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Follow-up evaluation of cognitive function in the randomized Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) and its Follow-up Study (ADAPT-FS)

ADAPT-FS research group

Abstract

Objective—The Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT) and follow-up study (ADAPT-FS) examined effects of naproxen and celecoxib on cognition in the elderly. We report here results describing trajectories of cognitive evaluation test scores.

Methods—2356 participants completed baseline and at least one follow-up cognitive evaluation between 2001-2004. Study treatments were discontinued in 2004, but participants were followed until 2007. 1537 participants were re-evaluated in 2010-2011. Outcomes include seven cognitive evaluations administered yearly in-person in ADAPT and three of these evaluations that were administered by telephone near the end of ADAPT and again in ADAPT-FS.

Results—There were no important differences over time by treatment group on any ADAPT cognitive measure, a global composite, or the three cognitive measures re-assessed in ADAPT-FS by telephone.

Conclusions—Treatment for 1 – 3 years with naproxen or celecoxib did not protect against cognitive decline in older adults with a family history of AD.

Keywords

prevention; clinical trial; Alzheimer's disease; cognitive function; non steroidal anti-inflammatory drug; naproxen; celecoxib

Background

Several lines of evidence from molecular and epidemiologic studies suggest that nonsteroidal anti-inflammatory drugs (NSAIDs) might protect against cognitive decline and impairment in the elderly (1-6), although not all studies have shown benefit (7-9). Motivated by these findings, the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) was initiated to test whether naproxen (a non-selective cyclooxygense [COX] inhibitor) or celecoxib (a selective COX-2 inhibitor) could delay the onset of dementia among cognitively intact older adults with a family history of Alzheimer's dementia. A secondary

aim was to examine whether the treatments could attenuate age-related decline on quantitative measures of cognitive function (10). This secondary aim was motivated by the supposition that the quantitative cognitive measures would provide more power to detect treatment effects than the dichotomous outcome of dementia.

ADAPT study treatments were stopped after a median of 14.8 months following randomization due to concerns about the cardiovascular safety of sustained NSAID use in the elderly (11). Reports over the treatment interval indicated that neither celecoxib nor naproxen prevented onset of dementia (12) or slowed cognitive decline over time (13). In fact, these initial findings suggested that the treatments might have increased the risk for dementia and exacerbated decline on global measures of cognition.

The ADAPT Follow-up Study (ADAPT-FS) was carried out to evaluate the cognitive function of ADAPT participants nearly six years after the end of study treatment. A recent report from ADAPT-FS confirmed that neither naproxen nor celecoxib prevented onset of AD over this extended follow-up (14). Here we describe the long term effects of naproxen and celecoxib on cognitive performance over time, including previously unreported data accumulated during in-person visits in the 1.5 years after the end of study treatments in ADAPT and the ADAPT and ADAPT-FS telephone evaluations.

Methods

Description of ADAPT and ADAPT-FS

ADAPT has been described elsewhere (15). Briefly, participants enrolled between March 2001 and December 2004 and were assigned in parallel to three treatment groups in a 1:1:1.5 ratio: 1) naproxen sodium (220 mg b.i.d.); 2) celecoxib (200 mg b.i.d.); or 3) placebo. Participants were recruited at six field sites and were age 70 years or older and had a history of at least one first-degree relative with Alzheimer-like dementia. Before enrollment, they completed a cognitive screening test intended to identify and exclude those with dementia or other cognitive disorders. The ADAPT protocol was approved by the Institutional Review Boards (IRBs) at each field site and the coordinating center.

Participants were seen in-person annually and were contacted by telephone between in-person visits. In December 2004, enrollment and treatment administration were suspended following announcement from the Adenoma Prevention with Celecoxib (APC) trial that celecoxib used in two doses (one of which was identical to that used in ADAPT) produced increased risks of cardiovascular death, myocardial infarction, and related events (16). Treatments were stopped permanently in March 2005, but double-masked follow-up of ADAPT participants continued until February 2007.

Nearly three years after the termination of ADAPT, a follow up study, ADAPT-FS, collected information on cognitive status of ADAPT participants who were alive, had not refused further contact during ADAPT, and had not received a diagnosis of dementia during ADAPT. Eligible participants were contacted by phone between February 2010 and February 2011. The procedures for ADAPT-FS have been published (14). Participants provided oral consent for the telephone assessment and written consent for any subsequent

in-person assessment. The ADAPT-FS protocol was also approved by the IRBs at the coordinating center and each of the six field sites.

Cognitive measures

ADAPT psychometrists administered an in-person Cognitive Assessment Battery (CAB) at baseline and at annual follow-up visits. The CAB included the Modified Mini-Mental State Examination (3MS-E) (17), Hopkins Verbal Learning Test – Revised (HVLT-R) (18), informant-rated Dementia Severity Rating Scale (DSRS) (19), Digit span tests (both forward and backward) (20), a generative verbal fluency test (21), narratives from the Rivermead Behavioral Memory Test (22), the Brief Visuospatial Memory Test –Revised (BVMT-R) (23), self-rating of memory functions (24), and the Geriatric Depression Scale (25). All of these measures except the self- and informant-rated scales for cognition and depression are considered here. We also calculated a global summary score from these seven measures as the unweighted mean of the standardized scores (z-scores) of the seven assessments using baseline norms.

In the final year of ADAPT and once during ADAPT-FS, a Telephone Assessment Battery (TAB) was administered. This battery included the Telephone Interview for Cognitive Status (TICS) (26), a test of generative verbal fluency (21), and the narratives subset of the Rivermead Behavioral Memory Test (RBMT) (22). For all cognitive assessments in the CAB and TAB included here, higher scores indicated better cognitive functioning.

ADAPT and ADAPT-FS participants whose CAB or TAB results fell below specified criteria, or those who were otherwise thought by a study clinician to require further evaluation, were asked to have an in-person Dementia Evaluation Visit (DEV). The CAB, TAB and DEV protocols have been described elsewhere (15, 27, 28). The DEV involved a more extensive neuropsychological assessment, a detailed medical history, neurological examination and global mental status examination, collateral interviews and, when appropriate, laboratory testing and neuroimaging. Participants continued to have annual cognitive assessment visits in ADAPT after dementia diagnoses for as long as they were willing and able (until the end of study).

Data analyses

Analyses included all available data with participants included in the treatment group to which they were assigned. By design, naproxen and celecoxib were both compared with placebo and not with one another. Estimates of the change from baseline to each follow-up time point and the change from the ADAPT TAB assessments to the ADAPT-FS TAB assessments were calculated for each applicable assessment and compared using t-tests and linear regression adjusting for clinic and age strata. Longitudinal analyses of change from baseline to all follow-up points were conducted using generalized estimating equation (GEE) regression assuming a exchangeable covariance structure for the within-person replicate measurements with robust standard errors and controlling for the randomization stratification variables (field site and age group). The GEE model provided estimates of the mean difference between the active treatment groups and those given placebo across all ADAPT follow-up times. Additionally, we calculated odds ratios using logistic regression

for each treatment compared with placebo using the outcome of a decline from baseline of either a specified number of points on the 3MS-E (5, 6, 7, 8, 9, or 10 points) or a specified effect size (0.50, 0.75, 1.00, or 1.25 SDs) on the global summary score at any time during follow-up.

A similar, but post-hoc, longitudinal GEE analysis was performed to examine the cognitive trajectories in those who did versus did not develop dementia (not by treatment group) over the course of in-person follow-up.

Sensitivity analyses for the GEE models of treatment effect were performed by testing for treatment interactions with the following variables 1) before versus after study-wide treatment termination; 2) by end-of-study dementia diagnostic status; 3) by end-of-study vital status; or 4) by presence of one or more APOE ε4 alleles. Although we attempted to exclude from enrollment people with cognitive impairment, 8 participants with dementia and 57 participants with cognitive impairment but not dementia (CIND) were not detected by the enrollment cognitive screener. We also constructed the GEE models after first excluding participants with prevalent dementia at baseline or after excluding those participants who had either prevalent dementia or CIND.

Results

Study population

Out of 2528 participants enrolled in ADAPT, 1537 also participated in ADAPT-FS. These ADAPT participants were highly educated and mostly Caucasian with a median age at randomization in ADAPT of 75. The participants who completed the ADAPT-FS cognitive assessment were similar to the original ADAPT sample. Detailed descriptions of baseline characteristics for all ADAPT participants (15, 27, 28) as well as for the participants who did complete versus did not complete cognitive assessment in ADAPT-FS (14) have been previously reported. Table 1 reviews baseline characteristics at the time of original randomization of the 2356 participants who completed at least one follow-up assessment in ADAPT or ADAPT-FS. At the time of ADAPT-FS enrollment, their median age was 82 years, and a large majority (85%) of them still lived in their own homes.

Cognitive function over time

Figure 1 shows the raw mean scores with 95% confidence intervals for each assessment using the CAB and TAB by follow-up visit or telephone contact. Table 2 shows the number of participants with data available at each ADAPT follow-up visit CAB and their mean change scores with confidence intervals by treatment group. In general, the participants experienced very small declines over time in the global summary score, 3MS-E score, GVF, and BVMT-R. These declines did not differ by treatment group except for small differences favoring placebo over both naproxen and celecoxib in year two; however, this did not continue in later years for the global summary score, 3MS-E or GVF. Scores on the RBMT, HVLT and digit span tests did not decline over time and did not differ by treatment group in any year of follow-up.

Figure 2 shows the global summary and 3MS-E scores over time for those who were diagnosed with dementia during ADAPT or ADAPT-FS versus all others. The global summary and 3MS-E scores for those who remained dementia-free shows remarkably little change over five years. The participants who received a dementia diagnosis at some point during follow-up scored significantly lower *at baseline* on the 3MS-E (-2.5 points [95%CI: -3.1, -1.8]; $p < 0.0001$) and the global summary score (-0.4 standardized points [-0.5, -0.3], $p < 0.0001$) than others. The difference was slightly smaller but remained highly significant after excluding from analysis those participants who had prevalent dementia or CIND at baseline (3MS-E: -1.9 [95%CI: -2.5, 1.3]; $p < 0.0001$; global summary: -0.3 [95% CI: -0.4, -0.2]; $p < 0.0001$).

Table 3 shows GEE estimates of the difference in mean change from baseline across all years of follow-up, confirming the findings from the yearly estimates. The difference in mean change on the GVF for celecoxib versus placebo is -0.40 (95% CI: -0.81, 0.00; $p = 0.05$) and for naproxen versus placebo is -0.39 (95% CI -0.80 to 0.02; $p = 0.06$), indicating slightly more decline in the active groups compared to placebo. Estimates for all other cognitive measures showed very little difference in change between the active groups and placebo (all $p > 0.05$).

As shown in Supplementary Table 1, odds ratios comparing each treatment group with placebo tended slightly toward more decline in the active groups compared with placebo for the global summary cutpoints and the 3MS-E cutpoints.

The ADAPT TAB and ADAPT-FS TAB were conducted a median (1^{st}, 3^{rd} quartile) of 48 months (44, 51) apart. The changes in TICS, RBMT and GVF between the ADAPT and ADAPT-FS TABs are shown in Table 4. In general, the TICS declined less than two points on average (out of maximum possible score of 41); the RBMT declined less than three points on average (out of maximum possible score of 21); and the GVF declined less than four points on average (out of maximum score in this population at baseline of 53). None of these changes differed by treatment group.

Sensitivity analyses

We conducted four tests for interactions (described in methods) for each of the eight cognitive measures (seven assessments plus global summary) to see how the two treatment effects varied in several subgroups of people or at different times. With a total of 64 interaction tests, we expected to see between three and four significant p-values (at the 0.05 level) by chance alone. However, we found no evidence for interactions between treatment group and a dummy variable indicating whether the visit occurred before or after the study-wide treatment termination date for the global summary, 3MS-E, RBMT, BVMT, HVLT or either digit span test. The treatment effect for naproxen versus placebo on the GVF was negative (favoring placebo) before the treatment termination and positive (favoring naproxen) after the treatment termination (interaction $p = 0.05$). Treatment effect estimates did not differ in those with and without end-of-study dementia diagnoses for any of the cognitive measures (all interaction $p > 0.05$). There was little evidence of a difference in either treatment effect by presence or absence of APOE ε4 with the possible exception of the HVLT-R. For the HVLT-R the average difference in decline of scores was larger in the

celecoxib than placebo group for those participants with [.epsilon]4 versus without (interaction p = 0.03). Also, for the HVLT-R only, comparing those participants who died versus those who survived over both ADAPT and ADAPT-FS, the difference in the rate of decline was larger in the active groups compared to placebo (celecoxib interaction p = 0.05; naproxen interaction p = 0.06). Given the number of tests performed and the general lack of consistent findings, we do not believe that the "statistically significant" interaction tests are meaningful.

We also repeated the longitudinal analyses excluding 1) people who were found to have dementia at baseline and 2) people with either dementia or CIND at baseline and found the magnitude of the treatment effect estimates to be virtually unchanged after both sets of exclusions (data not shown).

Discussion

Despite encouraging evidence from prior molecular and epidemiologic studies (1), the findings from ADAPT and ADAPT-FS do not support the conclusion naproxen or celecoxib (given over a relatively short interval) afford protection against cognitive impairment in the elderly. In a previous report using data from ADAPT and ADAPT-FS, we focused on the effects of naproxen and celecoxib on the primary outcome of dementia onset (14). Here, we examined the long term effects of these NSAIDs on quantitative measures of cognitive decline. These analyses were motivated by the consideration that quantitative measures may provide a more sensitive index of change in cognitive functioning than a dichotomous diagnosis of dementia, and therefore, yield greater power to detect any neurocognitive benefits of naproxen and celecoxib. Moreover, these measures might have captured certain domains of cognitive function that are preferentially protected by the treatments. However, our findings offer little evidence that the drugs attenuated age-related cognitive decline overall or in any specific domain, or that the treatment effects differed by follow-up time, eventual dementia onset, mortality, or *APOE* genotype status.

Several non-randomized prospective studies previously examined the relationship between NSAID use and cognitive decline over time. The majority of these, including three population based studies (2, 5, 29), a volunteer based study (30), and an ancillary study to a hypertension trial (31), found that NSAIDs were associated with less decline on certain global cognitive or brief cognitive screening measures. Two of these studies found that the protective association was more apparent among younger elderly (5, 31), and one suggested the protection was greater for those with an *APOE* ε4 allele (5). However, the findings have not been entirely consistent, with one of the most recent non-randomized studies reporting a lack of association between NSAID use and global cognitive decline (8).

ADAPT was the first study to examine this relationship in a randomized experiment among cognitively intact elderly. In an earlier analysis that included ADAPT data collected only until the end of study treatment, we reported that both naproxen and celecoxib were associated with slightly greater decline on global cognitive measures. Here, we found that over longer term observation after treatments had been stopped, the possible adverse effects of these treatments were no longer apparent. This was true for the global as well as specific cognitive measures.

The current study has several limitations that merit discussion. First, the duration of treatment administration was considerably less than planned due to the premature termination of the study in response to growing concerns about the safety of NSAID use in the elderly (11). As we noted before when describing the primary outcome of dementia onset, the median length of treatment for participants in ADAPT was less than 1.5 years, which is far shorter than the planned 7 years. It is quite possible that this duration of treatment was insufficient to alter cognitive trajectories in any meaningful way. A second concern is that we observed very little overall decline in cognitive functioning among trial participants who did not go on to develop dementia (Figure 2 shows the remarkable stability of these scores); although, there were small declines in the four years between the ADAPT and ADAPT-FS telephone assessments. This sort of observation has now been found in several studies (e.g., see Figure 1 in Wilson, et al. (32)). Certainly, the lack of variability in decline among ADAPT participants could have made it even more difficult to detect meaningful effects of the treatments on these trajectories. Also, the median age of those enrolled in ADAPT was older than several of the most notable observational studies suggesting an inverse association between NSAID use and AD, and it is notable that the studies that failed to find such an association generally had older samples than the remainder.

Possible neurocognitive benefits of NSAIDs in the elderly have been a focus of much interest and considerable debate. Initial enthusiasm sparked by suggestive findings from several molecular and epidemiological studies has been dampened by the disappointing results from randomized trials for the treatment of dementia, secondary prevention trials of effects on progression of mild cognitive impairment and now, with these results from ADAPT/ADAPT-FS the primary prevention of dementia (for review see Szekely and Zandi (33)). In ADAPT/ADAPT-FS, it can now be stated that the treatments did not appear to prevent the onset of dementia nor to attenuate decline in global cognition or specific cognitive domains over ten years of follow-up. Although the fact that the NSAID treatments were stopped prematurely may limit the inference possible from ADAPT/ADAPT-FS, it is clear the results of the trial do not support the hypothesis that naproxen and celecoxib, at least with brief exposure, provide meaningful neurocognitive benefits in the elderly.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Study data:

ADAPT and ADAPT-FS datasets are available upon request. All requests must be vetted by the Study Officers and must include an analysis plan. If the request is approved, the requestor must have IRB approval to receive data. Requests can be submitted to the address provided on the ADAPT or ADAPT-FS websites:

http://jhuccs1.us/adapt/default.htm

http://jhuccs1.us/adapt-fs/default.htm

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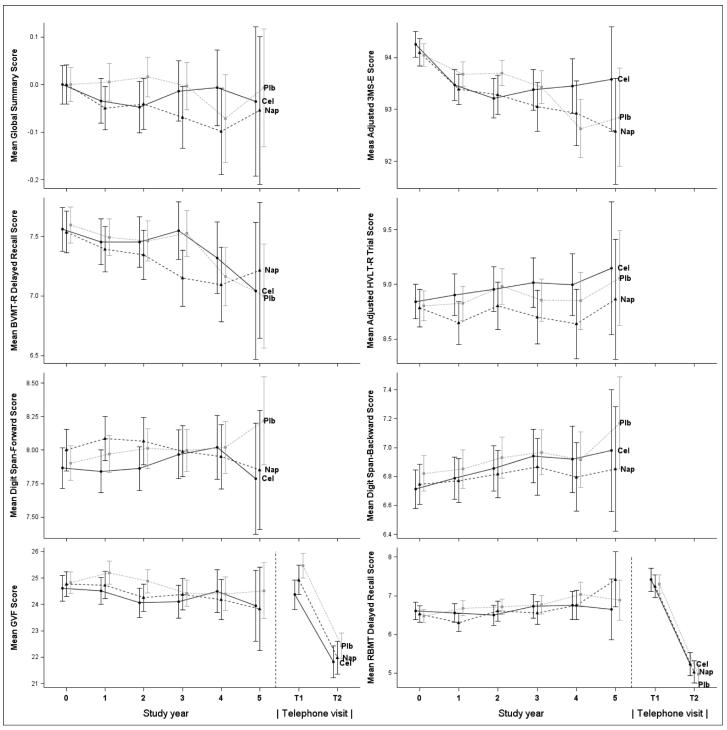

Available data at each time point are as follows: baseline (year 0), n = 2528; year 1, n = 2237; year 2, n = 2049; year 3, n = 1664; year 4, n = 1082; year 5, n = 323; T1, n = 1850; T2, n = 1537. BVMT-R, Brief Visuospatial Memory Test-Revised; HVLT-R, Hopkins Verbal Learning Test-Revised; RBMT, Rivermead Behavioral Memory Test; and 3MS-E, Modified Mini-Mental State Examination. T1 was the telephone assessment during ADAPT and T2 was the telephone assessment during ADAPT-FS; the T1 and T2 were a median of 48 months apart.

Figure 1.

Raw scores for each of the 7 tests of cognitive function and the global summary over time

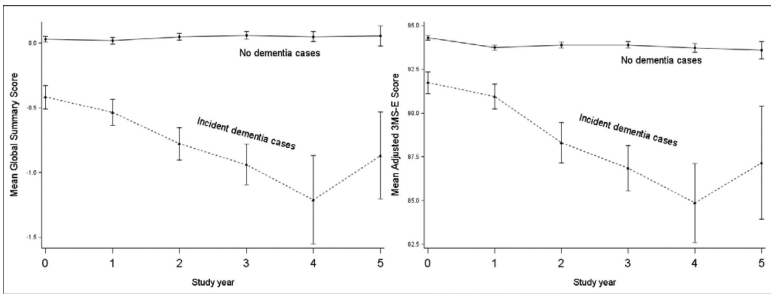

Figure 2.
Global summary and 3MS-E by dementia diagnosis (during ADAPT or ADAPT-FS)

Table 1

Characteristics at randomization of ADAPT participants with follow-up cognitive assessment

	Total	Celecoxib	Naproxen	Placebo
N	2356	677	667	1012
Characteristic				
Age, median	74.5	74.5	74.5	74.5
Age, %				
70-74	55.7	55.7	56.1	55.5
75-79	31.3	30.7	31.6	31.5
80-84	11.2	11.8	10.2	11.4
> 85	1.8	1.8	2.1	1.6
Sex, %				
Male	54.2	52.4	54	55.5
Female	45.8	47.6	46	44.5
Race/Ethnic origin, %				
White	96.8	96	96.9	97.3
African-American	1.5	1.8	1.9	1.1
Hispanic	0.8	1.5	0.3	0.6
Other	0.8	0.6	0.7	0.9
Did not answer	0.1	0.1	0.1	0.1
Education, %				
< High school	3.9	3.5	4.6	3.7
High school degree	19.2	20.7	16.8	19.9
College, no degree	27.4	27.5	28.5	26.6
College degree	19.2	19.4	16.8	20.7
Post graduate	30.3	29	33.3	29.2
Marital status, %				
Married	72.1	70.6	74.8	71.2
Widowed	18.3	19.9	16.2	18.6
Separated	0.6	0.4	0.3	0.8
Divorced	6.4	6.4	5.7	6.9
Never married	2.6	2.7	3	2.4
Not reported	0	0	0	0
Karnofsky score, %				
100	83.3	84.5	82	83.4
90	14.7	13.3	16.9	14.2
80	1.8	2.1	0.9	2.2
60-70	0.2	0.1	0.1	0.2
Cognitive score, median				
Adjusted 3MS-E	95.0	95.0	95.0	95.0
GVF	25.0	24.0	24.0	25.0
RBMT delayed recall	6.5	6.5	6.0	6.5

	Total	Celecoxib	Naproxen	Placebo
BVMT-R delayed recall	8.0	8.0	8.0	8.0
HVLT-R delayed recall	9.0	9.0	9.0	9.0
Digit Span- forward	8.0	8.0	8.0	8.0
Digit Span-backward	7.0	7.0	6.0	7.0

BVMT-R, Brief Visuospatial Memory Test-Revised; HVLT-R, Hopkins Verbal Learning Test-Revised; RBMT, Rivermead Behavioral Memory Test; and 3MS-E, Modified Mini-Mental State Examination

Table 2

Mean changes from baseline in cognitive function by treatment group for ADAPT visits

Measure	Celecoxib		Naproxen		Placebo		p-value*	
	N	Mean change (95% CI)	N	Mean change (95% CI)	N	Mean change (95% CI)	Celecoxib vs Placebo	Naproxen vs Placebo
Global summary								
1 year	651	−0.04 (−0.07, −.01)	633	−0.06 (−0.09, −.03)	951	−0.03 (−0.05, −.00)	0.57	0.14
2 years	601	−0.06 (−0.09, −.02)	578	−0.06 (−0.09, −.02)	870	−0.02 (−0.05, 0.00)	0.09	0.10
3 years	469	−0.05 (−0.09, −.00)	479	−0.10 (−0.15, −.06)	715	−0.05 (−0.08, −.02)	0.89	0.05
4 years	310	−0.05 (−0.10, 0.01)	311	−0.12 (−0.19, −.04)	461	−0.13 (−0.20, −.06)	0.10	0.82
5 years	94	−0.11 (−0.23, −.00)	88	−0.10 (−0.21, 0.01)	141	−0.11 (−0.20, −.03)	0.99	0.86
Adjusted 3MS-E								
1 year	651	−0.81 (−1.07, −0.55)	633	−0.70 (−0.97, −0.43)	951	−0.49 (−0.70, −0.29)	0.06	0.22
2 years	601	−1.12 (−1.45, −0.79)	578	−0.90 (−1.22, −0.58)	869	−0.46 (−0.68, −0.23)	0.00	0.02
3 years	468	−1.12 (−1.46, −0.77)	479	−1.19 (−1.59, −0.78)	715	−0.71 (−0.99, −0.44)	0.07	0.05
4 years	310	−1.01 (−1.46, −0.56)	311	−1.28 (−1.84, −0.72)	461	−1.59 (−2.09, −1.09)	0.11	0.43
5 years	94	−1.40 (−2.33, −0.48)	88	−1.89 (−2.79, −0.98)	141	−1.65 (−2.46, −0.83)	0.70	0.70
GVF								
1 year	651	−0.09 (−0.50, 0.33)	633	−0.10 (−0.54, 0.35)	951	0.31 (−0.05, 0.66)	0.16	0.16
2 years	601	−0.52 (−0.98, −0.06)	578	−0.67 (−1.14, −0.19)	868	−0.03 (−0.39, 0.34)	0.10	0.03
3 years	469	−0.62 (−1.11, −0.13)	479	−0.70 (−1.22, −0.18)	715	−0.51 (−0.94, −0.08)	0.75	0.58
4 years	310	−0.18 (−0.83, 0.48)	311	−0.67 (−1.35, 0.01)	460	−0.28 (−0.81, 0.25)	0.80	0.38
5 years	94	−1.72 (−2.94, −0.50)	88	−1.28 (−2.56, −0.01)	141	−1.04 (−2.01, −0.06)	0.38	0.76
RBMT delayed recall								
1 year	651	−0.07 (−0.33, 0.19)	633	−0.24 (−0.48, 0.01)	951	0.05 (−0.16, 0.25)	0.49	0.09
2 years	601	−0.14 (−0.41, 0.12)	578	0.06 (−0.21, 0.33)	869	0.06 (−0.16, 0.28)	0.25	1.00
3 years	468	0.01 (−0.27, 0.28)	478	−0.09 (−0.33, 0.16)	715	0.08 (−0.13, 0.29)	0.68	0.31
4 years	310	0.07 (−0.30, 0.44)	310	0.24 (−0.18, 0.65)	460	0.33 (0.00, 0.66)	0.30	0.73
5 years	94	−0.05 (−0.86, 0.76)	88	1.31 (0.53, 2.09)	141	0.32 (−0.26, 0.91)	0.45	0.04
BVMT-R delayed recall								
1 year	651	−0.14 (−0.32, 0.03)	633	−0.20 (−0.39, −0.02)	951	−0.21 (−0.34, −0.07)	0.57	0.98
2 years	600	−0.19 (−0.39, −0.00)	578	−0.28 (−0.48, −0.08)	867	−0.26 (−0.42, −0.10)	0.61	0.87

Measure	Celecoxib		Naproxen		Placebo		p-value*	
	N	Mean change (95% CI)	N	Mean change (95% CI)	N	Mean change (95% CI)	Celecoxib vs Placebo	Naproxen vs Placebo
3 years	465	−0.18 (−0.41, 0.05)	479	−0.50 (−0.73, −0.28)	714	−0.27 (−0.45, −0.09)	0.53	0.11
4 years	309	−0.41 (−0.72, −0.10)	310	−0.43 (−0.70, −0.15)	459	−0.62 (−0.87, −0.38)	0.29	0.30
5 years	94	−0.86 (−1.38, −0.34)	88	−0.70 (−1.19, −0.22)	141	−0.99 (−1.42, −0.57)	0.70	0.39
HVLT-R delayed recall								
1 year	651	0.02 (−0.17, 0.20)	633	−0.12 (−0.32, 0.07)	950	−0.10 (−0.24, 0.05)	0.34	0.83
2 years	601	0.01 (−0.18, 0.20)	578	0.04 (−0.17, 0.26)	869	0.06 (−0.10, 0.22)	0.72	0.88
3 years	468	0.06 (−0.15, 0.27)	478	−0.05 (−0.27, 0.18)	714	0.02 (−0.16, 0.19)	0.75	0.66
4 years	310	−0.08 (−0.37, 0.22)	310	−0.16 (−0.47, 0.14)	460	−0.04 (−0.27, 0.19)	0.85	0.52
5 years	94	0.18 (−0.39, 0.76)	88	−0.13 (−0.64, 0.39)	141	0.18 (−0.22, 0.58)	0.99	0.36
Digit span forward	650	−0.00 (−0.14, 0.13)	633	0.06 (−0.08, 0.19)	951	0.03 (−0.08, 0.14)	0.73	0.73
1 year	599	0.03 (−0.11, 0.17)	576	0.02 (−0.12, 0.17)	868	0.03 (−0.08, 0.15)	0.96	0.90
2 years	467	0.07 (−0.10, 0.23)	479	−0.14 (−0.31, 0.03)	715	−0.04 (−0.18, 0.09)	0.31	0.40
3 years	308	0.11 (−0.09, 0.32)	310	−0.15 (−0.35, 0.06)	460	−0.03 (−0.21, 0.15)	0.30	0.41
4 years	94	−0.05 (−0.35, 0.24)	88	−0.17 (−0.54, 0.20)	141	0.07 (−0.23, 0.37)	0.58	0.32
5 years								
Digit span backward								
1 year	648	0.08 (−0.05, 0.21)	633	0.00 (−0.13, 0.14)	951	−0.00 (−0.11, 0.11)	0.34	0.94
2 years	599	0.15 (0.00, 0.29)	577	0.01 (−0.13, 0.15)	866	0.05 (−0.07, 0.17)	0.32	0.68
3 years	466	0.24 (0.08, 0.41)	479	0.05 (−0.12, 0.22)	714	0.02 (−0.12, 0.15)	0.04	0.76
4 years	308	0.20 (−0.01, 0.41)	310	−0.05 (−0.26, 0.17)	460	−0.15 (−0.31, −0.00)	0.01	0.41
5 years	94	0.32 (−0.08, 0.71)	88	0.00 (−0.39, 0.39)	141	0.01 (−0.27, 0.29)	0.19	0.98

CI: confidence interval; BVMT-R: Brief Visuospatial Memory Test - Revised; GVF: generative verbal fluency; HVLT-R: Hopkins Verbal Learning Test - Revised; RBMT: Rivermead Behavioral Memory Test; 3MS-E: Modified Mini-Mental State Examination

* T test for differences: active compared to placebo. Negative values indicate decline in cognitive measure during follow-up visit

Table 3

Longitudinal effect of treatment on cognitive function for ADAPT visits only

Measure	Celecoxib vs Placebo		Naproxen vs Placebo	
	Estimated* difference in mean change from baseline (95% CI)	p-value	Estimated* difference in mean change from baseline (95% CI)	p-value
Global summary	−0.01 (−0.04 to 0.03)	0.72	−0.03 (−0.07 to 0.00)	0.08
Adjusted 3MS-E	−0.24 (−0.52 to 0.05)	0.11	−0.27 (−0.58 to 0.03)	0.08
GVF	−0.40 (−0.81 to 0.00)	0.05	−0.39 (−0.80 to 0.02)	0.06
RBMT delayed recall	−0.13 (−0.34 to 0.08)	0.22	−0.17 (−0.38 to 0.05)	0.13
BVMT-R delayed recall	0.04 (−0.12 to 0.21)	0.60	−0.10 (−0.27 to 0.06)	0.22
HVLT-R delayed recall	0.07 (−0.10 to 0.24)	0.44	−0.11 (−0.28 to 0.07)	0.24
Digit span forward	−0.02 (−0.14 to 0.10)	0.78	−0.01 (−0.13 to 0.12)	0.93
Digit span backward	0.08 (−0.05 to 0.20)	0.22	−0.03 (−0.15 to 0.10)	0.69

CI: confidence interval; BVMT-R: Brief Visuospatial Memory Test - Revised; GVF: generative verbal fluency; HVLT-R: Hopkins Verbal Learning Test - Revised; RBMT: Rivermead Behavioral Memory Test; 3MS-E: Modified Mini-Mental State Examination

* Calculated using generalized estimating equations (GEE) to account for within person correlation in repeated measures and adjusted for clinic and age strata. Negative values indicate more decline in active as compared to placebo

Table 4

Mean change* from ADAPT telephone assessment to ADAPT-FS telephone assessment by treatment group

Measure	Celecoxib	Naproxen	Placebo	p-value	
	Mean change (95% CI)	Mean change (95% CI)	Mean change (95% CI)	Celecoxib vs Placebo	Naproxen vs Placebo
TICS	−1.47 (−1.80, −1.14)	−1.66 (−1.98, −1.33)	−1.56 (−1.83, −1.30)	0.66	0.64
RBMT delayed recall	−2.48 (−2.81, −2.15)	−2.39 (−2.72, −2.07)	−2.41 (−2.67, −2.14)	0.73	0.95
GVF	−3.62 (−4.21, −3.03)	−3.20 (−3.78, −2.84)	−3.32 (−3.80, −2.84)	0.43	0.76

CI: confidence interval; TICS: Telephone Interview for Cognitive Status; GVF: Generative Verbal Fluency; RBMT: Rivermead Behavioral Memory Test

*Estimates are from linear regression adjusting for clinic and age strata. Negative values indicate decline in cognitive measure