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Aspirin and other non-steroidal anti-inflammatory drugs for the prevention of dementia (Review)

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[Intervention Review]

Aspirin and other non-steroidal anti-inflammatory drugs for the prevention of dementia

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ABSTRACT

Background

Dementia is a worldwide concern. Its global prevalence is increasing. At present, there is no medication licensed to prevent or delay the onset of dementia. Inflammation has been suggested as a key factor in dementia pathogenesis. Therefore, medications with anti-inflammatory properties could be beneficial for dementia prevention.

Objectives

To evaluate the effectiveness and adverse effects of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) for the primary or secondary prevention of dementia.

Search methods

We searched ALOIS, the specialised register of the Cochrane Dementia and Cognitive Improvement Group up to 9 January 2020. ALOIS contains records of clinical trials identified from monthly searches of several major healthcare databases, trial registries and grey literature sources. We ran additional searches across MEDLINE (OvidSP), Embase (OvidSP) and six other databases to ensure that the searches were as comprehensive and up-to-date as possible. We also reviewed citations of reference lists of included studies.

Selection criteria

We searched for randomised controlled trials (RCTs) and controlled clinical trials (CCTs) comparing aspirin or other NSAIDs with placebo for the primary or secondary prevention of dementia. We included trials with cognitively healthy participants (primary prevention) or participants with mild cognitive impairment (MCI) or cognitive complaints (secondary prevention).

Data collection and analysis

We used standard methodological procedures according to the *Cochrane Handbook for Systematic Reviews of Interventions*. We rated the strength of evidence for each outcome using the GRADE approach.

Main results

We included four RCTs with 23,187 participants. Because of the diversity of these trials, we did not combine data to give summary estimates, but presented a narrative description of the evidence.

We identified one trial (19,114 participants) comparing low-dose aspirin (100 mg once daily) to placebo. Participants were aged 70 years or older with no history of dementia, cardiovascular disease or physical disability. Interim analysis indicated no significant treatment effect and the trial was terminated slightly early after a median of 4.7 years' follow-up. There was no evidence of a difference in incidence of dementia between aspirin and placebo groups (risk ratio (RR) 0.98, 95% CI 0.83 to 1.15; high-certainty evidence). Participants allocated aspirin had higher rates of major bleeding (RR 1.37, 95% CI 1.17 to 1.60, high-certainty evidence) and slightly higher mortality (RR 1.14, 95% CI 1.01 to 1.28; high-certainty evidence). There was no evidence of a difference in activities of daily living between groups (RR 0.84, 95% CI 0.70 to 1.02; high-certainty evidence).

We identified three trials comparing non-aspirin NSAIDs to placebo. All three trials were terminated early due to adverse events associated with NSAIDs reported in other trials.

One trial (2528 participants) investigated the cyclo-oxygenase-2 (COX-2) inhibitor celecoxib (200 mg twice daily) and the non-selective NSAID naproxen (220 mg twice daily) for preventing dementia in cognitively healthy older adults with a family history of Alzheimer's disease (AD). Median follow-up was 734 days. Combining both NSAID treatment arms, there was no evidence of a difference in the incidence of AD between participants allocated NSAIDs and those allocated placebo (RR 1.91, 95% CI 0.89 to 4.10; moderate-certainty evidence). There was also no evidence of a difference in rates of myocardial infarction (RR 1.21, 95% CI 0.61 to 2.40), stroke (RR 1.82, 95% CI 0.76 to 4.37) or mortality (RR 1.37, 95% CI 0.78 to 2.43) between treatment groups (all moderate-certainty evidence).

One trial (88 participants) assessed the effectiveness of celecoxib (200 mg or 400 mg daily) in delaying cognitive decline in participants aged 40 to 81 years with mild age-related memory loss but normal memory performance scores. Mean duration of follow-up was 17.6 months in the celecoxib group and 18.1 months in the placebo group. There was no evidence of a difference between groups in test scores in any of six cognitive domains. Participants allocated celecoxib experienced more gastrointestinal adverse events than those allocated placebo (RR 2.66, 95% CI 1.05 to 6.75; low-certainty evidence).

One trial (1457 participants) assessed the effectiveness of the COX-2 inhibitor rofecoxib (25 mg once daily) in delaying or preventing a diagnosis of AD in participants with MCI. Median duration of study participation was 115 weeks in the rofecoxib group and 130 weeks in the placebo group. There was a higher incidence of AD in the rofecoxib than the placebo group (RR 1.32, 95% CI 1.01 to 1.72; moderate-certainty evidence). There was no evidence of a difference between groups in cardiovascular adverse events (RR 1.07, 95% CI 0.68 to 1.66; moderate-certainty evidence) or mortality (RR 1.62, 95% CI 0.85 to 3.05; moderate-certainty evidence). Participants allocated rofecoxib had more upper gastrointestinal adverse events (RR 3.53, 95% CI 1.17 to 10.68; moderate-certainty evidence). Reported annual mean difference scores showed no evidence of a difference between groups in activities of daily living (year 1: no data available; year 2: 0.0, 95% CI −0.1 to 0.2; year 3: 0.1, 95% CI −0.1 to 0.3; year 4: 0.1, 95% CI −0.1 to 0.4; moderate-certainty evidence).

Authors' conclusions

There is no evidence to support the use of low-dose aspirin or other NSAIDs of any class (celecoxib, rofecoxib or naproxen) for the prevention of dementia, but there was evidence of harm. Although there were limitations in the available evidence, it seems unlikely that there is any need for further trials of low-dose aspirin for dementia prevention. If future studies of NSAIDs for dementia prevention are planned, they will need to be cognisant of the safety concerns arising from the existing studies.

PLAIN LANGUAGE SUMMARY

Aspirin and other non-steroidal anti-inflammatory drugs for the prevention of dementia

Review question

The purpose of this review was to investigate if aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) could help in the prevention of dementia.

Background

Dementia is a worldwide healthcare concern. At present, there is no medicine that is proven to delay or prevent the onset of dementia. The biology of dementia is still poorly understood. However, there are reasons to believe that inflammation may be partly responsible for some of the brain changes seen in dementia. There are many medicines that have anti-inflammatory properties, including aspirin and NSAIDs that are often sold as pain killers. We wanted to see if these medicines had any effect on developing dementia. These medicines have a few potential side effects, including heart attack and bleeding, so we also assessed for any harmful effects of the medicines.

Study characteristics

We searched for relevant studies that had been published up to January 2020. We found four trials that met the inclusion criteria for this review (23,187 people). One trial was undertaken in the USA and Australia and three in the USA only. The trials included different populations. One was of aspirin in healthy people with no history of dementia, cardiovascular disease or physical disability. The other three were of NSAIDs other than aspirin and were conducted in healthy people with a family history of Alzheimer's disease, people with self-reported memory loss and people with mild cognitive impairment (a slight but noticeable and measurable decline in cognitive abilities, including memory and thinking skills). All of the included studies had limitations. The study of aspirin was stopped early due

to ineffectiveness. The three studies of other NSAIDs (celecoxib, naproxen and rofecoxib) were stopped early due to concerns around the safety.

Key results and quality of the evidence

The aspirin study found that low-dose aspirin (100 mg daily) did not prevent dementia in healthy older people, but resulted in higher rates of death and major bleeding compared to placebo (pretend tablet). We were very confident in this result. The NSAID studies did not find any evidence of a difference between the NSAIDs and placebo in terms of reducing the numbers of people developing dementia. In fact, in one of the studies, more people developed dementia in the NSAID group. One of the included NSAIDs studies reported more stomach bleeding and another reported other stomach problems, such as pain, nausea and gastritis. Other side effects were similar between groups. We were moderately confident in most of the results on NSAIDs.

Conclusions

This review found no evidence to support the use of either aspirin or other NSAIDs for the prevention of dementia and, in fact, there was some suggestion that they may cause harm. The studies had limitations, but, given the concerns over safety, further studies of low-dose aspirin for dementia prevention seem unlikely. If future studies of NSAIDs for dementia prevention are planned, then these will need to be mindful of the safety concerns arising from the studies included in this review and from other studies of the same medicines.

SUMMARY OF FINDINGS

Summary of findings 1. Aspirin compared to placebo for prevention of dementia

Aspirin compared to placebo for prevention of dementia

Patient or population: cognitively healthy older adults
Setting:
Intervention: aspirin
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with aspirin				
Incidence of dementia	30 per 1000	30 per 1000 (25 to 35)	**RR 0.98** (0.83 to 1.15)	19,114 (1 RCT)	⊕⊕⊕⊕ **High**	—
Adverse events (haemorrhage)	28 per 1000	38 per 1000 (32 to 44)	**RR 1.37** (1.17 to 1.60)	19,114 (1 RCT)	⊕⊕⊕⊕ **High**	—
Mortality	52 per 1000	59 per 1000 (52 to 66)	**RR 1.14** (1.01 to 1.28)	19,114 (1 RCT)	⊕⊕⊕⊕ **High**	—
Cognitive decline from baseline	—	—	—	—	—	Not measured.
Activities of daily living	23 per 1000	20 per 1000 (16 to 24)	**RR 0.84** (0.70 to 1.02)	19,114 (1 RCT)	⊕⊕⊕⊕ **High**	—
Health-related quality of life	—	—	—	—	—	Not measured.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Summary of findings 2. Other NSAIDs compared to placebo for the prevention of dementia in cognitively healthy older adults

Other NSAIDs compared to placebo for the prevention of dementia in cognitively healthy older adults

Patient or population: cognitively healthy older adults
Setting:
Intervention: NSAIDs
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with other NSAIDs				
Incidence of Alzheimer's disease	10 per 1000	19 per 1000 (9 to 41)	**RR 1.91** (0.89 to 4.10)	2125 (1 RCT)	⊕⊕⊕⊖ **Moderate** [a]	—
Adverse events –myocardial infarction	12 per 1000	15 per 1000 (7 to 29)	**RR 1.21** (0.61 to 2.40)	2500 (1 RCT)	⊕⊕⊕⊖ **Moderate** [a]	—
Adverse events – stroke	7 per 1000	12 per 1000 (5 to 29)	**RR 1.82** (0.76 to 4.37)	2500 (1 RCT)	⊕⊕⊕⊖ **Moderate** [a]	—
Mortality	17 per 1000	23 per 1000 (13 to 40)	**RR 1.37** (0.78 to 2.43)	2528 (1 RCT)	⊕⊕⊕⊖ **Moderate** [a]	—
Incidence of mild cognitive impairment	20 per 1000	26 per 1000 (15 to 46)	**RR 1.28** (0.72 to 2.28)	2072 (1 RCT)	⊕⊕⊖⊖ **Low** [a,b]	—
Activities of daily living	—	—	—	—	—	Not measured.
Health-related quality of life	—	—	—	—	—	Not measured.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **NSAID:** non-steroidal anti-inflammatory drug; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level due to imprecision: low event rate (i.e. total number of events was fewer than 300) (general guide).
[b]Downgraded one level due to risk of bias: failure to adhere to the intention-to-treat principle. Analysis for this outcome was per protocol.

Summary of findings 3. NSAIDs (celecoxib) compared to placebo for the delay of cognitive decline in older people with age-related memory loss

NSAIDs (celecoxib) compared to placebo for the delay of cognitive decline in older people with age-related memory loss

Patient or population: older people with age-related memory loss
Setting: community
Intervention: NSAIDs (celecoxib)
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with NSAIDs (celecoxib)				
Incidence of dementia	—	—	—	—	—	Not reported.
Adverse events – gastrointestinal	**Study population**		**RR 2.66** (1.05 to 6.75)	40 (1 RCT)	⊕⊕⊖⊖ **Low** [a,b]	—
	22 per 100	59 per 100 (23 to 100)				
Mortality	—	—	—	—	—	Not reported.
Cognitive decline from baseline across 6 domains	**Psychomotor speed:** Trailmaking A Digital Symbol: MD 2.40, 95% CI −3.41 to 8.21; WAIS-II Digital Symbol: MD −5.00, 95% CI −16.30 to 6.30. **Visuospatial functioning:** WAIS-III Block Design: MD −0.70, 95% CI −7.35 to 5.95; Complex Figure, Copy: MD 0.20, 95% CI −1.72 to 2.12.		—	40 (1 RCT)	⊕⊕⊖⊖ **Low** [a,b,c]	—

	Executive functioning: Trailmaking B: MD 7.20, 95% CI −17.85 to 32.25; Stroop Interference: MD −4.40, 95% CI −29.42 to 20.62; F.A.S. Letter Fluency: MD −3.30, 95% CI −13.80 to 7.20. **Learning:** Selective Reminding, Total Recall: MD −7.70, 95% CI −19.26 to 3.86); Verbal Paired Associations 1: MD −0.90, 95% CI −6.09 to 4.29; Benton Visual Retention: MD −0.40, 95% CI −2.26 to 1.46. **Delayed recall:** Selective Reminding Delayed Recall: MD −1.50, 95% CI −3.18 to 0.18; Complex Rigure, Recall: MD 0.50, 95% CI −4.23 to 5.23; Verbal Paired Associations 11: MD −0.70, 95% CI −2.19 to 0.79. **Language/semantic memory:** Boston Naming: MD −0.20, 95% CI −3.15 to 2.75; Animal Naming: MD 3.10, 95% CI −0.31 to 6.51.				
Activities of daily living	—	—	—	—	—	Not reported.
Health-related quality of life	—	—	—	—	—	Not measured.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **NSAID:** non-steroidal anti-inflammatory drug; **RCT:** randomised controlled trial; **RR:** risk ratio; **WAIS:** Wechsler Adult Intelligence Scale.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level due to imprecision: low event rate i.e. total number of events is fewer than 300 (general guide).
[b]Downgraded one level due to risk of bias: failure to adhere to the intention-to-treat principle. Analysis for this outcome was per protocol.
[c]Higher scores indicate better cognitive performance except for Trailmaking A and B, Benton Visual Retention, where lower scores indicate better performance.

Summary of findings 4. NSAIDs (rofecoxib) for the prevention of dementia in people with mild cognitive impairment

NSAIDs compared to placebo for the prevention of dementia in people with MCI

Patient or population: people with MCI
Setting: community
Intervention: NSAID
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with NSAID				
Incidence of Alzheimer's disease	112 per 1000	148 per 1000 (113 to 193)	**RR 1.32** (1.01 to 1.72)	1457 (1 RCT)	⊕⊕⊕⊖ **Moderate** [a]	—
Adverse events – cardiovascular	49 per 1000	53 per 1000 (34 to 80)	**RR 1.07** (0.68 to 1.66)	1457 (1 RCT)	⊕⊕⊕⊖ **Moderate** [a]	—
Adverse events – gastrointestinal	5 per 1000	19 per 1000 (6 to 58)	**RR 3.53** (1.17 to 10.65)	1457 (1 RCT)	⊕⊕⊕⊖ **Moderate** [a]	—
Mortality	20 per 1000	33 per 1000 (17 to 62)	**RR 1.62** (0.85 to 3.05)	1457 (1 RCT)	⊕⊕⊕⊖ **Moderate** [a]	—
Cognitive decline from baseline	—	—	—	—	—	Not measured.
Activities of daily living assessed with: BDRS	Study reported no differences between treatment groups in any of the annual mean BDRS scores: BDRS (difference rofecoxib minus placebo: year 1: no data available; year 2: 0.0, 95% CI −0.1 to 0.2; year 3: 0.1, 95% CI −0.1 to 0.3; year 4: 0.1, 95% CI −0.1 to 0.4.		—	1457 (1 RCT)	⊕⊕⊕⊖ **Moderate** [a]	—
Health-related quality of life	—	—	—	—	—	Not measured.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
BDRS: Blessed Dementia Rating Scale; **CI:** confidence interval; **MCI:** mild cognitive impairment; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level due to imprecision: a low event rate (i.e. total number of events is fewer than 300) (general guide).

BACKGROUND

Description of the condition

Dementia is a term used to describe a variety of illnesses which, although diverse in some respects, share common clinical manifestations. These include pervasive impairment of mental functioning, typically progressive memory loss, language difficulties, confusion and disorientation, and a decline in the skills required to carry out activities of daily living (Coteilli 2012). Dementia may also involve behavioural and psychological symptoms (Cohen-Mansfield 2000; Hoe 2005; Hoe 2006; Hoe 2007; Hoe 2009). As dementia progresses, the increasing severity of symptoms has a devastating effect on the quality of life of the affected person and their carers (World Health Organization 2012).

Current estimates suggest there are 46.8 million people living with dementia worldwide, and this is forecast to double every 20 years, reaching 74.7 million by 2030 and 131.5 million by 2050. Approximately 9.9 million new cases present each year, equating to one new case every 3.2 seconds. It is an expensive condition, costing an estimated USD 818 billion worldwide in 2015 (Prince 2015). Given the seriousness of the impact of dementia on all associated with the illness, its increasing prevalence, incidence and burden of cost, the World Health Organization (WHO) has declared dementia a world health priority (World Health Organization 2012). There is global interest in research into ways of preventing or delaying the onset of dementia.

Dementia: main subtypes and pathophysiology

Alzheimer's disease

Alzheimer's disease (AD) is considered the most common cause of dementia, accounting for approximately 60% to 70% of all cases. It has a prevalence of approximately 1% among people aged 60 to 64 years, increasing to 40% in people aged 85 years and older (Brookmeyer 1998). AD is a neurodegenerative disorder, characterised pathologically by amyloid plaques and neurofibrillary tangles, and clinically by gradually progressive cognitive decline, impairments in activities of daily living, and behavioural and psychological symptoms (Gorelick 2010). As yet, the precise mechanisms underlying the pathogenesis of AD are not understood fully, but the hypothesis that inflammatory processes are an integral part of the degeneration process was first posited over 25 years ago (Rogers 1988; McGeer 1995; McGeer 1997). Although dementia due to AD typically occurs in later life, there is an extended preclinical stage that is characterised by distinct neuropathological changes (Jack 2013). There are multiple risk factors for AD beyond increasing age. The greatest genetic risk is being a carrier of the *APOE*-ε4 allele of the gene for apolipoprotein E. Other risk factors include history of mild cognitive impairment (MCI), female sex, cardiovascular disease, obesity, diabetes mellitus and low socioeconomic status, defined as low income and low level of educational attainment (Barnes 2011; Yaffe 2013; Walter 2014).

Vascular dementia

Vascular dementia (VaD) is the second most common type of dementia. It is caused by cerebrovascular disease that directly or indirectly damages brain structures important for cognitive functioning (Roh 2014). Two factors are necessary for a diagnosis of VaD, namely, a cognitive disorder evident on neuropsychological testing, and a history of clinical stroke or cerebrovascular disease detected by neuroimaging which is plausibly linked to the cognitive disorder. VaD can be classified into 1. multi-infarct dementia, 2. strategic infarct dementia, 3. haemorrhagic dementia, 4. subcortical ischaemic vascular dementia (SIVD) and 5. other forms of VaD. The classic clinical picture of multi-infarct dementia is of step-wise progression, where periods of stability are interrupted by periods of rapid decline, fluctuation of symptoms and the presence of focal neurological signs. However, SIVD is associated with an insidious onset and gradual cognitive decline, mimicking the course of AD (Chui 2007). Other forms of VaD have heterogeneous causes, for example, vasculitis, cerebral amyloid angiopathy, and hereditary diseases such as cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (Seo 2007; Park 2013; Patel 2013). Risk factors for VaD include advancing age, male sex, history of cardiovascular disease (myocardial infarction (MI), history of stroke or transient ischaemic attack (TIA)), diabetes, obesity and smoking (McCullagh 2001).

Mixed dementia

It has become increasingly apparent that the boundaries between the different dementia subtypes are unclear and mixed forms exist, particularly in older people. For example, one retrospective clinico-pathological study of 1050 elderly people with a history of dementia showed that of the total cohort, 62.9% had a clinical diagnosis of probable or possible AD; 10% of VaD; 10.4% of non-specific degenerative dementia; 9.5% of Parkinson's disease with dementia; 1.5% of mixed dementia; and 5.7% of other dementias, including frontotemporal dementia, Huntington's and Creutzfeldt-Jakob diseases. Autopsy results, however, were significantly different: 86% had AD-related pathology but only 42.8% exhibited 'pure' AD while the remaining cases had mixed pathologies (Jellinger 2006).

Description of the intervention

Aspirin and other non-steroidal anti-inflammatory drugs

Aspirin and other NSAIDs are indicated for the alleviation of pain, inflammation and fever. Due to its anti-aggregation effects on platelets, aspirin is also indicated for the treatment and prevention of cardiovascular disease. Aspirin is used at low doses for cardiovascular prevention, whereas higher doses are used for analgesic effects.

Depending on the drug type, dose and duration of treatment, aspirin and other NSAIDs are associated with a variety of adverse events including serious cardiovascular events, hypertension, gastrointestinal ulcers, acute renal failure and worsening of pre-existing heart failure (Varga 2017).

Aspirin (a derivative of salicylate) was the original NSAID. It was introduced onto the market in the late 19th century. Further NSAIDs such as indomethacin and ibuprofen began to appear in the 1960s (Conaghan 2012). However, it was not until the early 1970s that the mechanism of action of aspirin (and by extension other NSAIDs) was elucidated by John Vane (Vane 1971). His work identified it as an inhibitor of the enzyme cyclo-oxygenase (COX). COX is responsible for the first stage in the production of prostaglandins, local hormones that have a range of physiological functions. Originally, it was thought that all prostaglandin synthesis was initiated by a single form of COX, but now at least two isoforms of COX are known to exist, termed COX-1 and COX-2. COX-1 is present in small amounts in most human tissues and acts as a 'housekeeping' enzyme,

involved in the regulation of normal physiological processes such as the maintenance of gastric mucosal integrity, kidney function and platelet aggregation. Conversely, COX-2 is undetectable in most tissues under normal physiological circumstances and is selectively upregulated after exposure to inflammatory mediators or trauma, contributing to subsequent inflammatory responses and pain.

NSAIDs may be classified according to their selectivity for COX-1 or COX-2, or both (Vane 1998). Early NSAIDs, including aspirin, are non-selective COX inhibitors. It was hypothesised that the therapeutic effects (that is analgesic, antipyretic and anti-inflammatory benefits) of all NSAIDs, including aspirin, were due to inhibition of COX-2 and that unwanted adverse effects were due to inhibition of COX-1 (Vane 1998). Hence, it was thought that if selective COX-2 inhibitors could be developed, such compounds should have a similar efficacy to non-selective NSAIDs but with an improved safety profile as they would allow the continued production of prostaglandins in locations such as the gastrointestinal tract and thus limit adverse effects such as mucosal ulceration (Hawkey 1999). Several COX-2 selective inhibitors were subsequently developed and marketed, including meloxicam, nimesulide and the even more highly selective COX-2 inhibitors known collectively as the 'coxibs'. However, some of these highly selective compounds (namely rofecoxib and valdecoxib) have subsequently been withdrawn from the market for safety reasons, due to increased cardiovascular risk. Such compounds are also not devoid of gastrointestinal problems, although the risk is less than with non-selective NSAIDs (Patricio 2013).

How the intervention might work

In recent years, a well-defined neuro-inflammatory response has been identified in AD (Kinney 2018). Considerable inflammation is observed around the plaques and tangles that represent the core histological features of the disease. COX enzymes and prostaglandin pathways have thus come to attention as a possible therapeutic target (McGeer 2000; Cudaback 2014; Kinney 2018). The anti-inflammatory properties of aspirin and other NSAIDs may interrupt or prevent inflammatory processes that are important in pathogenesis, thus preventing the onset of AD (Etminan 2003). Aspirin and other NSAIDs may also help to prevent VaD via their anti-inflammatory and antiplatelet effects (Devine 2003).

Besides their well-defined effects on COX enzymes and hence inflammatory pathways, it has also been suggested that certain NSAIDs have an effect on the formation of amyloid-beta (Aβ), the major component of the plaques associated with AD. The synthesis of Aβ requires the enzyme γ-secretase. Inhibitors of γ-secretase have been investigated as possible disease-modifying drugs in AD (Ozudogru 2012), with particular interest in selective drugs that do not interfere with the processing of other substrates for the enzyme (Crump 2013). Drugs with such properties are known as g-secretase modulators (GSMs). However, the NSAIDs that possess this GSM property (namely ibuprofen, flurbiprofen, indomethacin and sulindac) are only weak inhibitors of the enzyme in vitro and have low brain penetrability (Crump 2013), so the relevance of this property in a clinical setting has been questioned.

Our understanding of dementia pathogenesis continues to evolve. While early studies looking at inflammation had a specific neuroinflammation focus, more recent evidence suggests that systemic inflammation may also be a risk for development of dementia (Cunningham 2015). If this is true then reducing peripheral inflammation through anti-inflammatories may have indirect cognitive benefits even if there is no direct neural effect of the drug.

Why it is important to do this review

Epidemiological studies report a lower prevalence of AD in people who have regularly taken NSAIDs for the treatment of rheumatological disorders, suggesting that NSAIDs may have a protective effect against AD (McGeer 1996; Stewart 1997; In't Veld 2001). Reviews of epidemiological studies also suggest that the protective effects may be influenced by the type and duration of NSAID use. Long term use (defined as greater than 24 months) was associated with greater risk reduction than short term use (defined as less than 1 month) or intermediate term use (defined as 1 to 24 months) (Etminan 2003; Szekely 2004).

The effectiveness of aspirin and other NSAIDs as treatments for people with dementia due to AD and VaD has been evaluated in Cochrane systematic reviews (Rands 2000; Jaturapatporn 2012). The promising epidemiological evidence has not been reproduced in prospective randomised clinical trials, whose results have been largely disappointing.

As dementia, particularly AD and VaD, is such a major health concern worldwide, and in the absence of any known preventive or curative treatment, any intervention that can prevent or delay the onset of dementia would have a major public health impact. Therefore, we considered it important to assess in a systematic review the strength of the evidence on the efficacy and safety of these drugs for the primary and secondary prevention of dementia. We included as secondary prevention studies, trials in people with MCI, which is considered a high-risk state, and in many cases a precursor to dementia. This is the first Cochrane Review to evaluate the effects of aspirin and other NSAIDs for the prevention of dementia in this population.

OBJECTIVES

To evaluate the effectiveness and adverse effects of aspirin and other NSAIDs for the primary or secondary prevention of dementia.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and controlled clinical trials (CCTs) in which aspirin and other NSAIDs were administered for the primary or secondary prevention of dementia.

Types of participants

Participants were adults living in the community without a prior diagnosis of dementia. Participants were identified as cognitively healthy or with MCI. Participants identified as having MCI should have had: 1. objective evidence of cognitive decline greater than expected for age, and 2. no significant impairment in activities of daily living.

Types of interventions

Eligible experimental interventions were 1. aspirin at any dose or 2. other NSAIDs at any dose administered for the primary or

secondary prevention of dementia. The control intervention was placebo.

There is no consensus definition of primary and secondary prevention in dementia. For this review, we defined primary prevention as treating risk factors for the development of cognitive decline with the intention of slowing or arresting the underlying pathological process before any clinical features are evident. We defined secondary prevention as treatment designed to slow or arrest the pathological processes underlying cognitive decline where some evidence of cognitive impairment may be detectable but this is not yet sufficient to warrant a dementia label. In this rubric, we included MCI.

Types of outcome measures

Primary outcomes

- Incidence of dementia, diagnosed according to standard diagnostic criteria at the time the study was undertaken. We included data on any dementia pathological subtype, but, because NSAIDs may have specific effects in the pathological processes underlying AD, we favoured estimates of AD as our primary outcome where reported.
- Adverse events, for example, cardiovascular (specifically MI and stroke), gastrointestinal or renal events.
- Mortality.

Secondary outcomes

- Cognitive decline from baseline.
- Activities of daily living.
- Health-related quality of life.

Search methods for identification of studies

Electronic searches

The Information Specialist from the Cochrane Dementia and Cognitive Improvement Group searched ALOIS (www.medicine.ox.ac.uk/alois), the Cochrane Dementia and Cognitive Improvement Group Specialized Register on 9 January 2020. The search terms were: aspirin OR "cyclooxygenase 2 inhibitor" OR aceclofenac OR acemetacin OR celecoxib OR dexibruprofen OR dexketoprofen OR diclofenac sodium OR diflunisal OR diflusinal OR etodolac OR etoricoxib OR fenbufen OR fenoprofen OR flurbiprofen OR ibuprofen OR indometacin OR indomethacin OR ketoprofen OR lumiracoxib OR mefenamic OR meloxicam OR nabumetone OR naproxen OR nimesulide OR "anti-inflammatory" OR piroxicam OR sulindac OR tenoxicam OR tiaprofenic acid OR triamcinolone OR NSAIDS OR NSAID.

ALOIS is maintained by the Information Specialists for the Cochrane Dementia and Cognitive Improvement Group and contains studies in the areas of dementia prevention, dementia treatment and cognitive enhancement in healthy people. The studies are identified from the following.

- Monthly searches of a number of major healthcare databases: MEDLINE, Embase, CINAHL, PsycINFO and LILACS.
- Monthly searches of a number of trial registers: ISRCTN; UMIN (Japan's Trial Register); WHO International Clinical Trials Registry Platform portal (which covers ClinicalTrials.gov; ISRCTN; the Chinese Clinical Trials Register; the German Clinical Trials Register; the Iranian Registry of Clinical Trials; and the Netherlands National Trials Register, plus others).
- Quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL).
- Six-monthly searches of a number of grey literature sources: ISI Web of Science Core Collection.

To view a list of all sources searched for by ALOIS, see About ALOIS on the ALOIS website (www.medicine.ox.ac.uk/alois/content/about-alois).

The Information Specialists ran additional separate searches in many of the above sources to ensure that the search was as comprehensive and most up-to-date as possible. The search strategies used can be seen in Appendix 1.

Searching other resources

We reviewed citations of reference lists of included studies identified through the search strategy for additional studies and assessed their suitability for inclusion in the review.

Data collection and analysis

The methods that were undertaken in this review were designed in accordance with recommendations described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Selection of studies

Two review authors (FJ and DD) independently screened all titles and abstracts identified from searches to identify those which might meet the inclusion criteria. We retrieved in full text any papers identified as potentially relevant by at least one review author. Two review authors (from BMcG, PP or FJ) independently screened full-text articles for inclusion or exclusion. Any disagreements were resolved by discussion or, where necessary, we consulted a third review author (DD, TQ or KM).

Data extraction and management

For included trials, two review authors (FJ and DD) independently extracted study characteristics. Outcome data were extracted using data extraction sheets designed by one review author (CTS) and piloted by two review authors (CTS and FJ). Two of three review authors (CTS, FJ and TQ) independently extracted outcome data. Any discrepancies were resolved through discussion. All extracted data was entered into Review Manager 5 by one review author (FJ), and a second review author (CTS or TQ) checked the data for accuracy (Review Manager 2014).

Assessment of risk of bias in included studies

Two of three review authors (FJ, DD or TQ) independently assessed the methodological quality of all trials included in the review using the Cochrane 'Risk of bias' tool as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The domains assessed as potential sources of bias were: sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias.

Measures of treatment effect

Dichotomous data

For dichotomous data, where data were available, we presented the results as a risk ratio (RR) with 95% confidence intervals (CI).

Continuous data

For continuous data, where data were available, we presented the results using mean differences, with 95% CI. We planned to use the standardised mean differences if studies measured the same outcome but used different measurement scales (Higgins 2011).

Time-to-event data

We planned to analyse time-to-event data as described by Tierney (Tierney 2007), and detailed in Chapter 7, Section 7.7.6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Unit of analysis issues

Studies with multiple treatment groups

One of the included studies had two active treatment arms (one selective COX-2 and one non-selective NSAID) (ADAPT Research Group 2007/2006). We combined both arms to form a single 'NSAID' group for primary analysis but also presented the results from each arm of the trial separately.

Dealing with missing data

Where data were missing from included trials, we planned to contact the trial lead author. For each of the included trials, where data were available, we noted the level of attrition for each group, per outcome or group of outcomes.

Assessment of heterogeneity

Initial assessment of heterogeneity was clinical, based on populations, interventions and outcomes. Because we did not conduct any meta-analyses, we did not assess statistical heterogeneity between studies.

Assessment of reporting biases

This review included fewer than 10 trials so we did not formally assess publication bias using funnel plots.

Data synthesis

We prespecified the following comparisons.

- Aspirin at any dose versus placebo.
- Other NSAIDs at any dose versus placebo.

There are theoretical reasons to believe that selective COX-2 inhibitors may differ in their therapeutic and adverse effects from non-selective NSAIDs. Where selective and non-selective NSAIDs were available, we planned to combine data in a primary analysis, but also to present data separately.

Because of clinical diversity among the included trials, we did not conduct any meta-analyses, but rather we described the results for each of the included trials separately using a narrative summary approach.

Summarising and interpreting results

For each comparison, we produced a narrative 'Summary of Findings' table (Higgins 2011), using the GRADEpro Guideline Development Tool (GDT) (GRADEpro GDT). Where data were available, we summarised the certainty of the evidence for the primary and secondary outcomes detailed in the Types of outcome measures section.

Subgroup analysis and investigation of heterogeneity

We did not undertake any subgroup analyses to investigate heterogeneity because of the small numbers of included studies.

Sensitivity analysis

We did not perform any sensitivity analyses.

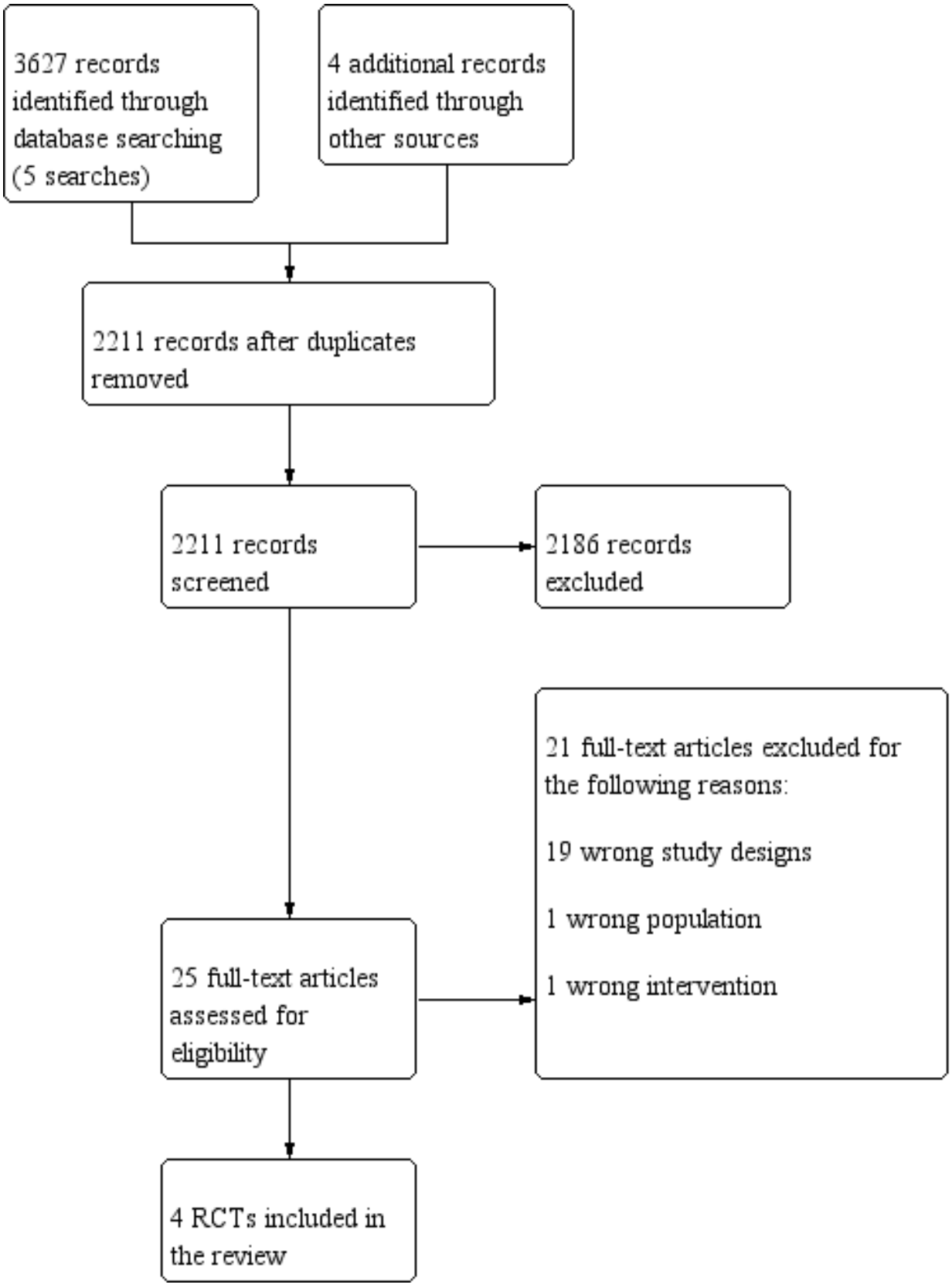
RESULTS

Description of studies

Results of the search

The results of the search are presented in Figure 1. Electronic searches retrieved 3627 citations, with four additional studies identified through other sources, giving a total of 3631 references. After the removal of duplicates, we screened the titles and abstracts of 2211 studies. We obtained the full text for 25 papers. We excluded 21 papers for reasons described in the Characteristics of excluded studies table.

Figure 1. Study flow diagram. RCT: randomised controlled trial.



Included studies

We included four RCTs with 23,187 participants (Thal 2005; ADAPT Research Group 2007/2006; Small 2008; ASPREE 2018). For full details, see Characteristics of included studies table.

Participants and setting

The Aspirin in Reducing Events in the Elderly (ASPREE) trial was a primary prevention study conducted in Australia and the US (ASPREE 2018). Participants (n = 19,114) were aged 70 years or older (or 65 years of age or older among Hispanic or black people in the USA) and free of dementia, chronic illness, or cardiovascular or cerebrovascular diseases at recruitment.

The Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) was a primary prevention trial conducted in six sites across the USA (ADAPT Research Group 2007/2006). Participants (n = 2528) were cognitively healthy volunteers, aged 70 years or more with a family history of AD. Participants were deemed cognitively healthy on the basis of predefined cut-off scores on a battery of cognitive tests.

Small 2008 was a secondary prevention trial conducted in a university research institute in California (US). Participants (n = 88) were volunteers, aged 40 to 81 years, with mild self-reported memory complaints but normal memory performance scores. They were recruited from community physician referrals, media coverage and advertising.

Thal 2005 was a secondary prevention study conducted across 46 study sites in the USA. Participants (n = 1457) were aged 65 years or older and had a clinical diagnosis of MCI. A diagnosis of MCI was determined using several criteria including self-report and informant report of memory decline in the previous year; a Mini-Mental State Examination (MMSE) score of 24 or greater; a Clinical Dementia Rating (CDR) global score of 0.5 with memory domain score of 0.5 or greater; a Blessed Dementia Rating Scale (BDRS) total score of 3.5 or less with no part 1 item score greater than 0.5; and an Auditory Verbal Learning Test (AVLT) total score of 37 or less.

Interventions

ASPREE 2018 evaluated the efficacy of low-dose aspirin for extending a disability-free life over a five-year period. Participants were randomly allocated to aspirin 100 mg or placebo once daily. After an interim analysis, the trial was terminated at a median of 4.7 years of follow-up, just five months ahead of schedule.

ADAPT Research Group 2007/2006 evaluated the efficacy and safety of the selective COX-2 inhibitor, celecoxib, and the non-selective NSAID, naproxen, for the primary prevention of AD. Participants were assigned randomly to celecoxib 200 mg twice daily (BID) or naproxen 220 mg BID or placebo BID. Initially this trial was intended to last for seven years, but was ended prematurely after increased cardiovascular risks associated with celecoxib were observed in the Adenoma Prevention with Celecoxib (APC) trial (Solomon 2005). Median follow-up times for participants were 733 days for celecoxib, 734 days for naproxen and 735 days for placebo.

Small 2008 studied the effects of the selective COX-2 inhibitor, celecoxib, on cognitive performance. Participants were assigned randomly to a daily dose of celecoxib 200 mg or 400 mg or placebo for a period of 18 months. Following the termination of the ADAPT trial, for the reasons stated earlier in the text, this trial was terminated at the same time (Small 2008). In the celecoxib group, mean follow-up was 17.6 (standard deviation (SD) 5.3) months and for the placebo group it was 18.1 (SD 4.7) months.

Thal 2005 studied the effectiveness of rofecoxib, a COX-2 inhibitor, in delaying conversion from MCI to dementia due to AD. Participants were assigned randomly to rofecoxib 25 mg or placebo once daily. This study was expected to run over four years. However, the study was terminated in April 2003, 11 months earlier than the planned termination date because Merck announced the voluntary withdrawal of rofecoxib from the market following reported association with increased cardiovascular risk in another trial (Bresalier 2005). Median duration for study participation was 115 weeks in the rofecoxib group and 130 weeks in the placebo group.

Outcomes measured in included trials that were relevant to this review

The primary endpoint in the ASPREE trial was a composite of dementia, physical disability and death (ASPREE 2018). Dementia was also reported as a secondary endpoint, diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders-IV criteria (DSM-IV) (APA 1994).

Incidence of AD was the primary outcome in ADAPT (ADAPT Research Group 2007/2006), diagnosed using the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association Criteria (NINCDS-ADRDA) (McKhann 1984). The trial also included incidence of all-cause dementia as a secondary outcome, which was diagnosed according to DSM-IV criteria (APA 1994).

Incidence of AD was the primary outcome in Thal 2005, diagnosed according to NINCDS-ADRDA criteria (McKhann 1984).

All trials reported adverse events (Thal 2005; ADAPT Research Group 2007/2006; Small 2008; ASPREE 2018).

Three trials reported mortality (Thal 2005; ADAPT Research Group 2007/2006; ASPREE 2018).

Two trials reported cognitive decline from baseline (ADAPT Research Group 2007/2006; Small 2008). Small 2008 measured a change in cognition from baseline across six cognitive domains: psychomotor speed, visuospatial functioning, executive functioning, learning, delayed recall and language/semantic memory. Thal 2005 reported annualised changes in cognition over a four-year period; data were presented as change per annum for each year and it was not possible to extrapolate a summary of total cognitive change from baseline.

ASPREE 2018 measured rates of MCI as an outcome, but results for this outcome are not published yet.

Incidence of MCI and AD prodromes were a secondary outcome in ADAPT (ADAPT Research Group 2007/2006). We regarded incident MCI as aligned with our outcome of cognitive decline because it represents a state of change from baseline normal cognition that is not sufficient to make a diagnosis of dementia. The trial administered the following battery of cognitive tests at baseline and at yearly follow-ups: the Modified Mini-Mental Sate Examination (3MS-E) (Teng 1987), the Hopkins Verbal Learning Test – Revised (HVLT-R) (Brandt 1991), informant-based Dementia

Severity Rating Scale (DSRS) (Clark 1996), Digit Span Test (Richardson 2007), Generative Verbal Fluency, narratives from the Rivermead Behavioural Memory test (Wilson 1989), Brief Visuospatial Test-Revised (Benedict 1996), and self-rating of memory functions (Squire 1979). It also included the Geriatric Depression Scale (GDS) (Yesavage 1983).

Two trials reported activities of daily living (Thal 2005; ASPREE 2018). Activities of daily living were measured in ASPREE 2018 using the Katz Index of Independence in Activities of Daily Living tool (Katz 1970). Thal 2005 measured activities of daily living using the BDRS (Morris 1988) at baseline, 24, 36 and 48 months, or at discontinuation from the study.

None of the trials reported health-related quality of life.

Excluded studies

We excluded 22 studies (see Characteristics of excluded studies table).

Risk of bias in included studies

We summarised the 'Risk of bias' results in Figure 2 and Figure 3. See Characteristics of included studies table.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

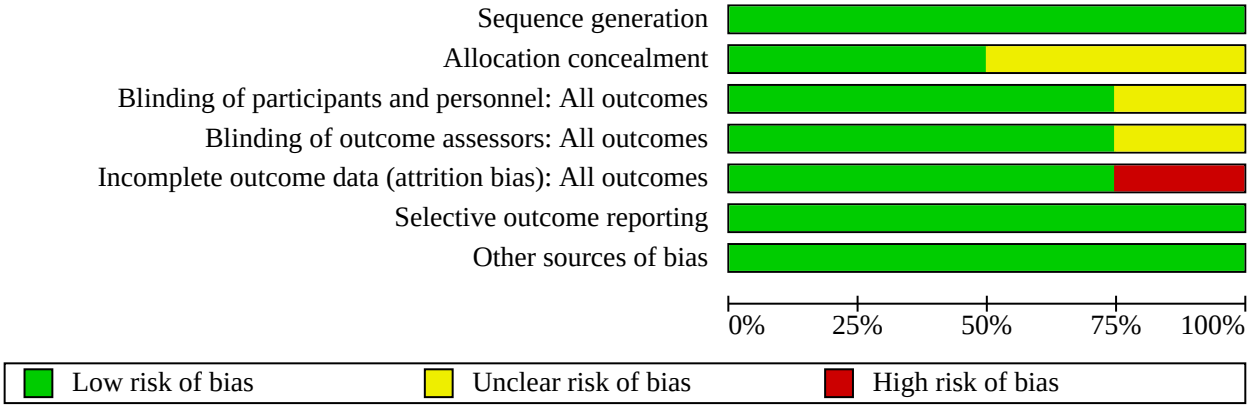
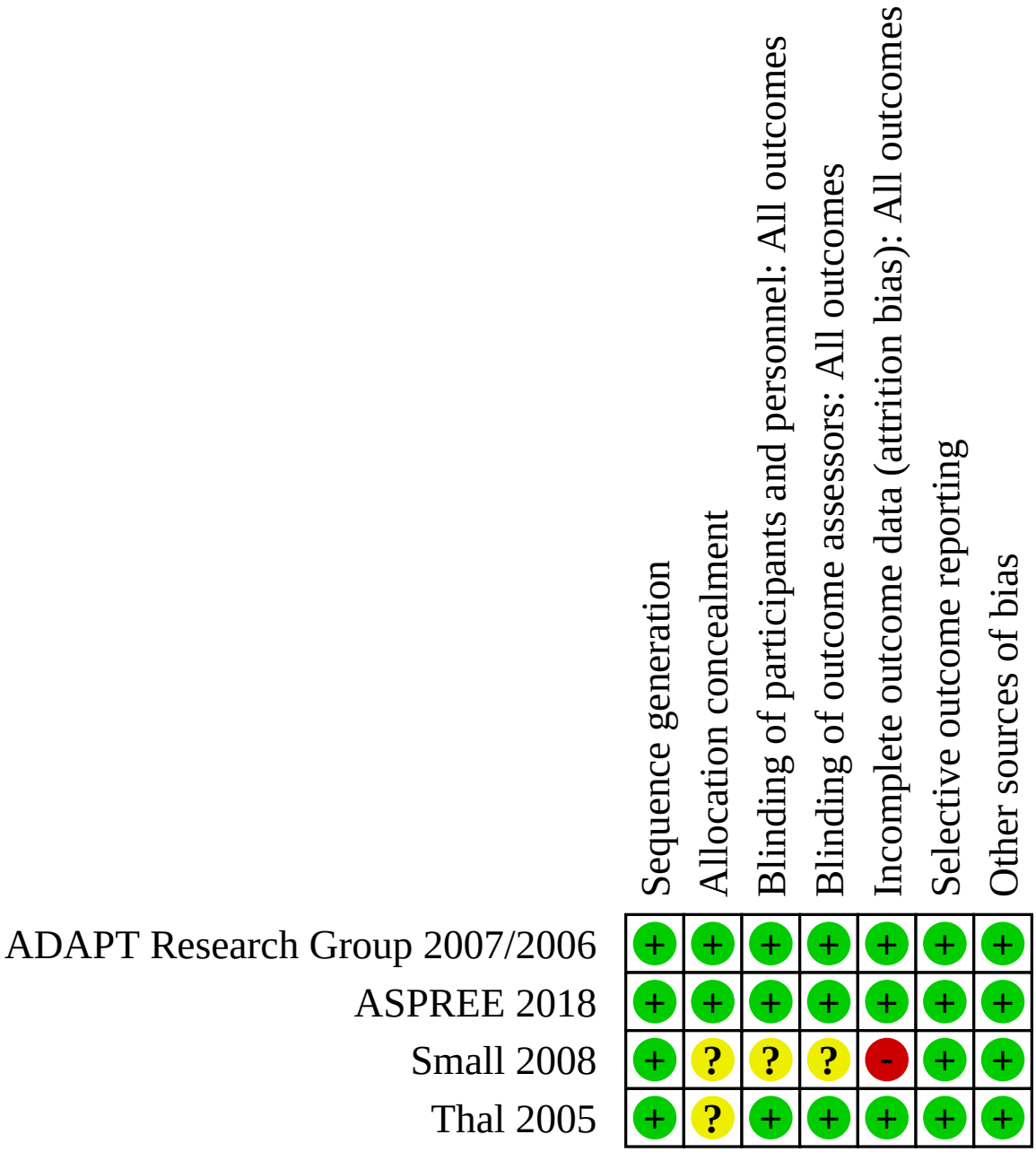


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

We judged all four included trials at low risk of bias in relation to sequence generation. We judged two trials at low risk of bias for allocation concealment (ADAPT Research Group 2007/2006; ASPREE 2018), and two trials at unclear risk because of lack of detail about allocation concealment in the reports (Thal 2005; Small 2008).

Blinding

We judged three trials at low risk of performance bias (blinding of participants and personnel) and low risk of detection bias

(blinding of outcome assessors) (Thal 2005; ADAPT Research Group 2007/2006; ASPREE 2018). We judged one trial at unclear risk of performance and detection bias because insufficient details were available to make a clear judgement (Small 2008).

Incomplete outcome data

We judged three trials at low risk of attrition bias (Thal 2005; ADAPT Research Group 2007/2006; ASPREE 2018). We judged one study at high risk of attrition bias as there was substantial attrition not accounted for in the analyses (Small 2008). One study reported per-protocol analysis excluding participants with known cognitive syndromes who were incorrectly enrolled into the trial (ADAPT Research Group 2007/2006). For the outcomes of interest to this review, we extracted and presented these per-protocol data. For each included study, details pertaining to loss to follow-up are presented in the Characteristics of included studies table.

Selective reporting

We judged all four trials at low risk of reporting bias because they reported all the outcome measures detailed in the methods sections of papers. Our assessment of reporting bias is in keeping with that described in our original protocol (Jordan 2015). We recognise that assessment of reporting bias has evolved and usual practice now would be to compare the study protocol to the published papers. Only two included studies had protocols available in the public domain (ADAPT Research Group 2007/2006; ASPREE 2018).

Other potential sources of bias

We did not identify any other high risks of bias. Two studies were funded by the pharmaceutical industry; their source of funding was reported in the trial publications and we did not judge this to pose a risk of bias (Thal 2005; ADAPT Research Group 2007/2006).

Effects of interventions

See: **Summary of findings 1** Aspirin compared to placebo for prevention of dementia; **Summary of findings 2** Other NSAIDs compared to placebo for the prevention of dementia in cognitively healthy older adults; **Summary of findings 3** NSAIDs (celecoxib) compared to placebo for the delay of cognitive decline in older people with age-related memory loss; **Summary of findings 4** NSAIDs (rofecoxib) for the prevention of dementia in people with mild cognitive impairment

1. Aspirin at any dose compared with placebo

See Summary of findings 1.

One trial compared aspirin versus placebo (ASPREE 2018).

Cognitively healthy older adults

Incidence of dementia: 575/19,114 (3%) participants had dementia across both treatment groups (283/9525 (3%) in the aspirin group and 292/9589 (3%) in the placebo group). There was no difference in incidence of dementia between treatment groups (RR 0.98, 95% CI 0.83 to 1.15; high-certainty evidence; Analysis 1.1).

Adverse events: at follow-up, 626/19,114 (3.3%) participants had experienced a major haemorrhagic event. The incidence of major bleeding was higher in the aspirin group (361/9525 (3.8%) than the placebo group (265/9589 (2.8%) (RR 1.37, 95% CI 1.17 to 1.60; high-certainty evidence; Analysis 1.2).

Mortality: at follow-up, 1050/19,114 (5.5%) participants had died. Mortality was slightly higher in participants allocated aspirin (558/9525 (5.8%) than those allocated placebo (494/9589 (5%) (RR 1.14, 95% CI 1.01 to 1.28; high-certainty evidence; Analysis 1.3).

Cognitive decline from baseline: the trial measure MCI but results are not yet published.

Activities of daily living: at follow-up, 412/19,114 (2.2%) participants experienced impairment in activities of daily living (188/9525 (2%) in the aspirin group and 224/9589 (2.3%) in the placebo group). There was no clear evidence of a difference in activities of daily living between groups (RR 0.84, 95% CI 0.70 to 1.02; high-certainty evidence; Analysis 1.4).

Health-related quality of life: the trial did not assess health-related quality of life.

2. Other NSAIDs at any dose compared with placebo

See Summary of findings 2; Summary of findings 3; Summary of findings 4.

Three trials compared other NSAIDs versus placebo (Thal 2005; ADAPT Research Group 2007/2006; Small 2008). We judged that outcome data from the three trials could not be combined because of clinically heterogeneous participants (participants in one trial were cognitively healthy, participants in another trial had age-related memory loss and participants in the other trial had MCI). Pooling of adverse events was not possible because of the diversity in the type of reported events. Findings for each of the outcomes reported in the individual trials and relevant to this review are presented separately.

Cognitively healthy older adults with a family history of Alzheimer's disease (ADAPT 2007/2006)

ADAPT Research Group 2007/2006 compared celecoxib, naproxen and placebo.

Incidence of dementia: the focus of this study was the primary prevention of AD. Of the total number of trial participants, 2125/2528 participants contributed to the analyses of cognitive outcomes. A total of 32/2125 (1.5%) participants were diagnosed with AD across all treatment groups (11/619 (1.8%) in celecoxib group, 12/598 (2%) in naproxen groups and 9/908 (1%) in placebo group). We combined findings from both NSAID treatment arms and found no evidence of a difference in the incidence of AD between participants allocated NSAIDs and those allocated placebo (RR 1.91, 95% CI 0.89 to 4.10; moderate-certainty evidence; Analysis 2.1). Similarly, there was no evidence of a difference in the incidence of AD between participants allocated celecoxib and those allocated placebo (RR 1.79, 95% CI 0.75 to 4.30; 1527 participants ; moderate-certainty evidence; Analysis 2.1), or between participants allocated naproxen and those allocated placebo (RR 2.02, 95% CI 0.86 to 4.78; 1506 participants; moderate-certainty evidence; Analysis 2.1). Analysis of the secondary outcome of all-cause dementia, excluding seven participants with prevalent dementia incorrectly enrolled into the trial, suggests a difference in incidence of all-cause dementia between participants allocated NSAIDs and those allocated placebo in favour of placebo (RR 2.45, 95% CI 1.05 to 5.68;

2118 participants; low-certainty evidence; Analysis 2.2). Results from the individual NSAIDs groups were compatible with little or no difference between groups (RR 2.50, 0.99 to 6.32; 1523 participants; low-certainty evidence; Analysis 2.2) and naproxen (RR 2.39, 95% CI 0.93 to 6.12; 1499 participants; low-certainty evidence; Analysis 2.2).

Adverse events: the trial reported cardiovascular adverse events. A total of 2528/2500 (98.9%) participants had follow-up for non-fatal events. Non-fatal cardiovascular events measured were MI, stroke, congestive heart failure (CHF), TIA and initiation of antihypertensive treatments. Results for each of the reported adverse events are presented below.

- MI: 34/2500 participants experienced a non-fatal MI across all treatment groups (8/717 (1.1%) in celecoxib group, 13/713 (1.8%) in naproxen group and 13/1070 (1.2%) in placebo group). Combining findings from both NSAID groups, we found no evidence of a difference in incidence of MI in participants allocated NSAIDs compared with those allocated placebo (RR 1.21, 95% CI 0.61 to 2.40; 2500 participants; moderate-certainty evidence; Analysis 2.3). This was true of both NSAIDs individually (celecoxib: RR 0.92, 95% CI 0.38 to 2.20; 1787 participants; moderate-certainty evidence; Analysis 2.3), naproxen: RR 1.50, 95% CI 0.70 to 3.22; 1783 participants; moderate-certainty evidence; Analysis 2.3).
- Stroke: 24/2500 participants experienced a stroke across all treatment groups (7/717 (1%) in celecoxib group, 10/713 (1.4%) in naproxen group and 7/1070 (0.6%) in placebo group). Combining findings from both NSAID groups, we found no evidence of a difference in incidence of stroke in participants allocated NSAIDs compared with those allocated placebo (RR 1.82, 95% CI 0.76 to 4.37; 2500 participants; moderate-certainty evidence; Analysis 2.4). This was also true of the individual NSAIDs (celecoxib: RR 1.49, 95% CI 0.53 to 4.24; 1787 participants; moderate-certainty evidence; Analysis 2.4, naproxen: RR 2.14, 95% CI 0.82 to 5.61; 1783 participants; moderate-certainty evidence; Analysis 2.4).
- CHF: 18/2500 participants experienced CHF across all treatment groups (3/717 (0.4%) in celecoxib group, 8/713 (1.1%) in naproxen group and 7/1070 (0.6%) in placebo group). Combining findings from both NSAID groups, we found no evidence of a difference in incidence of CHF in participants allocated NSAIDs compared with those allocated placebo (RR 1.18, 95% CI 0.46 to 3.02; 2500 participants; moderate-certainty evidence; Analysis 2.5). This was also true of the individual NSAIDs (celecoxib: RR 0.64, 95% CI 0.17 to 2.47; 1787 participants; moderate-certainty evidence; Analysis 2.5, naproxen: RR 1.72, 95% CI 0.62 to 4.71; 1783 participants; moderate-certainty evidence; Analysis 2.5).
- TIA: 27/2500 participants experienced TIA across all treatment groups (8/717 (1.1%) in celecoxib group, 9/713 (1.2%) in naproxen group and 10/1070 (0.9%) in placebo group). Combining findings from both NSAID groups, we found no evidence of a difference in incidence of TIA in participants allocated NSAIDs compared with those allocated placebo (RR 1.27, 95% CI 0.58 to 2.77; 2500 participants; moderate-certainty evidence; Analysis 2.6). This was also true of the individual NSAIDs (celecoxib: RR 1.19, 95% CI 0.47 to 3.01; 1787 participants; moderate-certainty evidence; Analysis 2.6, naproxen: RR 1.35, 95% CI 0.55 to 3.31; 1783 participants; moderate-certainty evidence; Analysis 2.6).
- Initiation of antihypertensive therapy: we had not prespecified this as an outcome of interest, but, because hypertension is a risk factor for dementia, we considered that it was important to include this reported adverse event. The proportion of participants receiving antihypertensive treatment was well-balanced across all treatment groups at baseline (39.4% in celecoxib group, 39.2% in naproxen group and 40.5% in placebo group). Across all treatment groups, 471/1521 participants initiated treatment for hypertension (160/440 (36%) in celecoxib group, 147/437 (34%) in naproxen group and 164/644 (25%) in placebo group). Combining findings from both NSAID groups, we found that a higher proportion of participants allocated NSAIDs were started on antihypertensive treatment compared with those allocated placebo (RR 1.37, 95% CI 1.17 to 1.61; 1521 participants; moderate-certainty evidence; Analysis 2.7). This was also true of the individual NSAIDs (celecoxib: RR 1.43, 95% CI 1.19 to 1.71; 1084 participants; moderate-certainty evidence; Analysis 2.7, naproxen: RR 1.32, 95% CI 1.10 to 1.59; 1081 participants; moderate-certainty evidence; Analysis 2.7).

Mortality: all 2528 participants contributed to analyses of mortality. Fifty-one participants died across all treatment groups (17/726 (2.3%) in celecoxib group, 16/719 (2.2%) in naproxen group and 18/1083 (1.7%) in placebo group). Combining findings from both NSAID groups, we found no evidence of a difference in incidence of mortality in participants allocated NSAIDs compared with those allocated placebo (RR 1.37, 95% CI 0.78 to 2.43; 2528 participants; moderate-certainty evidence; Analysis 2.8). This was true of both NSAIDs individually (celecoxib: RR 1.41, 95% CI 0.73 to 2.72; 1809 participants; moderate-certainty evidence; Analysis 2.8, naproxen: RR 1.34, 95% CI 0.69 to 2.61; 1802 participants; moderate-certainty evidence; Analysis 2.8).

Cognitive decline from baseline: a diagnosis of MCI was a secondary endpoint in this trial. Participants were supposed to be healthy adults at baseline but after randomisation 53 participants were diagnosed with cognitive impairment so the analyses for incidence of MCI, which we accepted as evidence of a change in cognition from baseline. excluded those 53 participants. At the end of the study, a total of 49 participants were diagnosed with MCI (16/605 (2.6%) in celecoxib group, 15/582 (2.6%) in naproxen group and 18/885 (2%) in placebo group). Combining findings from both NSAID groups, we found no evidence of a difference in the incidence of MCI between participants allocated NSAIDs and those allocated placebo (RR 1.28, 95% CI 0.72 to 2.28; 2072 participants; low-certainty evidence; Analysis 2.9). There was no evidence of a difference from placebo for either of the NSAIDs individually (celecoxib: RR 1.30, 95% CI 0.67 to 2.53; 1490 participants; low-certainty evidence; Analysis 2.9, naproxen: RR 1.27, 95% CI 0.64 to 2.49; 1467 participants; low-certainty evidence; Analysis 2.9) .

Activities of daily living: the trial did not report activities of daily living.

Health-related quality of life: the trial did not report health-related quality of life.

Adults with age-related memory loss (Small 2008)

Small 2008 compared celecoxib and placebo.

Incidence of dementia: the trial did not report the incidence of dementia.

Adverse events: of the 88 participants randomised, only 40 participants contributed to the analyses of adverse events. Thirteen (59%) participants allocated celecoxib and four (22%) participants allocated placebo experienced adverse gastrointestinal events, which included gastritis, nausea and abdominal pain (RR 2.66, 95% CI 1.05 to 6.75; 40 participants; low-certainty evidence; Analysis 3.1).

Mortality: the trial did not report mortality.

Cognitive decline from baseline: our analyses, undertaken at the individual cognitive test level within each of the six cognitive domains, found no evidence of a difference in cognition between participants allocated celecoxib and those allocated placebo (40 participants; low-certainty evidence for all cognitive measures across all six cognitive domains). The analyses for individual cognitive tests measured within each of the six cognitive domains are presented in Summary of findings 3. Contrary to our findings, the study reported significant between-group differences in the domains of executive functioning and language/semantic memory in favour of celecoxib. However, they used a different method of analysis. Within each domain, the raw data from the individual cognitive tests were converted to Z scores and the mean Z scores for each domain were used to compare groups.

Activities of daily living: the trial did not report activities of daily living.

Health-related quality of life: the trial did not report health-related quality of life.

Older adults with mild cognitive impairment (Thal 2005)

Thal 2005 compared rofecoxib versus placebo.

Incidence of dementia: 189 participants with MCI were diagnosed with AD over the period of the trial (107/725 (14.8%) in rofecoxib group and 82/732 (11.2%) in placebo group). Participants allocated to rofecoxib were more likely to convert to AD than those allocated placebo, although the result was imprecise and also compatible with little or no difference between the groups (RR 1.32, 95% CI 1.01 to 1.72; 1457 participants; moderate-certainty evidence; Analysis 4.1). The study reported an estimated annual rate of AD diagnosis of 6.4% in the rofecoxib group compared with 4.5% in the placebo group.

Adverse events: the trial reported the total number of cardiovascular and gastrointestinal adverse events. There were 74 cardiovascular adverse events across both treatment groups (38/725 (5.2%) in rofecoxib group and 36/732 (4.9%) in placebo group). There was no evidence of a difference in cardiovascular adverse events between treatment groups (RR 1.07, 95% CI 0.68 to 1.66; 1457 participants; moderate-certainty evidence; Analysis 4.2). There were 18 confirmed upper gastrointestinal ulcers, bleeds or perforations across both treatment groups (14/725 (1.9%) in rofecoxib group and 4/732 (0.55%) in placebo group). This represents a higher rate of gastrointestinal adverse events in participants allocated rofecoxib than in those allocated placebo (RR 3.53, 95% CI 1.17 to 10.68; 1457 participants; moderate-certainty evidence; Analysis 4.2).

Mortality: there were 39 deaths across both treatment groups (24/723 (3.3%) in rofecoxib group and 15/728 (2.1%) in placebo group), with no evidence of a difference in mortality between treatment groups (RR 1.62, 95% CI 0.85 to 3.05; 1457 participants; moderate-certainty evidence; Analysis 4.3).

Cognitive decline from baseline: the trial did not report cognitive decline from baseline. Data were presented for annual between-group differences in mean scores on cognitive tests including the Story Recall Test (SRT) – Summed Recall, SRT-Delayed Recall, Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog) and the MMSE. For each test, there was no evidence of an annual between-group difference.

Activities of daily living: data were presented for change in activities of daily living score for each year. Data for this outcome were not reported in a way suitable for our planned analyses so we reported the findings for this outcome directly from the study. The study reported no differences between treatment groups in any of the annual mean BDRS scores (BDRS: difference rofecoxib minus placebo: year 1: no data available; year 2: 0.0, 95% CI −0.1 to 0.2; year 3: 0.1, 95% CI −0.1 to 0.3; year 4: 0.1, 95% CI −0.1 to 0.4; 1457 participants; moderate-certainty evidence; data for this outcome are presented in Summary of findings 4).

Health-related quality of life: the trial did not report health-related quality of life.

DISCUSSION

Summary of main results

The objective of this review was to evaluate the effectiveness and safety of aspirin and other NSAIDs for the primary and secondary prevention of dementia.

For the comparison of aspirin with placebo, we included only one trial (ASPREE 2018). This trial evaluated the effects of low-dose aspirin for extending disability-free survival – an endpoint that combined dementia, all-cause death and physical disability – among healthy older people. There was no evidence of a difference between groups in rates of dementia and no difference in related outcomes such as functional status (i.e. ability to perform activities of daily living independently). However, participants allocated to aspirin had higher rates of mortality and higher rates of major haemorrhagic events compared with participants allocated placebo.

For the second comparison of other NSAIDs with placebo, we included three trials with 4073 participants. Due to heterogeneity between studies, we assessed each study separately.

One primary prevention trial evaluated the effectiveness of the selective COX-2 inhibitor celecoxib and the non-selective COX inhibitor naproxen in preventing dementia in cognitively healthy adults aged 70 years and older who were at risk of dementia by virtue of family history (ADAPT Research Group 2007/2006). The trial was supposed to run for seven years but was suspended after two years due to concerns around safety. Incidence of AD was the primary outcome in this trial. There was no evidence of a difference in the incidence of AD between treatment groups. The trial reported all-cause dementia, excluding participants with prevalent dementia, which indicated a potentially higher incidence of all-cause dementia in those prescribed NSAIDs. There was no evidence of a difference in cardiovascular adverse events and mortality between the groups. The trial did not report our other safety outcomes of interest, gastrointestinal bleeding and renal events.

Initiation of antihypertensives, a proxy for incident hypertension, was assessed and was higher in participants receiving NSAIDs. This trial measured incidence of MCI, which we included as a proxy for our outcome of cognitive decline from baseline; there was no difference in this outcome between groups. The trial did not report activities of daily living and health-related quality of life.

The second included trial for this comparison was a secondary prevention trial evaluating the effectiveness of the selective COX-2 inhibitor celecoxib 200 mg or 400 mg once daily in delaying cognitive decline in adults with age-related memory loss (Small 2008). This trial was planned to run for 18 months but was terminated early due to safety concerns. Gastrointestinal adverse events were more common in the celecoxib group. Our analysis found no difference in cognition between groups. However, the trial authors reported significant between-group differences in executive functioning and language/semantic memory in favour of celecoxib; this may be explained by the different methods used to analyse data, making a direct comparison of findings difficult.

The third included trial for this comparison was a secondary prevention trial that evaluated the effectiveness of the selective COX-2 inhibitor rofecoxib once daily in delaying a diagnosis of AD in participants with MCI (Thal 2005). The trial was planned to run for four years but was suspended early due to safety concerns. Results indicated that participants with MCI allocated rofecoxib had a higher conversion to AD compared with participants allocated placebo. There was no difference in cardiovascular adverse events between treatment groups but gastrointestinal adverse events were more common in the rofecoxib group. There was no evidence of a difference in mortality, cognitive decline from baseline and activities of daily living between treatment groups. The trial did not report health-related quality of life.

Overall completeness and applicability of evidence

This review sought to establish the evidence to support the use of aspirin and other NSAIDs for the primary and secondary prevention of dementia. The dose of aspirin used in ASPREE 2018 was low. It is plausible that higher doses of aspirin may be needed to have sufficient anti-inflammatory effects but, given the adverse events demonstrated with low-dose aspirin in this trial, future evaluations of higher doses of aspirin for dementia prevention may be limited by dose-dependent adverse effects.

Three NSAIDs were included in the review: celecoxib, rofecoxib (both COX-2 inhibitors) and naproxen (a non-selective COX inhibitor), thus we had relevant data on all drug classes within our 'anti-inflammatory' rubric. It seems likely that the results demonstrated in the two included trials indicate a class effect for NSAIDs.

Our primary outcomes of interest were incidence of dementia, adverse events and mortality. Three of the included studies had robust measures of dementia (Thal 2005; ADAPT Research Group 2007/2006; ASPREE 2018). In the two NSAID studies that measured dementia (ADAPT Research Group 2007/2006; ASPREE 2018), we favoured data on incident AD over undifferentiated dementia, as this is the dementia subtype that was hypothesised to be most amenable to modification through use of NSAIDs. Although all included papers reported adverse events, there was inconsistency in the data reported. NSAIDS often have adverse cardiovascular, gastrointestinal and renal effects, and it is plausible that important adverse event data were not included. Other important prespecified outcomes, such as health-related quality of life was not included in the available studies.

Quality of the evidence

This review included four trials. A meta-analysis of data was not possible for either comparison due to clinical heterogeneity in the populations studied; the interventions tested and the outcomes reported. All four trials were placebo-controlled RCTs and sample sizes in three of the included trial were large (Thal 2005; ADAPT Research Group 2007/2006; ASPREE 2018). One trial had a small sample size (Small 2008).

For the comparison of aspirin with placebo, ASPREE 2018 was a well-designed trial and the certainty of the evidence for each outcome was high. For the comparison of other NSAIDs compared with placebo, in two of the included trials the certainty of the evidence for each of the reported outcomes was moderate, downgraded by one level due to imprecision because event rates in both trials were low (Thal 2005; ADAPT Research Group 2007/2006). The certainty of the evidence in one NSAID trial was low, downgraded two levels due to imprecision as event rates were low and there was a risk of bias associated with on-treatment analyses (Small 2008). Loss to follow-up varied across the included trials. Reasons for loss to follow-up were provided in the individual trial reports and seemed unlikely to cause a systematic bias. All of the included trials were stopped early for safety rather than efficacy reasons, so for this reason the certainty of the evidence was not downgraded further.

Potential biases in the review process

We believe that in adhering to the recommended Cochrane search and review methods, we have identified all data of interest to the review question. We recognise that aspects of study inclusion are open to debate. Our interest was dementia prevention and so we did not include studies of prevalent dementia. We opted to include MCI, as this can be considered a high-risk state for future dementia and MCI is not included in other Cochrane Reviews of NSAIDs. Although our original remit was dementia prevention, we favoured outcomes relevant to AD rather than all-cause (undifferentiated) dementia where both were reported.

Agreements and disagreements with other studies or reviews

Much of the existing evidence to support the use of aspirin and other NSAIDs in the primary and secondary prevention of dementia stems from epidemiological studies. A systematic review and meta-analysis of these observational studies (Etminan 2003), included six cohort studies (13,211 participants) and three case-control studies (1443 participants). Contrary to findings from this review of trial evidence, the observational study review reported that aspirin and other NSAIDs lower the risk of AD, particularly with long-term use (defined as greater than 24 months). One updated systematic review and meta-analysis included both observational studies and RCTs evaluating NSAID use and the incidence of dementia (Wang 2015). It reported that findings from observational studies suggested that NSAIDs use was associated with a significant reduction in the risk of AD. The differences between these observational studies and the trial results in our review emphasises the danger of making causal inferences based on non-randomised data.

We found one trial that looked at aspirin for vascular disease that was relevant to our review question but did not contain our outcomes of interest (Price 2008). In a post-hoc study of a subgroup of participants, the research team administered a neuropsychological battery at one of the follow-up visits. This outcome does not represent incident dementia as there was no diagnostic formulation and does not represent 'cognitive decline from baseline' as only one assessment was made, albeit one may assume that participants were cognitively healthy at time of randomisation. Accepting these caveats, the results of this trial agree with the results from the trials included in this review in that aspirin showed no evidence of a beneficial cognitive effect.

AUTHORS' CONCLUSIONS

Implications for practice

The available evidence does not support the use of aspirin, celecoxib, naproxen or rofecoxib for the primary or secondary prevention of dementia, taken at the doses and for the periods of time detailed in this review. Aspirin did not demonstrate a protective effect but was associated with a higher rate of adverse events. The consistency of results across the various non-steroidal anti-inflammatory drugs (NSAIDs) would suggest that this is a class effect and our review findings probably apply to all NSAIDs. Similar to the aspirin study, NSAID use demonstrated a high rate of adverse events; this is in keeping with data from observational studies where chronic exposure to NSAIDs is a common cause of iatrogenic harm (García Rodríguez 2016).

Implications for research

Low-dose aspirin use demonstrated no protective effect but was associated with significant rates of adverse events. For this reason, it seems unlikely that there should be further trials of low-dose aspirin for dementia prevention. If future studies of NSAIDs for dementia prevention are planned, then these will need to take account of the safety concerns arising from the studies included in this review and from other NSAID trials. The results of this review do not mean that there is no potential for anti-inflammatory drugs to modify dementia risk. However, drugs with less potential to cause adverse events would be needed for future studies.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

ADAPT Research Group 2007/2006

Study characteristics	
Methods	**Study design:** RCT. **Data collection time points:** cognitive screening undertaken at baseline and once a year for trial period. Recruitment for trial started in March 2001. Initially, trial planned to last 7 years but treatments were suspended in December 2004 after there were increased cardiovascular risks with celecoxib in the Adenoma Prevention with Celecoxib (APC) trial.
Participants	**Setting:** 6 sites across the USA. **Inclusion criteria:** aged ≥ 70 years with family history of ≥ 1 first-degree relative with Alzheimer-like dementia. A suitable informant was available to provide information on the cognitive status of the participant and to assist with monitoring of trial medications, if needed. Sufficient fluency in written and spoken English to participate in study visits and neuropsychological testing. Willingness to limit use of the following for duration of study: vitamin E (at doses > 400 IU daily), non-aspirin NSAIDs, histamine H_2 receptor antagonists (e.g. cimetidine), corticosteroids, anti-inflammatory or analgesic doses of aspirin (> 81 mg daily) and Ginkgo biloba extracts. Ability and intention to participate in regular study visits, in the opinion of the study physician. Ability to provide informed consent. **Exclusion criteria:** history of peptic ulcer disease with bleeding or obstruction. Clinically significant liver or kidney disease. History of hypersensitivity to aspirin, ibuprofen, celecoxib, naproxen or other NSAIDs. Use of anticoagulant medication. Cognitive impairment or dementia. Current alcohol abuse or dependence. **Participants randomised:** total 2528, 726 allocated celecoxib, 719 allocated naproxen and 1083 allocated placebo. Of the total number of participants, 45.9% were women and 54.1% were men.

ADAPT Research Group 2007/2006 *(Continued)*

Interventions	**Intervention:** celecoxib 200 mg BID or naproxen 220 mg BID. **Control:** matching placebo. Median follow-up times: 733 days for celecoxib, 734 days for naproxen and 734.5 days for placebo.
Outcomes	**Outcome relevant to this review** • Diagnosis of AD, diagnosed according to NINCDS-ADRDA criteria. • Incidence of all-cause dementia diagnosed according to DSM-IV criteria. • Cardiovascular events, i.e. non-fatal MI, stroke, CHF, TIA and initiation of antihypertensive treatments. • Mortality. • Diagnosis of MCI or AD prodromes (compatible with our outcome of cognitive decline from baseline), assessed using a battery of cognitive tests, i.e. Brief Visuospatial Memory Test – Revised; generative verbal fluency; Hopkins Verbal Learning Test – Revised; Rivermead Behavioral Memory Test and a modified version of the MMSE (3MS-E).
Identification	**Authors name:** CG Lyketsos **Institution:** John Hopkins School of Medicine **E-mail:** kostas@jhmi.edu **Address:** Department of Psychiatry, Johns Hopkins Bayview, 5300 Alpha Commons Drive, 4th Floor, Baltimore, MD21224, USA.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence generation	Low risk	Quote: "The randomisation sequence was generated by the trial's coordinating centre in permuted blocks stratified by three age groups (ages 70–74, ages 75–79, and ages 80+) and the six field sites, with an assignment ratio of 1:1:1.5. Randomization was implemented via computer systems distributed to each of the six sites. The sequence of bin assignments was concealed from site personnel via encoding and password protection of the randomisation files. Before randomizations, site personnel were required to enter baseline data. The ADAPT computer system confirmed eligibility before releasing the bin assignment" (pg. 1801).
Allocation concealment	Low risk	Quote: "using a distributed computerized system that released treatment assignment only after baseline data were keyed and eligibility confirmed" (pg. 1801).
Blinding of participants and personnel All outcomes	Low risk	Judgement comment: treatments were administered using a double-blind method. Blinding was accomplished using placebos matching the celecoxib and naproxen treatments (without active ingredients). Treatment by study personnel during the trial remained blinded to assignment. The blinding for participants and study personnel remained in place until June 2007, when it was lifted via mailings to study participants revealing their assignment.
Blinding of outcome assessors All outcomes	Low risk	Judgement comment: blinding of the outcome assessors was referenced in the paper reporting cardiovascular and cerebrovascular events in ADAPT (ADAPT Research Group 2006). In the Data Collection paragraph of this paper, the authors stated that, "masked study personnel recorded participant reports of adverse events on data forms" (pg. e33).

ADAPT Research Group 2007/2006 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "As of December 17, 2004, ADAPT had recruited 2,528 participants. Figure 1 shows the flow of these participants from randomizations forward. Some 403 participants did not contribute to the analyses for one of three reasons: 1) their observations were censored before their first annual follow-up (n=179); 2) they did not return for cognitive follow-up (n=210); or 3) no information on cognition was available because they had refused or not completed a requested Dementia Evaluation. These losses were distributed proportionally across treatment groups (Fisher exact P = 0.54)" (pg.1802). Quote: "In all instances, we used the principle of intention-to-treat (ITT) when comparing the occurrence of diagnostic outcomes by assigned treatment" (pg. 1801).
Selective outcome reporting	Low risk	Judgement comment: outcomes were reported in 2 separate papers. The first paper (The ADAPT Research Group 2007) reported the primary outcome, i.e. diagnosis of AD, and secondary outcomes, i.e. incidence of all-cause dementia and MCI. Outcomes presented in the methods section were presented in the results section. Adverse events were reported in a second paper (The ADAPT Research Group 2006). All adverse events detailed in the methods section were presented in the results section.
Other sources of bias	Low risk	Judgement comment: no other sources of bias apparent. **Funding:** "Grant funding was received from the National Institute on Aging (U01 AG15477). Celecoxib and matching placebo were provided by Pfizer, Inc. Naproxen sodium and matching placebo were provided by Bayer Consumer Healthcare" (pg. 1800).

ASPREE 2018

Study characteristics	
Methods	**Study design:** RCT. **Data collection time points:** Trial participants had annual visits and six-monthly telephone calls. It was planned that participants reaching the study endpoints for dementia or disability would then be followed for the duration of the trial for mortality.
Participants	**Setting:** Australia and the USA. **Inclusion criteria:** community dwelling. Able to give informed consent. Able to attend a study visit. Men and women aged ≥ 70 years (no upper age limit) except for US black and Hispanic people who were aged ≥ 65 years (no upper age limit). **Exclusion criteria:** history of cardiovascular or cerebrovascular event. Clinical diagnosis of atrial fibrillation, dementia, physical disability, condition associated with a high risk of bleeding, condition likely to cause death within 5 years. Current continuous use of antiplatelet or anticoagulant medication. Current use of aspirin for secondary prevention. Uncontrolled hypertension. Unwilling to cease regular aspirin being taken for primary prevention. Tablet taking compliance < 80% during a 4-week placebo run-in phase. Current participation in another trial. **Participants randomised:** total 19,114 (16,703 in Australia and 2411 in US), 9525 allocated aspirin and 9589 allocated placebo
Interventions	**Intervention:** low-dose aspirin (100 mg daily) **Control:** matching placebo

ASPREE 2018 *(Continued)*

	Intervention delivered for median of 4.7 years, only 5 months ahead of the planned completion date.
Outcomes	• Dementia diagnosed according to DSM-IV criteria. • Mortality. • Adverse events: major haemorrhage. • Cardiovascular events, i.e. fatal coronary heart disease, non-fatal MI, fatal or non-fatal stroke, or hospitalisation for heart failure. • Diagnosis of MCI. • ADL.
Identification	**Authors name:** JJ McNeil **Institution:** Monash University, Melbourne **E-mail:** john.mcneill@monash.edu **Address:** Department of Epidemiology and Preventative Medicine, Monash University, 553 St Kilda Rd, Melbourne, VIC 30004, Australia
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence generation	Low risk	Participants allocated according to a computer-generated randomisation schedule.
Allocation concealment	Low risk	Study participants remotely randomised via the ASPREE web portal.
Blinding of participants and personnel All outcomes	Low risk	Quote: "Trial participants, study staff, investigators, and general practitioner associate investigators, were unaware of the trial group assignment until the publication of this article" (pg. 3).
Blinding of outcome assessors All outcomes	Low risk	All outcomes were adjudicated by an endpoint adjudication committee consisting of clinicians and research personnel who were blinded to group allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome analyses undertaken on an intention-to-treat basis. Quote: "By the last 12 months of the trial, 82% of participants were still attending annual follow-up visits, 5.5% had died, 9.7% were still being followed-up by regular telephone contact, or through access to clinical or other records, 1.2% had withdrawn, 1.6% were lost to follow-up. All participants contributed data to the analyses until the time of withdrawal or loss to follow-up" (pg. 6).
Selective outcome reporting	Low risk	Judgement comment: all outcomes detailed in the methods section were reported in the results section.
Other sources of bias	Low risk	Funded by grants from (quote): "the National Institute on Aging and the National Cancer Institute at the National Institutes of health, National Health and Medical research Council of Australia and by Monash University and the Victorian Cancer Agency" (pg. 9).

Small 2008

Study characteristics	
Methods	**Study design:** RCT. **Data collection time points:** baseline and 18-months for cognitive outcomes.
Participants	**Setting:** university research institute, USA. **Inclusion criteria:** aged ≥ 40 years with objective cognitive performance scores that were normal for their age group. All had mild age-related memory complaints. **Exclusion criteria:** taking drugs that could influence cognition (e.g. cholinesterase inhibitors, sedative-hypnotics) or modify COX-2 drug safety (e.g. aspirin) or supplements that could have such effects (e.g. phosphatidyl serine, ginkgo biloba). History of excessive alcohol or tobacco use. Evidence of depression or scoring < 26 on the MMSE. Meeting diagnostic criteria for dementia, MCI or other major psychiatric disorders. **Participants randomised:** 88 who met the inclusion criteria completed baseline clinical assessments, neuropsychological testing and scanning were randomised. 16 withdrew from participation after randomisation but before initiation of treatment. Of remaining 72 participants, 36 were randomised to the celecoxib group and 36 to the placebo group.
Interventions	**Intervention:** celecoxib 200–400 mg BID. **Control:** placebo.
Outcomes	• Change in cognition from baseline across 6 cognitive domains: psychomotor speed, visuospatial functioning, executive functioning, learning, delayed recall and language/semantic memory. • Adverse events.
Identification	**Authors name:** Dr Gary W Small **Institution:** The Semel Institute **E-mail:** gsmall@mednet.ucla.edu **Address:** Suite 88–201, 760 Westwood Plaza, Los Angeles 90024, CA, USA.
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Sequence generation	Low risk	Judgement comment: randomisation was undertaken using a randomisation table.
Allocation concealment	Unclear risk	Judgement comment: insufficient detail to make informed judgement.
Blinding of participants and personnel All outcomes	Unclear risk	Judgement comment: insufficient detail to make informed judgement.
Blinding of outcome assessors All outcomes	Unclear risk	Judgement comment: insufficient detail to make informed judgement.
Incomplete outcome data (attrition bias) All outcomes	High risk	Outcome analyses was not undertaken on an intention-to-treat basis.

Small 2008 *(Continued)*

		Quote: "A total of 88 subjects, who met the study inclusion criteria completed baseline clinical assessments, neuropsychological testing, and scanning, were randomized and 16 of them withdrew from participation after randomization but before initiation of treatment (Fig. 1). Of the remaining 72 subjects, 36 were randomized to the celecoxib group and 36 to the placebo group. Of the subjects randomized, a total of 40 completed the study, 22 in the celecoxib treatment arm and 18 in the placebo treatment arm. Subjects who withdrew from the study did not differ significantly from those who completed the study in mean age or baseline cognitive measures" (pg. 6).
Selective outcome reporting	Low risk	Judgement comment: all outcomes detailed in the methods section were reported in the results section.
Other sources of bias	Low risk	Funding bias: quote: "The University of California, Los Angeles, owns a U.S. patent (6,274,119) entitled “Methods for Labeling β-Amyloid Plaques and Neurofibrillary Tangles,” that has been licensed to Siemens. Drs. Small, Huang, and Barrio are among the inventors, have received royalties, and will receive royalties on future sales. Dr. Small reports having served as a consultant and/or having received lecture fees from Abbott, Brainstorming Co., Dakim, Eisai, Forest, Myriad Genetics, Novartis, Ortho-McNeil, Pfizer, Radica, Siemens, and VerusMed. Dr. Small also reports having received stock options from Dakim. Dr. Lavretsky reports having received lecture fees from Eisai, Janssen, and Pfizer and having received a grant from Forest. Dr. Huang reports having received lecture fees from GlaxoSmithKline. Dr. Barrio reports having served as a consultant and having received lecture fees from Nihon Medi-Physics Co, Bristol-Meyer Squibb, PETNet Pharmaceuticals, and Siemens. Drs. Ercoli, Siddarth, Miller, Phelps, and Bookheimer have no financial conflicts of interest" (pg. 1).

Thal 2005

Study characteristics	
Methods	**Study design:** RCT. **Data collection time points:** baseline, 1 month and every 4 months or at discontinuation from the trial. Study was expected to run over 4 years. However, the study was terminated in April 2003, 11 months earlier than the planned termination date because Merck announced the voluntary worldwide withdrawal of rofecoxib from the market.
Participants	**Setting:** 46 sites across the USA. **Inclusion criteria:** people aged ≥ 65 years who had completed ≥ 8 grades of education, and had a reliable informant who could accompany them to each clinic visit. Patients screened at study sites to determine if they met all the following criteria for MCI: patient-reported memory problem, or informant reports that patient has memory problem; informant reported that patient's memory had declined in the past year; MMSE score ≥ 24; CDR global score 0.5 with Memory Domain score ≥ 0.5; BDRS total score ≤ 3.5, with no part 1 item score > 0.5; Auditory Verbal Learning Test total score ≤ 37. **Exclusion criteria:** dementia. Inadequate motor or sensory capacities to comply with testing. Modified Hachinski Ischemic Scale score > 4; Hamilton Depression Scale (17-item version) score > 13 (to exclude people whose cognitive impairment may have been related to depression). History of angina or CHF with symptoms that occurred at res. Uncontrolled hypertension. History within past year of MI, coronary artery bypass, angioplasty or stent placement History within the past 2 years of stroke, multiple lacunar infarcts or TIA events. History within the past 3 months of gastrointestinal bleeding. Expected therapeutic need for chronic NSAID or oestrogen replacement therapy during study. Taking NSAIDs on a chronic basis (≥ 7 days per month for the 2 months prior to study entry). Taking oestrogen replacement therapy (excluding topical ointments) within 2 months of study entry or cholinesterase inhibitors within 1 month of study entry.

Thal 2005 *(Continued)*

	Participants randomised: total 1457, of whom, 725 were allocated rofecoxib and 732 were allocated placebo. The authors reported that of total number of participants allocated rofecoxib, 34.3% were women and of total number of participants allocated placebo, 31.1% were women.
Interventions	**Intervention:** rofecoxib 25 mg once daily **Control:** placebo Median duration for study participation: 115 weeks in rofecoxib group and 130 weeks in placebo group.
Outcomes	**Outcome relevant to this review:** • Clinical diagnosis of dementia. Diagnosis of possible or probable dementia was diagnosed according to the NINCDS-ADRDA criteria. • Adverse events. • Mortality. • ADL as measured by the BDRS (higher scores across Part 1 and Part 2 indicated greater impairment).
Identification	**Authors name:** Dr CR Lines **Institution:** Merck Research Laboratories **E-mail:** chris_lines@merck.com **Address:** 10 Sentry Parkway, Blue Bell, PA 19422, USA.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence generation	Low risk	Quote: "Randomization of patients at each study site was determined by a computer-generated allocation schedule" (pg. 1205).
Allocation concealment	Unclear risk	Quote: "The allocation schedule was generated by a statistician at Merck Research Laboratories according to in-house blinding conditions" (pg. 1205). Judgement comment: insufficient detail to make informed judgement.
Blinding of participants and personnel All outcomes	Low risk	Quote: "The rofecoxib and placebo tablets were visually identical" (pg. 1205).
Blinding of outcome assessors All outcomes	Low risk	Quote: "For patients who reached the end point of clinically diagnosed dementia, all relevant data were sent to an independent blinded adjudication committee consisting of three experts" (pg. 1206).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The analysis was based on a Cox proportional hazards model of time-to-event data (based on the initial diagnosis of AD) using an intention-to-treat approach, which included all randomised patients regardless of whether or not they were taking study medication" (pg. 1206). 656 participants discontinued treatment, 324 in rofecoxib group and 331 in placebo group. Loss to follow-up in each group was comparable. Judgement comments: high non-completion rates but primary efficacy analysis by intention-to-treat.

Thal 2005 *(Continued)*

Selective outcome reporting	Low risk	Judgement comment: a comparison of outcomes of interest reported in the methods section were consistent with those reported in the results section of the trial publication.
Other sources of bias	Low risk	Judgement comment: low risk. **Funding:** "This study was funded by Merck Research Laboratories. SH Ferris was a paid consultant for Merck Research Laboratories on this study. L Kirby received funding from Merck Research Laboratories to participate in this study. GA Block, CR Lines, E Yuen, C Assaid, ML Nessly, BA Norman, CC Baranak, and SA Reines were employees of Merck Research Laboratories at the time the study was performed (GA Block is currently an employee of Astra Zeneca, and SA Reines and E Yuen are currently employees of Johnson & Johnson)" (pg. 1213). Judgement comment: trial outcomes were not favourable to drug being tested so we deemed it unlikely that funding bias was an issue in this trial.

AD: Alzheimer's disease; ADAPT: Alzheimer's Disease Anti-inflammatory Prevention Trial; ADL: activities of daily living; ASPREE: Aspirin in Reducing Events in the Elderly; BDRS: Blessed Dementia Rating Scale; BID: twice daily; CDR: Clinical Dementia Rating; CHF: congestive heart failure; COX: cyclo-oxygenase; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders-IV criteria; MCI: mild cognitive impairment; MI: myocardial infarction; MMSE: Mini-Mental State Examination; NINCDS-ADRDA: Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association Criteria; NSAIDs: non-steroidal anti-inflammatory drugs; RCT: randomised controlled trial; SRT: Selective Recall Test; TIA: transient ischaemic attack.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
ADAPT-FS Research Group 2015	Study design did not meet inclusion criteria, i.e. not an RCT or CCT. Follow-up study to ADAPT trial.
Arai 2011	Study design did not meet inclusion criteria, i.e. not an RCT or CCT. A discussion paper on prevention and treatment strategies for dementia.
Arvanitakis 2008	Study design did not meet inclusion criteria, i.e. not an RCT or CCT.
Bertozzi 1996	Study design did not meet inclusion criteria, i.e. not an RCT or CCT.
Breitner 2009	Study design did not meet inclusion criteria, i.e. not an RCT or CCT.
Broe 2000	Study design did not meet inclusion criteria, i.e. not an RCT or CCT.
Bruce-Jones 1994	Study design did not meet inclusion criteria, i.e. not an RCT or CCT.
Clarke 2003	Population did not meet inclusion criteria, participants had dementia.
Gómez-Isla 2008	Intervention did not meet the inclusion criteria, i.e. aspirin or NSAID.
Hayden 2007	Study design did not meet inclusion criteria, i.e. not an RCT or CCT.
Ibáñez-Hernández 2008	Study design did not meet inclusion criteria, i.e. not an RCT or CCT.
Jonker 2003	Study design did not meet inclusion criteria, i.e. not an RCT or CCT.

Study	Reason for exclusion
Kang 2007	Study design did not meet the inclusion criteria, i.e. not an RCT or CCT. 'A cohort study' within an RCT.
Kern 2012	Study design did not meet inclusion criteria, i.e. not an RCT or CCT. A prospective, population-based cohort study
Kerst 2002	Study design did not meet inclusion criteria, i.e. not an RCT or CCT.
Marini 2013	Study design did not meet inclusion criteria, i.e. not an RCT or CCT.
May 1992	Study design did not meet inclusion criteria, i.e. not an RCT or CCT.
Price 2008	Contained none of the prespecified outcomes for this review.
Rist 2013	Study design did not meet inclusion criteria, i.e. not an RCT or CCT.
Silagy 1993	Study design did not meet inclusion criteria, i.e. not an RCT or CCT.
Sonnen 2010	Study design did not meet inclusion criteria, i.e. not an RCT or CCT.
Szekely 2008	Study design did not meet inclusion criteria, i.e. not an RCT or CCT.

CCT: controlled clinical trial; RCT: randomised controlled trial.

DATA AND ANALYSES

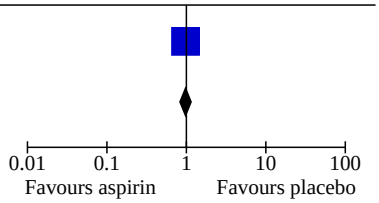
Comparison 1. Aspirin compared with placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Incidence of dementia	1	19114	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.83, 1.15]
1.2 Adverse events (haemorrhage)	1	19114	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [1.17, 1.60]
1.3 Mortality	1	19114	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [1.01, 1.28]
1.4 Activities of daily living	1	19114	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.70, 1.02]

Analysis 1.1. Comparison 1: Aspirin compared with placebo, Outcome 1: Incidence of dementia

Study or Subgroup	Aspirin Events	Aspirin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ASPREE 2018	283	9525	292	9589	100.0%	0.98 [0.83 , 1.15]
Total (95% CI)		**9525**		**9589**	**100.0%**	**0.98 [0.83 , 1.15]**
Total events:	283		292			

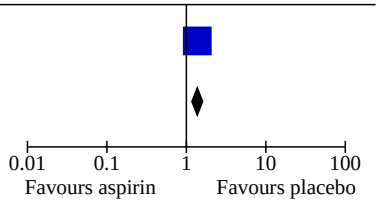
Heterogeneity: Not applicable
Test for overall effect: Z = 0.30 (P = 0.76)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Aspirin compared with placebo, Outcome 2: Adverse events (haemorrhage)

Study or Subgroup	Aspirin Events	Aspirin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ASPREE 2018	361	9525	265	9589	100.0%	1.37 [1.17 , 1.60]
Total (95% CI)		**9525**		**9589**	**100.0%**	**1.37 [1.17 , 1.60]**
Total events:	361		265			

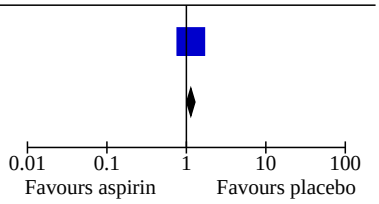
Heterogeneity: Not applicable
Test for overall effect: Z = 3.97 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Aspirin compared with placebo, Outcome 3: Mortality

Study or Subgroup	Aspirin Events	Aspirin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ASPREE 2018	558	9525	494	9589	100.0%	1.14 [1.01 , 1.28]
Total (95% CI)		**9525**		**9589**	**100.0%**	**1.14 [1.01 , 1.28]**
Total events:	558		494			

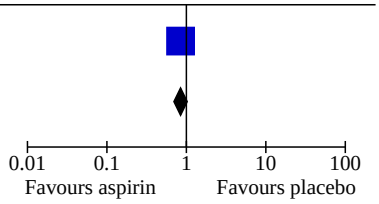
Heterogeneity: Not applicable
Test for overall effect: Z = 2.14 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Aspirin compared with placebo, Outcome 4: Activities of daily living

Study or Subgroup	Aspirin Events	Aspirin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ASPREE 2018	188	9525	224	9589	100.0%	0.84 [0.70 , 1.02]
Total (95% CI)		**9525**		**9589**	**100.0%**	**0.84 [0.70 , 1.02]**
Total events:	188		224			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.72 (P = 0.09)
Test for subgroup differences: Not applicable



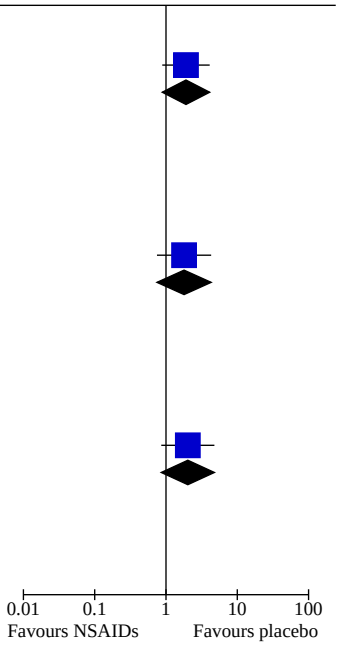
Comparison 2. NSAIDs compared with placebo: cognitively healthy adults with a family history of Alzheimer's disease (AD)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Incidence of dementia (AD)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1.1 All NSAIDs (celecoxib and naproxen combined)	1	2125	Risk Ratio (M-H, Fixed, 95% CI)	1.91 [0.89, 4.10]
2.1.2 Celecoxib	1	1527	Risk Ratio (M-H, Fixed, 95% CI)	1.79 [0.75, 4.30]
2.1.3 Naproxen	1	1506	Risk Ratio (M-H, Fixed, 95% CI)	2.02 [0.86, 4.78]
2.2 All-cause dementia	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.2.1 All NSAIDs (celecoxib and naproxen combined)	1	2118	Risk Ratio (M-H, Fixed, 95% CI)	2.45 [1.05, 5.68]
2.2.2 Celecoxib	1	1523	Risk Ratio (M-H, Fixed, 95% CI)	2.50 [0.99, 6.32]
2.2.3 Naproxen	1	1499	Risk Ratio (M-H, Fixed, 95% CI)	2.39 [0.93, 6.12]
2.3 Adverse effects – cardiovascular: myocardial infarction	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.3.1 All NSAIDs (Celecoxib and Naproxen combined)	1	2500	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.61, 2.40]
2.3.2 Celecoxib	1	1787	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.38, 2.20]
2.3.3 Naproxen	1	1783	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.70, 3.22]
2.4 Adverse effects – stroke	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.4.1 All NSAIDs (celecoxib and naproxen combined)	1	2500	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [0.76, 4.37]
2.4.2 Celecoxib	1	1787	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.53, 4.24]
2.4.3 Naproxen	1	1783	Risk Ratio (M-H, Fixed, 95% CI)	2.14 [0.82, 5.61]
2.5 Adverse effects – congestive heart failure	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.5.1 All NSAIDs (celecoxib and naproxen combined)	1	2500	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.46, 3.02]
2.5.2 Celecoxib	1	1787	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.17, 2.47]
2.5.3 Naproxen	1	1783	Risk Ratio (M-H, Fixed, 95% CI)	1.72 [0.62, 4.71]
2.6 Adverse effects – transient ischaemic attack	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.6.1 All NSAIDs (celecoxib and naproxen combined)	1	2500	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.58, 2.77]
2.6.2 Celecoxib	1	1787	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.47, 3.01]
2.6.3 Naproxen	1	1783	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.55, 3.31]
2.7 Adverse effects – antihypertensive therapy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.7.1 All NSAIDs (celecoxib and naproxen combined)	1	1521	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [1.17, 1.61]
2.7.2 Celecoxib	1	1084	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [1.19, 1.71]
2.7.3 Naproxen	1	1081	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [1.10, 1.59]
2.8 Mortality	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.8.1 All NSAIDs (celecoxib and naproxen combined)	1	2528	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.78, 2.43]
2.8.2 Celecoxib	1	1809	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.73, 2.72]
2.8.3 Naproxen	1	1802	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.69, 2.61]
2.9 Cognitive decline from baseline	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.9.1 All NSAIDs (celecoxib and naproxen combined)	1	2072	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.72, 2.28]
2.9.2 Celecoxib	1	1490	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.67, 2.53]
2.9.3 Naproxen	1	1467	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.64, 2.49]

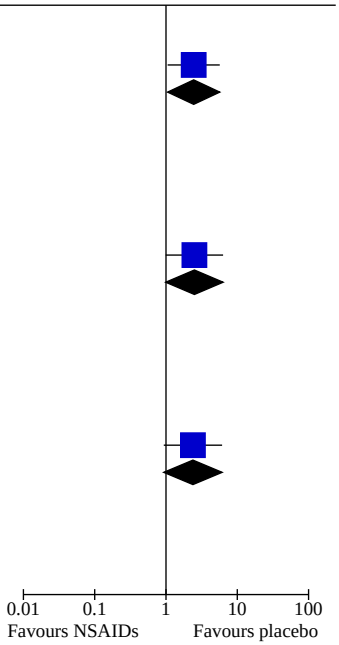
Analysis 2.1. Comparison 2: NSAIDs compared with placebo: cognitively healthy adults with a family history of Alzheimer's disease (AD), Outcome 1: Incidence of dementia (AD)

Study or Subgroup	NSAID Events	NSAID Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 All NSAIDs (celecoxib and naproxen combined)						
ADAPT Research Group 2007/2006	23	1217	9	908	100.0%	1.91 [0.89 , 4.10]
Subtotal (95% CI)		**1217**		**908**	**100.0%**	**1.91 [0.89 , 4.10]**
Total events:	23		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.65 (P = 0.10)						
2.1.2 Celecoxib						
ADAPT Research Group 2007/2006	11	619	9	908	100.0%	1.79 [0.75 , 4.30]
Subtotal (95% CI)		**619**		**908**	**100.0%**	**1.79 [0.75 , 4.30]**
Total events:	11		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.31 (P = 0.19)						
2.1.3 Naproxen						
ADAPT Research Group 2007/2006	12	598	9	908	100.0%	2.02 [0.86 , 4.78]
Subtotal (95% CI)		**598**		**908**	**100.0%**	**2.02 [0.86 , 4.78]**
Total events:	12		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.61 (P = 0.11)						
Test for subgroup differences: Chi^2 = 0.04, df = 2 (P = 0.98), I^2 = 0%						



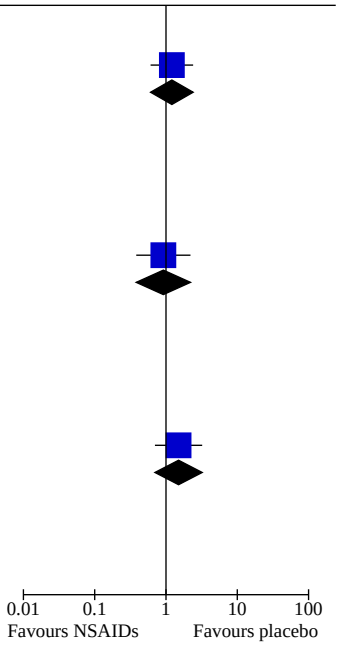
Analysis 2.2. Comparison 2: NSAIDs compared with placebo: cognitively healthy adults with a family history of Alzheimer's disease (AD), Outcome 2: All-cause dementia

Study or Subgroup	NSAID Events	NSAID Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.1 All NSAIDs (celecoxib and naproxen combined)						
ADAPT Research Group 2007/2006	23	1214	7	904	100.0%	2.45 [1.05 , 5.68]
Subtotal (95% CI)		**1214**		**904**	**100.0%**	**2.45 [1.05 , 5.68]**
Total events:	23		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.08 (P = 0.04)						
2.2.2 Celecoxib						
ADAPT Research Group 2007/2006	12	619	7	904	100.0%	2.50 [0.99 , 6.32]
Subtotal (95% CI)		**619**		**904**	**100.0%**	**2.50 [0.99 , 6.32]**
Total events:	12		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.94 (P = 0.05)						
2.2.3 Naproxen						
ADAPT Research Group 2007/2006	11	595	7	904	100.0%	2.39 [0.93 , 6.12]
Subtotal (95% CI)		**595**		**904**	**100.0%**	**2.39 [0.93 , 6.12]**
Total events:	11		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.81 (P = 0.07)						



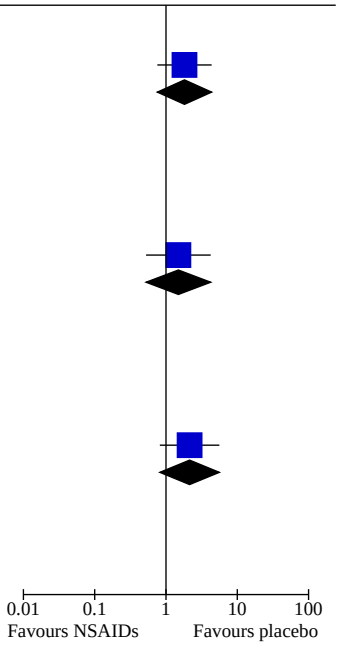
Analysis 2.3. Comparison 2: NSAIDs compared with placebo: cognitively healthy adults with a family history of Alzheimer's disease (AD), Outcome 3: Adverse effects – cardiovascular: myocardial infarction

Study or Subgroup	NSAID Events	NSAID Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.3.1 All NSAIDs (Celecoxib and Naproxen combined)						
ADAPT Research Group 2007/2006	21	1430	13	1070	100.0%	1.21 [0.61 , 2.40]
Subtotal (95% CI)		**1430**		**1070**	**100.0%**	**1.21 [0.61 , 2.40]**
Total events:	21		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.54 (P = 0.59)						
2.3.2 Celecoxib						
ADAPT Research Group 2007/2006	8	717	13	1070	100.0%	0.92 [0.38 , 2.20]
Subtotal (95% CI)		**717**		**1070**	**100.0%**	**0.92 [0.38 , 2.20]**
Total events:	8		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.19 (P = 0.85)						
2.3.3 Naproxen						
ADAPT Research Group 2007/2006	13	713	13	1070	100.0%	1.50 [0.70 , 3.22]
Subtotal (95% CI)		**713**		**1070**	**100.0%**	**1.50 [0.70 , 3.22]**
Total events:	13		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.04 (P = 0.30)						
Test for subgroup differences: Chi² = 0.69, df = 2 (P = 0.71), I² = 0%						



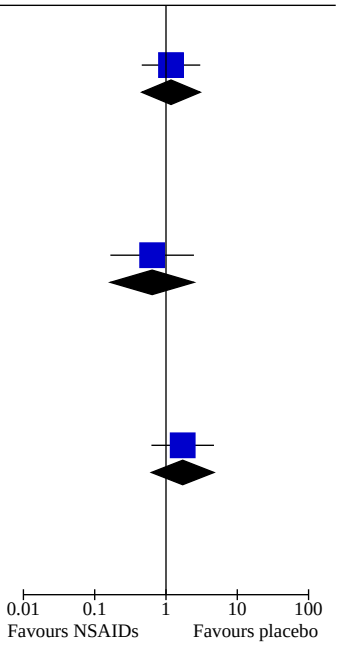
Analysis 2.4. Comparison 2: NSAIDs compared with placebo: cognitively healthy adults with a family history of Alzheimer's disease (AD), Outcome 4: Adverse effects – stroke

Study or Subgroup	NSAID Events	NSAID Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.4.1 All NSAIDs (celecoxib and naproxen combined)						
ADAPT Research Group 2007/2006	17	1430	7	1070	100.0%	1.82 [0.76 , 4.37]
Subtotal (95% CI)		**1430**		**1070**	**100.0%**	**1.82 [0.76 , 4.37]**
Total events:	17		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.34 (P = 0.18)						
2.4.2 Celecoxib						
ADAPT Research Group 2007/2006	7	717	7	1070	100.0%	1.49 [0.53 , 4.24]
Subtotal (95% CI)		**717**		**1070**	**100.0%**	**1.49 [0.53 , 4.24]**
Total events:	7		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.75 (P = 0.45)						
2.4.3 Naproxen						
ADAPT Research Group 2007/2006	10	713	7	1070	100.0%	2.14 [0.82 , 5.61]
Subtotal (95% CI)		**713**		**1070**	**100.0%**	**2.14 [0.82 , 5.61]**
Total events:	10		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.55 (P = 0.12)						
Test for subgroup differences: Chi² = 0.25, df = 2 (P = 0.88), I² = 0%						



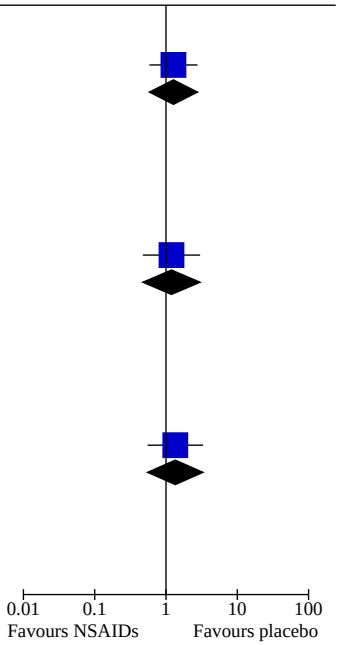
Analysis 2.5. Comparison 2: NSAIDs compared with placebo: cognitively healthy adults with a family history of Alzheimer's disease (AD), Outcome 5: Adverse effects – congestive heart failure

Study or Subgroup	NSAID Events	NSAID Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.5.1 All NSAIDs (celecoxib and naproxen combined)						
ADAPT Research Group 2007/2006	11	1430	7	1070	100.0%	1.18 [0.46 , 3.02]
Subtotal (95% CI)		**1430**		**1070**	**100.0%**	**1.18 [0.46 , 3.02]**
Total events:	11		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.34 (P = 0.74)						
2.5.2 Celecoxib						
ADAPT Research Group 2007/2006	3	717	7	1070	100.0%	0.64 [0.17 , 2.47]
Subtotal (95% CI)		**717**		**1070**	**100.0%**	**0.64 [0.17 , 2.47]**
Total events:	3		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.52)						
2.5.3 Naproxen						
ADAPT Research Group 2007/2006	8	713	7	1070	100.0%	1.72 [0.62 , 4.71]
Subtotal (95% CI)		**713**		**1070**	**100.0%**	**1.72 [0.62 , 4.71]**
Total events:	8		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.30)						
Test for subgroup differences: Chi² = 1.32, df = 2 (P = 0.52), I² = 0%						



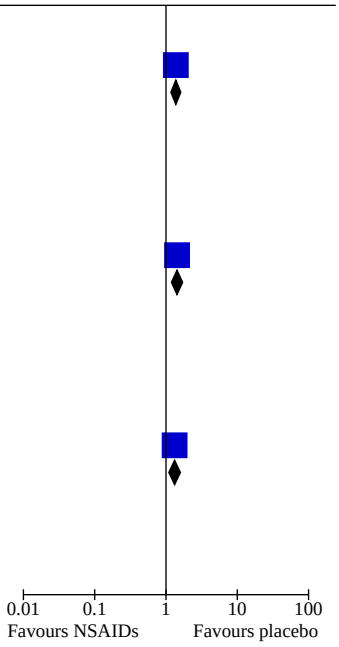
Analysis 2.6. Comparison 2: NSAIDs compared with placebo: cognitively healthy adults with a family history of Alzheimer's disease (AD), Outcome 6: Adverse effects – transient ischaemic attack

Study or Subgroup	NSAID Events	NSAID Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.6.1 All NSAIDs (celecoxib and naproxen combined)						
ADAPT Research Group 2007/2006	17	1430	10	1070	100.0%	1.27 [0.58 , 2.77]
Subtotal (95% CI)		**1430**		**1070**	**100.0%**	**1.27 [0.58 , 2.77]**
Total events:	17		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.61 (P = 0.54)						
2.6.2 Celecoxib						
ADAPT Research Group 2007/2006	8	717	10	1070	100.0%	1.19 [0.47 , 3.01]
Subtotal (95% CI)		**717**		**1070**	**100.0%**	**1.19 [0.47 , 3.01]**
Total events:	8		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.38 (P = 0.71)						
2.6.3 Naproxen						
ADAPT Research Group 2007/2006	9	713	10	1070	100.0%	1.35 [0.55 , 3.31]
Subtotal (95% CI)		**713**		**1070**	**100.0%**	**1.35 [0.55 , 3.31]**
Total events:	9		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
Test for subgroup differences: Chi² = 0.04, df = 2 (P = 0.98), I² = 0%						



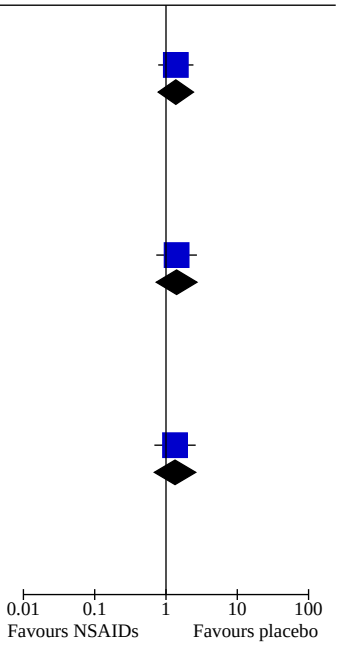
Analysis 2.7. Comparison 2: NSAIDs compared with placebo: cognitively healthy adults with a family history of Alzheimer's disease (AD), Outcome 7: Adverse effects – antihypertensive therapy

Study or Subgroup	NSAID Events	NSAID Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.7.1 All NSAIDs (celecoxib and naproxen combined)						
ADAPT Research Group 2007/2006	307	877	164	644	100.0%	1.37 [1.17 , 1.61]
Subtotal (95% CI)		**877**		**644**	**100.0%**	**1.37 [1.17 , 1.61]**
Total events:	307		164			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.90 (P < 0.0001)						
2.7.2 Celecoxib						
ADAPT Research Group 2007/2006	160	440	164	644	100.0%	1.43 [1.19 , 1.71]
Subtotal (95% CI)		**440**		**644**	**100.0%**	**1.43 [1.19 , 1.71]**
Total events:	160		164			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.86 (P = 0.0001)						
2.7.3 Naproxen						
ADAPT Research Group 2007/2006	147	437	164	644	100.0%	1.32 [1.10 , 1.59]
Subtotal (95% CI)		**437**		**644**	**100.0%**	**1.32 [1.10 , 1.59]**
Total events:	147		164			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.92 (P = 0.003)						
Test for subgroup differences: Chi² = 0.35, df = 2 (P = 0.84), I² = 0%						

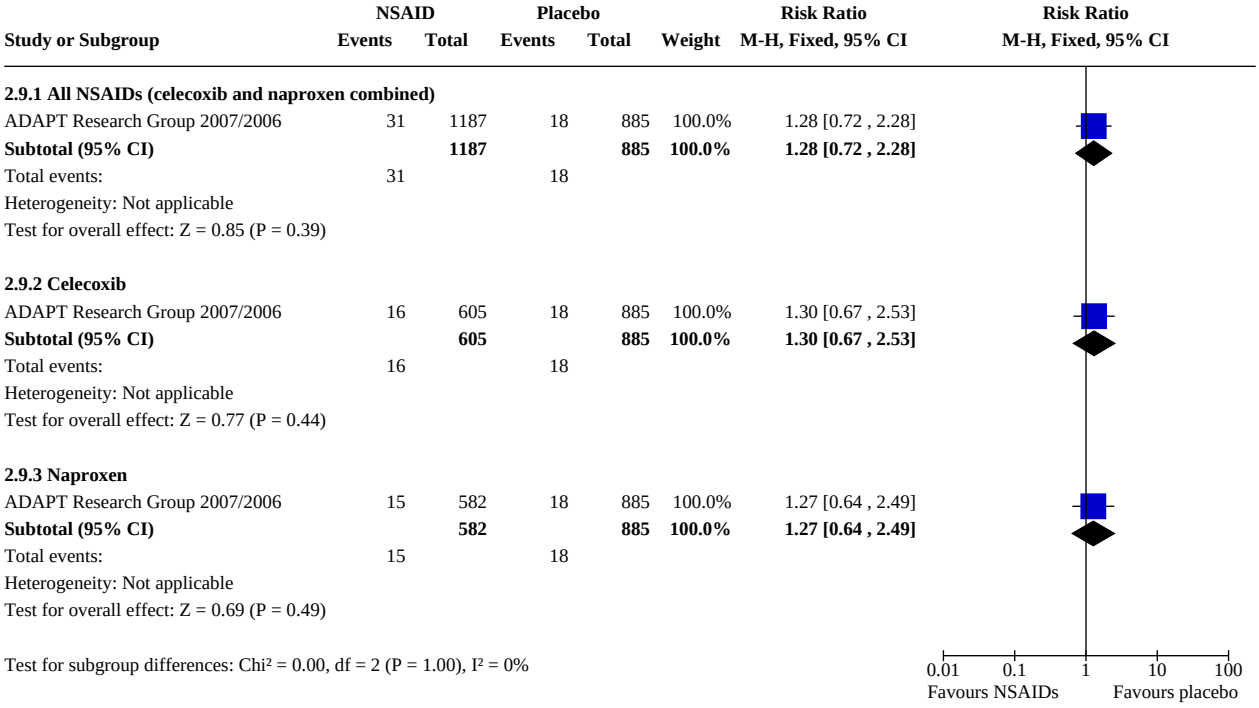


Analysis 2.8. Comparison 2: NSAIDs compared with placebo: cognitively healthy adults with a family history of Alzheimer's disease (AD), Outcome 8: Mortality

Study or Subgroup	NSAID Events	NSAID Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.8.1 All NSAIDs (celecoxib and naproxen combined)						
ADAPT Research Group 2007/2006	33	1445	18	1083	100.0%	1.37 [0.78 , 2.43]
Subtotal (95% CI)		**1445**		**1083**	**100.0%**	**1.37 [0.78 , 2.43]**
Total events:	33		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.09 (P = 0.27)						
2.8.2 Celecoxib						
ADAPT Research Group 2007/2006	17	726	18	1083	100.0%	1.41 [0.73 , 2.72]
Subtotal (95% CI)		**726**		**1083**	**100.0%**	**1.41 [0.73 , 2.72]**
Total events:	17		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.02 (P = 0.31)						
2.8.3 Naproxen						
ADAPT Research Group 2007/2006	16	719	18	1083	100.0%	1.34 [0.69 , 2.61]
Subtotal (95% CI)		**719**		**1083**	**100.0%**	**1.34 [0.69 , 2.61]**
Total events:	16		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.86 (P = 0.39)						
Test for subgroup differences: Chi² = 0.01, df = 2 (P = 0.99), I² = 0%						



Analysis 2.9. Comparison 2: NSAIDs compared with placebo: cognitively healthy adults with a family history of Alzheimer's disease (AD), Outcome 9: Cognitive decline from baseline



Comparison 3. NSAIDs compared with placebo: adults with age-related memory loss

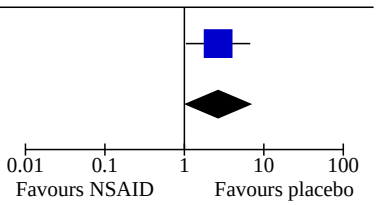
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Adverse events – gastrointestinal	1	40	Risk Ratio (M-H, Fixed, 95% CI)	2.66 [1.05, 6.75]
3.2 Cognitive decline from baseline (Psychomotor Speed)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.2.1 Trailmaking A Digital Symbol	1	40	Mean Difference (IV, Fixed, 95% CI)	2.40 [-3.41, 8.21]
3.2.2 WAIS II Digital Symbol	1	40	Mean Difference (IV, Fixed, 95% CI)	-5.00 [-16.30, 6.30]
3.3 Cognitive decline from baseline (Visuospatial Functioning)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.3.1 WAIS-III Block Design	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-7.35, 5.95]
3.3.2 Complex Figure, Copy	1	40	Mean Difference (IV, Fixed, 95% CI)	0.20 [-1.72, 2.12]
3.4 Cognitive decline from baseline (Executive Functioning)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.4.1 Trailmaking B	1	40	Mean Difference (IV, Fixed, 95% CI)	7.20 [-17.85, 32.25]
3.4.2 Stroop Interference	1	40	Mean Difference (IV, Fixed, 95% CI)	-4.40 [-29.42, 20.62]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.4.3 F.A.S. Letter Fluency	1	40	Mean Difference (IV, Fixed, 95% CI)	-3.30 [-13.80, 7.20]
3.5 Cognitive decline (Learning)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.5.1 Selective Reminding, Total Recall	1	40	Mean Difference (IV, Fixed, 95% CI)	-7.70 [-19.26, 3.86]
3.5.2 Verbal Paired Associations 1	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-6.09, 4.29]
3.5.3 Benton Visual Retention	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-2.26, 1.46]
3.6 Cognitive decline (Delayed Recall)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.6.1 Selective Reminding, Delayed Recall	1	40	Mean Difference (IV, Fixed, 95% CI)	-1.50 [-3.18, 0.18]
3.6.2 Complex Figure Recall	1	40	Mean Difference (IV, Fixed, 95% CI)	0.50 [-4.23, 5.23]
3.6.3 Verbal Paired Associations II	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-2.19, 0.79]
3.7 Cognitive decline (Language/Semantic Memory)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.7.1 Boston Naming	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-3.15, 2.75]
3.7.2 Animal Naming	1	40	Mean Difference (IV, Fixed, 95% CI)	3.10 [-0.31, 6.51]

Analysis 3.1. Comparison 3: NSAIDs compared with placebo: adults with age-related memory loss, Outcome 1: Adverse events – gastrointestinal

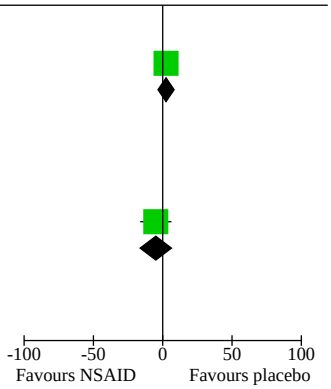
Study or Subgroup	NSAID Events	NSAID Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Small 2008	13	22	4	18	100.0%	2.66 [1.05 , 6.75]
Total (95% CI)		**22**		**18**	**100.0%**	**2.66 [1.05 , 6.75]**
Total events:	13		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.06 (P = 0.04)
Test for subgroup differences: Not applicable



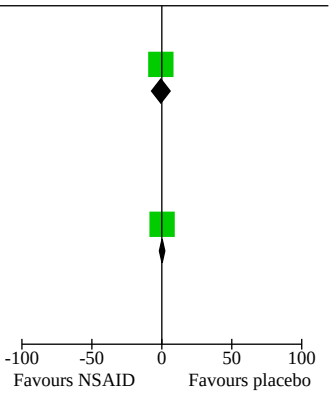
Analysis 3.2. Comparison 3: NSAIDs compared with placebo: adults with age-related memory loss, Outcome 2: Cognitive decline from baseline (Psychomotor Speed)

Study or Subgroup	NSAID Mean	NSAID SD	NSAID Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
3.2.1 Trailmaking A Digital Symbol								
Small 2008	30.7	9.7	22	28.3	9	18	100.0%	2.40 [-3.41 , 8.21]
Subtotal (95% CI)			**22**			**18**	**100.0%**	**2.40 [-3.41 , 8.21]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.81 (P = 0.42)								
3.2.2 WAIS II Digital Symbol								
Small 2008	69	17.8	22	74	18.4	18	100.0%	-5.00 [-16.30 , 6.30]
Subtotal (95% CI)			**22**			**18**	**100.0%**	**-5.00 [-16.30 , 6.30]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.87 (P = 0.39)								



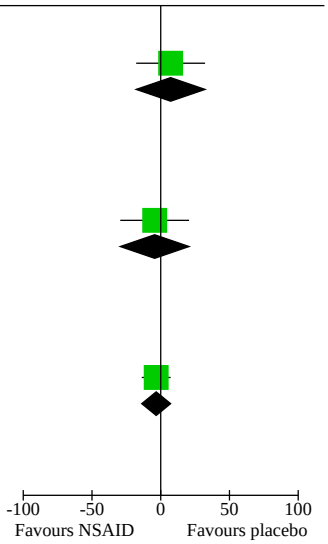
Analysis 3.3. Comparison 3: NSAIDs compared with placebo: adults with age-related memory loss, Outcome 3: Cognitive decline from baseline (Visuospatial Functioning)

Study or Subgroup	NSAID Mean	NSAID SD	NSAID Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
3.3.1 WAIS-III Block Design								
Small 2008	40.4	7.5	22	41.1	12.7	18	100.0%	-0.70 [-7.35 , 5.95]
Subtotal (95% CI)			**22**			**18**	**100.0%**	**-0.70 [-7.35 , 5.95]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.21 (P = 0.84)								
3.3.2 Complex Figure, Copy								
Small 2008	30.8	3.3	22	30.6	2.9	18	100.0%	0.20 [-1.72 , 2.12]
Subtotal (95% CI)			**22**			**18**	**100.0%**	**0.20 [-1.72 , 2.12]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.20 (P = 0.84)								
Test for subgroup differences: Chi^2 = 0.06, df = 1 (P = 0.80), I^2 = 0%								



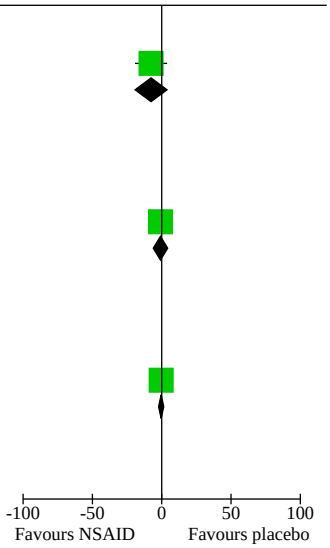
Analysis 3.4. Comparison 3: NSAIDs compared with placebo: adults with age-related memory loss, Outcome 4: Cognitive decline from baseline (Executive Functioning)

Study or Subgroup	NSAID Mean	NSAID SD	NSAID Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
3.4.1 Trailmaking B								
Small 2008	78.4	43.3	22	71.2	37.5	18	100.0%	7.20 [-17.85 , 32.25]
Subtotal (95% CI)			**22**			**18**	**100.0%**	**7.20 [-17.85 , 32.25]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.56 (P = 0.57)								
3.4.2 Stroop Interference								
Small 2008	121	30.5	22	125.4	46.6	18	100.0%	-4.40 [-29.42 , 20.62]
Subtotal (95% CI)			**22**			**18**	**100.0%**	**-4.40 [-29.42 , 20.62]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.34 (P = 0.73)								
3.4.3 F.A.S. Letter Fluency								
Small 2008	40.9	14.3	22	44.2	18.7	18	100.0%	-3.30 [-13.80 , 7.20]
Subtotal (95% CI)			**22**			**18**	**100.0%**	**-3.30 [-13.80 , 7.20]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.62 (P = 0.54)								
Test for subgroup differences: Chi² = 0.61, df = 2 (P = 0.74), I² = 0%								



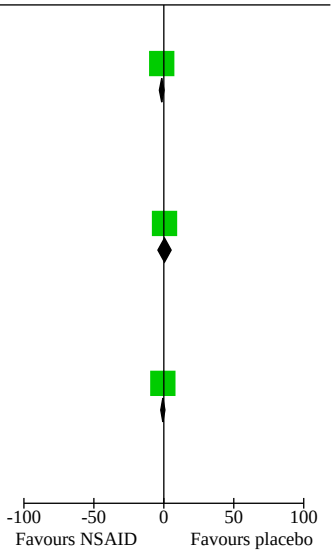
Analysis 3.5. Comparison 3: NSAIDs compared with placebo: adults with age-related memory loss, Outcome 5: Cognitive decline (Learning)

Study or Subgroup	NSAID Mean	NSAID SD	NSAID Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
3.5.1 Selective Reminding, Total Recall								
Small 2008	103.9	18	22	111.6	19	18	100.0%	-7.70 [-19.26 , 3.86]
Subtotal (95% CI)			**22**			**18**	**100.0%**	**-7.70 [-19.26 , 3.86]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.31 (P = 0.19)								
3.5.2 Verbal Paired Associations 1								
Small 2008	20.6	8	22	21.5	8.6	18	100.0%	-0.90 [-6.09 , 4.29]
Subtotal (95% CI)			**22**			**18**	**100.0%**	**-0.90 [-6.09 , 4.29]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.34 (P = 0.73)								
3.5.3 Benton Visual Retention								
Small 2008	4.3	2	22	4.7	3.6	18	100.0%	-0.40 [-2.26 , 1.46]
Subtotal (95% CI)			**22**			**18**	**100.0%**	**-0.40 [-2.26 , 1.46]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.42 (P = 0.67)								
Test for subgroup differences: Chi² = 1.51, df = 2 (P = 0.47), I² = 0%								



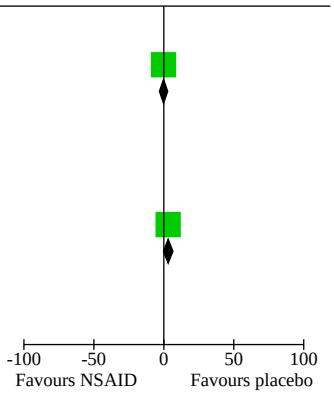
Analysis 3.6. Comparison 3: NSAIDs compared with placebo: adults with age-related memory loss, Outcome 6: Cognitive decline (Delayed Recall)

Study or Subgroup	NSAID Mean	NSAID SD	NSAID Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
3.6.1 Selective Reminding, Delayed Recall								
Small 2008	8.3	2.7	22	9.8	2.7	18	100.0%	-1.50 [-3.18 , 0.18]
Subtotal (95% CI)			**22**			**18**	**100.0%**	**-1.50 [-3.18 , 0.18]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.75 (P = 0.08)								
3.6.2 Complex Figure Recall								
Small 2008	17.3	7.7	22	16.8	7.5	18	100.0%	0.50 [-4.23 , 5.23]
Subtotal (95% CI)			**22**			**18**	**100.0%**	**0.50 [-4.23 , 5.23]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.21 (P = 0.84)								
3.6.3 Verbal Paired Associations II								
Small 2008	6.6	2.1	22	7.3	2.6	18	100.0%	-0.70 [-2.19 , 0.79]
Subtotal (95% CI)			**22**			**18**	**100.0%**	**-0.70 [-2.19 , 0.79]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.92 (P = 0.36)								
Test for subgroup differences: $Chi^2 = 0.88$, df = 2 (P = 0.64), $I^2 = 0\%$								



Analysis 3.7. Comparison 3: NSAIDs compared with placebo: adults with age-related memory loss, Outcome 7: Cognitive decline (Language/Semantic Memory)

Study or Subgroup	NSAID Mean	NSAID SD	NSAID Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
3.7.1 Boston Naming								
Small 2008	55.5	3.6	22	55.7	5.5	18	100.0%	-0.20 [-3.15 , 2.75]
Subtotal (95% CI)			**22**			**18**	**100.0%**	**-0.20 [-3.15 , 2.75]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.13 (P = 0.89)								
3.7.2 Animal Naming								
Small 2008	22.5	4.6	22	19.4	6.1	18	100.0%	3.10 [-0.31 , 6.51]
Subtotal (95% CI)			**22**			**18**	**100.0%**	**3.10 [-0.31 , 6.51]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.78 (P = 0.07)								



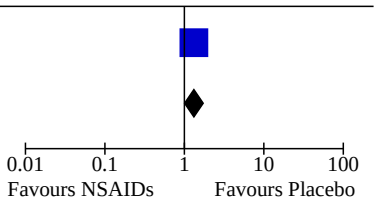
Comparison 4. NSAIDs compared with placebo: mild cognitive impairment

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
4.1 Incidence of dementia	1	1457	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [1.01, 1.72]
4.2 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.2.1 Cardiovascular	1	1457	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.68, 1.66]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
4.2.2 Gastrointestinal	1	1457	Risk Ratio (M-H, Fixed, 95% CI)	3.53 [1.17, 10.68]
4.3 Mortality	1	1457	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [0.85, 3.05]

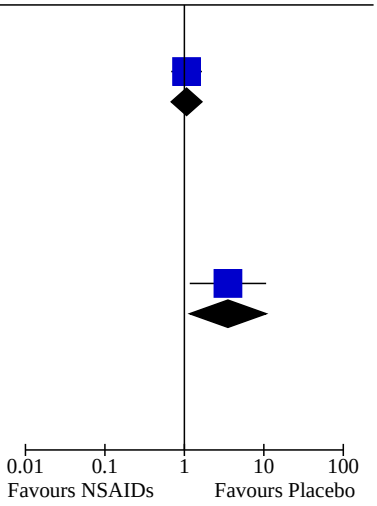
Analysis 4.1. Comparison 4: NSAIDs compared with placebo: mild cognitive impairment, Outcome 1: Incidence of dementia

	NSAID		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Thal 2005	107	725	82	732	100.0%	1.32 [1.01 , 1.72]	
Total (95% CI)		**725**		**732**	**100.0%**	**1.32 [1.01 , 1.72]**	
Total events:	107		82				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.01 (P = 0.04)							
Test for subgroup differences: Not applicable							



Analysis 4.2. Comparison 4: NSAIDs compared with placebo: mild cognitive impairment, Outcome 2: Adverse events

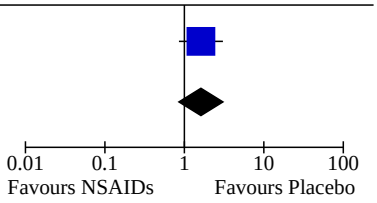
	NSAID		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
4.2.1 Cardiovascular							
Thal 2005	38	725	36	732	100.0%	1.07 [0.68 , 1.66]	
Subtotal (95% CI)		**725**		**732**	**100.0%**	**1.07 [0.68 , 1.66]**	
Total events:	38		36				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.28 (P = 0.78)							
4.2.2 Gastrointestinal							
Thal 2005	14	725	4	732	100.0%	3.53 [1.17 , 10.68]	
Subtotal (95% CI)		**725**		**732**	**100.0%**	**3.53 [1.17 , 10.68]**	
Total events:	14		4				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.24 (P = 0.03)							



Analysis 4.3. Comparison 4: NSAIDs compared with placebo: mild cognitive impairment, Outcome 3: Mortality

Study or Subgroup	NSAID Events	NSAID Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Thal 2005	24	725	15	732	100.0%	1.62 [0.85 , 3.05]
Total (95% CI)		**725**		**732**	**100.0%**	**1.62 [0.85 , 3.05]**
Total events:	24		15			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.48 (P = 0.14)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. Sources searched and search strategies

Source	Search strategy	Hits retrieved
ALOIS (Specialised Register searched via Cochrane Register of Studies) (Date of most recent search: 9 January 2020)	aspirin OR "cyclooxygenase 2 inhibitor" OR aceclofenac OR acemetacin OR celecoxib OR dexibruprofen OR dexketoprofen OR diclofenac sodium OR diflunisal OR diflusinal OR etodolac OR etoricoxib OR fenbufen OR fenoprofen OR flurbiprofen OR ibuprofen OR indometacin OR indomethacin OR ketoprofen OR lumiracoxib OR mefenamic OR meloxicam OR nabumetone OR naproxen OR nimesulide OR "anti-inflammatory" OR piroxicam OR sulindac OR tenoxicam OR tiaprofenic acid OR triamcinolone OR NSAIDS OR NSAID	Jan 2015: 9 Nov 2016: 1 Jan 2018: 1 Jan 2019: 0 Jan 2020: 17 Total: 28
CENTRAL (the Cochrane Library) cr-so.cochrane.org/SearchSimple.php (Date of most recent search: 9 January 2020)	#1 MeSH descriptor: [Aspirin] explode all trees #2 aspirin #3 "acetylsalicylic acid" #4 #1 or #2 or #3 #5 MeSH descriptor: [Anti-Inflammatory Agents, Non-Steroidal] explode all trees #6 "anti-inflammatory" #7 #5 or #6 #8 #4 or #7 #9 cognition #10 dementia #11 elderly #12 "old* adults" #13 MeSH descriptor: [Cognition] explode all trees #14 MeSH descriptor: [Dementia] explode all trees #15 MeSH descriptor: [Primary Prevention] explode all trees	Jan 2015: 626 Nov 2016: 43 Jan 2018: 352 Jan 2019: 209 Jan 2020: 291 Total: 1521

(Continued)

	#16 MeSH descriptor: [Secondary Prevention] explode all trees	
	#17 #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16	
	#18 #8 and #17 in Trials	
MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present (OvidSP) (Date of most recent search: 9 January 2020)	1. Aspirin/ 2. aspirin.ti,ab. 3. "acetylsalicylic acid".ti,ab. 4. "cyclooxygenase 2 inhibitor".ti,ab. 5. aceclofenac.ti,ab. 6. acemetacin.ti,ab. 7. celecoxib.ti,ab. 8. dexibruprofen.ti,ab. 9. dexketoprofen.ti,ab. 10. diclofenac sodium.ti,ab. 11. diflunisal.ti,ab. 12. diflusinal.ti,ab. 13. etodolac.ti,ab. 14. etoricoxib.ti,ab. 15. fenbufen.ti,ab. 16. fenoprofen.ti,ab. 17. flurbiprofen.ti,ab. 18. ibuprofen.ti,ab. 19. indometacin.ti,ab. 20. indomethacin.ti,ab. 21. ketoprofen.ti,ab. 22. lumiracoxib.ti,ab. 23. mefenamic.ti,ab. 24. meloxicam.ti,ab. 25. nabumetone.ti,ab. 26. naproxen.ti,ab. 27. nimesulide.ti,ab. 28. anti-inflammatory.ti,ab. 29. piroxicam.ti,ab. 30. sulindac.ti,ab. 31. tenoxicam.ti,ab.	Jan 2015: 352 Nov 2016: 42 Jan 2018: 128 Jan 2019: 56 Jan 2020: 60 Total: 638

(Continued)

32. tiaprofenic acid.ti,ab.
33. triamcinolone.ti,ab.
34. NSAIDS.ti,ab.
35. NSAIDS.ti,ab.
36. *Anti-Inflammatory Agents, Non-Steroidal/
37. Cyclooxygenase Inhibitors/
38. Triamcinolone/
39. Sulindac/
40. Piroxicam/
41. Sulfonamides/
42. Naproxen/
43. Mefenamic Acid/
44. Diclofenac/
45. Cyclooxygenase 2 Inhibitors/
46. Ketoprofen/
47. Indomethacin/
48. Indomethacin/
49. Ibuprofen/
50. Flurbiprofen/
51. Fenoprofen/
52. Diclofenac/
53. or/1-52
54. dement*.ti,ab.
55. exp Dementia/
56. (cognition or cognitive).ti,ab.
57. Cognition/
58. Cognition Disorders/
59. Secondary Prevention/ or Primary Prevention/
60. "pre-clinical AD".ti,ab.
61. "prodromal AD".ti,ab.
62. alzheimer*.ti,ab.
63. "healthy elderly".ti,ab.
64. (cognit* adj3 health*).ti,ab.
65. "older adult*".ti,ab.

(Continued)

	66. Aged/ or Middle Aged/	
	67. pensioner*.ti,ab.	
	68. "senior citizen*".ti,ab.	
	69. "community dwelling".ti,ab.	
	70. or/54-69	
	71. 53 and 70	
	72. randomized controlled trial.pt.	
	73. controlled clinical trial.pt.	
	74. (Randomized or randomised).ti,ab.	
	75. randomly.ab.	
	76. placebo*.ab.	
	77. or/72-76	
	78. (animals not (humans and animals)).sh.	
	79. 77 not 78	
	80. 71 and 79	
	81. 54 or 55 or 56 or 57 or 58 or 60 or 61 or 62 or 64	
	82. 63 or 65 or 66 or 67 or 68 or 69	
	83. 53 and 79 and 81 and 82	
	84. 55 and 59	
	85. 53 and 59 and 79	
	86. 84 or 85	
EMBASE (OvidSP) (Date of most recent search: 9 January 2020)	1. Aspirin/	Jan 2015: 405 Nov 2016: 17 Jan 2018: 46 Jan 2019: 46 Jan 2020: 31 Total: 545
	2. aspirin.ti,ab.	
	3. "acetylsalicylic acid".ti,ab.	
	4. "cyclooxygenase 2 inhibitor".ti,ab.	
	5. aceclofenac.ti,ab.	
	6. acemetacin.ti,ab.	
	7. celecoxib.ti,ab.	
	8. dexibruprofen.ti,ab.	
	9. dexketoprofen.ti,ab.	
	10. diclofenac sodium.ti,ab.	
	11. diflunisal.ti,ab.	
	12. diflusinal.ti,ab.	
	13. etodolac.ti,ab.	

(Continued)

14. etoricoxib.ti,ab.
15. fenbufen.ti,ab.
16. fenoprofen.ti,ab.
17. flurbiprofen.ti,ab.
18. ibuprofen.ti,ab.
19. indometacin.ti,ab.
20. indomethacin.ti,ab.
21. ketoprofen.ti,ab.
22. lumiracoxib.ti,ab.
23. mefenamic.ti,ab.
24. meloxicam.ti,ab.
25. nabumetone.ti,ab.
26. naproxen.ti,ab.
27. nimesulide.ti,ab.
28. anti-inflammatory.ti,ab.
29. piroxicam.ti,ab.
30. sulindac.ti,ab.
31. tenoxicam.ti,ab.
32. tiaprofenic acid.ti,ab.
33. triamcinolone.ti,ab.
34. NSAIDS.ti,ab.
35. NSAIDS.ti,ab.
36. *Anti-Inflammatory Agents, Non-Steroidal/
37. Cyclooxygenase Inhibitors/
38. Triamcinolone/
39. Sulindac/
40. Piroxicam/
41. Sulfonamides/
42. Naproxen/
43. Mefenamic Acid/
44. Diclofenac/
45. Cyclooxygenase 2 Inhibitors/
46. Ketoprofen/
47. Indomethacin/

(Continued)

48. Indomethacin/

49. Ibuprofen/

50. Flurbiprofen/

51. Fenoprofen/

52. Diclofenac/

53. or/1-52

54. dement*.ti,ab.

55. exp Dementia/

56. (cognition or cognitive).ti,ab.

57. Cognition/

58. Cognition Disorders/

59. Secondary Prevention/ or Primary Prevention/

60. "pre-clinical AD".ti,ab.

61. "prodromal AD".ti,ab.

62. alzheimer*.ti,ab.

63. "healthy elderly".ti,ab.

64. (cognit* adj3 health*).ti,ab.

65. "older adult*".ti,ab.

66. Aged/ or Middle Aged/

67. pensioner*.ti,ab.

68. "senior citizen*".ti,ab.

69. "community dwelling".ti,ab.

70. or/54-69

71. 53 and 70

72. 54 or 55 or 56 or 57 or 58 or 60 or 61 or 62 or 64

73. 63 or 65 or 66 or 67 or 68 or 69

74. randomly.ab.

75. randomized controlled trial/

76. controlled clinical trial/

77. rct.ti,ab.

78. placebo.ab.

79. "double-blind*".ti,ab.

80. "single-blind*".ti,ab.

81. or/74-80

(Continued)

	82. 53 and 72 and 73 and 81	
	83. primary prevention/	
	84. secondary prevention/	
	85. 83 or 84	
	86. 53 and 81 and 85	
	87. 54 or 55 or 57 or 64	
	88. 86 and 87	
	89. 82 or 88	
PSYCINFO (OvidSP) (Date of most recent search: 9 January 2020)	1. Aspirin/ 2. aspirin.ti,ab. 3. "acetylsalicylic acid".ti,ab. 4. "cyclooxygenase 2 inhibitor".ti,ab. 5. aceclofenac.ti,ab. 6. acemetacin.ti,ab. 7. celecoxib.ti,ab. 8. dexibruprofen.ti,ab. 9. dexketoprofen.ti,ab. 10. diclofenac sodium.ti,ab. 11. diflunisal.ti,ab. 12. diflusinal.ti,ab. 13. etodolac.ti,ab. 14. etoricoxib.ti,ab. 15. fenbufen.ti,ab. 16. fenoprofen.ti,ab. 17. flurbiprofen.ti,ab. 18. ibuprofen.ti,ab. 19. indometacin.ti,ab. 20. indomethacin.ti,ab. 21. ketoprofen.ti,ab. 22. lumiracoxib.ti,ab. 23. mefenamic.ti,ab. 24. meloxicam.ti,ab. 25. nabumetone.ti,ab. 26. naproxen.ti,ab.	Jan 2015: 305 Nov 2016: 13 Jan 2018: 7 Jan 2019: 13 Jan 2020: 12 Total: 350

(Continued)

27. nimesulide.ti,ab.
28. anti-inflammatory.ti,ab.
29. piroxicam.ti,ab.
30. sulindac.ti,ab.
31. tenoxicam.ti,ab.
32. tiaprofenic acid.ti,ab.
33. triamcinolone.ti,ab.
34. NSAIDS.ti,ab.
35. or/1-34
36. elderly.ti,ab.
37. "old* adult*".ti,ab.
38. "old* people".ti,ab.
39. "aged adults".ti,ab.
40. "middle age*".ti,ab.
41. cognition.ti,ab.
42. exp Cognition/
43. dementia.ti,ab.
44. exp Dementia/
45. seniors.ti,ab.
46. "community dwelling".ti,ab.
47. Aging/
48. or/36-47
49. 35 and 48
50. Drug Therapy/ or Clinical Trials/
51. placebo.ab.
52. randomly.ab.
53. "double-blind*".ti,ab.
54. "single-blind*".ti,ab.
55. RCT.ti,ab.
56. "randomised control* trial".ti,ab.
57. "randomized control* trial".ti,ab.
58. or/50-57
59. 49 and 58

CINAHL (EBSCOhost)	S1 TX aspirin	Jan 2015: 30

(Continued)

(Date of most recent search: 9 January 2020)	S2 TX "cyclooxygenase 2 inhibitor*"	Nov 2016: 5
	S3 TX "anti-inflammatory agent*"	Jan 2018: 16
	S4 TX aceclofenac OR acemetacin	Jan 2019: 10
	S5 TX betamethasone	Jan 2020: 60
	S6 TX celecoxib	Total: 121
	S7 TX cortisone	
	S8 TX deflazacort	
	S9 TX dexamenthasone OR TX dexibruprofen	
	S10 TX dexketoprofen	
	S11 TX “diclofenac sodium”	
	S12 TX diflunisal OR TX diflusinal	
	S13 TX etodolac OR TX etoricoxib	
	S14 TX fenbufen OR TX fenoprofen	
	S15 TX flurbiprofen	
	S16 TX hydrocortisone	
	S17 TX ibuprofen	
	S18 TX indometacin	
	S19 TX indomethacin	
	S20 TX Ketoprofen OR TX lumiracoxib	
	S21 TX “mefenamic acid” OR TX meloxicam	
	S22 TX methylprednisolone OR TX nabumetone	
	S23 TX naproxen OR TX nimesulide	
	S24 “non-steroid* anti-inflammatory agent*”	
	S25 TX prednisone OR TX piroxicam	
	S26 TX sulindac	
	S27 TX tenoxicam	
	S28 TX tiaprofenic acid OR TX triamcinolone	
	S29 (MH “Aspirin”)	
	S30 (MH "Antiinflammatory Agents, Non-Steroidal") OR (MH "Antiinflammatory Agents, Steroidal”)	
	S31 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30	
	S32 (MH “Cognition”)	
	S33 TX cognition	
	S34 TX dementia	

(Continued)

	S35 (MH “Dementia”) S36 TX elderly S37 TX “old* adults” S38 TX “aged adults” S39 TX “aged sample” S40 (MH "Aged") OR (MH "Aged, 80 and Over”) S41 TX "middle age*” S42 (MH “Middle Age”) S43 (MH "Randomized Controlled Trials”) S44 AB placebo S45 AB “double-blind*” S46 AB “single-blind*” S47 AB RCT S48 AB “random* allocat*” S49 AB “random* divide*” S50 AB “allocat* random*” S51 S32 OR S33 OR S34 OR S35 S52 S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 S53 S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 S54 S31 AND S51 AND S52 AND S53 S55 (MH "Preventive Health Care") S56 S31 AND S53 AND S55 S57 S54 OR S56	
ISI Web of Science – core collection (Date of most recent search: 9 January 2020)	TOPIC: (aspirin OR "acetylsalicylic acid" OR "anti-inflammatory agent*" OR NSAID*) AND TOPIC: ("old* age*" OR "middle age*" OR elderly OR "old* adults" OR seniors OR "senior citizens" OR "community dwelling") AND TOPIC: (randomly OR randomised OR randomized OR RCT OR "controlled trial" OR "double blind" OR "single blind") AND TOPIC: (cognition OR "prevent* dement*" OR "prevent alzheimer*" OR MMSE OR "executive function*" OR memory OR attention)	Jan 2015: 168 Nov 2016: 9 Jan 2018: 28 Jan 2019: 2 Jan 2020: 1 Total: 208
LILACS (BIREME) (Date of most recent search: 9 January 2020)	aspirin OR “agentes antiagregantes” OR “acetylsalicylic acid” OR “anti-inflammatory” OR NSAID$ OR “cyclooxygenase 2 inhibitor$” OR ibuprofen OR naproxen OR COX-2 OR rofecoxib [Words] and dementia OR elderly OR cognition OR "old$ adult$" OR cognitive OR anciano OR demencia OR cognición [Words] and and trial OR group OR randomly OR randomised OR randomized OR RCT OR "double blind" OR "single-blind" OR placebo OR "control group"	Jan 2015: 61 Nov 2016: 2 Jan 2018: 3 Jan 2019: 2 Jan 2020: 2

(Continued)

		Total: 70
ClinicalTrials.gov (www.clinicaltrials.gov) (Date of most recent search: 9 January 2020)	([condition] dementia OR cognitive OR cognition OR elderly OR memory OR alzheimer* OR MCI) AND ([interventions] aspirin OR "acetylsalicylic acid" OR "cyclooxygenase 2 inhibitor" OR NSAIDS)	Jan 2015: 30 Nov 2016: 2 Jan 2018: 1 Jan 2019: 2 Jan 2020: 8 Total: 43
ICTRP (apps.who.int/trialsearch) (Date of most recent search: 9 January 2020)	([condition] dementia OR cognitive OR cognition OR elderly OR memory OR alzheimer* OR MCI) AND ([interventions] aspirin OR acetylsalicylic acid OR cyclooxygenase 2 inhibitor OR NSAIDS)	Jan 2015: 17 Nov 2016: 24 Jan 2018: 41 Jan 2019: 13 Jan 2020: 8 Total: 103
TOTAL before deduplication		3627
TOTAL after deduplication		2207

HISTORY

Protocol first published: Issue 1, 2015
Review first published: Issue 4, 2020

CONTRIBUTIONS OF AUTHORS

FJ: principal author.

DD, BMcG, PP, CTS, TQ and KM: roles detailed in the Methods.

JK: advised on the pharmacological aspects of the review.

DECLARATIONS OF INTEREST

FJ: none.

TQ: none.

BMcG: none.

PP: none.

JK: none.

CTS: none.

KM: none.

DD: none.

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Internal sources

- National University of Ireland, Galway, Ireland

External sources

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- NIHR, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We included the primary outcome, incidence of dementia, which included all types of dementia. Where differing dementia diagnoses were presented, we favoured AD as this is the pathology thought to be most closely related to inflammation.

For the comparator 'other NSAIDs compared with placebo', we included three 'Summary of findings' tables reflecting the different populations included for this comparator. We had not prespecified initiation of antihypertensive therapy as an outcome of interest in the protocol (Jordan 2015), but decided to include this under the adverse events outcome because of the importance of hypertension as a risk factor for dementia.

We performed no subgroup or sensitivity analyses due to the small number of included studies.

INDEX TERMS

Medical Subject Headings (MeSH)

Activities of Daily Living; Alzheimer Disease [epidemiology] [prevention & control]; Anti-Inflammatory Agents, Non-Steroidal [administration & dosage] [adverse effects] [*therapeutic use]; Aspirin [administration & dosage] [adverse effects] [*therapeutic use]; Celecoxib [administration & dosage] [adverse effects] [therapeutic use]; Cyclooxygenase 2 Inhibitors [administration & dosage] [adverse effects] [therapeutic use]; Dementia [epidemiology] [mortality] [*prevention & control]; Hemorrhage [chemically induced] [epidemiology]; Incidence; Lactones [therapeutic use]; Myocardial Infarction [epidemiology]; Naproxen [therapeutic use]; Randomized Controlled Trials as Topic; Stroke [epidemiology]; Sulfones [therapeutic use]

MeSH check words

Adult; Aged; Aged, 80 and over; Humans; Middle Aged