

## Low dose aspirin and cognitive function in the women's health study cognitive cohort

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### ABSTRACT

**Objective** To determine whether low dose aspirin protects women aged 65 or more against cognitive decline.

**Design** Cohort study within both arms of the women's health study, a randomised, double blind, placebo controlled trial of low dose aspirin for the primary prevention of cardiovascular disease and cancer, 1992-5.

**Setting** Women's health study, 1998-2004.

**Participants** 6377 women aged 65 or more.

**Interventions** Low dose aspirin (100 mg on alternate days) or placebo for a mean of 9.6 years.

**Main outcome measures** Women had three cognitive assessments at two year intervals by telephone. The battery to assess cognition included five tests measuring general cognition, verbal memory, and category fluency. The primary prespecified outcome was a global score, averaging performance across all tests. The key secondary outcome was a verbal memory score, averaging performance on four measures of verbal memory.

**Results** At the initial assessment (mean 5.6 years after randomisation) cognitive performance in the aspirin group was similar to that of the placebo group (mean difference in global score -0.01, 95% confidence interval -0.04 to 0.02). Mean decline in the global score from the first to the final cognitive assessment was also similar in the aspirin compared with placebo groups (mean difference 0.01, -0.02 to 0.04). The risk of substantial decline (in the worst 10th centile of decline) was also comparable between the groups (relative risk 0.92, 0.77 to 1.10). Findings were similar for verbal memory; however, a 20% lower risk was observed for decline in category fluency with aspirin (relative risk 0.80, 0.67 to 0.97).

**Conclusion** Long term use of low dose aspirin does not provide overall benefits for cognition among generally healthy women aged 65 or more.

### INTRODUCTION

Increasingly, research has focused on reducing the risk of early cognitive decline, a strong predictor of dementia.<sup>1,2</sup> Randomised trials<sup>3-7</sup> have generally found no benefits of aspirin and other anti-inflammatory drugs for patients with Alzheimer's disease, although the trials were short and the disease may have been advanced. Several anti-inflammatory drugs have been implicated in cardiovascular disease<sup>8</sup>; however, low dose aspirin has been shown to provide vascular benefits, particularly in those aged 65 or more.<sup>9,10</sup>

We tested the effect of long term use of low dose aspirin on overall cognitive decline over four years among a subset of women aged 65 or more from the women's health study.<sup>10</sup>

### METHODS

The women's health study was a randomised, placebo controlled trial of low dose aspirin and vitamin E in the prevention of cardiovascular disease and cancer among 39 876 US women.<sup>11</sup> Women were randomised from 1992-5: 19 934 to aspirin, 19 942 to placebo. Most participants are white (95%).

In 1998 we started a substudy of cognitive function among women aged at least 65 (see [bmj.com](http://bmj.com)). Overall, 6377 of the 7175 women (88.9%) selected completed the initial cognitive assessment by telephone (see [bmj.com](http://bmj.com)). Telephone assessments were administered an average of 5.6 years after randomisation. A further two assessments took place, at two year intervals.

The cognitive battery was administered by trained nurses masked to treatment. The five tests measured general cognition (telephone interview of cognitive status), verbal memory (immediate and delayed recalls of the east Boston memory test and delayed recall of the telephone interview of cognitive status 10 word list), and category fluency (naming as many animals as possible in one minute).

Our primary, prespecified outcome was a global composite score averaging performance across all tests. Because verbal memory is a strong predictor of Alzheimer's disease,<sup>1</sup> our key, secondary outcome was a composite score of verbal memory, averaging performance on four tests (the immediate and delayed recalls of both the east Boston memory test and the 10 word list).

### Statistical analysis

We examined mean performance at each assessment using repeated measures analysis of means as well as mean change from the initial assessment over time. We treated scores and change in scores as repeated continuous outcomes and we modelled the treatment effect with a time by treatment interaction. Because the trends for test scores over time were non-linear, we used general linear models of response profiles, modelling time nominally rather than linearly.<sup>12</sup> We fitted all models by maximum likelihood, incorporating the longitudinal correlation within participants, using

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unstructured covariance structures; for statistical testing, we used Wald tests.<sup>12</sup> All linear models were fitted using Proc Mixed in SAS (version 9).

In secondary analyses we evaluated whether aspirin influenced the risk of “substantial decline,” defined as the worst 10th centile of decline. We also examined effect modification by key risk factors for cognitive decline (see *bmj.com*). We performed all tests of effect modification by evaluating the interaction terms in the models of mean change.

## RESULTS

Characteristics at randomisation were similar among women assigned to aspirin or placebo (see *bmj.com*). At the first cognitive assessment the average duration of treatment was 5.6 years and the mean time between the first and the last assessment was 4.0 years; thus the average total follow-up from randomisation to final evaluation was 9.6 years. At the final assessment, 70.0% in both groups reported taking at least two thirds of the assigned pills.

No mean differences were observed between the groups for global score or verbal memory score at each assessment (table 1). The aspirin group performed better for category fluency than the placebo group at all three assessments, and this difference was statistically significant at the final assessment (mean difference 0.37 points, 95% confidence interval 0.10 to 0.65).

No differences were observed in mean change in cognition by treatment for any of the cognitive outcomes (see *bmj.com*). The mean difference in change over time between the aspirin and placebo groups was 0.01

(95% confidence interval  $-0.02$  to  $0.04$ ) for global score,  $0.01$  ( $-0.03$  to  $0.04$ ) for verbal memory score,  $0.02$  ( $-0.11$  to  $0.16$ ) for the telephone interview of cognitive status, and  $0.11$  ( $-0.12$  to  $0.34$ ) for category fluency.

The risk of substantial decline on the global score from the first to final assessments for the aspirin group was not lower than the placebo group; compared with women in the placebo group the relative risk of substantial decline for aspirin users was 0.92 (0.77 to 1.10). Only for category fluency did aspirin users have a statistically significant 20% lower risk of substantial decline than placebo users (relative risk 0.80, 0.67 to 0.97; table 2).

## Secondary analyses

Few interactions were found between aspirin use and cognitive risk factors (see *bmj.com*). A significant interaction ( $P$  for interaction 0.03) was found between cigarette smoking and aspirin use. Among current smokers, the aspirin group experienced significantly less cognitive decline than the placebo group (difference in mean decline 0.13, 95% confidence interval 0.03 to 0.22). In contrast, little difference was found in mean change between the treatment groups among never smokers or former smokers. Significant differences were observed in effects of aspirin in relation to cholesterol levels, with aspirin providing cognitive benefits among women with hyperlipidaemia (difference in mean decline 0.05, 95% confidence interval 0.01 to 0.09) but not among those without ( $-0.02$ ,  $-0.06$  to  $0.02$ ). The study results did not change materially when women who were not compliant to treatment assignment were excluded.

**Table 1** | Cognitive function at each cognitive assessment

Cognitive test (assessment)	Aspirin group		Placebo group		Mean difference* (95% CI)
	No of participants	Adjusted mean (SE)	No of participants	Adjusted mean (SE)	
Global score†:					
First	3215	-0.01 (0.01)	3162	0.00 (0.01)	-0.01 (-0.04 to 0.02)
Second	2873	0.07 (0.01)	2819	0.06 (0.01)	0.01 (-0.03 to 0.04)
Third	2630	0.02 (0.01)	2596	0.02 (0.01)	0.00 (-0.04 to 0.04)
Verbal memory score‡:					
First	3215	-0.01 (0.01)	3162	0.01 (0.01)	-0.02 (-0.05 to 0.02)
Second	2873	0.13 (0.01)	2819	0.13 (0.01)	0.00 (-0.04 to 0.04)
Third	2630	0.09 (0.02)	2596	0.11 (0.02)	-0.02 (-0.06 to 0.02)
TICS test:					
First	3208	34.18 (0.05)	3154	34.26 (0.05)	-0.08 (-0.22 to 0.05)
Second	2871	34.07 (0.05)	2817	34.12 (0.05)	-0.05 (-0.20 to 0.10)
Third	2630	34.09 (0.06)	2596	34.11 (0.06)	-0.02 (-0.19 to 0.14)
Category fluency test:					
First	3202	17.58 (0.09)	3151	17.46 (0.09)	0.12 (-0.13 to 0.36)
Second	2871	18.13 (0.10)	2817	18.02 (0.10)	0.12 (-0.15 to 0.39)
Third	2629	17.76 (0.10)	2596	17.38 (0.10)	0.37 (0.10 to 0.65)

TICS=telephone interview of cognitive status.

\*From longitudinal linear models by treatment assignment of mean cognitive performance.

†Composite of five tests: TICS, immediate and delayed recalls of east Boston memory test, delayed recall of 10 word list, and category fluency.

‡Composite of four tests: immediate and delayed recalls of both 10 word list and east Boston memory test.

## DISCUSSION

In a randomised, placebo controlled trial with nearly 10 years of treatment among over 6000 women aged 65 or more, women taking low dose aspirin had similar overall cognitive performance to those taking placebo. Compared with women receiving placebo, women taking aspirin did not differ in overall performance at any of the cognitive assessments, from the first assessment after 5.6 years of treatment to the third after a mean 9.6 years, and also did not differ in their average cognitive decline during 3-6 years of follow-up.

There was some suggestion that aspirin users performed better in category fluency, particularly at the final assessment; women assigned to aspirin were 20% less likely to develop substantial decline in category fluency. Because this test partially assesses executive function—a cognitive system influenced by vascular disease<sup>13</sup>—it is biologically plausible that low dose aspirin may help preserve executive function. However, because category fluency was the only test that measured executive function, and this was not a primary outcome of our trial, this result should be interpreted with caution.

Among the subset of women with high cholesterol levels, aspirin protected against cognitive decline; this is consistent with the results from the primary trial of cardiovascular events, where aspirin seemed more

protective against major cardiovascular events among women with hyperlipidaemia than those without.<sup>10</sup> Also, among current smokers, aspirin users experienced less cognitive decline than placebo users; in contrast, among women who never smoked or had quit smoking, aspirin had no effect on cognition. These results were the opposite of those found in the primary trial of cardiovascular events,<sup>10</sup> where aspirin seemed protective against major cardiovascular events only among women who never smoked or had quit smoking. Chance cannot be ruled out to explain these findings.

#### Limitations of the study

A limitation of our trial is that the study population consisted of mainly healthy white “young-old” (mean age 72) women, so whether the results are generalisable to older women or other races is unknown. The age of the study population may have contributed to the lack of major decline in cognitive function over follow-up, although we have detected other risk factors for cognitive decline in these women over a similar period.<sup>14,15</sup> In addition, we started testing a mean 5.6 years after randomisation, thus we were unable to measure change in cognition from randomisation. However, at randomisation risk factors for cognitive impairment were similarly distributed across the groups, and it is highly likely that cognitive function was also comparable. Thus the lack of a true baseline assessment should not have a major influence on our ability to detect effects. Although there may have been some transient, short term benefits of aspirin on cognition just during the first 5.6 years, this seems biologically implausible given that cognitive changes develop over long periods. Finally, loss to follow-up did not differ by group; however, greater losses to follow-up occurred among those who developed cardiovascular disease (15%) compared with the entire cohort (8%). Some bias towards the null may therefore have occurred; however, such bias would

be minimal as the proportion of women with cardiovascular events was low.

Although many observational studies have investigated non-steroidal anti-inflammatory drugs in relation to cognitive decline,<sup>16</sup> few<sup>17-20</sup> have specifically examined aspirin use. These have generally shown inconsistent associations between aspirin and cognitive decline, largely supporting our null results. Our study contributes to the existing literature in that biases related to the indication for aspirin treatment are minimised owing to randomisation and the length of treatment (almost 10 years), allowing for strong conclusions about the specificity of the role of aspirin in cognitive changes.

Biologically our null results should be interpreted in light of the dose and drug selected. Although the low aspirin dose used in this trial (100 mg on alternate days) has shown antiplatelet activity, it confers limited anti-inflammatory effects.<sup>21</sup> In addition, aspirin lacks the ability to modulate the processing of the amyloid precursor protein,<sup>22</sup> believed to be critical in the pathogenesis of Alzheimer’s disease.

The most likely mechanism by which low dose aspirin might influence cognitive decline is that it reduces platelet aggregation, improves cerebral blood flow, and prevents cardiovascular disease. Although, overall, aspirin did not reduce major cardiovascular events in the primary trial of the women’s health study,<sup>10</sup> treatment conferred a modest protective effect among the subset of women aged 65 or more.

Several studies<sup>23-27</sup> have reported adverse relations between vascular risk factors in middle age and cognitive impairment later in life, implying that for prevention, early modification of cardiovascular risk may be important. Although we found no cognitive benefits of aspirin, it remains possible that benefits require years to noticeably affect cognitive decline.

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**Competing interests:** None declared.

**Ethical approval:** The trial was approved by the institutional review board of Brigham and Women’s Hospital.

**Table 2 | Relative risk of substantial cognitive decline\***

Cognitive test	No of women	Relative risk of substantial decline (95% CI)	P value
Global score†:			
Placebo	270	1.00	
Aspirin	253	0.92 (0.77 to 1.10)	0.36
Verbal memory score‡:			
Placebo	260	1.00	
Aspirin	263	1.00 (0.83 to 1.20)	0.99
TICS test:			
Placebo	297	1.00	
Aspirin	294	0.98 (0.82 to 1.16)	0.79
Category fluency:			
Placebo	268	1.00	
Aspirin	222	0.80 (0.67 to 0.97)	0.02

TICS=telephone interview of cognitive status.

\*Worst 10% of distribution of decline from first to third assessment (global score -0.8 points, verbal memory score -0.9 points, TICS -4 points, category fluency -7 points).

†Composite of five tests: TICS, immediate and delayed recalls of east Boston memory test, delayed recall of 10 word list, and category fluency.

‡Composite of four tests: immediate and delayed recalls of both 10 word list and east Boston memory test.

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## WHAT IS ALREADY KNOWN ON THIS TOPIC

Laboratory and epidemiological evidence suggests that aspirin and other anti-inflammatory drugs may be protective against dementia

Data from randomised studies to date have been inconclusive

## WHAT THIS STUDY ADDS

Low dose aspirin did not provide overall cognitive benefits in generally healthy ageing women participating in a large, long term randomised trial

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## Social inequalities in self reported health in early old age: follow-up of prospective cohort study

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### ABSTRACT

**Objective** To describe differences in trajectories of self reported health in an ageing cohort according to occupational grade.

**Design** Prospective cohort study of office based British civil servants (1985-2004).

**Participants** 10 308 men and women aged 35-55 at baseline, employed in 20 London civil service departments (the Whitehall II study); follow-up was an average of 18 years.

**Main outcome measures** Physical component and mental component scores on SR-36 measured on five occasions.

**Results** Physical health deteriorated more rapidly with age among men and women from the lower occupational grades. The average gap in physical component scores between a high and low grade civil servant at age 56 was 1.60 and this gap increased by 1 over 20 years. The average physical health of a 70 year old man or woman who was in a high grade position was similar to the physical health of a person from a low grade around eight

years younger. In mid-life, this gap was only 4.5 years. Although mental health improved with age, the rate of improvement is slower for men and women in the lower grades.

**Conclusions** Social inequalities in self reported health increase in early old age. People from lower occupational grades age faster in terms of a quicker deterioration in physical health compared with people from higher grades. This widening gap suggests that health inequalities will become an increasingly important public health issue, especially as the population ages.

### INTRODUCTION

Health in general tends to deteriorate as people get older. There may, however, be social inequalities in the trajectories of age related health decline. Cross sectional evidence suggests that the prevalence of ill health in people aged 50-59 from routine and manual social classes is greater than among older people from professional and managerial social classes.<sup>1</sup> If people