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NSAIDs, Aspirin, and Cognitive Function in the Baltimore Longitudinal Study of Aging

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Abstract

Objective—To examine the relations of non-aspirin, nonsteroidal anti-inflammatory drug (NSAID) and aspirin use to age-related change in multiple domains of cognitive function among non-demented, community-dwelling individuals.

Design—Longitudinal with measures obtained on one to eighteen occasions over up to 45 years.

Setting—General community.

Participants—A volunteer sample of up to 2,300 participants from the Baltimore Longitudinal Study of Aging, free of diagnosed dementia.

Measurements—At each visit, reported NSAID or aspirin use (yes/no) and tests of verbal and nonverbal memory, attention, perceptuo-motor speed, confrontation naming, executive function, and mental status.

Results—Mixed-effects regression models revealed that NSAID use was associated with less prospective decline on the Blessed Information-Memory-Concentration (I-M-C) Test - a mental status test weighted for memory and concentration ($p < .0001$), and Part B of the Trail Making Test - a test of perceptuo-motor speed and mental flexibility ($p < .05$). In contrast, aspirin use was related to greater prospective decline on the Blessed IMC Test ($p < .05$), and the Benton Visual Retention Test - a test of visual memory ($p < .0001$).

Conclusions—Consistent with studies of incident dementia, non-demented NSAID users displayed less prospective decline in cognitive function, but on only two cognitive measures. In contrast, aspirin use was associated with greater prospective cognitive decline on select measures,

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potentially reflecting its common use for vascular disease prophylaxis. Effect sizes were small; thus clinical significance is questioned although overall public health significance may be meaningful.

Keywords

NSAIDs; aspirin; cognitive function; neuropsychology

Introduction

Alzheimer's disease and vascular dementia commonly co-occur (1), and inflammatory mechanisms may play a critical role in the pathogenesis of both diseases (2). Use of nonsteroidal anti-inflammatory drugs (NSAIDs) other than aspirin (referred to hereafter as NSAID use) has been associated with a reduced incidence and prevalence of Alzheimer's disease in a recent meta-analysis of available data (3). All subtypes of NSAIDs appear to confer similar benefit (4). In't Veld concluded that NSAID use conferred protection against Alzheimer's disease but not vascular dementia (5). Aspirin, which is frequently prescribed for vascular disease prophylaxis, and which also has strong anti-inflammatory properties, may also confer protection with respect to Alzheimer's disease (6,7,8). However, some studies have found no benefit (9,10,11), or even increased incidence of Alzheimer's disease (12) or vascular dementia (13) among aspirin users.

Early neuroprotection may be beneficial to both types of disease pathogenesis. Yet, relatively little is known about the potential cognitive benefit of NSAID or aspirin use among non-demented persons or on specific domains of cognitive function. In that regard, diminished prospective decline has been found in conjunction with NSAID or aspirin use on the Short Portable Mental Status Questionnaire (SPMSQ) - a mental status test (14,15). Recent data revealed a relation between NSAID use and less prospective decline on a different mental status test (i.e., the Modified Mini Mental State Examination or 3MS), but only when use was begun in midlife rather than older age (16). Further, this association was more pronounced among persons having one or more APOE e4 alleles. Cross-sectional relations between aspirin and better cognitive function have also been noted (17).

Here, we examined both cross-sectional and longitudinal relations of both NSAID and aspirin use to cognitive function among non-demented participants in the Baltimore Longitudinal Study of Aging (BLSA). A prior report from the BLSA noted that the relative risk of Alzheimer's disease among NSAID users was one-half that of non-users (11). Following exclusion of persons with diagnosed dementia, we examined prospective relations of NSAID and aspirin use to performance on two commonly used mental status tests, and on tests reflecting a greater number of domains of cognitive function than examined previously - verbal and nonverbal memory, attention, perceptuo-motor speed, executive functions, and language.

Methods

Participants

The BLSA is a prospective study of community-dwelling volunteers initiated by the National Institute on Aging in 1958. Approximately every two years, participants visit the Gerontology Research Center in Baltimore for medical, psychological, and cognitive testing (18). Beginning in 1986, participants 60 years and older were administered a more extensive neuropsychological test battery. Therefore, the majority of tests examined herein were available only during visits occurring on or after January 1, 1986. Two thousand five hundred forty-seven BLSA participants [ages 17 to 102; M=52.3 ($\pm$ 17.7)] were available for potential inclusion in the present analyses. We excluded persons with dementia (n=247; see reference 19 for determination of dementia status) at all assessment visits, both prior to and after

diagnosis. Persons with stroke or renal failure were censored from the visit at which diagnosis was recorded. Two thousand three hundred participants (1,381 men and 919 women) were included in the analyses. Baseline characteristics of participants are presented in Table 1. Because the BLSA utilizes continuous enrollment procedures, participants have differential start times in the project, numbers of visits, and follow-up intervals. The total number of participants by number of visits is listed in Table 2. These participants had an average of 3.8 (± 3.4 ; range = 1 to 18) visits, and the average time between visits was 3.4 (± 1.7) years. Over the course of the study, 648 participants died and 125 formally withdrew from the investigation; rate of attrition was therefore 33.6%. Institutional Review Board approval was obtained from the Johns Hopkins Bayview Medical Center prior to 2002, and the MedStar Research Institute after 2002. All participants provided written informed consent. Data analyses were approved by the Institutional Review Board of the University of Maryland, Baltimore County.

Neuropsychological Tests

Standard neuropsychological tests were administered at each BLSA visit by highly trained psychometricians (20). The numbers that follow each test indicate respective sample sizes due to test-specific missing data associated with variability of the neuropsychological battery during different epochs of the BLSA, as well as scheduling constraints. The Digits Forward ($n=1,394$) and Backward ($n=1,397$) portions of the Wechsler Adult Intelligence Scale – Revised assessed attention and concentration. The California Verbal Learning Test (CVLT) ($n=1,313$) measured verbal learning and memory (i.e., learning slope, short and long free recall). The CVLT learning slope quantifies rate of learning by estimating the slope of item acquisition over the 5 learning trials, with positive slopes indicating a benefit of additional learning trials. The Benton Visual Retention Test ($n=2,300$) evaluated nonverbal memory. The Trail Making Test Parts A ($n=1,004$) and B ($n=987$) assessed attention, perceptuo-motor speed, visuomotor scanning, and mental flexibility (an executive function). Letter Fluency ($n=1,008$) and Category Fluency (1,002) examined phonetic and semantic association fluency, respectively, and executive function. The Boston Naming Test ($n=847$) assessed confrontation naming (i.e., word finding). The Mini-Mental State Examination ($n=1,018$) and the Blessed Information-Memory-Concentration (I-M-C) Test ($n=1,810$) are mental status tests.

NSAID and Aspirin Use

Use of NSAIDs and aspirin was self-reported as “yes” or “no” at each BLSA visit and coded as a binary, fully time-dependent variable. Quantity/frequency measures were not obtained.

Covariates

Age and education were assessed in years. A cardiovascular co-morbidity indicator variable (absent/present) reflected history of chronic cerebrovascular disease, coronary artery disease, and peripheral arterial disease, coded as a time-dependent binary variable. Diagnosed diabetes was coded as a time-dependent binary variable. An inflammatory disease index included osteoarthritis, rheumatoid arthritis, and rheumatism- conditions for which regular NSAID use might be indicated - coded as a time-dependent binary variable. Hypertension was defined time-dependently as having systolic blood pressure ≥ 140 , diastolic blood pressure ≥ 90 , or self-reported antihypertensive medication use. Resting brachial systolic and diastolic blood pressure (SBP, DBP) values were obtained three times bilaterally with participants in the seated position following a 5-minute resting period. SBP and DBP were defined by Korotkoff phases I and V, respectively.

Data Analyses

Mixed-effects regression analyses were conducted to examine longitudinal relations of NSAID and aspirin use (included in the same models) to cognitive function. Mixed-effects models are

the preferred method of analyzing data with different numbers of repeated outcome measurements that are obtained at non-uniform intervals (21,22). These models examine the unique effects of individual predictors adjusted for all other predictors in the model, include both fixed and random effects, account for the correlation among repeated measurements on the same participant, and are unaffected by randomly missing data. Because concurrent measures of NSAID and aspirin use, and cognitive function were available at all visits, results of the present mixed-effects regression indicates age-related change in cognitive performance as a function of concurrently reported NSAID or aspirin use (and all relevant covariates).

To maximize the unique information provided by each neuropsychological test, separate regression models were constructed for each test as a dependent measure. Age and years of education were treated as continuous covariates, and sex and all comorbidity indexes were treated as categorical covariates. Other than sex, all covariates were treated as time varying. Age was modeled as a random effect to index time (21). All main effects and two-way interactions of NSAIDs or aspirin with age were entered into each model.

Statistical analyses were conducted using SAS version 9.1 (Cary, NC). Significant main effects of NSAID or aspirin use indicate that the cognitive outcome (collapsed across all available testing sessions) is associated with overall differences in usage patterns regardless of longitudinal change. Longitudinal change in cognitive outcome associated with NSAID or aspirin use is indicated by the interaction term of NSAID (or aspirin) and age. The latter reflects age-related differences in cognitive decline as a function of prospectively-assessed NSAID or aspirin use. Graphs were created to visualize the significant longitudinal relations using the prototypical values of the predictors as a function of age (21). Each graph depicts the predicted changes in the cognitive outcome over time using all of the information in the analyses regardless of the number of repeated assessments. Because our primary focus is on age-related change, each graph shows change in a cognitive test performance as a function of age.

Results

Significant main effects of NSAID and aspirin and their interactions with age are depicted in Table 3. Significant interaction of NSAID use and age (indicating change over time) was found for the Blessed I-M-C Test and Trail Making Part B such that NSAID use was associated with lesser decline in performance over time (see Figure 1). Significant main effects of NSAID use (that were not qualified by an age interaction) were noted for the Benton Visual Retention Test, the Boston Naming Test, the California Verbal Learning Test's learning slope, and short and long free recall, and Digits Backward. With the exception of the Boston Naming Test, NSAID use was associated with better test performance across all testing sessions.

Significant interactions of aspirin use and age were noted for the Blessed I-M-C Test and the Benton Visual Retention Test (see Figure 2). However, aspirin was associated with a steeper gradient of cognitive decline on these tests. Significant main effects of aspirin use (that were not qualified by an age interaction) were noted for the Benton Visual Retention Test, the California Verbal Learning Test's learning slope and short free recall, and Mini-Mental State Examination and indicated better average levels of function for aspirin users.

Discussion

Knowledge of longitudinal trajectories in cognitive performance associated with NSAID or aspirin use among non-demented persons is minimal, and few studies examine both cross-sectional and prospective relations. Further, most prior studies only used mental status tests to index cognitive function. Accordingly, the present study examined cross-sectional and longitudinal relations of NSAID and aspirin use to performance on tests reflecting multiple

domains of cognitive function in dementia-free persons. Results indicated that with increasing age, NSAID use was associated with less prospective decline on the Blessed I-M-C Test - a mental status test weighted for memory and concentration, and Part B of the Trail Making Test - a test of perceptuo-motor speed and mental flexibility (an executive function). In contrast, aspirin use was associated with greater prospective decline on the Blessed I-M-C Test and the Benton Visual Retention Test - a test of visual memory. Importantly, and as is illustrated in Figures 1 and 2, effect size magnitudes were particularly small for the longitudinal associations of NSAID and aspirin use with rate of change in cognitive performance over time. Clinical significance of these findings on an individual level is therefore questioned, although overall public health significance may be meaningful.

Despite the paucity of longitudinal findings, there were a multitude of cross-sectional associations of NSAID or aspirin use with cognitive performance. Specifically, NSAID use was related to better average levels of performance across all testing sessions on measures of verbal and visual learning and memory, as well as concentration (or working memory), yet diminished confrontation naming. Use of aspirin was also related to better average performance across testing sessions on measures of verbal and visual learning and memory, and global mental status. It is unclear whether this apparent benefit is attributable to medication use per se, or other characteristics of the individuals who choose to take these medications over time.

Prior prospective investigations have been mixed with respect to the positive, negative, or neutral relation of aspirin to cognitive function (6-11), and an increased incidence of Alzheimer's disease or vascular dementia was noted in two studies (12,13). In that regard, it may be important to recall that aspirin is frequently prescribed among those with existing vascular disease. Thus, a decline in cognitive performance among aspirin users may be attributable, in part, to the neurobiological impact of cardiovascular disease or its risk factors (see 23), that may ultimately influence the development of both vascular dementia and Alzheimer's disease (1). Despite that we adjusted for hypertension and other cardiovascular disease diagnoses in the present data analyses, residual confounding is possible due to potential differences in severity of extent of vascular disease between those with and without aspirin use even among those with cardiovascular disease by our indicator variable. It would also be important to conduct a standard assessment of subclinical cardiovascular disease to more fully evaluate this possibility. In addition, select individuals are "aspirin resistant" and thus may not benefit from its use with respect to clinical outcomes (24) with a concomitant lack of protection against disease-related cognitive decline. That aspirin use was related to greater decline on the Benton Visual Retention Test may be of interest because performance on this test has been shown to predict Alzheimer's disease up to 10 years prior to its diagnosis in the BLSA (25, 26).

Other prior studies of NSAID and aspirin use have employed a variety of mental status tests that screen for dementia. Our findings are partially consistent with those noted in prior epidemiologic investigations in which lesser decline on the SPMSQ or 3MS was found among NSAID users (14,16). In the present investigation, NSAID use was associated with lesser decline on the Blessed I-M-C Test - a screening measure that is more heavily weighted toward assessment of memory and concentration than the SPMSQ (or 3MS) and that may be a more sensitive screening measure for cognitive difficulties. Also benefited was performance on Part B of the Trail Making Test, a measure that requires perceptuo-motor speed and mental flexibility (or set shifting), a component of executive functioning. Thus, future longitudinal work might include a broader assessment of executive functions which are weakly (or not) represented on most cognitive screening measures.

Our findings may, in part, reflect that the Blessed I-M-C Test and Benton Visual Retention Test were the two measures available for the greatest number of BLSA participants although

this concern does not relate to the Trail Making Test. Nevertheless, it is striking that neither NSAID nor aspirin use conferred protection against prospective decline on any other clinical neuropsychological or mental status measure. Indeed, the preponderance of our findings suggest that NSAID and aspirin use were associated with greater average levels of performance on multiple measures of learning, memory and verbal fluency across all testing sessions. Prior cross-sectional findings have revealed weak relations of aspirin use to better word recall and word fluency (17), and relations of NSAID use to better concentration (27). However, fewer tests of cognitive function were employed in these investigations. The cross-sectional findings here and elsewhere raise the question of whether NSAID or aspirin use confers habitual neuroprotection or whether persons taking these medications differ from those who do not on other dimensions that may protect the brain and cognitive function. Discussed extensively elsewhere, there are several plausible biological mechanisms whereby NSAID and aspirin use may preserve cognitive function (see 28,29). These include reduced production of cytokines, diminished platelet aggregation (and therefore decreased beta-amyloid), the scavenging of free radicals, reduced endothelial damage, and vasodilatation.

Strengths of this investigation include the greatest number of repeated, concurrent assessments of NSAID or aspirin use and cognitive function available to date. Use of an extensive neuropsychological test battery is also an advantage. Limitations to this investigation include the use of a highly educated and predominantly White convenience sample that limits the study's generalizability. Another limitation is the binary assessment of NSAID and aspirin use rather than measurement of quantity and frequency, or use of pharmacy records. Yet, prior work has suggested no incremental benefit of increased dosage (5,27). Thus even habitual, low-level use may confer benefit.

In sum, NSAID users displayed less prospective decline on a mental status measure weighted for memory and concentration and a test of perceptuo-motor speed and mental flexibility. Thus, only select protection against cognitive decline was apparent in the present non-demented sample – an understudied group in this literature. In contrast, aspirin use was associated with greater prospective cognitive decline on the mental status measure described above and a visual memory test, potentially reflecting its common use for vascular disease prophylaxis. It is therefore possible that inception of aspirin use must precede even subclinical vascular disease to confer the greatest benefit. Further understanding of the longitudinal trajectories of cognitive function associated with NSAID and aspirin use may provide optimal information regarding potential maintenance of cognitive function, or attenuation of decline, with aging.

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Figure 1. Longitudinal change in performance on the Blessed I-M-C Test and Part B of the Trail Making Test as a function of NSAID use. Because age was modeled as a random effect in the data analyses, this figure displays change in cognitive performance over time (i.e., as individuals grow older during the course of the study) as a function of concurrently assessed NSAID use. Higher scores on each test indicate poorer performance.

Figure 2.

Longitudinal change in performance on the Blessed I-M-C Test and the Benton Visual Retention Test (BVRT) as a function of aspirin use. Because age was modeled as a random effect in the data analyses, this figure displays change in cognitive performance over time (i.e., as individuals grow older during the course of the study) as a function of concurrently assessed aspirin use. Higher scores on each test indicate poorer performance.

Table 1

Characteristics of Study Sample at First Assessment

Variable	Mean (SD)	Range
Age, y	50.6 ($\pm$ 17.4)	17-96
Education, y	16.6 ($\pm$ 2.7)	4-24
Gender, % male	60.0	
Race, % white	82.9	
Hypertension, %	36.7	
Cardiovascular disease [*] , %	11.8	
Diabetes, %	3.9	
Inflammatory disease [†] , %	22.5	
NSAID use, %	16.2	
Aspirin use, %	11.1	
Concurrent NSAID and aspirin use, %	3.9	

^{*} Cardiovascular disease included chronic cerebrovascular disease, coronary artery disease, and peripheral arterial disease, coded as a time-dependent binary variable.

[†] Inflammatory disease included osteoarthritis, rheumatoid arthritis, and rheumatism, coded as a time-dependent binary variable.

Table 2

Sample Size by Number of BLSA Visits: Available Data for the Present Data Analyses

Number of Visits	# (% of Sample)
1	2300 (100.0)
2	1548 (67.3)
3	1123 (48.8)
4	885 (38.5)
5	691 (30.0)
6	541 (23.5)
7	433 (18.8)
8	348 (15.1)
9	279 (12.1)
10	199 (8.7)
11	155 (6.7)
12	105 (4.6)
13	70 (3.0)
14	42 (1.8)
15	21 (0.9)
16	10 (0.4)
17	4 (0.2)
18	2 (0.09)

Table 3

Mixed-effects Regression Models Predicting Neuropsychological Test Performance from NSAID Use, Aspirin Use, and Covariates: Significant Main and Interactive Effects of NSAID or Aspirin Use

Neuropsychological Test	NSAIDS Use		Aspirin Use		NSAIDS Use × Age		Aspirin Use × Age	
	<i>b</i>	SE	<i>b</i>	SE	<i>b</i>	SE	<i>b</i>	SE
Blessed IMC (n=1,810)	.611 *	.163	-.422 *	.175	-.011 *	.003	.006 *	.003
Benton Visual Retention Test (n=2,300)	-.150 *	.069	-2.02 *	.315	--	--	.030 *	.005
Boston Naming Test (n=847)	-.290 *	.144	.017	.131	--	--	--	--
CVLT Learning Slope (n=1,313)	.090 *	.020	.071 *	.019	--	--	--	--
CVLT Free Recall Short Delay (n=1,313)	.242 *	.093	.199 *	.090	--	--	--	--
CVLT Free Recall Long Delay (n=1,313)	.259 *	.094	.154	.091	--	--	--	--
Digits Backward (n=1,397)	.255 *	.073	.003	.070	--	--	--	--
Mini-Mental State Examination (n=1,018)	-.011	.053	.096 *	.049	--	--	--	--
Trail Making Test – Part B (n=987)	22.2	11.8	-1.33	1.22	-.319 *	.163	--	--

* $p < .05$

Note: Coefficients associated with main effects of NSAIDS or aspirin use indicate the magnitude and direction of the relation between the variables; coefficients associated with the interaction terms are not directly interpretable and are clarified in Figures 1 and 2.