

What Are the Effects of Long-Term NSAID Therapy on Cognition in Older Adults? A Literature Review

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Dementia is a major neurocognitive disorder characterized by deterioration in memory, thinking, and behavior, which results in the inability to perform activities of daily living. Alzheimer's disease is the most common type of dementia. Preventative approaches against neurocognitive disease in older adults described in the literature have focused on the use of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs). The CINAHL and PubMed databases were searched for previous studies, of which sixteen were analyzed, but these studies showed no strong evidence that NSAIDs have an effect on slowing the progression of cognitive decline in community-dwelling older adults. The results on the effects of NSAIDs on cognitive function are mixed. Based on the current evidence, there is no medical recommendation to initiate NSAID therapy in order to prevent cognitive decline. *Keywords:* NSAIDs, aspirin, dementia, older adults

INTRODUCTION

Dementia is a major neurocognitive disorder characterized by deterioration in memory, thinking, and behavior, resulting in the inability to perform activities of daily living. Dementia is a progressive and incurable disease. There are various etiologies of dementia, including Alzheimer's disease, frontotemporal lobar degeneration, Lewy body disease, vascular disease, and others (APA, 2013). Alzheimer's disease is the most common type of dementia, which constitutes 60 to 70 percent of all cases of dementia (WHO, 2015).

Approximately 47.5 million older adults worldwide have dementia, and its incidence is projected to triple by 2050 (WHO, 2015). Alzheimer's disease is the third most costly disease in the United States, including \$100 billion of the yearly government spending (CDC & NCCDPHP, 2000). The National Institutes of Health funding for Alzheimer's disease and Alzheimer's disease related dementias ranges from \$600 to \$900 million a year (NIH, 2016).

Research trials focus on treatment, diagnostics, prevention, and quality of life (Alzheimer's Association, 2017). Prevention trials aim at finding ways to prevent the onset of dementia, and these trials have the most potential to minimize the impact of dementia. Typically, prevention trials are conducted in populations identified as being at higher risk for neurocognitive disease. Preventative interventions studied include certain drugs, vitamins or supplements, or lifestyle changes (Alzheimer's Association, 2017). Due to the multifactorial etiology of dementia, including inflammatory or vascular disease, dementia-preventative interventions are similar to drug regimens initiated for inflammatory or vascular diseases. For example, clients with untreated rheumatoid arthritis (RA) are at a significantly higher risk for dementia than non-RA

controls, due to the inflammatory processes inherent in RA (Ungprasert, Wijarnpreecha, & Thongprayoon, 2016). Similarly, clients with chronic vascular disease (e.g. chronic diabetic hyperglycemia, hypercholesterolemia, hypertension, thrombosis) are more likely to suffer from post-stroke (vascular) dementia.

Preventative approaches against neurocognitive disease in older adults described in the literature have focused on the use of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs are used to treat many pain and inflammation conditions, which are heavily concentrated in the elderly population. The most common therapeutic use of aspirin is prophylaxis against stroke, because aspirin is hypothesized to have benefit in reducing the risk for vascular dementia (Rands and Orrell, 2000-2012). Other NSAIDs (which will be called non-aspirin NSAIDs from now on), particularly ibuprofen, naproxen, and celecoxib, are often prescribed to treat certain inflammatory diseases, such as rheumatoid arthritis and pain in other musculoskeletal disorders, such as osteoarthritis (OA) or ankylosing spondylitis.

A biological rationale exists for why NSAIDs may be able to prevent neurocognitive impairment in older adults. Because dementia most likely results from inflammation in the brain (neuroinflammation), anti-inflammatory drugs, such as NSAIDs, are hypothesized to at least ameliorate the signs and symptoms of dementia or otherwise to slow its progression.

While abundant research exists on dementia prevention, the overall results are unclear. This paper's goal is to evaluate the scientific literature on the association between NSAID use and cognitive function in older adults. Specifically, focus will be on answering the question: Is there evidence that NSAIDs have an effect on slowing the progression of cognitive decline in community-dwelling older adults?

METHOD

CINAHL and PubMed were the databases used to gather relevant scientific literature. Searched terms included any variations of the four main terms (depending on whether CINAHL or PubMed was used): (i) non-steroidal anti-inflammatory drugs (e.g. “NSAIDS”), (ii) cognitive function (e.g. “COGNITION”), (iii) older adults (e.g. “AGED”), and (iv) population sample (e.g. “COMMUNITY-DWELLING”). The terms were then added by the “AND” command. Publications were selected for the literature review if they investigated the pathophysiology of neurocognitive disease or efficacy of NSAIDs in the prevention of neurocognitive disease among the population sample of older adults.

RESULTS

Based on the comprehensive literature review, 16 studies were identified, which examined the effects of NSAIDs on cognitive function in older adults. These studies are summarized in Appendixes A-C and are categorized into three groups. Group I (Appendix A: Table 1) focuses on studies analyzing the effects of aspirin only, Group II (Appendix B: Table 2) on NSAIDs in general, including aspirin, and Group III (Appendix C: Table 3) on non-aspirin NSAIDs. These categories provide the framework for organizing this review. The studies are labeled IA to IIF to indicate the assignment to one of the three groups (I, II, or III) as well as number of studies in the group (A to F).

Out of these studies, only four (IA, IC, IIA, and IIB) provide some evidence and five (IB, ID, IIC, IID, and IIF) provide no evidence of protective effect of aspirin on cognitive function. One study (IID) provides evidence of a deleterious effect of aspirin on cognitive function. With regard to non-aspirin NSAIDs, six studies (IIA, IID, IIE, IIIA, IIIC, and IIIF) provide some evidence and six (IIB, IIF, IIIB, IIID, IIIE, and IIIF) provide no evidence of protective effect of non-aspirin NSAIDs on cognitive function, three of which (IIC, IIIB, and IIIF) provide evidence of deleterious effect of non-aspirin NSAIDs on cognitive function. Further, five studies (IIA, IIB, IIC, IID, and IIF) included both aspirin and non-aspirin NSAID in the analyses. Of these combined drug studies, ten provide at least some evidence and eleven provide no evidence of protective effect of NSAIDs on cognitive function, including four which provide evidence of deleterious effect of NSAIDs on cognitive function. Therefore, the results on the effects of NSAIDs on cognitive function are mixed.

Effects of NSAIDs on Cognitive Function

Aspirin. Four aspirin studies were analyzed: one non-interventional (IA), one systematic review (IB), and two randomized-controlled trials (IC and ID): see Appendix A: Table 1. Generally, there was no substantial evidence of

protective effect of aspirin use on cognitive function in any of the studies: no evidence in IB and ID and some evidence in IA and IC. There was some evidence of protective effect of “as needed” use of aspirin on cognitive function (IA); there was some evidence of substantial decline on cognitive measure of category fluency, i.e. naming as many animals as possible in one minute, with low-dose aspirin (IC).

There were no statistically significant differences in the characteristics and baseline performance on cognitive measures between aspirin takers and non-takers in any of the studies. However, there was a higher proportion of women and obesity, impaired mobility, no regular physical activity, light alcohol consumption, angina, headache, joint pain, and depression in the aspirin-taking group in study IA. The East Boston Senior Health Project of EPESE (IA) had the most limited cognitive assessment battery. Despite this and it being a non-interventional study, it did find some evidence of protective effect of “as needed” use of aspirin on cognitive function compared to deleterious effect of high-frequency use of aspirin on cognitive function. This finding is consistent with previous research, stating that aspirin taken in high doses may be related to cognitive decline among older adults (Karplus & Saag, 1998).

The aspirin study with the largest sample (N=6,377) was the Women’s Health Study (IC). The second and third largest studies were the East Boston Senior Health Project of EPESE (IA) and AAT of Central Scotland (ID). They both had similar sample sizes (N=3,809 and 3,350, respectively). The East Boston Senior Health Project of EPESE (IA) determined that low-frequency aspirin users (“as needed”) had a 16-percent reduction in risk for cognitive decline. Conversely, aspirin users who used aspirin at a high frequency (more than two aspirin doses daily) had a 31-percent increase in risk for cognitive decline.

The study with the most comprehensive cognitive assessment battery is the AAT of Central Scotland (ID), followed by the Women’s Health Study (IC). In the Women’s Health Study (IC), aspirin users performed similar to non-aspirin users on cognitive measures of general cognition, verbal memory, and global score. However, on cognitive fluency (naming as many animals as possible in one minute), aspirin users had a 20-percent lower risk of substantial decline than non-aspirin users.

The systematic review of RCTs summarizing the evidence for efficacy and safety of aspirin to treat vascular dementia (IB) failed to find any study that would meet the inclusion criteria. Therefore, despite the wide prescription of aspirin for vascular dementia, there is still no scientific evidence to support such practice.

NSAIDs (Aspirin Included). Six NSAID (aspirin included) studies were analyzed, and all of them were non-interventional (see Appendix B: Table 2). Generally, there was mixed evidence with regards to the effect of NSAID use on cognitive function across all of the studies. One large study (IIA) provided evidence for the effectiveness of general NSAID use (aspirin as well as non-aspirin NSAIDs)

in the prevention of cognitive decline. Study IIB found evidence of protective effect of aspirin on cognitive decline, simultaneously finding no evidence of protective effect of non-aspirin NSAIDs on cognitive decline. Study IID provided inverted results (evidence of protective effect of non-aspirin NSAIDs and no evidence of protective effect), additionally showing a deleterious effect of aspirin on cognitive function. In study IIC, the deleterious effect on cognitive function was found in non-aspirin NSAID instead of aspirin use. Lastly, study IIF found no evidence of protective effect of either aspirin or non-aspirin NSAIDs on cognitive function.

All of the six NSAID (aspirin included) studies analyzed were non-interventional and longitudinal, except for IIE, which was cross-sectional. Generally, NSAID users were mostly female and had positive histories of vascular disease (refer to Appendix B: Table 2.2 for more details). The largest study was the East Boston EPESE (IIA), followed by the similarly sized IIF and IID, and IIC and IIB (N=7,671; 2,422; 2,300; 1,019; and 1,007, respectively). In the East Boston EPESE (IIA), chronic NSAID users had a lower incidence rate of cognitive decline than non-NSAID users. The LASA (IIB) found that aspirin users 75 years of age or younger performed better on the cognitive measure of immediate recall than non-NSAID users, indicating a three-time lower risk of memory decline. On the other hand, not only did the BLSA (IID) determine that aspirin had no protective effect on cognitive function, but also that there was greater prospective decline on Information-Memory-Concentration Test and Benton Visual Retention Test in aspirin users compared to non-aspirin NSAID users. Conversely, non-aspirin NSAID users had less prospective decline on Information-Memory-Concentration Test and Part B of Trial Making Test than aspirin users. Aspirin use was found in IIF to have a higher risk for cognitive impairment within next 10 years than no aspirin use. However, there was no statistically significant difference in longer-term use.

Study IIE had the smallest sample size (N=75) and was also cross-sectional. However, it still provided valuable evidence of different temporal lobe volumes in aging (non-aspirin) NSAID users and aging (non-aspirin) non-NSAID users. Studies IIC and IIE confirmed that NSAID use was associated with changes in the brain. In Study IIC, all of the deceased study participants had at least some Alzheimer's disease pathology in their brain autopsies. The deceased who used ibuprofen specifically had increased level of global AD pathology, including neuritic plaques, diffuse plaques, and tangles. However, Study IIE found that elderly non-NSAID users had lower temporal lobe volumes than (non-aspirin) NSAID users, meaning that there is greater temporal volume loss with age in (non-aspirin) non-NSAID users than (non-aspirin) NSAID users.

In five out of six studies, the cognitive battery was comprehensive. The only study with limited cognitive battery was the East Boston EPESE (IIA). The most general study was also IIA, which did find evidence of protective

effect of NSAIDs on cognitive function. Nonetheless, it cannot be determined which type of NSAID, whether aspirin or non-aspirin NSAID, positively influenced the results. In most studies, the statistical analyses was conducted separately for aspirin and non-aspirin NSAIDs (IIB, IIC, IID, and IIF). This enabled the investigators to draw separate conclusions for aspirin and non-aspirin NSAIDs.

Non-Aspirin NSAIDs. Six non-aspirin NSAID studies were analyzed (see Appendix C: Table 3). Generally, there was no evidence of protective effect of non-aspirin NSAID use on cognitive function, except for one non-interventional study, which found evidence of NSAID use on cognitive function based on NSAID use frequency and dose (IIIA). The remaining five studies analyzed the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT), which was conducted between 2001 and 2004. The general conclusion was that neither celecoxib nor naproxen sodium protected against cognitive decline.

Five of the six non-aspirin NSAID studies were publications related to the ADAPT Trial. All of them were non-interventional, except for one, the parent ADAPT study, which was an RCT (IIIB). There were no statistically significant differences in the characteristics and baseline performance on cognitive measures between NSAID takers and non-NSAID takers in all of the studies. Generally, there was no evidence of protective effect of either celecoxib or naproxen sodium on cognitive function. However, the Duke EPESE (IIIA) determined that although there was no substantial or consistent evidence of protective effect of prescription non-aspirin NSAID use on cognitive function, there was some evidence of (i) protective effect of NSAID use on cognitive impairment in indeterminate NSAID users, (ii) improved concentration in continuous NSAID users, and (iii) improved memory in low-dose NSAID users.

In the Duke EPESE (IIIA), the cognitive outcomes were measured with tests of mental status (SPMSQ) and orientation, memory, and concentration (OMCT). Mental status improved in indeterminate NSAID users ("as needed"), concentration improved in continuous NSAID users compared to non-NSAID users, and memory improved in low-dose NSAID users compared to moderate-to-high dose NSAID users. The ADAPT was randomized placebo-controlled multi-center NIA-sponsored primary prevention trial. The community-dwelling older adults were randomized into either one of the two interventions (200 mg celecoxib twice daily or 220 mg naproxen sodium twice daily) or placebo. Neither celecoxib nor naproxen sodium was found to be protective of cognitive decline. There were mixed results for naproxen sodium. Firstly, naproxen sodium treatment group was found to have lower global summary scores over time (IIIB). Secondly, there was scant evidence of protective effect of naproxen sodium on incidence of Alzheimer's disease after two to four years in participants who were cognitively intact at baseline.

The last study, IIIF, analyzed the results of the ADAPT study, which considered the stage of cognitive decline in

participants. The study obtained progressive results using growth mixture models. The results were mixed, depending on which of the three cognitive-decline classes participants belonged to: (i) no-decline (class 1), (ii) slow-decline (class 2), and (iii) fast-decline (class 3). Slow-decliners declined at similar rates whether they were in the celecoxib treatment group, the naproxen sodium treatment groups, or on placebo. However, fast-decliners on naproxen sodium performed worse on the cognitive measure of mental status (3MS-E) than those on celecoxib or placebo. Conversely, fast-decliners on celecoxib performed better on the cognitive measure of mental status (3MS-E) than those on naproxen sodium or placebo. Nevertheless, fast decliners on celecoxib performed worse on the cognitive measure of dementia severity (DSRS) than those on naproxen sodium and placebo.

DISCUSSION

Neither aspirin nor non-aspirin NSAIDs have protective effects on cognitive function in community-dwelling older adults. Likewise, previous reviews were unable to establish a statistically significant relationship between NSAID use and improved neurocognitive outcomes (Jaturapatporn, MGEKN, McCleery, & Tabet, 2012).

The first major limitation of the research studies is the failure to distinguish between different types of neurocognitive disease. The exception is the Alzheimer's disease trials, which focus exclusively on AD. Treating all neurocognitive diseases as general "cognitive decline" is an oversimplification of the complex pathophysiologies of individual neurocognitive diseases.

The second limitation is the lack of standardized criteria for what constitutes "NSAID use." The definitions vary from self-reported use of at least one NSAID for two consecutive weeks to medications taken three years prior to the baseline assessment. Non-compliance would contribute to an underestimation of drug effects, which may partially explain why the studies generally fail to provide any substantial evidence of the positive effect of NSAIDs on cognition.

Although most studies recruited cognitively intact older adults, participants may have beginnings of cognitive decline with the absence of any signs or symptoms. Rarely do studies specify which level of prevention they target. Primary prevention is the recently-emerged goal of cognitive prevention trials based on the finding that NSAIDs may actually lose their protective effect approximately two years prior to the onset of dementia (Breitner, 2003).

The last important limitation involves dosing of NSAIDs. Because high dose NSAID use is associated with cognitive impairment (Karplus & Saag, 1998), its protective effect is attributed to lower doses. However, lower doses are unable to control pain adequately which is a main therapeutic purpose for taking NSAIDs. There is evidence that OA pain remains undertreated among the community-dwelling

elderly (Marcum et al., 2012), which may affect performance on neurocognitive. It would be statistically valuable to include pain assessment as part of the neurocognitive testing in future trials.

Further research, addressing the limitations in this body of literature, is needed to investigate the potential role of NSAIDs on cognitive function. If effective, NSAIDs could be a readily-available, cost-effective preventative treatment. The discovery of interventions to prevent and treat cognitive decline is vitally important given the demographic imperative of global aging and the prevalence of Alzheimer's disease and related dementias in the aging population.

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Appendix A

Table 1. Studies Investigating the Effects of Aspirin on Cognitive Function

Study	Population	Definition of Aspirin Use	Intervention	Re)assessment	Effectiveness (Y/N)	Cognitive Measures
IA Non-interventional; progressive longitudinal; correlational	Established Populations for Epidemiologic Studies of Elderly, East Boston Senior Health Project (East Boston EPESE); 3,809 men & women; community-dwelling older adults (65 y.o. ≤); asymptomatic of cognitive deterioration	“Aspirin use” defined as intake of any aspirin-containing drugs 2 weeks prior to initial assessment; “dose” = # pills/day (frequency hypothesized to have greater effect than dose)	None	Y1 (1982/1983) → baseline cognitive assessment Y3 (1985/1986) → f/u cognitive assessment Y6 (1988/1989) → final cognitive assessment	Generally, NO: no <i>substantial</i> evidence of protective effect of aspirin use on cognitive function However, <i>some</i> evidence of protective effect of “as needed” use of aspirin on cognitive function	- East Boston Memory Test (EBMT) - Short Portable Mental Status Questionnaire (SPMSQ)
IB Systematic review of RCTs for efficacy & safety of aspirin in Tx of vascular dementia	Any age; diagnosed vascular dementia	None (it is systematic review of interventional studies)	Low-dose (75 – 300 mg) aspirin	Min. 6-month f/u	Unknown; lack of studies eligible for inclusion	- Cognition: validated scales - Behavior: validated scales - Global function
IC RCT	Women’s Health Study (1998-2004); 6,377 women; community-dwelling older adults (65 y.o. ≤); asymptomatic of cognitive deterioration	-	Low-dose (100 mg on alternate days) aspirin	Y1 (1998) → baseline cognitive assessment Y2 (2000) → f/u cognitive assessment Y4 (2002) → f/u cognitive assessment Y6 (2004) → final cognitive assessment	Generally, NO: no <i>substantial</i> evidence of protective effect of aspirin use on cognitive function However, <i>some</i> evidence of protective effect of aspirin on substantial decline on cognitive measure of category fluency	Telephone Cognitive Battery (TCB): - Telephone interview of cognitive status (adaptation of MMSE for use by telephone) - East Boston Memory Test (EBMT; immediate & delayed recall) - Category fluency: naming as many animals as possible in 1 minute - Global score
ID RCT	Asymptomatic Atherosclerosis Trial (AAT; Central Scotland; 1998-2006); 3,350 men & women; community middle-aged & older adults (aged 50-75 y.o.); asymptomatic of cognitive deterioration	-	Low-dose (100 mg daily) aspirin	Y1 → baseline cognitive assessment Y5 → f/u & final cognitive assessment	NO; no evidence of protective effect of aspirin use on cognitive function	- Mill Hill vocabulary scale (combined version of the Junior and Senior Form A) - National Adult Reading Test (NART) - Mini-Mental State Examination (MMSE) - Verbal Fluency Test (VFT) - Raven’s Progressive Matrices

- Auditory Verbal Learning Test (AVLT)
 - Trial Making Test (TMT)
 - Digits Symbol Test
 - Hospital Anxiety & Depression Scale

Notes. AVLT = Auditory Verbal Learning Test; EBMT = East Boston Memory Test; f/u = follow-up; q = every; HTN = hypertension; Hx = history; MI = myocardial infarction; MMSE = Mini-Mental State Examination; NART = National Adult Reading Test; RCT = randomized controlled trial; SPMSQ = Short Portable Mental Status Questionnaire; SXS = symptoms; TCB = Telephone Cognitive Battery; TMT = Trial Making Test; Tx = treatment; VFT = Verbal Fluency Test; Y = year.

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Appendix B

Table 2. Studies Investigating Effects of NSAIDs, Including Aspirin, on Cognitive Function

Study	Population	Definition of NSAID Use	Intervention	(Re)assessment	Effectiveness (Y/N)	Cognitive Measures
IIA Non-interventional; progressive longitudinal; correlational	Established Populations for Epidemiologic Studies of the Elderly, East Boston site (East Boston EPESE; 1982-1988); 7,671 men & women; community-dwelling older adults (65 ≤ y.o.); asymptomatic of cognitive deterioration; 21% chronic NSAID users	“NSAID use” defined as intake of any NSAID 2 weeks prior to initial assessment; “chronic NSAID use” defined as intake of any NSAID for 3 years prior to baseline cognitive assessment in 1985; NSAIDs reported: aspirin, other salicylates, diclofenac sodium, sulindac, piroxicam, etodolac, nabumetone, indomethacin, ibuprofen, oxaprozin, fenopufen, flurbiprofen, ketoprofen, & naproxen	None	Y1 (1982) → NSAID use assessment Y3 (1985) → chronic NSAID use assessment + baseline cognitive assessment Y6 (1988) → f/u cognitive assessment	YES; evidence of protective effect of NSAIDs on cognitive function	Short Portable Mental Status Questionnaire (SPMSQ)
IIB Non-interventional; progressive	Longitudinal Aging Study Amsterdam (LASA; 1993-	NSAID use defined as intake of any NSAID at both baseline	None	Y1 (1993) → NSAID use assessment +	YES; evidence of protective effect of aspirin on cognitive function	- Mini-Mental State Examination (MMSE)

longitudinal; correlational	1996) 1,007 men & women; community-dwelling older adults (62-85 y.o.); asymptomatic of cognitive deterioration	assessment & f/u, & for at least 1 year prior to f/u		baseline cognitive assessment Y3 (1996) → f/u cognitive assessment	in older adults 75≤ y.o. NO; no evidence of protective effect of non-aspirin NSAIDs on cognitive function	- Auditory Verbal Learning Test (AVLT; immediate & delayed recall; Dutch version) - Information processing speed: coding task (adjusted version)
IIC Non-interventional; progressive longitudinal; correlational	Religious Orders Study (1994-2007); 1,019 Catholic clergy men & women	NSAID use was computed using ratio of # of self-reported NSAID use (whenever participant said that they were using NSAIDs) to # of assessments (total # of assessments completed by participant); e.g. if participant self-reported NSAID use at baseline & 1 st f/u, then # of self-reported NSAID use is 2, which divided by total of 2 assessments yields 2/2, i.e. ratio of 1	None	12 f/u's q1yr (from 1994 until 2007)	NO; no evidence of protective effect of NSAIDs on cognitive function or incidence of AD Evidence of brain AD-like pathologic changes in deceased participants	- Global cognition (based on average of 19 tests) - Memory: episodic, semantic, & working - Perceptual speed - Visuo-spatial ability - Brain autopsies on participants deceased during course of study: standard techniques
IID Non-interventional; progressive longitudinal; correlational	Baltimore Longitudinal Study of Aging (BLSA; 1958-1986); 2,300 men & women; community-dwelling adults (17-102 y.o.); asymptomatic of cognitive deterioration	NSAID use & aspirin use were defined as self-reported "yes" or "no" at each assessment; dose &/or frequency were not considered	None	1-18 f/u's up to 45 yrs. (from 1958 until 1986); average of 3.8 ± 3.4 visits; average time between visits of 3.4 ± 1.7 yrs.	YES; evidence of protective effect of non-aspirin NSAIDs on cognitive function NO; no evidence of protective effect of aspirin on cognitive function Evidence of deleterious effect of aspirin on cognitive function	- Wechsler Adult Intelligence Scale-Revised (WAIS-R; Digits Forward & Backward portions) - California Verbal Learning Test (CVLT) - Benton Visual Retention Test (BVRT) - Trail Making Test (TMT; Parts A & B) - Letter Fluency & Category Fluency - Boston Naming Test (BNT) - Mental status: Mini-Mental State Examination (MMSE) - Blessed Information-Memory-Concentration Test (I-M-C)

IIE Non-interventional; cross-sectional; correlational	75 men & women; community-dwelling middle-aged & older adults (mean age 58.04 ± 7.10 yrs.); asymptomatic of cognitive deterioration	“NSAID use” defined as self-reported intake of any NSAID at least once/week for min. 6 months prior to initial assessment; NSAIDs reported: ibuprofen, diclofenac sodium, etodolac, meloxicam, nabumetone, piroxicam, rofecoxib (no aspirin)	None	Single assessment (cross-sectional study)	YES; evidence of greater temporal lobe volume in aging (non-aspirin) NSAID users than non-NSAID users; greater temporal volume loss with age in non-NSAID users than (non-aspirin) NSAID users	<ul style="list-style-type: none"> - Auditory Verbal Learning Test (AVLT) - Brief Visual Memory Test (BVMT) - Trail Making Test (TMT; Parts A & B) - Center for Epidemiologic Studies Depression Scale (CES-D) - State-Trait Anxiety Inventory (STAI) - Magnetic resonance imaging (MRI) scans of brains
IIF Non-interventional; progressive longitudinal; correlational	Epidemiology of Hearing Loss Study (EHLS; 1988-2000); 2,422 men & women; middle-aged & older adults (43-84 y.o.); asymptomatic of cognitive deterioration	“Aspirin use” defined as intake of aspirin at least twice/week for more than 3 months prior to initial assessment, or inclusion of any aspirin-containing medication in list of medications from last month; “non-aspirin NSAID use” defined as inclusion of any non-aspirin-NSAID-containing medication in list of medications from last month	None	Y1 (2000) → baseline cognitive assessment (only MMSE) Y2 (2005) → f/u cognitive assessment (only MMSE) Y3 (2010) → f/u cognitive assessment (MMSE + other cognitive tests)	NO; no evidence of protective effect of NSAIDs on cognitive function	<ul style="list-style-type: none"> - Mini-Mental State Examination (MMSE) - Trial Making Test (TMT) - Digit Symbol Substitution Test (DSST) - Verbal Fluency Test (VFT) - Auditory Verbal Learning Test (AVLT) - Mild cognitive impairment (MCI) & dementia questionnaires (based on National Institute on Aging-Alzheimer’s Association criteria)

Notes. AD = Alzheimer’s disease; ApoE = apolipoprotein E; AVLT = Auditory Verbal Learning Test; BNT = Boston Naming Test; BVMT = Brief Visual Memory Test; BVRT = Benton Visual Retention Test; CES-D = Center for Epidemiologic Studies Depression Scale; CVD = cardiovascular disease; CVLT = California Verbal Learning Test; DM = diabetes mellitus; DSST = Digit Symbol Substitution Test; f/u = follow-up; I-M-C = Information-Memory-Concentration Test; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NSAID = non-steroidal anti-inflammatory drugs; HTN = hypertension; Hx = history; SPMSQ = Short Portable Mental Status Questionnaire; STAI = State-Trait Anxiety Inventory; TMT = Trail Making Test; WAIS-R = Wechsler Adult Intelligence Scale-Revised; VFT = Verbal Fluency Test; Y = year; yr./yrs. = year/s.

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IIB: Jonker, C., Comijs, H. C., & Smit, J. H. (2003). Does aspirin or other NSAIDs reduce the risk of cognitive decline in elderly persons? Results from a population-based study. *Neurobiology of Aging*, 24, 583-88.

IIC: Arvanitakis, Z., Grodstein, F., Bienias, J. L., Schneider, J. A., Wilson, R. S., Kelly, J. F., . . . Bennett, D. A. (2008). Relation of NSAIDs to incident AD, change in cognitive function, and AD pathology. *Neurology*, 70, 2219-25.

IID: Waldstein, S. R., Wendell, C. R., Seliger, S. L., Ferrucci, L., Metter, E. J., & Zondermann, A. B. (2010). Nonsteroidal anti-inflammatory drugs, aspirin, and cognitive function in the Baltimore Longitudinal Study of Aging. *Journal of the American Geriatrics Society*, 58, 38-43. doi: 10.1111/j.1532-5415.2009.02618.x.

IIE: Bendlin, B. B., Newman, L. M., Ries, M. L., Puglielli, L., Carlsson, C. M., Sager, M. A., . . . Johnson, S. C. (2010). NSAIDs may protect against age-related brain atrophy. *Frontiers in Aging Neuroscience*, 2(35). doi: 10.3389/fnagi.2010.00035.

IIF: Wichmann, M. A., Cruickshanks, K. J., Carlsson, C. M., Chappell, R., Fischer, M. E., Klein, B. E., . . . Schubert, C. R. (2016). NSAID use and incident cognitive impairment in a population-based cohort. *Alzheimer Disease and Associated Disorders*, 30(2), 105-112. doi: 10.1097/WAD.0000000000000098.

Appendix C

Table 3. Studies Investigating the Effects of Non-Aspirin NSAIDs on Cognitive Function

Study	Population	Definition of Non-Aspirin NSAID Use	Intervention	(Re)assessment	Effectiveness (Y/N)	Cognitive Measures
IIIA Prospective, longitudinal, correlational	Established Populations for Epidemiologic Studies of the Elderly, Duke University site (Duke EPESE; 1986-1990; 2,765 men & women; community-dwelling older adults (65 ≤ y.o.)	“Non-aspirin NSAID use” was determined from computerized files of participants’ data & defined as use of ≥1 regularly scheduled prescription NSAID; “duration of prescription NSAID use” was defined as: (i) continuous, if used at both baseline & f/u; (ii) current, if used at f/u only; (iii) prior, if used at baseline only; (iv) indeterminate, if used “as-needed” (PRN), or if over-the-counter (OTC) ibuprofen was used at both baseline & f/u; and (v) non-use, if no NSAIDs were used at baseline & f/u Aspirin use was <i>not</i> considered	None (non-interventional study)	Y1 (1986 & 1987) → baseline cognitive assessment Y3 (1989 & 1990) → f/u cognitive assessment	Generally, NO: no <i>substantial</i> or <i>consistent</i> evidence of protective effect of prescription non-aspirin NSAID use on cognitive function Evidence of: (i) protective effect of NSAID use on cognitive impairment in indeterminate NSAID users, (ii) improved concentration in continuous NSAID users, & (iii) improved memory in low-dose NSAID users	- Short Portable Mental Status Questionnaire (SPMSQ): scores yielded 2 measures, (1) continuous variable representing change in SPMSQ score between baseline Y3, & (2) dichotomous measure based on standard cut-off scores adjusted for education & race, which indicated whether, at Y3, participant was cognitively impaired or intact - Orientation-Memory-Concentration Test (O-M-C)
IIIB RCT	Alzheimer’s Disease Anti-Inflammatory Prevention Trial (ADAPT; 2001-2004; randomized, placebo-controlled, multicenter, NIA-sponsored primary prevention trial); 2,528 men & women; community-dwelling older adults (70 ≤ y.o.); asymptomatic of	-	(1) Celecoxib 200 mg bid (2) Naproxen sodium 220 mg bid	Y1 (2001) → baseline cognitive assessment Y2 (2002) → f/u cognitive assessment Y3 (2003) → f/u cognitive assessment Y4 (2004) → f/u cognitive assessment December 17, 2004 → trial suspended due to increased cardiovascular risk w/ celecoxib	NO: no evidence of protective effect of celecoxib or naproxen sodium use on cognitive function Evidence of <i>deleterious</i> effect of naproxen sodium on cognitive function	- Modified Mini-Mental State Examination (3MS-E) - Hopkins Verbal Learning Test-Revised (HVLTR) - Informant-rated Dementia Severity Rating Scale (DSRS) - Digit Span Test - Rivermead Behavioral Memory Test (RBMT) - Brief Visuo-spatial Memory

	cognitive deterioration but w/ family Hx of at least 1 first-degree relative AD-like dementia					Test-Revised (BVMT-R) - Self-rating of memory functions - Geriatric Depression Scale - Global summary score
IIC Extended results of ADAPT (IIIB) Non-interventional; progressive longitudinal	Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT; 2001-2004; randomized, placebo-controlled, multicenter, NIA-sponsored primary prevention trial); 2,528 men & women; community-dwelling older adults (70 ≤ y.o.); asymptomatic of cognitive deterioration but w/ family Hx of at least 1 first-degree relative AD-like dementia	-	None	18-25 months after termination on December 17, 2004; observation until 2007	NO: no evidence of protective effect of celecoxib or naproxen sodium use on incidence of AD Evidence of deleterious effect of celecoxib & naproxen sodium on cognitive function in later stages of AD	- Incidence of AD - Cerebrospinal fluid (CSF) analysis
IIID Results of follow-up study to ADAPT (IIIB) Non-interventional; progressive longitudinal	Alzheimer's Disease Anti-Inflammatory Prevention Trial – Follow-Up Study (ADAPT-FS; 2010-2011); 1,537 men & women; community-dwelling older adults (70 ≤ y.o.); asymptomatic of cognitive deterioration but w/ family Hx of at least 1 first-degree relative AD-like dementia	-	None	6-7 yrs. after termination on December 17, 2004; telephone f/u in 2010-2011	NO: no evidence of protective effect of celecoxib or naproxen sodium use on incidence of AD in older adults w/ family Hx of AD-like dementia	I. Telephone Assessment Battery (TAB): - Telephone Interview for Cognitive Status (TICS) - Test of Generative Verbal Fluency (GVF) - Rivermead Behavioral Memory Test (RBMT) II. In-person Dementia Evaluation Visit (DEV)
IIIE Follow-up evaluation of ADAPT (IIIB) & ADAPT-FS (IIID) Non-interventional; progressive longitudinal	Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT; 2001-2004) & Alzheimer's Disease Anti-Inflammatory Prevention Trial – Follow-Up Study (ADAPT-FS; 2010-2011);	-	None	6-7 yrs. after termination on December 17, 2004; telephone f/u in 2010-2011	NO: no evidence of protective effect of celecoxib or naproxen sodium use for 1 to 3 yrs. on cognitive function in older adults w/ family Hx of AD-like dementia	I. In-person Cognitive Assessment Battery (CAB): - Modified Mini-Mental State Examination (3MS-E) - Hopkins Verbal Learning Test-Revised (HVLT-R)

<p>IIIF Result analysis of ADAPT (IIIB) Non-interventional; retrospective longitudinal</p>	<p>2,356 men & women; community-dwelling older adults (70 ≤ y.o.); asymptomatic of cognitive deterioration but w/ family Hx of at least 1 first-degree relative AD-like dementia</p>	<p>-</p>	<p>Intervention in ADAPT: (1) Celecoxib 200 mg bid (2) Naproxen sodium 220 mg bid</p>	<p>Y1 (2001) → baseline cognitive assessment Y2 (2002) → f/u cognitive assessment Y3 (2003) → f/u cognitive assessment Y4 (2004) → f/u cognitive assessment</p>	<p>YES: evidence differs based on participant membership in one of three cognitive-decline classes: (i) no-decline (class 1), (ii) slow-decline (class 2), & (iii) fast-decline (class 3) No evidence of protective effect of celecoxib or naproxen sodium in slow-decliners; in fact, evidence of deleterious effect of naproxen sodium in fast-decliners; however, evidence of protective effect of celecoxib in fast-decliners</p>	<p>- Informant-rated Dementia Severity Rating Scale (DSRS) - Digit Span Test - Rivermead Behavioral Memory Test (RBMT) - Brief Visuo-spatial Memory Test-Revised (BVM-T-R) - Self-rating of memory functions - Geriatric Depression Scale - Global summary score II. Telephone Assessment Battery (TAB): - Telephone Interview for Cognitive Status (TICS) - Generative Verbal Fluency (GVF) - Rivermead Behavioral Memory Test (RBMT) III. In-person Dementia Evaluation Visit (DEV)</p>	<p>Cognitive measures used for statistical analyses: - Modified Mini-Mental State Examination (3MS-E) - Informant-rated Dementia Severity Rating Scale (DSRS)</p>
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Notes. 3MS-E = Modified Mini-Mental State Examination; AD = Alzheimer's disease; ApoE = apolipoprotein E; CVD = cardiovascular disease; DEV = Dementia Evaluation Visit; DM = diabetes mellitus; DSST = Digit Symbol Substitution Test; f/u = follow-up; GVF = Generative Verbal Fluency; I-M-C =

Information-Memory-Concentration Test; MMSE = Mini-Mental State Examination; NSAID = non-steroidal anti-inflammatory drugs; HTN = hypertension; Hx = history; RBMT = Rivermead Behavioral Memory Test; SPMSQ = Short Portable Mental Status Questionnaire; TICS = Telephone Interview for Cognitive Status; TMT = Trail Making Test; Y = year; yr./yrs. = year/s.

- IIIA: Hanlon, J. T., Schmader, K. E., Landerman, L. R., Horner, R. D., Fillenbaum, G. G., Pieper, C. F., . . . Cohen, H. J. (1997). Relation of prescription non-steroidal anti-inflammatory drug use to cognitive function among community-dwelling elderly. *Annals of Epidemiology*, 7(2), 87-94. doi: 10.1016/S1047-2797(96)00124-X.
- IIIB: Martin, B. K., Szekely, C., Brandt J., Piantadosi, S., Breitner J. C. S., Craft, S., . . . Mullan, M. (2008). Cognitive function over Time in the Alzheimer's Disease Antiinflammatory Prevention Trial (ADAPT): Results of a randomized, controlled trial of naproxen and celecoxib. *Archives of Neurology*, 65(7), 896-905. doi: 10.1001/archneur.2008.65.7.nct70006.
- IIIC: Breitner, J. C., Baker, L. D., Montine, T. J., Meinert, C. L., Lyketsos, C. G., & Ashe, K. H., . . . Tariot, P. N. for the ADAPT Research Group. (2011). Extended results of the Alzheimer disease anti-inflammatory prevention trial (ADAPT). *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, 7(4), 402-11. doi: 10.1016/j.jalz.2010.12.014.
- IIID: Martin, B. K., Szekely, C., Brandt J., Piantadosi, S., Breitner J. C. S., Craft, S., . . . Mullan, M. The Alzheimer's Disease Anti-Inflammatory Prevention Trial Research Group. (2013). Results of a follow-up study to the randomized Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT). *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, 9(6). doi: 10.1016/j.jalz.2012.11.012.
- IIIE: ADAPT-FS Research Group. (2015). Follow-up evaluation of cognitive function in the randomized Alzheimer's Disease Anti-Inflammatory Prevention Trial and its follow-up study. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, 11(2), 216-25. doi: 10.1016/j.jalz.2014.03.009.
- IIIF: Leoutsakos, J.-M. S., Muthen, B. O., Breitner, J. S., Lyketsos, C. G., & For the ADAPT Research Team. (2011, May 10). Effects of non-steroidal anti-inflammatory drug treatments on cognitive decline vary by phase of pre-clinical Alzheimer's disease: Findings from the randomized controlled Alzheimer's Disease Anti-inflammatory Prevention Trial. *International Journal of Geriatric Psychiatry*, 27(4), 364-74. doi: 10.1002/gps.2723.