American Journal of Epidemiology

Vol. 143, No. 7
Printed in U.S.A.

Aspirin Use and Cognitive Function in the Elderly

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Decline in cognitive function in the elderly is common and represents a major clinical and public health concern. Aspirin may reduce the decline in cognitive function by influencing multi-infarct dementia, but data are sparse. The East Boston Senior Health Project is a population-based cohort study that enrolled 3,809 community-dwelling residents aged 65 years and older in 1982–1983 and followed them with home visits every 3 years until 1988–1989. Trained interviewers assessed cognitive function by using the Short Portable Mental Status Questionnaire and assessed medication use, including over-the-counter drugs. Response to the Short Portable Mental Status Questionnaire was scored as high, medium, or low, and decline was defined as transition to a lower category. Participants who used drugs containing aspirin in the 2 weeks prior to the interview were classified as aspirin users. Multiple logistic regression was used to obtain adjusted odds ratios and their 95% confidence intervals for decline of cognitive function. The estimating equation approach was used to adjust the standard errors for repeated measurements. Aspirin users had an odds ratio for cognitive decline of 0.97 (95% confidence interval 0.82–1.15). Low frequency of aspirin use (less than daily) was associated with an odds ratio of 0.87 (95% confidence interval 0.69–1.09). Although no substantial effect was observed, the data are also compatible with a modest benefit of aspirin, especially with intermittent use, on decline of cognitive function. Concern about small residual biases from self-selection or confounding suggests that randomized trials will be necessary to provide definitive data on this question. *Am J Epidemiol* 1996;143: 683–91.

aging; Alzheimer's disease; aspirin; cognition; cohort studies; dementia, multi-infarct; incidence

Two to four million Americans are estimated to suffer from dementia, and of those, about 1.5 million are thought to have severe dementia requiring constant care, either in institutions or in their homes (1, 2). Assessment is difficult in noninstitutionalized populations, so precise estimates of the prevalence of dementia are uncertain. The prevalence increases with age, with estimates ranging from 24 percent (3) to over 47 percent (4) in those aged 85 years and above. The continuing aging of the US population will yield large increases in numbers of affected individuals. The high prevalence, important implications, and concern about availability and cost of care result in dementia being one of the major health problems for the elderly.

Despite extensive work, no major modifiable risk factor has been identified for senile dementia of the Alzheimer's type. Recent publications have focused on the association between the effect of cholinesterase inhibitors (5–7) as well as anti-inflammatory drug use (8–10) on cognitive decline. Multi-infarct dementia is the second most common cause of dementia, comprising up to 50 percent of dementias in the elderly (3, 11–14). High blood pressure is its major risk factor (15), whose alteration may be beneficial (16).

During the past decade, the anti-aggregatory properties of acetylsalicylic acid (aspirin) have been shown to prevent transient cerebral ischemic attacks and atherothrombotic strokes (17–19). Since the pathology of multi-infarct dementia involves major as well as minor cerebral infarctions, aspirin could potentially reduce its occurrence or alter its course. This hypothesis has been addressed in one small randomized trial that enrolled subjects at high risk of multi-infarct

Received for publication March 8, 1995, and in final form September 6, 1995.

Abbreviations: CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; SPMSQ, Short Portable Mental Status Questionnaire.

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dementia (20). Cerebral perfusion values and cognitive performance scores were significantly improved among aspirin-treated subjects at each of three annual follow-up evaluations (21), but the study was not placebo controlled, and this finding has not been replicated so far.

The aim of the present analysis is to examine in prospective data whether aspirin use affected decline of cognitive function among persons aged 65 years and older in East Boston, Massachusetts, by using data gathered in the Established Populations for the Epidemiologic Studies of the Elderly project.

MATERIALS AND METHODS

Population

The study population is 3,809 elderly residents of East Boston who participated in the Senior Health Project. East Boston is a geographically defined, urban, working-class community of approximately 32,000 persons and is one of four centers of the US National Institute on Aging Established Populations for Epidemiologic Studies of the Elderly project. Beginning in 1982, a community census was performed. All dwelling units were visited by interviewers to ascertain the identity, sex, and age of each resident. All noninstitutionalized individuals aged 65 years or older were invited to participate in the study by responding to a structured questionnaire administered in their homes by trained interviewers. Virtually all (99.8 percent) households in the community were enumerated in the census.

Of the 4,497 eligible residents, 3,809 (84.7 percent) participated in the baseline study and form the cohort. The cohort was followed by in-home interviews and examinations after 3 and 6 years and by telephone interview in the intervals. Of the 3,223 participants alive at the time of the 3-year follow-up, 2,773 (86.0 percent) had in-person interviews including cognitive assessment. Of the 2,556 participants alive at the time of the 6-year follow-up, 2,023 (79.1 percent) had in-person interviews with cognitive assessment. For this analysis, we used the in-home interviews, and the follow-up period was divided into two 3-year intervals (baseline to the 3-year follow-up and the 3-year follow-up to the 6-year follow-up).

Assessment

Medication use was assessed at baseline and at the follow-up examinations by an interviewer after examination of all medication containers for prescription and nonprescription drugs taken during the previous 2 weeks. In addition, the frequency of administration for each medication was assessed and grouped according to the number of pills taken per day. Drugs taken less than once per day were assigned to an "as needed" category. All identified drugs were coded using an updated version of the Drug Product Information Coding System (22). Codes of medications containing acetylsalicylic acid (aspirin) were grouped by using the 1982, 1986, and 1993 editions of the *Physicians' Desk Reference* (23), as well as other sources. Since the possible effect of aspirin was hypothesized to be more dependent on frequency than on dose, mean daily dose was not used in the analyses.

Cognitive function was measured at each interview by use of a memory test (East Boston Memory Test) and a short portable mental status questionnaire (SPMSQ). The nine-item SPMSQ was derived from an earlier instrument by Kahn et al. (24) and is similar to Pfeiffer's Short Portable Mental Status Questionnaire (25) (the question "What is the name of this place" was dropped because pretesting revealed that participants objected to being asked this question in their homes). Response was scored into three categories: high (8–9 correct answers), medium (6–7 correct answers), and low (5 or fewer correct answers). The sensitivity and specificity of both tests has been estimated by using a stratified sample of 467 participants who underwent detailed clinical evaluation including neurologic, neurophysiologic, psychiatric, and laboratory examinations, which categorized participants as having no impairment, mild impairment, or moderate/severe impairment (26). With the middle SPMSQ and mild impairment categories excluded, sensitivity of the SPMSQ for identifying moderate/severe cognitive impairment was 85 percent and specificity was 96 percent (27).

The following variables were thought to be potential confounders because of possible associations with aspirin use or cognitive decline: age (five 6-year categories), sex, education (0, 1–6, 7–8, 9–11, and 12 or more years of formal schooling), obesity (body mass index > 29.5 kg/m^2), hypertension (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 95 mmHg, based on the mean of three seated measurements, or taking antihypertensives), current smoking (yes/no), impaired mobility (any negative answer to one of the following questions: can you do work around the house, can you climb stairs without help, and can you walk half a mile), no regular physical activity (no regular exercise at least once a week and not taking frequent walks in good weather), alcohol use (grams of pure alcohol calculated from the number of bottles of beer, glasses of wine, and drinks of liquor consumed in the month prior to the interview according to the Framingham classification (28); categorized into 0, 15 g a day or less, and more than 15 g a day),

diabetes (two categories: self-report without medication; taking hypoglycemics), history of myocardial infarction (self-report), angina (according to the Rose questionnaire (29)), headache (any headache within the year prior to the interview), joint pain (pain in any joint on most days for at least 1 month in the year prior to the interview), and symptoms of depression (four or more affirmative answers to a shorter form of the Center for Epidemiologic Studies Depression Scale symptoms index (30)). Whenever values of these variables were missing at the beginning of the second interval, those from baseline were used, if available. Current values of at least one covariate (frequently body mass index) were missing at the beginning of the second interval for 219 participants who had values for these variables at baseline. If these second intervals were deleted from analyses, estimated aspirin effects changed little, although their standard errors increased slightly.

Analysis

We used direct standardization on age and sex with weights based on the overall number of individuals in each stratum to calculate the distribution of possible confounders at baseline according to aspirin use. Differences in rates of characteristics between aspirin users and nonusers and 95 percent confidence intervals also used these weights. For primary analyses, decline in cognitive function, defined as a transition in SPMSQ categories (high to medium or low, or medium to low) separately in each 3-year period, was the dependent variable with aspirin use as the independent variable. Subjects with low cognitive function at the beginning of an interval could not decline on this scale and were therefore excluded from these analyses for the corresponding interval. Stratum-specific rates of decline by aspirin use and SPMSQ category at the beginning of the interval were calculated. We used Mantel-Haenszel estimates for the odds ratios and their 95 percent confidence intervals adjusted for age, sex, and SPMSQ category at the beginning of the interval.

Multiple logistic regression was then used to estimate odds ratios and their 95 percent confidence intervals as measures of the relative proportion of decline in aspirin users versus nonusers after possible confounders were entered as covariates. We evaluated confounding by introducing variables into the model and examining the change in the aspirin parameter estimate (31). Effect modification of the association of aspirin with decline in cognitive function was tested by introducing interaction terms between aspirin use and all covariates. Since individuals could contribute information on two intervals and these changes might be correlated, the estimating equation approach was used to adjust the standard errors for repeated measurements (32). We used a score test (33) to compare rates of cognitive decline across categories formed by frequency of aspirin use (never, as needed, 1–2 per day, more than two per day).

As an alternative analytic strategy that considers change in the original nine-level scale of the SPMSQ, we used a normal scores transformation to obtain a measure of change independent of the initial score (34). This was done by first ranking the individual differences between baseline and 3-year follow-up (defined as 3-year level minus baseline level of SPMSQ) combined with those between 3- and 6-year follow-up (defined as 6-year level minus 3-year level of SPMSQ) separately within each level of SPMSQ score at the beginning of an interval. Second, these ranks were transformed to the value, or normal score, that corresponds to the percentile of a normal distribution with mean 0 and variance 1. These normal scores were then used as the dependent variable in multiple linear regression models. These models included the same independent variables as the logistic regression models to control for confounding. Additional analyses used age, years of formal schooling, systolic pressure, and body mass index as continuous variables. However, results changed little, so these additional analyses are not shown. Because, as before, individuals could contribute changes during each of two intervals that might be correlated, we used a general linear model, as described by Jennrich and Schluchter (35), to estimate these effects. We assumed an unstructured covariance matrix for the repeated measures and obtained maximum likelihood estimates from the BMDP program 5V (36).

Because nonsteroidal anti-inflammatory drugs (NSAIDs) may have effects on cognitive function that are similar to aspirin, we estimated effects in individuals not using NSAIDs in addition to analyses that controlled for use of these drugs. Since values of cognitive decline may more likely be missing in those who actually declined, we assessed the impact of missing data in a separate logistic regression model, which treated individuals with partial or proxy interview at the end of each 3-year interval as having declined in cognitive function. We also looked at the association between aspirin use and participation with cognitive assessment over both intervals by using an age-and sex-adjusted logistic regression. To provide some evaluation of regular aspirin use, we fitted a separate logistic regression model among individuals whose aspirin use did not change between baseline and the 3-year follow-up and examined the impact of aspirin

use at both times on decline from the 3-year follow-up to the 6-year follow-up.

We also performed additional stratified analyses. Because it may be difficult to control for the effects of preexisting cardiovascular disease on both aspirin use and the risk of death, we fitted separate multivariate models in those with cardiovascular disease (history of angina, myocardial infarction, stroke, or current use of digoxin or loop diuretics) and those without any of these conditions. Separate multivariate models were also fitted among those with a high level of SPMSQ at the beginning of an interval and among those with a medium level.

RESULTS

In table 1, the follow-up and mental status categories are presented for the entire cohort of 3,809 elderly residents of East Boston. At baseline, the SPMSQ was administered to 3,631 individuals (95.3 percent). The cognitive function of 178 subjects could not be assessed at baseline because they had only partial interviews or a proxy was interviewed. Three years later, at the 3-year follow-up, the SPMSQ was administered to 2,773 individuals (86.0 percent of all living). After 6 years (6-year follow-up), the SPMSQ was administered to 2,023 individuals (79.1 percent of all living).

The number of cohort members alive and the proportion participating in the cognitive function assessment are presented in table 2 by baseline age and time of evaluation. Participation declined uniformly from 98 percent at baseline in the youngest two age groups to 42 percent at the 6-year follow-up in the oldest.

Of the 3,793 (99.6 percent) individuals with available information on medication use at baseline, 975 (25.7 percent) took aspirin in the 2 weeks prior to the interview and 2,818 did not; 477 (12.6 percent) used aspirin less than daily (as needed), 294 (7.8 percent) took one to two aspirin a day, and 204 (5.4 percent) took more than two aspirin a day. In table 3, we present the distribution of various potential confounding factors according to aspirin use at baseline. The age distribution of those taking aspirin is similar to the distribution of those not taking aspirin. The proportion of women is higher in the group taking aspirin than in the group not taking aspirin. Obesity, impaired mobility, not having regular physical activity, light alcohol consumption, angina, headache, joint pain, and depression are all more common in aspirin users than in nonusers. The opposite is seen for the proportion of individuals taking acetaminophen, which is lower in aspirin users than in nonusers, indicating differential use of these drugs. All other variables were comparable between aspirin users and nonusers.

Table 4 presents the number of individuals with high or medium SPMSQ category (at risk of decline) at baseline or the 3-year follow-up as well as the proportions who declined in cognitive function over the first and second 3-year periods. Only individuals with cognitive function assessed at the beginning and the end of an interval are included in these analyses. Combining both categories at baseline, 30.6 percent of 1,852 individuals not taking aspirin declined in cognitive function, compared with 31.8 percent of 679 taking aspirin. Aspirin use was therefore associated with a 7 percent increased risk of decline in the interval from baseline to the 3-year follow-up ($p = 0.49$). The corresponding numbers for the second interval (from the 3-year follow-up to the 6-year follow-up) are very similar: 28.1 percent of 1,305 not taking aspirin declined in cognitive function compared with 27.1 percent of those taking aspirin, leading to a 7 percent decreased risk of decline in aspirin users ($p = 0.56$).

TABLE 1. Description of follow-up and cognitive function categories in a population-based cohort of the elderly, East Boston Senior Health Project, 1982–1989

	Baseline (1982–1983)	3-year follow-up (1985–1986)	6-year follow-up (1988–1989)
SPMSQ* category			
High	2,002	1,383	1,061
Medium	1,199	974	697
Low	430	416	265
Total with SPMSQ measured	3,631	2,773	2,023
Partial/proxy interview	178	236	325
Refused/lost	0	214	208
Deceased	0	586	1,253
Total	3,809	3,809	3,809

* SPMSQ, Short Portable Mental Status Questionnaire.

TABLE 2. Participation in cognitive function assessments by baseline age and time of evaluation, East Boston Senior Health Project, 1982–1989

Age at baseline (years)	Baseline (1982–1983)		3-year follow-up (1985–1986)		6-year follow-up (1988–1989)	
	No.*	%†	No.*	%†	No.*	%†
65–70	1,541	98	1,402	90	1,221	84
71–76	1,124	98	987	89	810	82
77–82	669	93	525	83	365	71
83–88	344	88	237	68	129	47
89–103	131	76	72	46	31	42
Total	3,809	95	3,223	86	2,556	79

* Number of cohort members originally in this age group who were alive at this evaluation.

† Percent of those alive who completed the Short Portable Mental Status Questionnaire.

TABLE 3. Distribution of various potential risk indicators, according to aspirin use, in a population-based cohort of the elderly, East Boston Senior Health Project, 1982–1989

	No aspirin	Aspirin	Mean difference	95% CI*
Interviewed (no.†)	2,818	975		
Age (years) (%)				
65–70	40.6	39.9		
71–76	29.2	30.8		
77–82	17.6	17.3		
83–88	9.2	8.4		
88–103	3.4	3.6		
Women (%)	60.5	66.1		
With potential risk indicators (%)‡				
Less than 9 years of formal education	51.5	53.5	2.1	−1.5 to 5.6
Obesity (body mass index§ >29.5)	23.7	27.5	3.8	0.5 to 7.1
Hypertension (blood pressure ≥160/95 mmHg or taking antihypertensive medication)	56.8	59.0	2.2	−1.5 to 5.8
Current smoking	19.5	19.9	0.3	−2.5 to 3.1
Impaired mobility	47.9	53.4	5.5	2.1 to 9.0
No regular physical activity	45.9	50.2	4.3	0.8 to 7.7
Alcohol use (≤15 g/day)	33.0	36.4	3.5	0.0 to 6.9
Alcohol use (>15 g/day)	20.4	21.7	1.4	−1.5 to 4.2
Diabetes (taking antiglycemics)	9.7	8.0	−1.6	−3.7 to 0.4
Myocardial infarction (self-report)	10.5	11.4	0.9	−1.4 to 3.2
Angina (Rose questionnaire)	4.3	7.1	2.9	1.1 to 4.6
Headache	42.3	58.0	15.8	12.2 to 19.3
Joint pain	31.9	43.3	11.3	7.8 to 14.9
Depression	26.0	32.4	6.4	2.9 to 9.9
SPMSQ* medium category	31.4	32.0	0.6	−2.8 to 4.0
SPMSQ low category	11.4	10.9	−0.5	−2.6 to 1.7
Taking other NSAIDs*	9.4	10.9	1.5	−0.7 to 3.7
Taking acetaminophen	19.0	9.0	−10.0	−12.3 to −7.7

* CI, confidence interval; SPMSQ, Short Portable Mental Status Questionnaire; NSAIDs, nonsteroidal anti-inflammatory drugs.
† Number in each aspirin category at baseline (16 with missing values).
‡ Adjusted for age (6-year categories) and sex.
§ Weight (kg) divided by height (m^2).

In table 5, we present the results of the multivariate models. The second and third columns refer to models that included individuals using NSAIDs, whereas the fourth and fifth columns exclude those taking NSAIDs. Effects in the latter are slightly more pronounced and are presented here. The models are based on 2,262 (89.4 percent of all eligible) individuals in the first and 1,657 (95.0 percent of all eligible) individuals in the second interval because of missing covariates. For any aspirin use versus none, aspirin users had a 6 percent decreased risk of decline in cognitive function ($p = 0.50$). When different frequencies of aspirin use were examined, a low frequency of use (as needed) was associated with a 16 percent reduction in risk of cognitive decline ($p = 0.15$). In contrast, a higher frequency of use (more than two aspirin per day) was associated with a 31 percent increase in risk of decline ($p = 0.14$). Taking one to two aspirin per day was associated with a 9 percent reduction in risk of decline ($p = 0.52$). Testing the equality of all categories simultaneously revealed a nonsignificant effect of the aspirin frequencies in the model that excluded NSAIDs users ($p = 0.15$).

In table 6, we present the effect of aspirin use on change in cognitive function over 3 years based on the normal scores transformation of changes in SPMSQ. Estimated effects above zero represent a change in cognitive function that is above the median after 3 years for a given initial level, whereas results below zero represent changes below the median. A value of zero therefore stands for a median change and does not mean no change. The results are very similar to those shown in table 5. Aspirin users have a slight, nonsignificant increased cognitive function compared with

TABLE 4. Proportions with decline in cognitive function according to aspirin use, baseline cognitive function, and observation period, East Boston Senior Health Project, 1982–1989

	No aspirin		Aspirin		OR*	95% CI*
	No.	% decline	No.	% decline		
Decline from baseline to the 3-year follow-up						
SPMSQ† high category	1,200	36.4	433	37.0	1.05	0.83–1.32
SPMSQ† medium category	652	19.9	246	22.8	1.13	0.78–1.64
Total‡	1,852	30.6	679	31.8	1.07	0.88–1.30
Decline from the 3-year follow-up to the 6-year follow-up						
SPMSQ† high category	799	35.9	272	33.5	0.89	0.66–1.19
SPMSQ† medium category	506	15.6	167	16.8	1.05	0.65–1.71
Total‡	1,305	28.1	439	27.1	0.93	0.72–1.19

* Odds ratios (OR) and confidence intervals (CI) adjusted for age and sex (Mantel-Haenszel estimates).
† SPMSQ, Short Portable Mental Status Questionnaire. Includes only individuals with valid categories at beginning and end of interval.
‡ Crude % decline. OR and 95% CI adjusted for age, sex, and SPMSQ category at the beginning of interval (Mantel-Haenszel estimates).

TABLE 5. Multivariate odds ratio of decline in cognitive function according to aspirin use, East Boston Senior Health Project, 1982–1989

	Including NSAIDs* users (n = 2,386; 3,919 3-year intervals)		Excluding NSAIDs users (n = 2,292; 3,550 3-year intervals)	
	OR†	95% CI‡	OR†	95% CI‡
Use of aspirin				
None	1.00	Referent	1.00	Referent
Any	0.97	0.82–1.15	0.94	0.79–1.12
Use of NSAIDS				
None	1.00	Referent		
Any	0.89	0.69–1.16		
Aspirin use§				
As needed	0.87	0.69–1.09	0.84	0.66–1.06
1–2 per day	0.95	0.72–1.26	0.91	0.68–1.22
More than 2 per day	1.30	0.93–1.81	1.31	0.92–1.88

* NSAIDs, nonsteroidal anti-inflammatory drugs.
† Odds ratio (OR) combining both 3-year periods, adjusted for age (6-year categories), sex, education (five levels), obesity, hypertension, smoking, mobility, physical activity, alcohol use (three levels), diabetes (three levels), angina, headache, joint pain, depressive symptoms, acetaminophen use, and Short Portable Mental Status Questionnaire category at start of intervals.
‡ Confidence interval (CI) adjusted for repeated measurements using the estimating equation approach.
§ Aspirin use in the 2 weeks prior to the interview.

nonusers that is slightly more pronounced with a low frequency of use and is again nonsignificant.

None of the interaction terms between aspirin use and the covariates used in the models was significant, indicating no major effect modification. Additional models that assumed that individuals with partial or proxy interview declined in cognitive function and models that considered aspirin use at both baseline and 3-year follow-up (11 percent were aspirin users at both times) show results very similar to those presented in table 5 (data not shown). When categorizing missing cognitive function information at the end of each interval as a decline in cognitive function or aspirin consumption according to information at baseline and the 3-year follow-up, aspirin use was associated with a 3 percent ($p = 0.70$) or 2 percent ($p = 0.92$) reduction in risk of cognitive decline, respectively.

Separate multivariate analyses of those with and those without cardiovascular disease found a nonsignificant ($p = 0.23$) 12 percent decreased risk of decline in cognitive function associated with aspirin use in those without cardiovascular disease (odds ratio (OR) = 0.88, 95 percent confidence interval (CI) 0.72–1.08), whereas among those with cardiovascular disease, aspirin use was associated with a nonsignificant ($p = 0.28$) 20 percent increased risk of decline in cognitive function (OR = 1.20, 95 percent CI 0.87–1.66). Multivariate analyses stratified by high or medium level of SPMSQ at the beginning of an interval found a slight reduction in risk of decline associated with aspirin use among those with initially high SPMSQ (OR = 0.91, 95 percent CI 0.74–1.11) and a slight increase in risk of decline among those with initially medium SPMSQ (OR = 1.14, 95 percent CI 0.82–1.59).

DISCUSSION

The East Boston cohort appears to be well suited to study the influence of aspirin use on cognitive decline in the elderly. It is a population-based study of the elderly who are at the highest risk of the outcome.

TABLE 6. Predicted 3-year normalized change in cognitive function according to aspirin use, East Boston Senior Health Project, 1982–1989

	Including NSAIDs* users		Excluding NSAIDs users	
	Change†	95% CI‡	Change†	95% CI‡
Aspirin use§				
None	0.0	Referent	0.0	Referent
Any	0.008	−0.052 to 0.068	0.011	−0.050 to 0.072
NSAIDs use				
None	0.0	Referent		
Any	0.081	−0.008 to 0.17		
Aspirin use§				
None	0.0	Referent	0.0	Referent
As needed	0.037	−0.042 to 0.116	0.048	−0.032 to 0.129
1–2 per day	0.014	−0.082 to 0.110	0.012	−0.086 to 0.111
More than 2 per day	−0.078	−0.198 to 0.041	−0.087	−0.208 to 0.034

* NSAIDs, nonsteroidal anti-inflammatory drugs.

† Predicted normalized change combining both 3-year periods in a multivariate regression model, adjusted for age (6-year categories), sex, education (five levels), obesity, hypertension, smoking, mobility, physical activity, alcohol use (three levels), diabetes (three levels), angina, headache, joint pain, depressive symptoms, acetaminophen use, and Short Portable Mental Status Questionnaire category at start of interval.

‡ Confidence interval (CI) from the multivariate regression model.

§ Aspirin use in the 2 weeks prior to the interview.

Detailed information on medication use and cognitive function was assessed three times over a 6-year interval, allowing evaluation of prospective data. The tests used to assess cognitive function have been validated by extensive medical examination using a sample of the cohort, many possible risk factors have been ascertained, and the follow-up is excellent because of extensive efforts and a stable population.

Overall, aspirin users did not have a significantly reduced risk of cognitive decline, and 95 percent confidence intervals excluded increases or decreases of risk beyond 20 percent. Exploratory analyses of the frequency of aspirin use and cognitive decline showed variable effects, but these were also consistent with chance.

These data must be interpreted with caution. Measurement error regarding long-term aspirin use as well as decline in cognitive function is likely to be present, and the direction and magnitude of the bias introduced is not always obvious. Aspirin use in the 2 weeks prior to each observation period is used as exposure. Since medication use was assessed by in-home interviewers asking explicitly for aspirin and other over-the-counter drugs and cross-checking this information with drugs actually present in the medicine cabinet, aspirin use in this period is likely to be accurate. On the other hand, the possible effect of aspirin on cognitive decline is likely to be most pronounced in subjects with chronic aspirin use (preventing more mini-infarctions over time), which has not been assessed in this cohort. Although long-term use of analgesics, including salicylates, has previously been assessed successfully over a 10-year period (37), the assessment of aspirin use over intermediate time periods is at least impractical, if not impossible. This is due to the widespread intermittent use of the drug as well as the lack of prescription information. Misclassification is likely to be nondifferential and therefore will likely bias the results toward observing no association. A separate multivariate model classifying aspirin exposure by using information from baseline and the 3-year follow-up interviews (present if aspirin was used at both baseline and the 3-year follow-up and absent if aspirin use was absent at both interviews) showed very similar results with the limitation that it is based on many fewer individuals.

On the other hand, measurement error regarding decline in cognitive function is very likely. The shortcomings of assessments of cognitive function by brief screening tools, especially when administered outside the hospital setting, are well known (38, 39). In this context, it is important to consider the sensitivity and specificity of the SPMSQ coding in members of the cohort who underwent detailed medical examination. Both were found to be very high (85 and 96 percent, respectively). Although a high specificity is usually regarded as sufficient to avoid major bias of ratio measures in a cohort study, in this setting with a high prevalence of disease the number of false negatives resulting from a lower sensitivity might be equally or even more important. Pfeiffer (25) found the reliability of the SPMSQ to be good with test-retest correlations of 0.82 and 0.83, respectively, when two groups of elderly subjects were given the SPMSQ twice at ap-

proximately 4-week intervals. Misclassification is likely to be nondifferential and would therefore tend to bias the results toward observing no association. On the other hand, we found strong associations of known risk factors with cognitive decline (data not shown), making major nondifferential misclassification unlikely.

Since decline in cognitive function is likely to be a cause of missing data, the occurrence of missing data is an inherent problem in studies regarding cognitive function in the elderly. Since missing data in the outcome measure can be assumed to be positively associated with cognitive decline, they are not random. The analyses presented are based on individuals without missing values and might be biased. We estimated the extent of this bias in two ways. First, we found only a modest, nonsignificant association between aspirin use at the beginning of each interval and subsequent participation with cognitive assessment at the end of the interval (combining both intervals, age- and sex-adjusted odds ratio of participation at the next examination associated with aspirin use = 1.13; 95 percent CI 0.99–1.29) (data not shown). Second, we ran a separate multivariate model, assuming that individuals with partial or proxy interview (SPMSQ category missing) at the end of a 3-year period actually had a decline in cognitive function. A similar approach has been used previously in a longitudinal study (40). The aspirin effect is almost identical in this model (data not shown), indicating that no major bias is introduced by restricting the analysis to those with assessment of cognitive function. Furthermore, the strongest predictor of missing data on cognitive function, i.e., age (table 2), is not associated with aspirin use (table 3).

Any association between aspirin use and cognitive decline is very likely confounded by a variety of known and unknown factors. Strong associations of aspirin use and factors possibly related to cognitive decline were found in this study (table 2) and were controlled for in the multivariate analyses. Nevertheless, many of the cutoff points chosen are subjective, and these factors themselves are not measured without error, leaving the possibility for residual confounding. On the other hand, factors known to be the strongest predictors of cognitive function testing, such as age and education, were adequately controlled for in the analyses. Furthermore, an additional model that used continuous variables instead of the categorical ones gave very similar results (data not shown). Some of the factors, such as mobility, might be on the causal pathway for some of the effects of aspirin on cognitive decline. Since the causal pathway is not completely clear and is most probably complex, overcontrolling cannot be excluded in this context.

When all of the above considerations are taken into account, this study indicates little benefit of aspirin use on decline in cognitive function in an elderly population, although the data are consistent with a possible small beneficial effect associated with intermittent use. On the other hand, the above considerations also indicate that the hypothesis is unlikely to be proven or rejected in an observational setting since the amount of uncontrollable confounding or bias in any observational study is similar to the magnitude of a plausible small-to-moderate benefit of 20–30 percent (41). A randomized trial in this age group will therefore be needed to answer the question definitively.

ACKNOWLEDGMENTS

Supported by a contract from the National Institute on Aging (AG02107). Dr. Stürmer was a recipient of a training grant from the Swiss National Science Foundation (823B-33287)

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