall drug use in persons with dementia.

In conclusion, our results suggest that long-term use of NSAIDs has a beneficial effect on the risk of Alzheimer's disease. Primary-prevention trials should be undertaken to confirm this finding and show whether the benefits of such therapy outweigh the potential risks.

Supported by the Inspectorate for Health Care, the Netherlands Incentives Program for Geriatric Research, the Netherlands Organization for Scientific Research, and the municipality of Rotterdam.

We are indebted to the general practitioners and pharmacists of Ommoord and of the Rotterdam Regional Institute for Ambulatory Mental Health Care, Noord Rotterdam, for their collaboration.

REFERENCES

1. Aisen PS. Inflammation and Alzheimer's disease: mechanisms and therapeutic strategies. Gerontology 1997;43:143-9.
2. *Idem.* Inflammation and Alzheimer disease. Mol Chem Neuropathol 1996;28:83-8.
3. McGeer PL, McGeer EG. The inflammatory response system of brain: implications for therapy of Alzheimer and other neurodegenerative diseases. Brain Res Brain Res Rev 1995;21:195-218.
4. Lehmann JM, Lenhard JM, Oliver BB, Ringold GM, Kliewer SA. Peroxisome proliferator-activated receptors alpha and gamma are activated by indomethacin and other non-steroidal anti-inflammatory drugs. J Biol Chem 1997;272:3406-10.
5. Ricote M, Li AC, Willson TM, Kelly CJ, Glass CK. The peroxisome proliferator-activated receptor-gamma is a negative regulator of macrophage activation. Nature 1998;391:79-82.
6. Leveugle B, Fillit H. Proteoglycans and the acute-phase response in Alzheimer's disease brain. Mol Neurobiol 1994;9:25-32.
7. Breitner JC. Inflammatory processes and antiinflammatory drugs in Alzheimer's disease: a current appraisal. Neurobiol Aging 1996;17:789-94.
8. Andersen K, Launer LJ, Ott A, Hoes AW, Breteler MM, Hofman A. Do nonsteroidal anti-inflammatory drugs decrease the risk for Alzheimer's disease? The Rotterdam Study. Neurology 1995;45:1441-5.
9. Broe GA, Henderson AS, Creasey H, et al. A case-control study of Alzheimer's disease in Australia. Neurology 1990;40:1698-707.
10. Heyman A, Wilkinson WE, Stafford JA, Helms MJ, Sigmon AH, Weinberg T. Alzheimer's disease: a study of epidemiological aspects. Ann Neurol 1984;15:335-41.
11. Graves AB, White E, Koepsell TD, et al. A case-control study of Alzheimer's disease. Ann Neurol 1990;28:766-74.
12. Li G, Shen YC, Li YT, Chen CH, Zhau YW, Silverman JM. A case-control study of Alzheimer's disease in China. Neurology 1992;42:1481-8.
13. French LR, Schuman LM, Mortimer JA, Hutton JT, Boatman RA, Christians B. A case-control study of dementia of the Alzheimer type. Am J Epidemiol 1985;121:414-21.
14. Jenkinson ML, Bliss MR, Brain AT, Scott DL. Rheumatoid arthritis and senile dementia of the Alzheimer's type. Br J Rheumatol 1989;28:86-8.
15. Beard CM, Kokman E, Kurland LT. Rheumatoid arthritis and susceptibility to Alzheimer's disease. Lancet 1991;337:1426.
16. McGeer PL, McGeer E, Rogers J, Sibley J. Anti-inflammatory drugs and Alzheimer disease. Lancet 1990;335:1037.
17. Amaducci LA, Fratiglioni L, Rocca WA, et al. Risk factors for clinically diagnosed Alzheimer's disease: a case-control study of an Italian population. Neurology 1986;36:922-31.
18. Henderson AS, Jorm AF, Korten AE, et al. Environmental risk factors for Alzheimer's disease: their relationship to age of onset and to familial or sporadic types. Psychol Med 1992;22:429-36.
19. Breitner JC, Gau BA, Welsh KA, et al. Inverse association of anti-inflammatory treatments and Alzheimer's disease: initial results of a co-twin control study. Neurology 1994;44:227-32.
20. Breitner JC, Welsh KA, Helms MJ, et al. Delayed onset of Alzheimer's disease with nonsteroidal anti-inflammatory and histamine H2 blocking drugs. Neurobiol Aging 1995;16:523-30.
21. The Canadian Study of Health and Aging: risk factors for Alzheimer's disease in Canada. Neurology 1994;44:2073-80.
22. Brooks W, Grayson D, Nicholson G, et al. APOE-E4 predicts, but anti-inflammatory drugs do not prevent, incident Alzheimer's disease in an elderly community sample. Neurobiol Aging 1998;19:Suppl 4:S140. abstract.
23. Anthony JC, Breitner JC, Zandi PP, et al. Reduced prevalence of AD in users of NSAIDs and H2 receptor antagonists: the Cache County study. Neurology 2000;54:2066-71.
24. Kukull WA, Larson EB, Stergachis A, et al. Non-steroidal anti-inflammatory drug use and risk of Alzheimer's disease. Neurology 1994;44:Suppl 2:A237. abstract.
25. Fourrier A, Letenneur L, Begaud B, Dartigues JF. Nonsteroidal anti-inflammatory drug use and cognitive function in the elderly: inconclusive results from a population-based cohort study. J Clin Epidemiol 1996;49:1201.
26. Stewart WF, Kawas C, Corrada M, Metter EJ. Risk of Alzheimer's disease and duration of NSAID use. Neurology 1997;48:626-32.

27. Henderson AS, Jorm AF, Christensen H, Jacomb PA, Korten AE. Aspirin, anti-inflammatory drugs and risk of dementia. Int J Geriatr Psychiatry 1997;12:926-30.
28. Beard CM, Waring SC, O'Brien PC, Kurland LT, Kokmen E. Nonsteroidal anti-inflammatory drug use and Alzheimer's disease: a case-control study in Rochester, Minnesota, 1980 through 1984. Mayo Clin Proc 1998; 73:951-5.
29. in 't Veld BA, Launer LJ, Hoes AW, et al. NSAIDs and incident of Alzheimer's disease: the Rotterdam Study. Neurobiol Aging 1998;19:607-11.
30. Cornelius C, Fratiglioni L, Fastbom J, Guo Z, Viitanen M, Winblad B. No support for a protective effect of NSAIDs against Alzheimer's disease from a follow-up population-based study. Neurobiol Aging 1998;19: Suppl 4:S28. abstract.
31. Hofman A, Grobbee DE, de Jong PT, van de Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. Eur J Epidemiol 1991;7:403-22.
32. Slooter AJ, Tang MX, van Duijn CM, et al. Apolipoprotein E epilson4 and the risk of dementia with stroke: a population-based investigation. JAMA 1997;277:818-21.
33. Ott A, Breteler MM, van Harskamp F, Stijnen T, Hofman A. Incidence and risk of dementia: the Rotterdam Study. Am J Epidemiol 1998; 147:574-80.
34. Ott A, Breteler MMB, van Harskamp F, et al. Prevalence of Alzheimer's disease and vascular dementia: association with education: the Rotterdam Study. BMJ 1995;310:970-3.
35. World Health Organization. Anatomical therapeutic classification (ATC) index including defined daily doses (DDD) for plain substances. Oslo, Norway: World Health Organization, 1994.
36. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-98.
37. Copeland JR, Kelleher MJ, Kellett JM, et al. A semi-structured clinical interview for the assessment of diagnosis and mental state in the elderly: the Geriatric Mental State Schedule. I. Development and reliability. Psychol Med 1976;6:439-49.
38. Roth M, Tym E, Mountjoy CQ, et al. CAMDEX: a standardised instrument for the diagnosis of mental disorder in the elderly with special reference to the early detection of dementia. Br J Psychiatry 1986;149:698-709.
39. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34: 939-44.
40. Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN International Workshop. Neurology 1993;43:250-60.
41. Cox DR. Regression models and life-tables. J R Stat Soc [B] 1972;34: 187-220.
42. Time-varying explanatory variables. In: Clayton D, Hills M. Statistical models in epidemiology. Oxford, England: Oxford University Press, 1993: 307-18.
43. Greenland S. Dose-response and trend analysis in epidemiology: alternatives to categorical analysis. Epidemiology 1995;6:356-65.
44. Checkoway H, Pearce N, Dement JM. Design and conduct of occupational epidemiology studies. II. Analysis of cohort data. Am J Ind Med 1989;15:375-94.
45. Gilbert ES, Marks S. An analysis of the mortality of workers in a nuclear facility. Radiat Res 1979;79:122-48.
46. Checkoway H, Pearce N, Hickey JL, Dement JM. Latency analysis in occupational epidemiology. Arch Environ Health 1990;45:95-100.

IMAGES IN CLINICAL MEDICINE

The *Journal* welcomes consideration of new submissions for Images in Clinical Medicine. Instructions for authors and procedures for submissions can be found on the *Journal*'s Web site at www.nejm.org. At the discretion of the editor, images that are accepted for publication may appear in the print version of the *Journal*, the electronic version, or both.