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Risk of Alzheimer's disease and duration of NSAID use

Walter F. Stewart, PhD, MPH; Claudia Kawas, MD; Maria Corrada, ScM; and E. Jeffrey Metter, MD

Article abstract—In a longitudinal study of 1,686 participants in the Baltimore Longitudinal Study of Aging, we examined whether the risk of Alzheimer's disease (AD) was reduced among reported users of aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs). In addition, we examined use of acetaminophen, a pain-relief medication with little or no anti-inflammatory activity, to assess the specificity of the association between AD risk and self-reported medications. Information on use of medications was collected during each biennial examination between 1980 and 1995. The relative risk (RR) for AD decreased with increasing duration of NSAID use. Among those with 2 or more years of reported NSAID use, the RR was 0.40 (95% confidence interval [CI]: 0.19-0.84) compared with 0.65 (95% CI: 0.33-1.29) for those with less than 2 years of NSAID use. The overall RR for AD among aspirin users was 0.74 (95% CI: 0.46-1.18), and no trend of decreasing risk of AD was observed with increasing duration of aspirin use. No association was found between AD risk and use of acetaminophen (RR = 1.35; 95% CI: 0.79-2.30), and there was no trend of decreasing risk with increasing duration of use. These findings are consistent with evidence from cross-sectional studies indicating protection against AD risk among NSAID users and with evidence suggesting that one stage of the pathophysiology leading to AD is characterized by an inflammatory process.

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Increasing evidence indicates that inflammation is involved in the pathogenesis of Alzheimer's disease (AD). Neuritic plaques, a cardinal neuropathologic marker of AD, are composed of amyloid peptides and numerous other proteins indicative of an inflammatory response.[1-8] The latter includes chronically activated microglia, complement cascade and defense proteins, cytokines, acute phase reactants, and protease inhibitors. If inflammation is part of the causal pathway leading to AD, anti-inflammatory medications may be effective in slowing disease progression or preventing onset of AD.

In population-based case-control and cross-sectional studies, evidence consistently supports an association between reported use of NSAIDs and a lower risk of AD.[9-14] However, previous studies have relied on retrospective recall or surrogate interviews for information on drug use. Moreover, the cross-sectional design of most studies raises concerns that reporting bias (e.g., cases or informants underreport use of NSAIDs) or selection bias (e.g., healthy survivor effect, higher education, and use of medical care) may explain the observed association. Finally, there is no evidence to date to support a dose-response relationship between use of NSAIDs and risk of AD.

To determine whether duration of NSAID use is

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associated with a reduced risk of AD, we used self-reported prospective data on medications from the Baltimore Longitudinal Study of Aging/National Institute on Aging (BLSA/NIA).[15] We also examined the association between AD risk and use of acetaminophen, a pain-relief medication with little or no anti-inflammatory activity, to assess the specificity of the association between AD risk and self-reported medications.

Methods. The BLSA is a prospective study of "normal aging" conducted at the Gerontology Research Center/National Institute on Aging.[15] The cohort consists of volunteers who have been continuously recruited from the Baltimore/Washington area since 1958. To date, 1,532 (64.6%) men and 839 (35.4%) women have been enrolled. The study was initially limited to men; recruitment of women began in 1978. Subjects are predominantly white (93%) and from middle to upper-middle socioeconomic brackets. Over one-half the participants attained at least a college degree. As of September 1995, 1,165 of the 2,357 enrollees (49%) were active (i.e., had an examination within 2 years), 370 (16%) were inactive (i.e., alive but no visit in 2 years), 172 (7%) had withdrawn from the study, and 650 (28%) were deceased. This report is limited to BLSA participants who were actively followed for 1 year or more between 1980 and 1995.

Participants return biennially to the Gerontology Research Center for 2.5 days of multidisciplinary evaluations.[15] All subjects over age 65 had a standardized neurologic examination and neuropsychological testing in addition to the usual BLSA protocols.[15] Neuropsychological evaluations included the Blessed IMC Test,[16] Mini-Mental State Examination,[17] Immediate and Delayed Cued Recall,[18] Boston Naming Test,[19] Controlled Verbal Fluency,[20]Trail Making Tests A and B,[21] Clock Drawing[22] and other constructions,[23] Center for Epidemiologic Studies Depression Scale,[24] Pfeffer Functional Activities Questionnaire,[25] and the National Adult Reading Test.[26] The Blessed IMC Test was administered to all subjects 55 to 64 years of age. Those with a Blessed IMC score greater than 3 were clinically examined and administered the above test battery.

Clinical diagnosis. The diagnostic status of each participant was assigned in a multi-disciplinary conference without knowledge of medication history. All information available on each subject, including the neurologic examination, neuropsychological testing, Dementia Questionnaire,[27] and personal medical records, were used to determine cognitive status. A clinical diagnosis of dementia was made according to DSM-III–R[28] criteria for dementia and the NINCDS-ADRDA[29] criteria for possible and probable AD. Age at AD diagnosis was defined as the earliest age at which the above clinical criteria were met.

Use of aspirin, NSAIDs, or acetaminophen. Information on medication use was collected during each biennial examination. Since 1979, subjects have been asked to list all medicines used since their last visit (or the last 2 years for those completing their first visit) and to include vitamins, aspirin, nasal spray, laxatives, as well as medicines for specific conditions. For each medication listed, questions were asked about the type (e.g., pill, cream), schedule of use (e.g., two times per day), frequency of use (i.e., regular use, occasional use, stopped since last visit), and duration of time used. Reported drug names were individually reviewed and coded as aspirin, NSAID, or acetaminophen. If a reported drug contained both NSAIDs and either acetaminophen or aspirin it was categorized as an NSAID.

Use of aspirin, NSAIDs, and acetaminophen were each defined as time-dependent cumulative-exposure variables. Risk of AD was assessed in relation to a binary variable for exposure and by cumulative duration of use. For each visit during which relevant drug use was reported, a subject was assumed to be exposed from the midpoint between the visit of the report and the previous visit to the midpoint between the visit of the report and the subsequent visit. If use of aspirin, NSAIDs, or acetaminophen were reported on the last visit, the subject was assumed to be exposed from the midpoint between the last visit and the previous visit to the last visit.

Analysis. The relative risk (RR) of AD associated with medication use was estimated from Cox proportional hazards regression.[30] Subjects with AD contributed person-time up to their age at diagnosis. Others were censored on the calendar date that they were lost to follow-up (i.e., inactive or deceased subjects on whom reliable information could not be obtained), died, had their last visit, or had a phone follow-up. Potential confounders examined in the regression model included education, calendar year of follow-up (a time-dependent variable in the Cox model), and gender. Education was not retained in the regression model because it was neither a significant predictor of AD risk (the BLSA cohort has a high level of education compared with other cohorts) and had no effect on the coefficients for reported use of NSAIDs, aspirin, or acetaminophen. Survival time in the Cox model was defined by age at follow-up. Use of NSAIDs increased substantially after 1979 as ibuprofen became widely available as an over-the-counter medication. Follow-up time was from 1980 to 1995, a period during which more than 80% of the use of NSAIDs and acetaminophen was reported in the BLSA.

SAS Proc PHREG was used to estimate the hazard function for AD in relation to use of aspirin, NSAIDs, and acetaminophen. Use of these specific pain medications was defined as a time-dependent binary variable (non-user versus ever user during follow-up) and a time-dependent categorical duration-of-use variable (0 years, <2 years, 2+ years). The cut-points for duration of medication use were defined to ensure an adequate number of individuals in each group for each type of drug. Relative risk estimates for aspirin, NSAIDs, and acetaminophen were derived with and without adjustment for each other.

In the analysis, lagging,[31,32] a method for assessing latency in person-time analysis, was used to determine whether there was a minimum latency between the time of reported drug use and protection against AD. By using this method, follow-up time is lagged by some assumed latency period of "y" years (e.g., 2 years) relative to exposure time. Effectively, the first y-years of follow-up are ignored. The exposure level assigned to the last year of follow-up is that which accumulated y-years earlier. We examined the effect of 0 to 5 years of lagging. Since the results did not differ substantially when exposure was lagged from 2 to 5 years, we display findings for no lagging and 2 years of lagging.

Table 1 *Profile of BLSA cohort members followed for 1 or more years between 1980 and 1995*

Variable	Category	Number of subjects		Person-years (PY) of observation		AD cases
		Number	%	Number	%	
Gender	Male	984	58.4	8,344	61.8	44
	Female	702	41.6	5,160	38.2	37
Education level	<High school	28	1.7	219	1.6	2
	High school	118	7.0	922	6.8	10
	Some college	277	16.4	2,156	16.0	12
	College degree	411	24.4	3,064	22.7	23
	More than college	852	50.5	7,143	52.9	34
Age at enrollment	<55	1,012	60.0	8,905	65.9	13
	55–64	224	13.0	1,719	12.7	13
	65–69	119	7.1	840	6.2	10
	70–74	132	7.8	935	6.9	14
	75–79	98	5.8	646	4.8	15
	80+	101	6.0	459	3.4	16
Year of enrollment	1958–64	220	13.0	2,255	16.7	13
	1965–69	182	10.8	1,920	14.2	14
	1970–74	120	7.1	1,201	8.9	2
	1975–79	239	14.2	2,664	19.7	12
	1980–84	309	18.3	3,018	22.3	27
	1985–90	414	24.6	2,129	15.8	10
	1990+	202	12.0	317	2.3	3
Duration of follow-up (yrs)* between 1980 and 1995	<5	506	30.0	1,135	8.4	20
	5–9	442	26.2	3,057	22.6	35
	10–14	654	38.8	8,052	59.6	24
	15+	84	5.0	1,260	9.3	2
Total number of visits between 1980 and 1995	1	160	9.5	312	2.3	8
	2–3	515	30.5	2,462	18.2	18
	4–5	435	25.8	3,491	25.9	29
	6–7	340	20.2	4,007	29.7	15
	8–10	236	14.0	3,232	23.9	11

* The time interval from first enrollment to last known status.
BLSA = Baltimore Longitudinal Study on Aging.

Results. A total of 1,686 BLSA participants were followed for 1 or more years between 1980 and 1995 (table 1). Eighty-one individuals were diagnosed with AD during the 16-year follow-up period. Of the 1,686 participants, 58% were men, 75% completed college, 45% were less than 55 years at enrollment, and 45% enrolled before 1980. About 80% of the subjects were followed for 5 or more years, and 90% completed two or more visits between 1980 and 1995. A total of 52% of the person-time between 1980 and 1995 occurred when participants were below age 65 (data not shown).

Since 1980, reported use of aspirin has been relatively high, ranging from 38.5 to 43.8%. Frequency of NSAID use also increased substantially after 1980 when ibuprofen was available over the counter (table 2). Reported use of NSAIDs more than tripled between 1980–84 and 1990–95. Ibuprofen accounted for 49.7% of the reported use of drugs in this category, followed in order by naproxen (15.3%), indomethacin (8.2%), fenoprofen (1.6%), flurbiprofen (1.4%), and a variety of prescription NSAIDs. Women reported use of NSAIDs on one or more visits more often than men (53% versus 31% of visits). No difference in NSAID use was found by level of education.

Overall, a statistically significant lower risk of AD (RR = 0.50; 95% confidence interval [CI]: 0.30-0.85) was associated with reported use of NSAIDs defined as a binary variable (table 3). Although the risk of AD was reduced among aspirin users, the RR was not significantly different from 1.0 (RR = 0.81; 95% CI: 0.52-1.28). There was no evidence of reduced risk of AD among reported users of acetaminophen (RR = 1.23; 95% CI: 0.73-2.07).

Lagging had little or no effect on relative risks for binary medication use variables (see table 3). In contrast, the RRs by duration of use of NSAIDs varied by lagging (table 4). In particular, the RRs for the two durations of use groups (i.e., <2 years, 2+ years) were similar when no lag was employed. In contrast, with a 2-year lag, the RRfor those with less than 2 years of reported NSAID use increased to 0.65 (95% CI: 0.33-1.29); the RR for those with 2 or more years of NSAID use decreased to 0.40 (95% CI:

Table 2 *Reported use of NSAIDs during each visit by calendar period*

Type of medication	1980–84 Number of visits	1980–84 Reported use (%)*	1985–89 Number of visits	1985–89 Reported use (%)*	1990–95 Number of visits	1990–95 Reported use (%)*
Aspirin	850	40.0	893	38.5	1,362	43.8
NSAIDs	203	9.6	411	17.7	1,023	32.9
Acetaminophen	273	12.9	358	15.5	651	21.0

* Percent of total visits during which use was reported.
NSAID = nonsteroidal anti-inflammatory drug.

0.19-0.84). The results were essentially the same for lagging up to 5 years (data not shown).

Duration of aspirin use and the risk of AD were also examined (see table 4), but no statistically significant RRs were observed. Moreover, in contrast to NSAIDs, there was no trend of decreasing risk with increasing duration of use (figure). Lagging did not affect the duration of exposure risk relationship.

Table 3 *Relative risk of AD associated with use of aspirin, NSAIDs, and acetaminophen defined as binary variables, BLSA, 1995*

Type of drug	Years of lagging	Relative risk	95% CI
NSAIDs	0	0.50*	0.30–0.85
	2	0.52†	0.30–0.91
Aspirin	0	0.81	0.52–1.28
	2	0.74	0.46–1.18
Acetaminophen	0	1.23	0.73–2.07
	2	1.35	0.79–2.30

* $p < 0.01$.
† $p < 0.05$.
NSAID = nonsteroidal anti-inflammatory drug; BLSA = Baltimore Longitudinal Study on Aging.

Table 4 *Relative risk of AD associated with use of aspirin, NSAIDs, and acetaminophen defined by duration of use, BLSA, 1995*

Type of medication	Lagging duration	Duration of use (years)	Relative risk	95% CI
NSAIDs	0	<2	0.52	0.25–1.12
		2+	0.46*	0.24–0.86
	2	<2	0.65	0.33–1.29
		2+	0.40*	0.19–0.84
Aspirin	0	<2	0.74	0.36–1.51
		2+	0.85	0.53–1.37
	2	<2	0.58	0.28–1.18
		2+	0.82	0.50–1.36
Acetaminophen	0	<2	0.87	0.40–1.93
		2+	1.58	0.86–2.93
	2	<2	1.19	0.60–2.38
		2+	1.59	0.80–3.16

* $p < 0.05$.

No association was observed between risk of AD and duration of acetaminophen use, regardless of how the variable was defined or the amount of lagging. The RR for users-versus nonusers was 1.23 (1.35 for a 2-year lag). No meaningful trend was observed by duration of use (see figure).

Discussion. Evidence from this study supports an association between NSAID use and reduced risk of AD. In the past, the relationship between NSAID use and AD was assessed in either the cross-sectional or case-control design.[9-14] The primary concern with past studies has been that the observed protective effect of NSAIDs might be due to underreporting of NSAIDs among AD cases or their surrogates compared with non-cases. In this longitudinal study of BLSA participants, information on drug use was reported prospectively, thus avoiding the limitations of past studies. To our knowledge, this is the first study to demonstrate that increasing duration of NSAID use is associated with a decreasing risk of AD.

To determine whether the observed association between AD risk and NSAIDs was specific and not simply a product of self-reported use of medications (e.g., differential reporting between AD cases in the early stages of disease and non-cases), we examined the use of acetaminophen, a drug with little or no anti-inflammatory properties. No association was found with use of acetaminophen and risk of AD, nor was there a difference in the RR by duration of use of acetaminophen.

Although aspirin use may confer some protection against AD, the RR estimate from our study was not statistically significant and no trend of decreasing risk with increasing duration of use was observed. The less consistent evidence for aspirin use may be explained by an increasing proportion of elderly individuals taking a prophylactic dose (i.e., 65 to 85 mg/day) to prevent heart disease. Prophylactic use of aspirin for venous and arterial thrombosis was first examined in clinical trials in the late 1960s and early 1970s. Aspirin use was shown to reduce the risk of recurrent myocardial infarction[33] in the early 1980s, and to reduce the risk of first-time myocardial infarction in the late 1980s.[34] Clinical recommendations for prophylactic aspirin use may have begun before 1980. Although low-dose aspirin may be sufficient to affect platelet aggregation, a low dose of 65

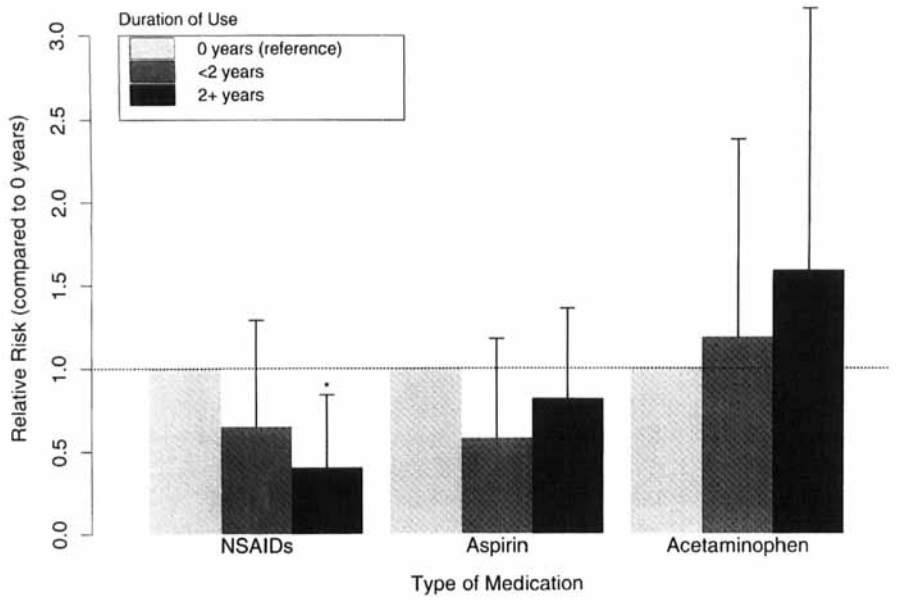

Figure. Relative risk of AD (2-year lag) by type and duration of medication use (Baltimore Longitudinal Study of Aging, 1996).

to 80 mg may not be adequate for anti-inflammatory effects in the CNS.

In this study, use of NSAIDs was reported by 26% of AD cases and 48% of non-cases. In general, the observed protective effect of NSAIDs is consistent with recent evidence regarding inflammatory activity in the pathophysiology of AD, although the specific mode of action is not clear. Neuritic plaques contain complement proteins, activated microglia, cytokines, and acute phase proteins.[7,8,34,35] Complement proteins may induce migration of microglia and, in turn, the synthesis or release of a number of inflammatory intermediaries including interleukin-1 and prostaglandins. Activated microglia may cause neurodegeneration through the chronic release of cytotoxic host defense factors and possibly other agents that may mediate this process (e.g., glutamate, nitric oxide, superoxide). NSAIDs may influence inflammation through a number of mechanisms such as interference with activation of complement proteins and the formation and release of chemical mediators that inhibit cyclooxygenase and, in turn, prostaglandin production.

One limitation of our study is that we were unable to accurately determine when and for how long a medication was used relative to the time that use was reported during a visit. We interpreted an affirmative report of medication use to mean that exposure occurred, on average, from the midpoint between the previous visit and the visit of the report and continued to the midpoint between the visit of the report and the next visit. Given this assumption, we are likely to overestimate use in some individuals and misclassify individuals with little drug use as exposed. Information on duration of drug use was not consistently obtained from subjects during each visit. Consequently, we could not examine the validity of this assumption. Moreover, we cannot state how reduction in risk is related to actual duration of use of NSAID. Rather, duration of use is a surrogate variable that allowed us to categorize individuals by their relative duration of use of NSAIDs and other drugs.

Nonetheless, we found that AD risk decreased with increasing duration of NSAID use with a lag of 2 years. In this analysis, the 2-year lag effectively ignores exposure to medications in the 2-year period before diagnosis. There are two reasons why lagging may have helped. First, to be effective, NSAIDs may have to be taken a number of years before AD diagnosis. That is, NSAIDs may not be effective in the late preclinical phase of AD (e.g., in the 2 years before diagnosis) because the disease process has either advanced beyond the inflammatory phase or deterioration is too advanced to alter the course of the disease. Misclassification of exposure may have been introduced by including information on exposure to NSAIDs near the time of diagnosis because NSAIDs used during this time may not have been effective.

Lagging may also have reduced the potential problem of reporting differences between AD cases and non-cases. Individuals in the preclinical phase of AD may tend to underreport recent drug use compared with age- and gender-matched cognitively normal individuals. In the absence of lagging, reporting bias of this type would result in a greater apparent protective benefit from NSAID use. We found no support for this type of reporting bias (see RRs in table 3 with and without lagging).

The conclusions in this study are essentially in line with those reported in a recent abstract.[36] The earlier analysis differs, however, in that it encompassed all subjects, regardless of the calendar year of follow-up. In the earlier analysis, we were concerned about the known correlation between calendar year of follow-up (before 1980 versus on or after 1980) and older age and greater risk of AD, and the inverse correlation between calendar year of follow-up and use of NSAIDs. These correlations were an inherent problem when all data were used and introduced

confounding which could not be adequately controlled. The problem of confounding was resolved by limiting the analysis to follow-up time occurring on or after 1980.

Although NSAID prophylaxis offers promise as a strategy for the prevention or delayed onset of AD, it is not possible to conclude that a protective benefit is attributable to any one particular NSAID. Randomized trials will be essential to prove that a specific NSAID confers protection. In addition, trials will be critical to identify an appropriate point of intervention based on age, cognitive status, or genetic susceptibility, as well as a medication and dose that confer protective benefits with minimal adverse events. Because chronic use of NSAIDs is associated with potentially serious adverse events (e.g., gastric irritation and bleeding, peptic ulcer disease, impaired renal function, nephrotoxicity, and in rare instances renal failure), the risk of problems associated with long-term prophylactic use of these drugs must be balanced by the risk of AD.[34,35,37] Depending on the frequency and severity of adverse events, prophylactic oral administration of some of the currently available NSAIDs may only be suitable for clinical trials of high-risk individuals.

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Assessment of CSF levels of tau protein in mildly demented patients with Alzheimer's disease

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Article abstract—CSF levels of tau protein are increased in many patients with Alzheimer's disease (AD). Studies disagree on whether the increase is found in moderate or severe AD to a greater extent than in mild AD, and in two reports there was an inverse correlation between tau levels and cognitive scores. To readdress this question, we measured CSF tau in a group of mildly impaired patients with AD (Mini-Mental State Examination [MMSE] scores ≥20/30) and compared their tau levels with those in age-comparable normal and neurologic controls. We found that the mean level of CSF tau was significantly increased in the AD group compared with the controls, and 29 of 36 patients with AD had levels that exceeded a cutoff determined in a previous study. CSF tau levels did not correlate with MMSE scores. These findings and those of previous studies show that elevated CSF tau levels are found in most patients with AD, occur early in the course of dementia, and may be useful in supporting the diagnosis of AD.

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The accuracy of the clinical diagnosis of Alzheimer's disease (AD) at centers specializing in the evaluation and treatment of dementia is over 80%, as shown by several prospective studies with autopsy follow-up.[1-5] This degree of accuracy was achieved by extensively evaluating patients and following them to demonstrate the progression of dementia over time and to obtain autopsies. However, the diagnosis may be more difficult in a more typical clinical setting, especially in individuals in the early stages of AD who may have memory complaints that could be compatible with aging alone or in patients who have not been observed longitudinally. To assist in the diagnosis of AD, biological markers have been sought systemically and in CSF. An important question for any potential biological marker is whether its use helps to identify patients early in the course of AD.

Eleven studies, involving over a thousand subjects, have all concluded that CSF levels of the microtubule associated protein tau are significantly increased in subjects with AD compared with nondemented controls or with patients with other neurologic diseases or dementias.[6-16] Tau is the major constituent of neurofibrillary tangles (NFTs), which are markers of neuronal pathology in AD. In clinical-pathologic studies, counts of NFTs correlate with the severity of dementia in AD. The published reports on CSF tau do not agree on whether tau levels correlate with the level of cognitive impairment. If CSF tau elevation identifies mainly mid- to late-stage AD patients, as suggested by two reports in which tau levels correlated inversely with Mini-Mental State Examination (MMSE) scores,[10,13] its usefulness is restricted to this group of patients. Conversely, if increased CSF tau levels are present in very early stages of AD, the clinical utility should be much higher. Since each previous study included relatively few subjects with mild levels of dementia, we analyzed CSF tau levels in a group of patients with AD with MMSE scores of 20 (out of 30) or higher.

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