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Aspirin, steroidal and non-steroidal anti-inflammatory drugs for the treatment of Alzheimer's disease (Review)

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[Intervention Review]

Aspirin, steroidal and non-steroidal anti-inflammatory drugs for the treatment of Alzheimer's disease

Darin Jaturapatporn[1], Mokhtar Gad El Kareem Nasr Isaac[2], Jenny McCleery[3], Naji Tabet[4]

[1]Department of Family Medicine, Ramathibodi Hospital, Mahidol University, Bangkok and Baycrest Centre for Geriatric Care, University of Toronto, Toronto, Canada. [2]Old Age Psychiatry, Sussex Partnership NHS Foundation Trust, Eastbourne, UK. [3]Cochrane Dementia and Cognitive Improvement Group, University of Oxford, Oxford, UK. [4]Institute of Postgraduate Medicine, Brighton and Sussex Medical School & Cognitive Treatment and Research Unit, Sussex Partnership NHS Foundation Trust, Brighton, UK

Contact: Darin Jaturapatporn, Department of Family Medicine, Ramathibodi Hospital, Mahidol University, Bangkok and Baycrest Centre for Geriatric Care, University of Toronto, Toronto, Canada. drdarinj@yahoo.com.

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ABSTRACT

Background

Alzheimer's disease (AD) is the most common form of dementia. The incidence of AD rises exponentially with age and its prevalence will increase significantly worldwide in the next few decades. Inflammatory processes have been suspected in the pathogenesis of the disease.

Objectives

To review the efficacy and side effects of aspirin, steroidal and non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment of AD, compared to placebo.

Search methods

We searched ALOIS: the Cochrane Dementia and Cognitive Improvement Group's Specialized Register on 12 April 2011 using the terms: aspirin OR "cyclooxygenase 2 inhibitor" OR aceclofenac OR acemetacin OR betamethasone OR celecoxib OR cortisone OR deflazacort OR dexamethasone OR dexibruprofen OR dexketoprofen OR diclofenac sodium OR diflunisal OR diflusinal OR etodolac OR etoricoxib OR fenbufen OR fenoprofen OR flurbiprofen OR hydrocortisone OR ibuprofen OR indometacin OR indomethacin OR ketoprofen OR lumiracoxib OR mefenamic OR meloxicam OR methylprednisolone OR nabumetone OR naproxen OR nimesulide OR "anti-inflammatory" OR prednisone OR piroxicam OR sulindac OR tenoxicam OR tiaprofenic acid OR triamcinolone OR NSAIDS OR NSAID. ALOIS contains records of clinical trials identified from monthly searches of a number of major healthcare databases (including MEDLINE, EMBASE, PsycINFO, CINAHL, LILACS), numerous trial registries (including national, international and pharmacuetical registries) and grey literature sources.

Selection criteria

All randomised controlled trials assessing the efficacy of aspirin, steroidal and non-steroidal anti-inflammatory drugs in AD.

Data collection and analysis

One author assessed risk of bias of each study and extracted data. A second author verified data selection.

Main results

Our search identified 604 potentially relevant studies. Of these, 14 studies (15 interventions) were RCTs and met our inclusion criteria. The numbers of participants were 352, 138 and 1745 for aspirin, steroid and NSAIDs groups, respectively. One selected study comprised two

separate interventions. Interventions assessed in these studies were grouped into four categories: aspirin (three interventions), steroids (one intervention), traditional NSAIDs (six interventions), and selective cyclooxygenase-2 (COX-2) inhibitors (five interventions). All studies were evaluated for internal validity using a risk of bias assessment tool. The risk of bias was low for five studies, high for seven studies, and unclear for two studies.There was no significant improvement in cognitive decline for aspirin, steroid, traditional NSAIDs and selective COX-2 inhibitors. Compared to controls, patients receiving aspirin experienced more bleeding while patients receiving steroid experienced more hyperglycaemia, abnormal lab results and face edema. Patients receiving NSAIDs experienced nausea, vomiting, elevated creatinine, elevated LFT and hypertension. A trend towards higher death rates was observed among patients treated with NSAIDS compared with placebo and this was somewhat higher for selective COX-2 inhibitors than for traditional NSAIDs.

Authors' conclusions

Based on the studies carried out so far, the efficacy of aspirin, steroid and NSAIDs (traditional NSAIDs and COX-2 inhibitors) is not proven. Therefore, these drugs cannot be recommended for the treatment of AD.

PLAIN LANGUAGE SUMMARY

Aspirin, steroid and non-steroidal anti-inflammatory drugs use for treating Alzheimer's disease

Inflammation may play an important role in the development of Alzheimer’s disease. There is also some evidence from community surveys that people receiving anti-inflammatory drugs for various medical conditions may be less likely to develop Alzheimer's disease. Fourteen studies met our inclusion criteria for this review and none of the exclusion criteria. Aspirin, steroid and non-steroidal anti-inflammatory drugs (NSAIDs) (traditional and the selective cyclooxygenase-2 (COX-2) inhibitors) showed no significant benefit in the treatment of Alzheimer's disease. Therefore, the use of these drugs cannot be recommended for the treatment of Alzheimer's disease.

BACKGROUND

Alzheimer's disease (AD) is the most common form of dementia, and its incidence increases exponentially with age. AD affects 1-2% of people aged 65-70 and approximately 20% of those over 80 years (Jorm 2003). It results in a progressive deterioration of intellect, memory and personality. AD is an important health problem that has a significant impact on national economies. In the United States, there are approximately 5.2 million AD patients and the cost of care for an average patient is about 24,500 dollars per year (Wimo 2005). By 2030, an estimated 7.7 million Americans aged 65 and older will have AD (Hebert 2003). The disease is increasing worldwide.

The exact mechanism underlying the pathogenesis of AD is still unclear and remains a topic of intense debate. However, two hypotheses revolving around amyloid and inflammation have been particularly influential in trying to understand the neuropathological processes underlying AD. Beta amyloid (AB) is a proteolytic fragment of 40-42 residues derived from Amyloid Precursor Protein (APP). In vitro, the longer AB-42 fragment aggregates much more readily, and is hypothesised to be the main pathological agent in the pathogenesis of AD (Joachim 1992; Selkoe 1991; Younkin 1995). Altered production, aggregation and deposition of AB may play a critical role in the development of AD (Citron 1992; Haass 1994). Significantly, it is suspected that this deposition of amyloid may directly contribute to the inflammatory environment seen (Ruan 2009; Salminen 2009). The inflammatory hypothesis of AD proposes that specific inflammatory mechanisms, including the cytokine-driven acute-phase response, complement activation and microglial activation, contribute to neurodegeneration (Aisen 1994; McGeer 1989). In addition, AD may be associated with loss of the capacity to control inflammation in the brain (Bazan 2009).

In view of the strong association between inflammation and AD, attempts have been made to assess whether anti-inflammatory pharmaceutical agents may have a role in the management of AD. An important mechanism of attenuating inflammatory processes can be achieved through inhibition of the activity of the enzyme cyclooxygenase (COX) which is critical to the production of prostaglandins (Fiebich 1997). This inhibition can occur through the use of various non-steroidal anti-inflammatory drugs (NSAIDs) which might thereby diminish the inflammatory response in degenerative dementias. There is evidence that the enzyme cyclooxygenase-2 (COX-2) might be involved in neurodegenerative mechanisms in AD (Ho 1999; Pasinetti 1998). This has given rise to the hypothesis that drugs which inhibit COX-2 in the brain, including certain steroids, aspirin, traditional non-steroidal anti-inflammatory drug (NSAIDs) and selective COX-2 inhibitors could possibly slow the rate of progression or alleviate the symptoms of AD. Likewise, it has also been suspected that corticosteroids (namely synthetic glucocorticoids) may offer some neuroprotection in AD patients (Aisen 1998) through their well characterised anti-inflammatory action.

Anti-inflammatory medications such as non-selective and selective NSAIDs and corticosteroids have been the subject of epidemiological (Launer 2003) and clinical research in AD. The possibility of benefit from non-selective COX inhibitors (such as indomethacin, naproxen, ibuprofen and diclofenac) and/or selective COX-2 inhibitors (such as celecoxib and meloxicam) is supported by several lines of evidence. Less work has been carried out for corticosteroids such as prednisolone, but their potential usefulness is of interest.

Epidemiological studies have found a lower prevalence of dementia in people who have regularly taken NSAIDs, usually for rheumatological disorders (McGeer 1996, Stewart 1997). There has also been a cohort study reporting a lower incidence of AD in users of NSAIDs than in non-users (In't Veld 2001). There is *in vitro* evidence that, independently of their inhibition of prostaglandin synthesis, some NSAIDs can directly influence the processing of amyloid precursor protein (APP) which is thought to be implicated in the pathogenesis of AD (Avramovich 2002; Blasko 2001). Likewise, an open-label pilot study of low-dose prednisolone showed the suppression of peripheral markers of the acute phase response and complement activation in AD without systemic toxicity (Aisen 1996).

In recent years attempts have been made to determine whether anti-inflammatory agents may be efficacious in the treatment of AD. The purpose of this review is to establish the effectiveness, or otherwise, of such medication. It is now known that all anti-inflammatory drugs, including selective COX-2 inhibitors, can carry significant side effects profile and may occasionally be fatal. Hence, it is now important to ascertain whether there is a place for these drugs in the treatment of AD.

OBJECTIVES

To systematically review the evidence examining the efficacy and side effects of aspirin, steroidal and non-steroidal anti-inflammatory drugs in the treatment of AD.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials assessing the efficacy of aspirin, steroidal and non-steroidal anti-inflammatory drugs in the treatment of AD.

Types of participants

Patients of any age diagnosed with probable AD according to internationally recognised criteria including the 'National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA), the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the World Health Organisation classification of mental and behavioural disorders (ICD-10) (APA 1995; McKhann 1984; WHO 1992) .

Types of interventions

Aspirin, steroidal and non-steroidal anti-inflammatory agents (traditional and selective COX-2 inhibitors) at any dose.

Types of outcome measures

Primary outcomes

- Cognition (using objective psychometric rating instruments, e.g. the Alzheimer's disease assessment scale - cognitive sub-scale or ADAS-COG) or Mini-Mental Status Examination (MMSE)

- Adverse events
- Death

Secondary outcome

- Clinical global impression of change
- Mood/depression
- Behavioural disturbance
- Activities of daily living
- Quality of life
- Caregiver burden
- Institutionalization

Search methods for identification of studies

Electronic searches

We searched ALOIS (www.medicine.ox.ac.uk/alois) - the Cochrane Dementia and Cognitive Improvement Group's Specialized Register on 12 April 2011. The search terms used were: aspirin OR "cyclooxygenase 2 inhibitor" OR aceclofenac OR acemetacin OR betamethasone OR celecoxib OR cortisone OR deflazacort OR dexamethasone OR dexibruprofen OR dexketoprofen OR diclofenac sodium OR diflunisal OR diflusinal OR etodolac OR etoricoxib OR fenbufen OR fenoprofen OR flurbiprofen OR hydrocortisone OR ibuprofen OR indometacin OR indomethacin OR ketoprofen OR lumiracoxib OR mefenamic OR meloxicam OR methylprednisolone OR nabumetone OR naproxen OR nimesulide OR "anti-inflammatory" OR prednisone OR piroxicam OR sulindac OR tenoxicam OR tiaprofenic acid OR triamcinolone OR NSAIDS OR NSAID.

ALOIS is maintained by the Trials Search Co-ordinator for the Cochrane Dementia Group and contains studies in the areas of dementia prevention, dementia treatment and cognitive enhancement in healthy. The studies are identified from:

1. Monthly searches of a number of major healthcare databases: Medline, Embase, Cinahl, Psycinfo and Lilacs
2. Monthly searches of a number of trial registers: ISRCTN; UMIN (Japan's Trial Register); the WHO 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)
3. Quarterly search of *The Cochrane Library*'s Central Register of Controlled Trials (CENTRAL)
4. Six-monthly searches of a number of grey literature sources: ISI Web of Knowledge Conference Proceedings; Index to Theses; Australasian Digital Theses

To view a list of all sources searched for ALOIS see About ALOIS on the ALOIS website.

Details of the search strategies used for the retrieval of reports of trials from the healthcare databases, CENTRAL and conference proceedings can be viewed in the 'methods used in reviews' section within the editorial information about the Dementia and Cognitive Improvement Group.

Additional searches were performed in many of the sources listed above to cover the timeframe from the last searches performed for ALOIS to ensure that the search for the review was as up-to-date and as comprehensive as possible. The search strategies used can be seen in Appendix 1.

Details of the initial search carried out for this review can be viewed in Appendix 2.

The latest search (April 2011) retrieved a total of 1223 results. After a first-assess and a de-duplication of these results the authors were left with 116 references/records to further assess.

Searching other resources

The first authors of important identified RCTs that were potentially suitable for inclusion were contacted to request additional information on related new, unpublished, or in press studies.

Data collection and analysis

Selection of studies

Two authors (DJ, MI) independently examined the titles and abstracts of the trials identified in the search and considered them for inclusion according to the pre-determined eligibility criteria. Any disparity was resolved by retrieval of the cited articles and further discussion with the third author (NT).

Data extraction and management

A double-check process was used for risk of bias and outcome data including clinical outcomes and side effects. As mentioned, there were 14 included studies with 15 interventions as one study was comprised two interventions. Initially, the first author (DJ) extracted the data on all 14 included studies (15 interventions) and this was followed by verification by the other two authors (MI and NT). All authors had a data extraction form for this process. Any disagreements were resolved by discussion between DJ and the other author involved (either MI or NT depending on the study in question).

Assessment of risk of bias in included studies

The quality of the methods used in each study was examined by the two reviewers using the domain-based evaluation as shown in Table 1. In conclusion, risk of bias are summarised for each study as described in Table 2. The Grades of Recommendation, Assessment, Development and Evaluation Working Group (GRADE Working Group) approach was used to define the quality of data presented in this systematic review. The GRADE approach specifies four levels of quality as shown in Table 3.

Measures of treatment effect

The data presented in this review included dichotomous and continuous data. In dichotomous data (side effects, institutionalisation and death), each individual outcome comprised two possible categorical responses. Continuous data included the rest of clinical outcomes which were presented in a numerical quantity as a score format.

For dichotomous outcome, we used risk ratio (relative risk) to compare intervention and placebo. Risk ratio describes the probability with which side effects, institutionalisation and death will occur in the intervention group compared to placebo. In addition to risk ratio, 95% confidence interval was also calculated to determine the range of the effect.

For continuous data, we used both the mean difference (MD) and the standardized mean difference (SMD).

Mean difference was used for all outcomes that used the same scale. If an outcome was measured using more than one scale, then we calculated a standardised mean difference (SMD) where

$$SMD = \frac{\text{Difference in mean outcome between group}}{\text{SD of outcome among participants}}$$

Heterogeneity may exist among studies in a meta-analysis and whenever possible the causes of the heterogeneity need to be explored. One way of exploring this is to carry out a subgroup analysis. However, this approach is problematic when there are very few included studies in each meta-analysis which is the case in this review Another approach to address the potential consequences of heterogeneity is to use the random-effects meta-analysis (Cochrane Handbook). In this review, and in line with current guidelines, I^2 was used to quantify inconsistency across studies which then move the focus away from testing whether heterogeneity is present to assessing its impact on the meta-analysis (Cochrane Handbook). Here, the intention was to use I^2 level of >30% (this is a conservative estimate and was preferred to 40%) as an indicator of potential heterogeneity. Hence, for I^2<30%, the fixed-effects meta-analysis method was determined to be appropriate. For I^2>30% the random-effects meta-analysis method would be more fitting. This division is not ideal but is in line with current guidelines and does represent an effort to deal with the possible effects of heterogeneity on meta-analysis results.

Unit of analysis issues

In this review only Aisen 2003a had two active interventions: a traditional NSAIDs and a selective COX-2 inhibitor group. The approach to overcome a potential unit-of-analysis error for such a study which included multiple groups but with clear separation of subgroups was to “split” the shared group (the placebo group) into two subgroups each with a smaller sample size.

Dealing with missing data

Missing data could be a source of bias and affect the validity of the study. For considered studies with potential missing data, the authors were contacted to request more information.

In studies where the SD for continuous outcomes was missing, then SD was calculated from available P value.

For included studies with high risk of bias because of missing data, a sensitivity analyses was conducted to take into account the high bias risk. This was applied to studies with both dichotomous and continuous outcome data.

Subgroup analysis and investigation of heterogeneity

For this review, interventions were grouped according to the established and accepted classification of the different groups of drugs studied (aspirin, steroid and NSAIDs). As aspirin, steroid and NSAID drugs differed significantly in chemical structure and mode of action, overall analyses under "anti-inflammatory drugs" would not have been useful. Therefore, separate analyses were needed to differentiate between the potential efficacy and adverse events of these three groups of drugs. As far as the NSAID drugs are concerned, a subgroup analysis was justified to differentiate between the traditional NSAIDs and selective COX-2 inhibitors subgroups. In essence, they were similar enough to be included as one group in the initial analysis and different enough to justify a further subgroup analyses. Hence, analyses undertaken included: aspirin VS Placebo; steroids VS Placebo; NSAIDs VS Placebo, then traditional NSAIDs VS Placebo and selective COX-2 inhibitors VS Placebo.

Heterogeneity was quantified using the I^2 statistic which was interpreted as follows:

- 0%-40%: might not be important
- 30%-60%: may represent moderate heterogeneity
- 50%-90%: may represent substantial heterogeneity
- 70%-100%: considerable heterogeneity

RESULTS

Description of studies

Results of the search

604 references were retrieved by the electronic searches, from which 14 relevant RCTs were selected. Kappa statistic for agreement among 2 authors was 0.793 as shown in Appendix 3 which implied excellent agreement.

Included studies

From 15 interventions (14 studies in total), there were three interventions for aspirin, one for steroids, six for traditional NSAIDs and five interventions for selective COX-2 inhibitors. One study had two interventions including both a traditional NSAIDs and a selective COX-2 inhibitor (Aisen 2003a). The 14 selected studies enrolled a total of 2445 AD patients. The characteristics of participants in each study are presented in Table 4.

Excluded studies

Studies were excluded if they were non-RCTs, did not include AD patients and did not use one of the drugs under investigation. In total:

- 529 studies were excluded because they were not RCTs; (Of these 470 studies were excluded at the begining if they were reviews or animal studies, therefore, there were only 59 studies included in the references for the excluded studies)
- 35 RCTs were excluded because participants were not diagnosed as suffering from AD;
- 18 RCTs were excluded because the interventions were not aspirin, steroidal or non-steroidal anti-inflammatory drugs;
- 6 RCTs were excluded because they were based on the same data used in other included RCTs;
- 2 RCTs identified from trial registers were excluded because there was no published data and no response from the authors to a request for information.

Flurbiprofen, a traditional NSAID, was included as a search term. Several studies were identified which proved on closer investigation to have used R-flurbiprofen. This enantiomer has little activity against cyclooxygenase, the target of traditional NSAIDs, and undergoes minimal chiral conversion in humans to the cyclooxygenase-inhibiting S-enantiomer. It cannot, therefore, be classed as an NSAID, but has been investigated as a potential

modulator of AB-42 production in AD (Wilcock 2006a). Trials using R-flurbiprofen were therefore excluded from this review.

Risk of bias in included studies

Risk of bias assessment tool was used to assess the validity of each included study. A range from low (five studies) to high (seven studies) was observed. Two studies had unclear risk of bias (Figure 1 and Figure 2).

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

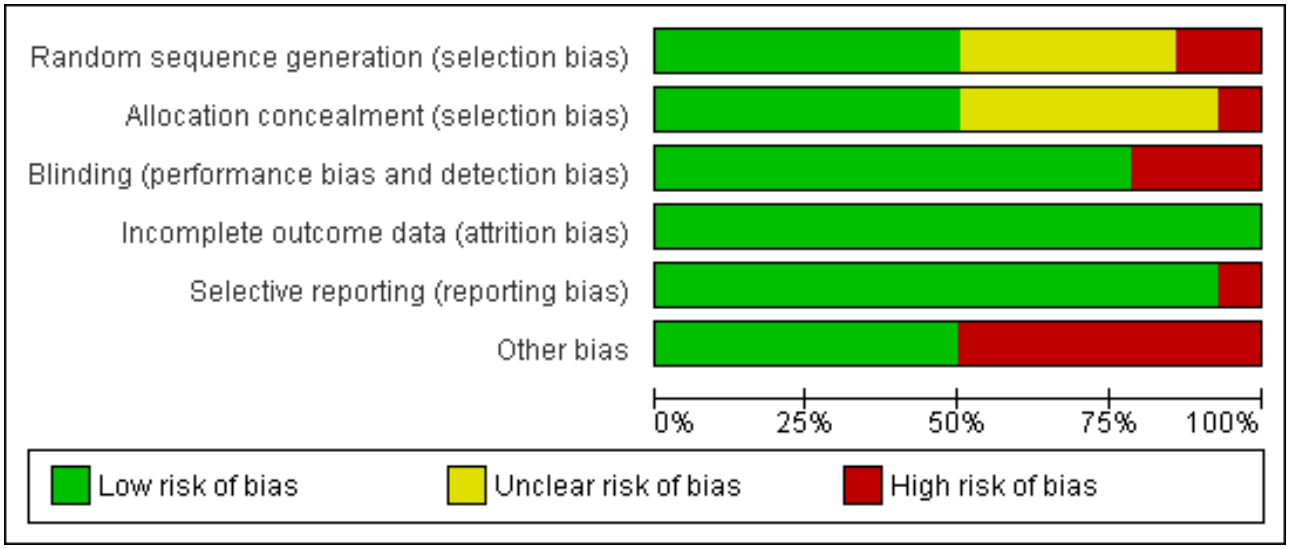
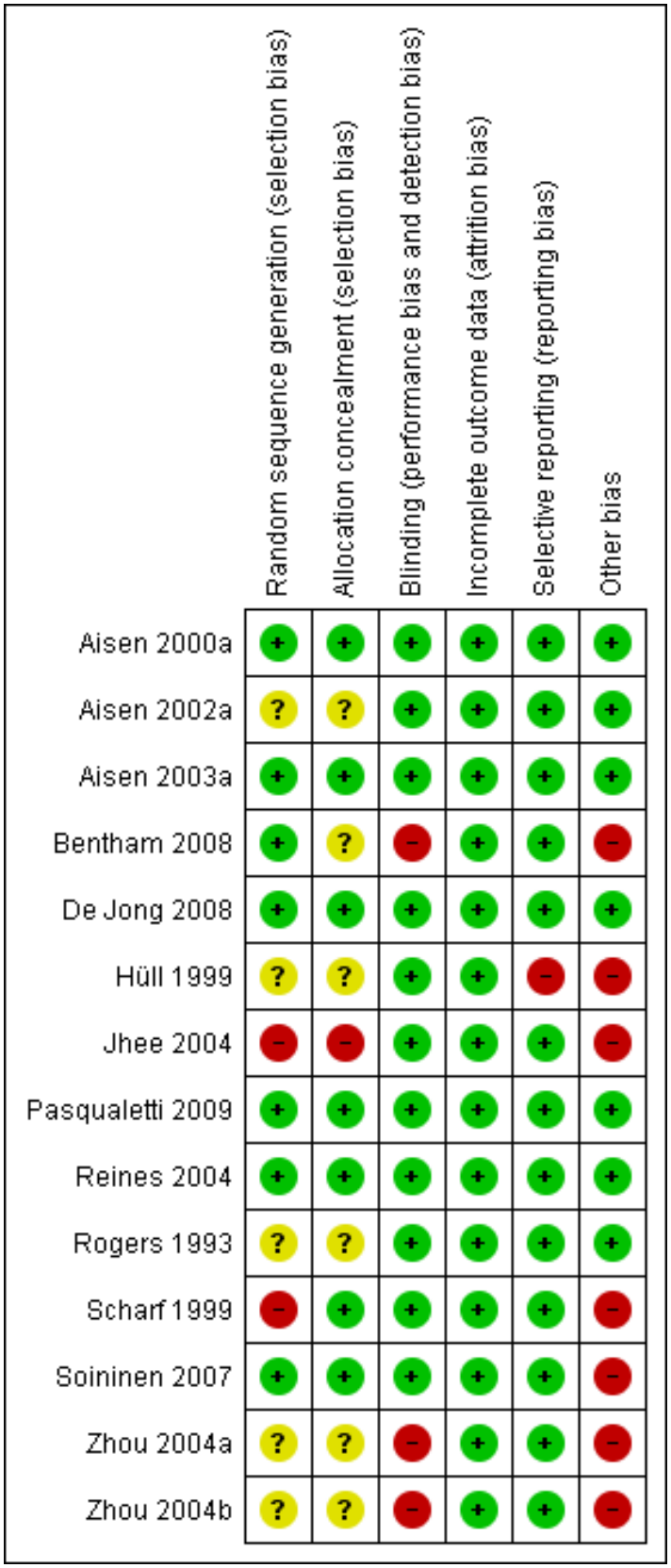


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

There were seven included studies that used proper allocation concealment method, while six studies were unclear and only Jhee 2004 did not apply allocation concealment.

Blinding

Eleven included studies properly blinded participants and outcome assessors. The remaining three studies were open-label studies (Bentham 2008; Zhou 2004a; Zhou 2004b).

Incomplete outcome data

All studies properly addressed the issue of incomplete outcome data and reasons for missing outcome data were unlikely to be related to true outcome.

Selective reporting

Of all included studies, only Hüll 1999 did not report all stated outcomes. In this particular study the data was presented in an abstract form and no full text article was available. This could have resulted from negative findings or no measurement for these outcomes. This may represent a selective reporting bias.

Effects of interventions

Aspirin

All three selected studies (Bentham 2008; Zhou 2004a; Zhou 2004b) were open-label and unsuitable for meta-analysis due to clinical and methodological heterogeneity. Total numbers of participants from both Zhou 2004a and Zhou 2004b were 42, compared to 310 in Bentham 2008. Bentham 2008, Zhou 2004b and Zhou 2004a had different follow up time length which was 3 years, 36 weeks and 6 months respectively. Further, most patients (75%) in Bentham 2008 study took donepezil in the control group, while patients from Zhou 2004a and Zhou 2004b took hyperzine and nigocerline. All three studies also used different doses of aspirin, namely 75 mg, 150 mg and 50 mg per day.

In addition, an issue of lacking and missing data should be taken into account as neither Zhou 2004 nor Zhou 2004a provided data on side effects and detailed data on cognitive improvements. For example, there was no specific p-value or mean difference shown in the studies.

None of these studies reported significant cognitive improvement in the group treated with aspirin.

However, Bentham 2008 showed significant bleedings from various sites (RR 7.90, 95% CI 2.43 to 25.69; Analysis 1.1), but there was no difference in terms of death (RR 1.01, 95% CI 0.70 to 1.46; Analysis 1.2) and institutionalisation rate (RR 0.93, 95% CI 0.50 to 1.74; Analysis 1.3), compared to aspirin avoidance group.

Steroid

Only one selected study assessed a steroidal anti-inflammatory agent, prednisone (Aisen 2000a).This study was classified as being at low risk of bias. A total of 138 subjects with probable AD were randomised to either the drug or the placebo groups. This was a double-blind two-group parallel design comparing prednisone treatment with placebo. The primary outcome measure for this trial was the 1-year change in the cognitive subscale of the AD Assessment Scale (ADAS-cog) score.

No significant effect on cognition or mood at 12 months was observed (Analysis 2.1). Prednisone was associated with hyperglycaemia (RR 5.00, 95% CI 1.14 to 21.99; Analysis 2.3), abnormal lab results (RR 2.55, 95% CI 1.38 to 4.70; Analysis 2.4) and face edema (RR 1.87, 95% CI 1.10 to 3.17; Analysis 2.5).

NSAIDs

Ten studies investigated NSAIDs in AD. There were eleven interventions: six traditional NSAIDs and five selective COX-2 inhibitors. Analysis was initially undertaken on the NSAIDs group as a whole (all 11 interventions). Subsequently, subgroup analysis was carried out to establish whether any difference existed between traditional NSAIDs and selective COX-2 inhibitors.

All NSAIDs interventions used ADAS-cog scores as an outcome measure, but there was not enough data from Jhee 2004 to perform an analysis. In these studies, which included 1745 participants, the meta-analysis showed no significant difference between the scores of the treatment and placebo groups (MD -1.41, 95% CI -3.13 to 0.32; Analysis 3.1). Six studies involving 1268 participants also used the MMSE as an outcome measure (De Jong 2008; Pasqualetti 2009; Reines 2004; Rogers 1993; Scharf 1999; Soininen 2007). These studies showed no significant change in rate of MMSE scores decline in the treatment group (MD -1.08, 95%CI -2.21 to 0.12; Analysis 3.2).

In the subgroup analyses, no significant difference in the rate of cognitive decline overall was observed in the traditional NSAIDs group for ADAScog (MD -3.81, 95% CI -7.94 to 0.33; Analysis 3.1) and MMSE scores (MD -3.22, 95% CI -6.58 to 0.14; Analysis 3.2). Similarly, for the selective COX-2 inhibitors studies, no overall significant change was reported for both ADAScog (MD 0.30, 95% CI -0.99 to 1.60; Analysis 3.1) and MMSE scores (MD 0.34, 95% CI -0.07 to 0.76; Analysis 3.2). For all NSAIDs, no significant improvement was obtained for Clinician's Interview-Based Impression of Change (CIBIC+) (MD 0.04; 95% CI -0.09 to 0.16: Analysis 3.3). The same also applied for the Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB), neuropsychiatric inventory (NPI) and other measures where no significant differences between the treatment and the placebo groups were observed (Analysis 3.4 to Analysis 3.12).

Gastrointestinal side effects were more common in the NSAIDs group (RR 1.94, 95% CI 1.36 to 2.77; Analysis 3.13) compared to placebo based on analysis of data from 1675 participants in 9 studies. Both traditional NSAIDs and selective COX-2 inhibitors had higher rate of gastrointestinal side effects (RR 1.43, 95% CI 0.68 to 3.00 and RR 2.03, 95% CI 1.37 to 3.03; from Analysis 4.2 and Analysis 5.1, respectively).

For traditional NSAIDs, common side effects compared to placebo included nausea and vomiting (RR 4.81, 95% CI 0.24 to 95.58; Analysis 4.1), elevated creatinine (RR 4.30, 95% CI 0.54 to 34.30; Analysis 4.3), elevated liver function test (RR 4.04, 95% CI 0.48 to 33.98; Analysis 4.4), and hypertension (RR 3.36, 95% CI 0.84 to 13.34; Analysis 4.5). For selective COX-2 inhibitors, common side effects compared to placebo included hypertension (RR 8.65, 95% CI 0.51 to 146.03; Analysis 5.2), heart disease (RR 7.52, 95% CI 1.47 to 38.41; Analysis 5.3), and rash (RR 3.47, 95% CI 1.00 to 12.04; Analysis 5.4). The hypertension results came from only 229 participants in Aisen 2003b resulting from the use of rofecoxib. For cardiac side effects, subgroup analysis was performed for rofecoxib and celecoxib separately. There was no direct comparison between the two products. The result showed that celecoxib caused significant

heart problems in AD (RR 20.21, 95% CI 1.23 to 331.79; Analysis 5.3), while rofecoxib did not (RR 2.73, 95% CI 0.29 to 25.86; Analysis 5.3).

Death rate was higher in the NSAIDs group although this did not reach statistical significant (RR 1.67, 95% CI 0.85 to 3.31; Analysis 3.3). Death rate for traditional NSAIDs (RR 0.72, 95% CI 0.18 to 2.87; Analysis 4.15) and selective COX-2 inhibitor groups (RR 1.88, 95% CI 0.87 to 4.07; Analysis 5.14). Data presented in this meta-analysis was from 1711 participants from 9 included studies.

DISCUSSION

Aspirin, steroids and NSAIDs (traditional NSAIDs and selective COX-2 inhibitors) do not slow down the decline in cognitive function in AD patients and do not improve non-cognitive and behavioural outcome measures such as depression, behavioral disturbance, activity of daily living, quality of life, clinical global impression of change and caregiver burden.

All anti-inflammatory agents are known to be associated with a host of side effects. In the selected studies aspirin significantly increased bleeding in AD patients. Steroid medication was associated with hyperglycaemia, abnormal laboratory parameters, and face edema. Traditional NSAIDs were associated with nausea, vomiting, elevated creatinine, elevated liver function tests, and hypertension. Selective COX-2 inhibitors were associated with hypertension, heart problems, and rash. Celecoxib tended to cause higher rate of heart problems compared to rofecoxib, however the baseline characteristic of celecoxib group had significantly higher rate of hypertension, diabetes and higher numbers of bypass patients. Gastrointestinal side effects were commonly found in both traditional NSAIDs and Selective COX-2 inhibitors. Significantly, death rate was higher in selective COX-2 inhibitors, compared to traditional NSAIDs. Meta-analysis of side effects that included more than 1000 participants included gastrointestinal, cerebrovascular and other side effects as well as death.

There is a wealth of epidemiological data supporting a role for anti-inflammatory treatment in the protection against the development of cognitive dysfunction. In addition, a role for inflammatory processes in the pathogenesis of AD is now widely recognised. Nevertheless, such data has not been translated into clinical benefit to patients with AD. Anti-inflammatory drugs do not seem, based on current evidence, to achieve any noticeable improvement in any of the various outcomes assessed, and foremost among them cognitive measures. It cannot be discounted that most, in fact all of the studies assessing the efficacy of anti-inflammatory agents have been for a relatively short duration not usually exceeding 12 months. Further, patients selected are likely to have well established disease. It is accepted that the disease pathological process begins many years before the start of any symptoms associated with AD. Hence, one cannot comment on any potential efficacy for anti-inflammatories such as NSAIDs in those with very early stages of asymptomatic and silent disease. In fact epidemiological studies showing a benefit for anti-inflammatories has tended to assess patients with mainly rheumatological disorders on long term treatment with anti-inflammatory drugs. This may explain the discrepancy between the widely observed data from epidemiological studies and RCTs.

It is tempting to speculate whether a potential difference may exist between traditional NSAIDs and selective COX-2 inhibitors. It remains unclear whether this may relate to mechanism of action beyond COX-2 inhibition. In recent years more interest has been directed at selective COX-2 inhibitors, in part, due to the earlier perceived supremacy of this class of NSAIDs when it comes to side effects. In recent years, however, the benefit/risk profile of these drugs has been evaluated and earlier enthusiasm about their use has been critically reassessed. It will be of benefit that future work continues to include traditional NSAIDs as well as the newer COX-2 inhibitors.

Summary of main results

Aspirin, steroid and NSAIDs (traditional NSAIDs and selective COX-2 inhibitors) do not slow down cognitive decline in AD patients. They also do not improve behavioural and all other non-cognitive outcome measures such as depression, behavioral disturbance, activity of daily living, quality of life, clinical global impression of change and caregiver burden.

All anti-inflammatory agents are known to be associated with a host of side effects. In the selected studies aspirin significantly increased bleeding in AD patients. Steroid medication was associated with hyperglycaemia, abnormal laboratory parameters, and face edema.Traditional NSAIDs were associated with nausea, vomiting, elevated creatinine, elevated liver function tests, and hypertension. Selective COX-2 inhibitors were associated with hypertension, heart problems and rash. Death rate was higher in selective COX-2 inhibitors, compared to traditional NSAIDs.

Overall completeness and applicability of evidence

All patients in this review were diagnosed as having probable AD by NINCDS-ADRDA criteria or DSM 4. MMSE ranged from 10-26; hence patients in these studies had mild to moderate disease. Most recruitment took place in out-patient settings, except for two studies that were conducted in in-patient settings (42 participants) (Zhou 2004b; Zhou 2004a) and one study (Hüll 1999) in both out-patient and in-patient settings (10 participants). Minimum participants' age was 46 years. The studies were conducted in different countries including USA, UK, Netherlands, Australia, Belgium, Finland, France, Germany, Italy and China. Interventions included Aspirin, Steriods and NSAIDs.

Quality of the evidence

The three aspirin studies were rated 'moderate' in quality as they were not double-blind randomised controlled trials. The steroid study had low risk of bias and high quality rating. For NSAIDs, high rating for quality was obtained for four studies (Aisen 2003a; De Jong 2008; Pasqualetti 2009; Reines 2004). Moderate rating for quality was for three studies (Aisen 2002a; Rogers 1993; Soininen 2007) while low rating for quality was achieved by another three studies (Hüll 1999; Jhee 2004; Scharf 1999).

Potential biases in the review process

There were 2 studies by Beck 2000 and Taylor 1999 that met all inclusion criteria, but data could not be retrieved and the authors could not be contacted. Inability to include this unpublished data could have led to publication bias as the articles might not be published due to the nature and direction of the results. However, for this review thorough search of multiple databases

was performed and is expected to have identified all registered trials and possible unpublished articles.

Duplicate publication bias

There were 15 studies in this review that were found to be repetitive or overlapped substantially with the included studies. It was crucial to identify all redundant and multiple publication as it can lead to overestimation of intervention effects.

Location bias

It was found that trials published in low or non-impact factor journals were more likely to report significant results than those published in high-impact journals and that the quality of the trials was also associated with the journal of publication. In this systematic review, high risk of bias studies such as Zhou 2004b, Hüll 1999 and Scharf 1999 tended to provided more significant positive outcome toward intervention group than those of low risk.

Language bias

Reviews have often been exclusively based on studies published in English. Although the number of systematic reviews that restricted their search to studies reported in English had been decreased from 72% to 16%, it remained a challenge of the review process. In this review there was no language restriction which resulted in including 2 Chinese language studies. Although no total translation for the two Chinese language studies was done, data was extracted using a translation sheet from Cochrane as shown in Appendix 4. The process was done to help reduce language bias in the review.

Outcome reporting bias

Of all included studies only one Hüll 1999 did not report all stated outcomes. A reason for this may have been because the data was presented in an abstract form. For the remainder of the included studies, at least the stated primary outcomes were reported. For Jhee 2002, the ADAScog was not reported and data could not be retrieved although the author could be contacted. For side effects, Soininen 2007 study only reported side effects where more than 10% of participants complained. Hence, less common side effects were not reported.

Selection bias

In Soininen 2007 study the intervention group included higher number of subjects with pre-existing hypertension, diabetes and heart bypass. Hence, in this sponsored study the results obtained as far as side effects are concerned need to be interpreted with caution.

Agreements and disagreements with other studies or reviews

Results from cross-sectional, cohort and case-control studies tended to be positive toward the use of NSAIDs in AD (Imbimbo 2004; In't Veld 2001; Landi 2003; McGeer 1996; Rich 1995). There was also evidence from a systematic review that people who took NSAIDs had a lower risk of developing AD (Etminan 2003). Theoretically, aspirin, steroid and NSAIDs should be able to decrease inflammatory process (Aisen 1994; Aisen 1996; Aisen 1998; Harris 2002; Ho 1999; McGeer 1989; Pasinetti 1998; Thomas 2001) which in turn would help improve AD.

In this systematic review, all three classes of drug were found to be associated with more side effects than placebo. The selective COX-2 inhibitor group experienced more hypertension and heart problems. Patients treated with NSAIDs, particularly COX-2 inhibitors had a higher death rate than the placebo group.

In patients with osteoarthritis and rheumatoid arthritis, selective COX-2 inhibitors have been associated with fewer gastrointestinal side effects than traditional NSAIDs (Deek 2002). Among the AD patients studied, gastrointestinal side effects occurred at a similar rate in both groups for AD.

AUTHORS' CONCLUSIONS

Implications for practice

There no evidence to support the use of aspirin, steroidal or NSAIDs (both traditional NSAIDs and selective COX-2 inhibitors) in AD. None of the assessed drugs can be recommended for the treatment of AD.

Implications for research

The results of this review show that currently available evidence does not support the use of aspirin, steroid and NSAIDs (traditional NSAIDs and COX-2 inhibitors) for treating AD. These results are not in line with the majority of epidemiological data supporting a protective role for anti-inflammatories in the development of cognitive impairment. However, all of the selected studies were of relatively short duration and in symptomatic people with well established disease. As it is now widely accepted that inflammatory processes contribute to the pathogenesis of AD, future clinical trials need to assess a prophylactic role for anti-inflammatories. Participants should include those with Mild cognitive impairment and those with normal cognition but with evidence of early disease pathology such as amyloid deposits as assessed on Pet imaging and tau/amyloid ratio in the cerebrospinal fluid. Agents used should not be restricted to COX-2 inhibitors but need to include traditional NSAIDs as well.

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CHARACTERISTICS OF STUDIES

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

Aisen 2000a

Methods	Double blind randomised controlled trial, 12 months
Participants	138 participants (69 intervention, 69 control) who had MMSE 13-26, aged>50 years, were out-patient in USA
Interventions	Intervention: Prednisone 20 mg oral x 4 weeks then 10 mg x1year, follow by gradual taper over an additional 16 weeks of observation Control: placebo
Outcomes	Cognition (ADAScog 0-70 lower score = improvement) at 12 months (CDR-sob lower score = improvement) at 12 months Mood and depression (BPRS 7-126 lower score = improvement at 12 months (Ham-D 0-54 lower score = improvement) at 12 months (BDRS lower score = improvement) at 12 months
Notes	Supported by a grant from the national institutes of health. Prednisone and matching placebo were provided by Pharmacia and Upjohn, Inc

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote** "Codes were randomised at the packaging centre (supposed it is computer), the randomisation scheme was approved by the Alzheimer's disease Cooperative study (ADCS) statistic core. Randomization was stratified by site and utilized a block size of eight" **Comment:** Codes were generated at the packaging centre, probably using computer.
Allocation concealment (selection bias)	Low risk	**Quote 1** "Scratch-off code breakers were used so that instances of unbinding would be documented. All code breakers were collected at the end of the trial" **Quote 2** "Randomization codes were broken in two instances. In each case, the code was broken by investigators at local sites to determine whether stress-dose glucocorticoid treatment was necessary for subjects who required surgical procedures" **Comment:** It mentioned about using the code as a number. Probably done
Blinding (performance bias and detection bias) All outcomes	Low risk	**Quote 1**"Matching placebo tablets were assembled into identical containers with coded labels to blind participants" **Quote 2** "Adequacy of masking was assesses by questionnaires completed by subjects, caregivers, psychometrists, and site investigators" **Comment:** Blinding of participants ensured and unlikely that the blinding could have been broken
Incomplete outcome data (attrition bias) All outcomes	Low risk	The reasons for early discontinuation of study medication were caregiver issues and perceived lack of efficacy. No subjects discontinued medication because of serious adverse events attributed to the treatment

Aisen 2000a *(Continued)*

		1 year: 19/69 missing from intervention group, 11/69 missing from placebo **Comment:** Reasons for missing outcome data likely to be related to true outcome
Selective reporting (reporting bias)	Low risk	Report all outcome state in methodology **Comment:** The study protocol is not available, but all of the study's pre-specified outcomes have been reported in the pre-specified way in methodology
Other bias	Low risk	**Comment:** The study appears to be free of other sources of bias

Aisen 2002a

Methods	Double blind randomised controlled trial, 12 weeks
Participants	40 participants (21 intervention, 19 placebo) who has probable AD with stable medical condition, were out-patient in USA, age-not limited
Interventions	Intervention: Nimesulide 100 mg oral twice Control: Placebo
Outcomes	Cognition (ADAScog 0-70 lower score = improvement) (CDR-sob lower score = improvement) (MMSE 0-30 higher score = improvement) Mood and depression (BPRS 7-126 lower score = improvement) (Ham-D 0-54 lower score = improvement) Activity of daily living (Blessed ADL score higher score = improvement)
Notes	Sources of funding not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Quote**: The randomisation schedule was generated in the research pharmacy **Comment:** Insufficient information about the sequence generation process to permit judgement of yes or no
Allocation concealment (selection bias)	Unclear risk	**Comment** Insufficient information to permit judgement of Yes or No
Blinding (performance bias and detection bias) All outcomes	Low risk	**Quote 1** : All investigators and study personnel remained blind to group assignment of participants until completion of data collection

Aisen 2002a *(Continued)*

		Quote 2 : Participants were treated twice daily with Nimesulide or identical placebo tablets **Comment:** done
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** Reasons for missing outcome data unlikely to be related to true outcome
Selective reporting (reporting bias)	Low risk	**Comment:** The study protocol is not available, but all of the study's pre-specified outcomes have been reported in the pre-specified way in methodology
Other bias	Low risk	**Comment:** The study appears to be free of other sources of bias

Aisen 2003a

Methods	Double blind randomised controlled trial, 12 months
Participants	351 participants (240 intervention, 111 control) who had MMSE 13-26, aged > 50 years, were out-patient in USA
Interventions	Intervention 1: Naproxen sodium 220 mg oral twice (118 participants) Intervention 2: Rofecoxib 25 mg oral once (122 participants) Control: Placebo
Outcomes	Cognition (ADAScog 0-70 lower score = improvement) at 6, 12 months (CDR-sob lower score = improvement) at 6, 12 months (NPI 0-144 lower score = improvement) at 6, 12 months Activity of daily living (ADCS-ADL 0-78 higher score = improvement) at 6, 12 months Qulity of life (QoL-AD higher score = improvement) at 6, 12 months
Notes	source of funding: a grant from the national institute on aging and the general clinical research centre program of the national centre for research resources

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**Quote**: The randomisation process used a permuted block design with block size of 3 stratified by site. The randomisation sequence was generated by the ADCS data centre **Comment:** done

Aisen 2003a *(Continued)*

Allocation concealment (selection bias)	Low risk	**Quote 1:** Scratch-off code-breakers were used so that instances of unbinding would be documented. All code breakers were collected at the end of the trial. **Comment:** Probably done
Blinding (performance bias and detection bias) All outcomes	Low risk	**Quote 1**: Rofecoxib tablets were over-encapsulated to allow preparation of an identical placebo capsule. Naproxen sodium tablets and identical placebo tables were supplied by?.. **Quote 2**: Adequacy of masking was assessed by questionnaires completed by participants, caregivers, psychometrists, and site investigators. The results of questionnaires at 12 months indicated that the percentage of participants and informants who believed they were taking active study medication and active study medication also did not differ significantly across the treatment group, indicating that blinding was adequately maintained. **Quote3**: the randomisation code was broken in 1 instance, based on clinical need for the management of an acute medical problem **Comment:** acceptable
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Quote 1:** Reason for loss follow up are caregiver issue and adverse event **Comment:** Reasons for missing outcome data unlikely to be related to true outcome Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across group
Selective reporting (reporting bias)	Low risk	All primary outcomes were reported, but not all secondary outcome such as institutionalisation **Comment:** The study protocol is not available, but all of the study's pre-specified outcomes have been reported in the pre-specified way in methodology
Other bias	Low risk	**Comment:** The study appears to be free of other sources of bias

Bentham 2008

Methods	Open-label randomised controlled trial, 3 years
Participants	310 participants (156 intervention, 154 control) who had a DSM-4 diagnosis of probable dementia of AD without a coexisting diagnosis of vascular dementia, aged 46-90, were out-patient in the UK. 75% took Donepezil.
Interventions	Intervention: aspirin 75 mg oral once Control: avoid aspirin
Outcomes	Cognition (MMSE 0-30 higher score = improvement) at 12 wk, 1,2,3 years (NPI 0-144 lower score = improvement) at 12 wk, 1,2,3 years

Bentham 2008 *(Continued)*

	Activity of daily living (BALDS 0-60 higher score = improvement) at 12 wk, 1,2,3 years Caregiver burden (GHQ for care give 0-30 lower score = improvement) at 12 wk, 1,2,3 years
Notes	funding from research and development directorate of the west midlands region or national health service executive

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote**: Eligible patients were randomly assigned to take open-label aspirin or to take no aspirin. Treatment allocation was obtained by telephone from the central trial office and used minimised randomisation generated by a computer program to balance allocations by age, severity of dementia, the presence of absence of vascular dementia, parkinsonian and psychotic symptoms. **Comment:** done
Allocation concealment (selection bias)	Unclear risk	No statement **Comment:** Probably not done
Blinding (performance bias and detection bias) All outcomes	High risk	**Quote 1**: No blinding and the outcome or outcome measurement is likely to be influenced by lack of blinding. This is an open-label study **Quote 2:** The potential for biased assessment by patients or raters was judged insufficient to justify the cost of packaging aspirin and placebo for this long-term study. **Comment:** Not done
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Quote 1** **Comment:** Reasons for missing outcome data unlikely to be related to true outcome Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	**Comment:** The study protocol is not available, but all of the study's pre-specified outcomes have been reported in the pre-specified way in methodology
Other bias	High risk	**Comment:** Had a potential source of bias related to the specific study design used

De Jong 2008

Methods	Double blind randomised controlled trial, 12 months
Participants	51 participants (26 intervention, 25 control) who had a diagnosis of

De Jong 2008 *(Continued)*

	probable AD by NINCDS/ADRDA with MMSE 10-26, were out-patient in Netherlands, aged-not limited
Interventions	Intervention: Indomethacin 50 mg oral twice Control: Placebo
Outcomes	Cognition (ADAScog 0-70 lower score = improvement) at 6,12 months (MMSE higher score = improvement) at 6,12 months (CIBIC+ 1-7 lower score = improvement) at 6,12 months (NPI 0-144 lower score = improvement) at 6,12 months Activity of daily living (IDDD lower score = improvement) at 6,12 months Caregiver burden (NPI-D lower score = improvement) at 6,12 months
Notes	Funding from grants from Zon-MW Innovational Research, Hersenstichting Nederland

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote**: the statistician provided computer-generated lists of random numbers allocating patients in a 1:1 ratio to receive indomethacin or placebo. For each centre, a separate randomisation list was provided **Comment:** done
Allocation concealment (selection bias)	Low risk	**Quote 1:** Randomization codes were held by the pharmacy of the Radboud University Nijmegen Medical Centerthat labelled and dispensed all trial medication. Allocation was concealed from all investigators and patients. **Comment:** done
Blinding (performance bias and detection bias) All outcomes	Low risk	**Quote 1**: The indomethacin and placebo tablets were of identical appearance. Neither the patients nor the investigators knew which treatment they received or dispensed. The blinding process remained complete until all data was entered in the trial database and the accuracy of the data and the database was confirmed. Afterward, the database was forwarded to the statistician for analysis **Comment:** done
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Quote 1:** **Comment:** Reasons for missing outcome data unlikely to be related to true outcome Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across group
Selective reporting (reporting bias)	Low risk	**Comment:** The study protocol is not available, but all of the study's pre-specified outcomes have been reported in the pre-specified way in methodology

De Jong 2008 *(Continued)*

Other bias	Low risk	**Comment:** The study appears to be free of other sources of bias

Hüll 1999

Methods	Double blind randomised controlled trial, 6 months
Participants	10 Participants (7 intervention, 3 control) who had AD diagnosis, unclear if they were out-patient or in-patient, in Germany, aged 55-75
Interventions	Intervention: Piroxicam-B-cyclodextrin 10 mg oral once Control: Placebo
Outcomes	Cognition (ADAScog 0-70 lower score = improvement) at 6 months
Notes	Sources of funding not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**No information** **Comment:** probably not done
Allocation concealment (selection bias)	Unclear risk	**No information** **Comment:** Probably not done
Blinding (performance bias and detection bias) All outcomes	Low risk	**Quote 1**: all patients received either 10 mg piroxicam B Cyclodextrin or placebo **Comment:** Probably done, but there is only information for participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** Reasons for missing outcome data unlikely to be related to true outcome
Selective reporting (reporting bias)	High risk	Only report ADAS-cog **Comment:** not all of the study's pre-specified primary outcomes have been reported. The study report fails to include results for a key outcome that would be expected to have been reported for such a study
Other bias	High risk	**Comment:** had a potential source of bias related to the specific study design used Selection bias due to baseline imbalance

Jhee 2004

Methods	Double blind randomised controlled trial, 4 weeks
Participants	21 participants (16 intervention, 5 control) who had a diagnosis of probable AD. Subjects had to meet the NINCDS-ADRDA and DSM4 criteria for probable AD, had modified Hachinski Ischemia Scale score of less than or equal to 4, MMSE score between 10-24 inclusive and had been diagnosed with probable AD for at least a six month period. They were out-patient, aged>/=60 y in USA
Interventions	Interventions: Celecoxib dose 50. 200 and 400 mg oral twice Control: Placebo
Outcomes	Cognition (ADAScog 0-70 lower score = improvement) at 4 weeks (MMSE higher score = improvement) at 4 weeks
Notes	Sources of funding not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	**Quote**: Subjects with AD were randomly allocated a treatment arm in the order in which they were enrolled in the study **Comment:** Sequence generated by some rule based on the number they enrolled in the study
Allocation concealment (selection bias)	High risk	**No information** **Comment:** Probably not done
Blinding (performance bias and detection bias) All outcomes	Low risk	**Quote 1**: All study medication had the same appearance and was provided as celecoxib 50 mg and 200 mg capsules and matching placebo. **Comment:** Probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** Reasons for missing outcome data unlikely to be related to true outcome
Selective reporting (reporting bias)	Low risk	**Comment:** The study protocol is not available, but all of the study's pre-specified outcomes have been reported in the pre-specified way in methodology
Other bias	High risk	**Comment:** The study appears to have some degrees of selective bias as patients' age in each group were difference.

Pasqualetti 2009

Methods	Double blind randomised control trial, 52 weeks
Participants	132 participants (66 intervention, 66 control) who had a diagnosis of probable AD by ADRdA-NINCDS criteria with MMSE 16-25 and Clinical Dementia Rating =0.5-1, in Italy, aged 65 years or older and be cared for by a reliable caregiver, Out-patient setting
Interventions	Intervention: Ibuprofen 400 mg twice a day plus esomeprazole 20 mg Control: Placebo
Outcomes	Cognition (MMSE 0-30 higher score = improvement) at 52 weeks (ADAScog 0-70 lower score = improvement) at 52 weeks (CDR-sob lower score = improvement) at 52 weeks (CIBIC+ 1-7 lower score = improvement) at 52 weeks (NPI 0-144 lower score = improvement) at 52 weeks Mood (GDS 0-15 lower score = improvement) at 52 weeks Basic and instrumental activities of Daily LIving Scales (lower score = improvement) at 52 weeks Caregiver burden (NPI-stress CG subscale lower score = improvement) at 52 weeks (STAI-Y1, STAI-Y2) at 52 weeks (Beck Depression Inventory) at 52 weeks (CBI) at 52 weeks
Notes	The study was supported by a grant from the Italian Health Department. Active drug tablets and relative placebos were supplied by Angelini SpA for Ibuprofen and by Astra-Zeneca Pharmaceuticals.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote**: Randomization was performed with a permuted block design with a block size of 10, allocation rate 1:1, stratified by recruitment site. The randomisation sequence was provided by the Statistical Analysis Center, according to a pseudo-random computerized generator. **Comment:** Sequence generated by some rule based on the number they enrolled in the study
Allocation concealment (selection bias)	Low risk	**Quote**: Randomization was performed with a permuted block design with a block size of 10, allocation rate 1:1, stratified by recruitment site. **Comment:** Done
Blinding (performance bias and detection bias) All outcomes	Low risk	**Quote 1**: Tablets of the active drug and the placebo were undistinguishable, as were the gastroprotective agent and the relative placebo. Code-breaking was possible only at the level of the statistical Analysis Center an upon motivated request, resulting in simultaneous discontinuation of the patient from the study. **Comment:**

Pasqualetti 2009 *(Continued)*

		Done
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** Reasons for missing outcome data unlikely to be related to true outcome
Selective reporting (reporting bias)	Low risk	**Comment:** The study protocol is not available, but all of the study's pre-specified outcomes have been reported in the pre-specified way in methodology
Other bias	Low risk	**Comment:** The study appears to be free of other sources of bias

Reines 2004

Methods	Double blind randomised controlled trial, 12 months
Participants	692 participants (346 intervention, 346 control) who aged at least 50 years, met standard research criteria for possible or probable AD and had mild or moderate dementia as measured by MMSE score from 14-26 inclusive, unclear if they were out-patient or in-patient, in USA
Interventions	Intervention: Rofecoxib 25 mg oral once Control: Placebo
Outcomes	Cognition (ADAScog 0-70 lower score = improvement) at 6, 12 months (CDR-sob lower score = improvement) at 6, 12 months (MMSE 0-30 higher score = improvement) at 6, 12 months (CIBIC+ 1-7 lower score = improvement) at 6, 12 months Activity of daily living (ADCS-ADL 0-78 higher score = improvement) at 6, 12 months
Notes	Funding from Merck Research Laboratories

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**Quote**: Randomization of patients at each study site was determined by a computer-generated allocation schedule and was stratified according to MMSE score (14-20 and > 20) to try to ensure equal distributions of dementia severity in each treatment group **Comment:** done
Allocation concealment (selection bias)	Low risk	**Quote**: A statistician at Merck Research Laboratories generated the allocation schedule according to in-house blinding conditions. The rofecoxib and placebo tables were visually identical. **Comment:** done
Blinding (performance bias and detection bias) All outcomes	Low risk	**Quote 1**: A The rofecoxib and placebo tables were visually identical.

Reines 2004 *(Continued)*

		Quote 2: Any adverse events occurring during the study were recorded and rated by the investigator, while still blinded. Any serious vascular events including cardiac, peripheral vascular and cerebrovascular events were reviewed by independent blinded adjudication committees **Comment:** done
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** Reasons for missing outcome data unlikely to be related to true outcome Reason for missing outcome data unlikely to be related to true outcome
Selective reporting (reporting bias)	Low risk	**Comment:** The study protocol is not available, but all of the study's pre-specified outcomes have been reported in the pre-specified way in methodology
Other bias	Low risk	**Comment:** The study appears to be free of other sources of bias

Rogers 1993

Methods	Double blind randomised control trial, 6 months
Participants	28 participants (14 intervention, 14 control) who had a diagnosis of probable AD and MMSE of 16 or more, unclear if they are out-patient or in-patient, in USA, aged, not limited
Interventions	Intervention: Indomethacin oral once 100 mg/day for weight < 100 pounds, 125 mg/day for weight 101-150 pounds, 150 mg/day for weight > 150 pounds Control: Placebo
Outcomes	Cognition (MMSE 0-30 higher score = improvement) at 6 months (ADAScog 0-70 lower score = improvement) at 6 months (BNT 0-60 higher score = improvement) at 6 months (TK higher score = improvement) at 6 months
Notes	Sources of funding not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were then randomly assigned to one of two treatment conditions in a double-blind protocol, no information about sequence generation **Comment:** probably not done
Allocation concealment (selection bias)	Unclear risk	No information **Comment:** Probably not done

Rogers 1993 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	**Quote 1**: Patients were then randomly assigned to one of two treatment conditions in a double-blind protocol **Comment:** probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** Reasons for missing outcome data unlikely to be related to true outcome
Selective reporting (reporting bias)	Low risk	**Comment:** The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified.
Other bias	Low risk	**Comment:** The study appears to be free of other sources of bias

Scharf 1999

Methods	Double blind randomised control trial, 25 weeks
Participants	27 participants (12 intervention, 15 placebo) who had a diagnosis of AD according to DSM-4 criteria that was of mild to moderate severity, defined by a MMSE score of 11-25, aged >/= 50 years, were out-patient in Australia
Interventions	Intervention: Unknown dose of diclofenac and misoprostol oral Control: Placebo
Outcomes	Cognition (ADAScog 0-70 lower score = improvement) at 12, 25 weeks (MMSE 0-30 higher score = improvement) at 12, 25 weeks Clinical global impression of change at 12, 25 weeks (GDS lower score = improvement) at 12, 25 weeks (CGIC lower score = improvement) at 12, 25 weeks Behavioral disturbance (ADAS-noncog lower score = improvement) at 12, 25 weeks (ADAS-total lower score = improvement) at 12, 25 weeks Activity of daily living (IADL lower score = improvement) at 12, 25 weeks Quality of life (PSMS lower score = improvement) at 12, 25 weeks Caregiver burden (CGIC lower score = improvement) at 12, 25 weeks

Scharf 1999 *(Continued)*

Notes	source of funding from postgraduate medical research scholarship

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	**Quote**: Randomization was performed by the manufacturer of the medication before delivery to the study centre. For patients 1 to 20, 50% received diclofenac/misoprostol (D/M) and 50% placebo; for patients 21-41, two thirds received D/M and one third placebo. **Comment:** Sequence generated by some rule based on hospital or clinic record number
Allocation concealment (selection bias)	Low risk	**Quote:** The identity code was concealed in sequentially numbered opaque envelopes. **Quote 2**: The medication and envelopes were stored in a pharmacy separate from the study site. The medication was supervised and dispensed by independent pharmacist trained in the conduct of randomised double-blind clinical trials. **Quote 3:** Medication codes were broken after completion of the trial or if a patient was withdrawn prematurely due to an adverse event. **Comment:** Done
Blinding (performance bias and detection bias) All outcomes	Low risk	**Quote 1**: Patients were randomly assigned in a double-blind fashion to receive either D/M as a single table twice a day or identical placebo twice daily for 25 weeks. **Comment:** Blinding of participants ensured and unlikely that the blinding could have been broken
Incomplete outcome data (attrition bias) All outcomes	Low risk	Side effects are more significant in D/M group. **Comment:** Reasons for missing outcome data unlikely to be related to true outcome
Selective reporting (reporting bias)	Low risk	Report all outcome state in methodology **Comment:** The study protocol is not available, but all of the study's pre-specified outcomes have been reported in the pre-specified way in methodology
Other bias	High risk	**Comment:** Selection bias: baseline are different between intervention and placebo

Soininen 2007

Methods	Double blind randomised control trial, 12 months

Soininen 2007 *(Continued)*

Participants	461 participants (308 intervention, 153 control) who aged >/= 50 years with early to moderate AD by MMSE and global deterioration scale (GDS) scores of 3-5, meeting NINCDS or DSM 4 criteria for probable AD with symptoms present for at least one year, were out-patient in USA, Australia, Belgium, Finland, France, Germany, Netherlands and the UK.
Interventions	Intervention: Celecoxib 200 mg oral twice Control: Placebo
Outcomes	Cognition (ADAScog 0-70 lower score = improvement) at 6, 12 months (CIBIC+ 1-7 lower score = improvement) at 6, 12 months Clinical global impression of change (NOSGER 30-150 lower score = improvement) at 6, 12 months Behavioral disturbance (Behave-AD 0-75 lower score = improvement) at 6, 12 months
Notes	Funding from Pfizer

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** Patients were assigned to receive the study medication in the order of enrolment according to a computer-generated randomisation schedule prepared by the sponsor prior to the start of the study. **Comment:** done
Allocation concealment (selection bias)	Low risk	**Quote**: Patients and study personnel were blinded to the allocation of treatments throughout, and the randomisation code was only to be broken for a specific patient in an emergency situation when the investigator's opinion required this action. **Comment:** Probably done
Blinding (performance bias and detection bias) All outcomes	Low risk	**Quote 1:** Eligible patients were randomised to receive the 52-week dosing regimen of either celecoxib 200 mg bid or matching placebo in the ration of 2:1 **Quote 2:** Patients and study personnel were blinded to the allocation of treatments throughout. **Comment:** Blinding of participants and unlikely to introduce bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** Reasons for missing outcome data unlikely to be related to true outcome
Selective reporting (reporting bias)	Low risk	All primary outcomes were reported, but not all secondary outcomes were reported **Comment:** The study protocol is not available, but all of the study's pre-specified outcomes have been reported in the pre-specified way in methodology

Soininen 2007 *(Continued)*

Other bias	High risk	Celecoxib group has more hypertension, diabetes and by pass patients, trans cerebral ischemias, coronary artery disease and aspirin use, compared to placebo **Comment:** Selection bias

Zhou 2004a

Methods	Open-label randomised controlled trial, 6 months
Participants	16 participants (8 intervention, 8 control) who had a diagnosis of AD, were in-patient. in China, aged-not limited
Interventions	Intervention: Hyperzine A 0.15 mg oral twice, Nicegoline 20 mg oral twice and enteric-coated aspirin oral 50 mg once Control: Hyperzine A 0.15 mg oral twice, Nicegoline 20 mg oral twice
Outcomes	Cognition (MMSE 0-30 higher score = improvement) at 3,6 months Activity of daily living (Blessed ADL score higher score = improvement) at 3,6 months
Notes	Sources of funding not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**No information** **Comment:** probably not done
Allocation concealment (selection bias)	Unclear risk	**No information** **Comment:** Probably not done
Blinding (performance bias and detection bias) All outcomes	High risk	**Quote 1**: This is an open-label trial **Comment:** Only outcome assessors were blinded, incomplete blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** Reasons for missing outcome data unlikely to be related to true outcome
Selective reporting (reporting bias)	Low risk	**Comment:** The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified.
Other bias	High risk	**Comment:** Performance bias due to the nature of open-label trial

Zhou 2004b

Methods	Open-label randomised controlled trial, 36 weeks
Participants	26 participants (13 intervention, 13 control) who had a diagnosis of AD, were in-patient in China, aged-not limited
Interventions	Intervention: Hyperzine A 0.15 mg oral twice and aspirin oral 150 mg once Control: Hyperzine A 0.15 mg oral twice
Outcomes	Cognition (MMSE 0-30 higher score = improvement) at 36 weeks Activity of daily living (Blessed ADL score higher score = improvement) at 36 weeks
Notes	Sources of funding not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**No information** **Comment:** probably not done
Allocation concealment (selection bias)	Unclear risk	**No information** **Comment:** Probably not done
Blinding (performance bias and detection bias) All outcomes	High risk	**Quote 1**: This is an open-label trial **Comment:** Only outcome assessors were blinded, incomplete blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** Reasons for missing outcome data unlikely to be related to true outcome
Selective reporting (reporting bias)	Low risk	**Comment:** The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified.
Other bias	High risk	**Comment:** Performance bias due to the nature of open-label trial

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

Study	Reason for exclusion
ADAPT 2008	not RCT

Study	Reason for exclusion
Aisen 1996a	no comparison group
Aisen 2000b	Repeat study to Aisen2000a
Aisen 2000c	not RCT
Aisen 2002b	not RCT
Aisen 2003b	not RCT
Aisen 2008a	not RCT
Aisen 2008b	not RCT
Aizen 2005	not RCT
Allain 2007	not RCT
Anthony 2000a	not RCT
Anthony 2000b	not RCT
Asthana 1999	RCT, AD, but intervention is physostigmine which is not aspirin, steroids or NSAIDS
Baum 2008	RCT, AD, but intervention is curcurmin which is not aspirin, steroids or NSAIDS
Beck 2000	This study met all inclusion criteria, but information of the study from the authors could not be obtained.
Belanoff 2002a	RCT, AD, but intervention is mifepristone which is not aspirin, steroids or NSAIDS
Belanoff 2002b	not RCT
Bernardi 2000	not RCT
Bertozzi 1996	not RCT
Black 2006	RCT, AD, but intervention is R-flurbiprofen which is not aspirin, steroids or NSAIDS
Breitner 1995	not RCT
Breitner 2000	RCT, but for AD prevention
Breitner 2009	RCT, but in MCI and normal elderly
Browne 1999	not RCT
Bruce-Jones 1994	RCT, but for healthy elderly
Brunner 2006	not RCT
Budge 2000	RCT, but for non-specified dementia, not AD
Bullock 2004	not RCT

Study	Reason for exclusion
Bussiere 2005	RCT, but for non-specified dementia
Canigueral 2008	RCT, but not in AD
Chang 2005	RCT, AD, but intervention is Ginko biloba which is not aspirin, steroids or NSAIDS
Clarke 2003a	RCT, but for non-specified dementia, not AD
Clostre 1999	not RCT
Diener 2007	RCT, but for ischemic stroke, not AD
Diener 2008	RCT, but ofr ischemic stroke, not AD
Doraiswamy 1996	not RCT
Fisk 2000	Repeat study to Bentham2008
Forssell 1989	RCT, AD, but intervention is choline chloride and lecithin which is not aspirin, steroids or NSAIDS
Fotuhi 2008	not RCT
Geldmacher 2004	RCT, AD, but intervention is pioglitazone which is not aspirin, steroids or NSAIDS
Gomez-Isla 2008	RCT, but in MCI, not AD
Green 2009	RCT, AD, but intervention is Tarenflurbil
Group 2007	RCT, but in elderly with family history of AD, not AD
Hollander 1987	RCT, AD, but intervention is RS 86 (Cholinomimetic drug) which is not aspirin, steroids or NSAIDS
Jackson 2005	RCT, AD, but intervention is propranolol which is not aspirin, steroid, or NSAIDS
Jacobs 2009	not RCT
Jacoby 2002	RCT, but for non-specified dementia
Jeong 2004	not RCT
Jiang 2008	not RCT
Jin 2008	not RCT
Kimball 2008	RCT, but in atopic dermatitis
Landi 2003	not RCT
Laughlin 2006	RCT, AD, but intervention is R-flurbiprofen which is not aspirin, steroid, or NSAIDS
Leblhuber 2004	not RCT
Leuchtenberger 2006	not RCT

Study	Reason for exclusion
Lucca 1994	not RCT
Martin 2006	RCT, but in patients with family history of AD
Martin 2008	RCT, but in patients with family history of AD
McIntyre 2006	not RCT
Meinert 2009	not RCT
Meinerta 2008	RCT, but in TIA or Stroke patients
Meyer 1989	not RCT
Meyer 2002	RCT, but in multi-infarct dementia
Nawata 2002	RCT, but in vascular dementia
Nourhashemi 1998	not RCT
O'Shea 2007	RCT, but in premature infact
Pasinetti 2002	not RCT
Pfizer 2004	Repeat study to Soininen2007
Pfizer 2005	Repeat study to Soininen2007
Pomara 1985	RCT, AD, but intervention is naltrexone which is not aspirin, steroid or NSAIDs
Pomara 2006	RCT, AD, but intervention is mifepristone which is not aspirin, steroid or NSAIDs
Reid 2005	RCT, but in cocaine dependent subjects
Relkin 2003	RCT, AD, but intervention is donepezil which is not aspirin, steroid or NSAIDs
Sainati 2000	Repeat study to Soininen2007
Simon 1998	RCT, but in osteoarthritis and rheumatoid arthritis patients
Small 1999	RCT, but in MCI
Small 2008	RCT, but in non demented volunteer with mild age-related memory decline
Solomon 2008	not RCT
Souza-Talarico 2008	not RCT
Steiger 1991	RCT, but in healthy men
Stevenson 2004	Repeat study to Jhee2004
Stewart 1997	not RCT
Stoppe 1996	not RCT

Study	Reason for exclusion
Szekely 2008	not RCT
Szekely 2010	not RCT
Taylor 1999	This study met all inclusion criteria, but information of the study from the authors could not be obtained.
Thal 2005	RCT, but in MCI
Tsartsalis 2011	not RCT
Tuppo 2005	not RCT
Turini 2002	not RCT
Usui 2006	not RCT
Uttner 2005	RCT, but in multiple sclerosis
Van Niekerk 2001	RCT, but in men aged 62-76
van Reekum 1999	not RCT
Visser 2005	not RCT
Vlad 2008	not RCT
Walker 2005	not RCT
Walther 2011	RCT, but in 2 patients with unspecified dementia
Watson 2004	RCT, but in both AD and MCI and intervention is rosiglitasone which is not aspirin, steroid or NSAIDs
Whitehouse 1998	not RCT
Widimsky 2008	RCT, but in stable angina group A
Wilcock 1999	RCT, but in non-specified AD
Wilcock 2004	RCT, AD, but intervention is R-flurbiprofen which is not aspirin, steroid and NSAIDs
Wilcock 2006	not RCT
Wilcock 2008	RCT, AD, but intervention is tarenflurbil which is not aspirin, steroid and NSAIDs
Williams 2004	not RCT
Windisch 2000	not RCT
Wisloff 1996	RCT, but in multiple myeloma
Wolkowitz 2003	RCT, AD, but intervention is a steroid that does not have anti-inflammatory effect
Wollheim 2000	not RCT

Study	Reason for exclusion
Woodward 2002	not RCT
Xia 2007	RCT, but in premature infant
Yaqub 1999	not RCT
Yip 2005	not RCT
Young 1999	RCT, but in normal male volunteers
Zandi 2005	not RCT
Zaragoza 2005	not RCT
Zerovnik 2010	not RCT
Zhai 2010	RCT, but in vascular cognitive impairment
Ziebell 2010	not RCT

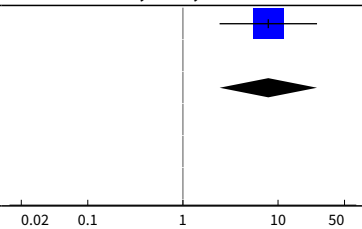
DATA AND ANALYSES

Comparison 1. Aspirin vs. aspirin avoidance

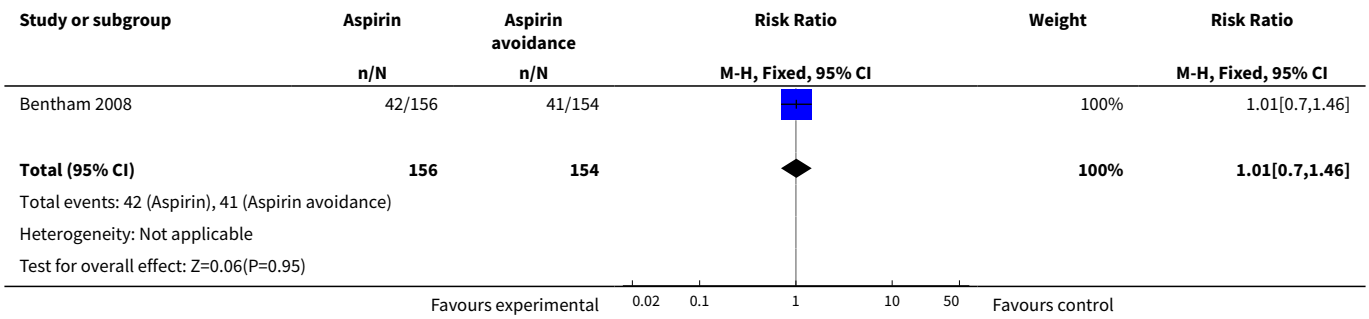
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Bleeding	1	310	Risk Ratio (M-H, Fixed, 95% CI)	7.90 [2.43, 25.69]
2 Death	1	310	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.70, 1.46]
3 Institutionaliation	1	310	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.50, 1.74]

Analysis 1.1. Comparison 1 Aspirin vs. aspirin avoidance, Outcome 1 Bleeding.

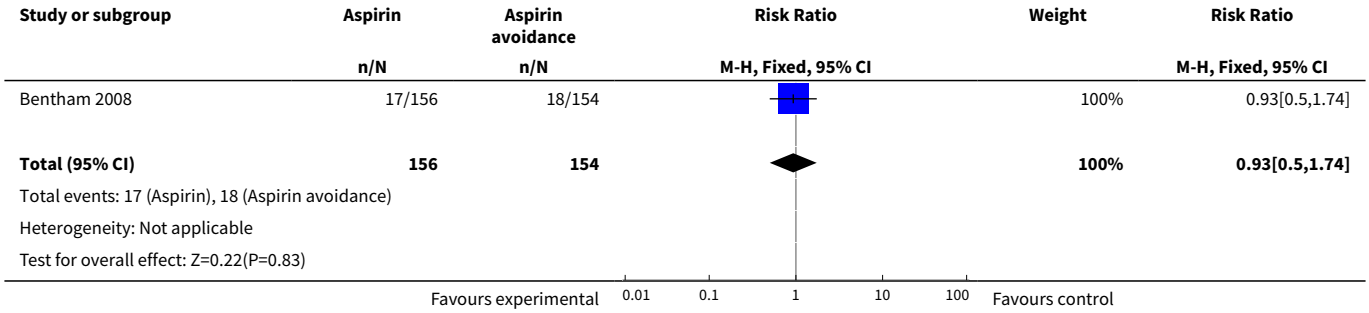
Study or subgroup	Aspirin n/N	Aspirin avoidance n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bentham 2008	24/156	3/154		100%	7.9[2.43,25.69]
Total (95% CI)	**156**	**154**		**100%**	**7.9[2.43,25.69]**
Total events: 24 (Aspirin), 3 (Aspirin avoidance)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.43(P=0)					



Analysis 1.2. Comparison 1 Aspirin vs. aspirin avoidance, Outcome 2 Death.



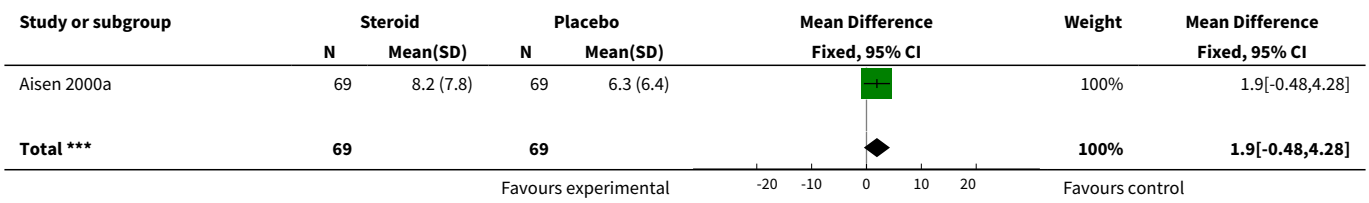
Analysis 1.3. Comparison 1 Aspirin vs. aspirin avoidance, Outcome 3 Institutionaliation.

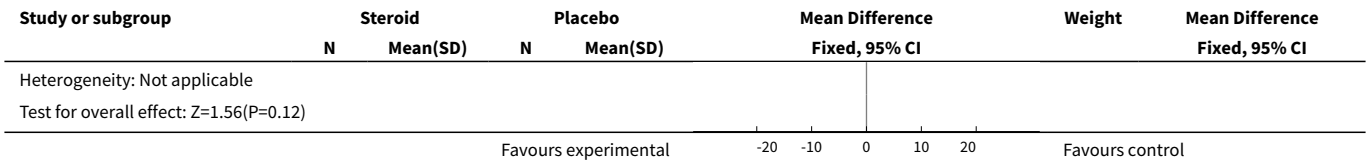


Comparison 2. Steroids vs. placebo

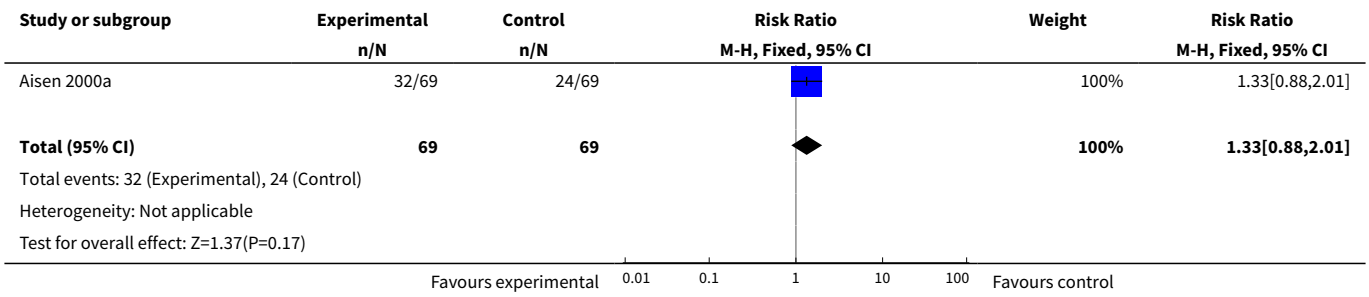
Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 ADAScog	1	138	Mean Difference (IV, Fixed, 95% CI)	1.90 [-0.48, 4.28]
2 Confusion	1	138	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.88, 2.01]
3 hyperglycemia	1	138	Risk Ratio (M-H, Random, 95% CI)	5.0 [1.14, 21.99]
4 Abnormal lab results	1	138	Risk Ratio (M-H, Fixed, 95% CI)	2.55 [1.38, 4.70]
5 Face edema	1	138	Risk Ratio (M-H, Fixed, 95% CI)	1.87 [1.10, 3.17]

Analysis 2.1. Comparison 2 Steroids vs. placebo, Outcome 1 ADAScog.

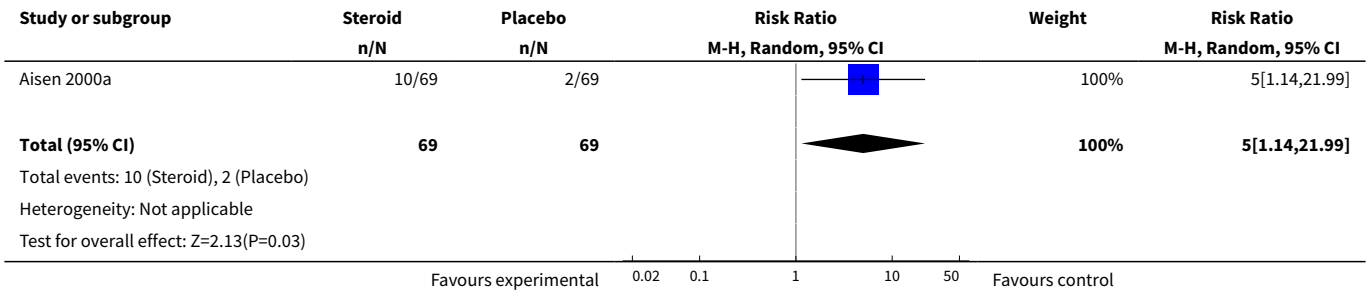




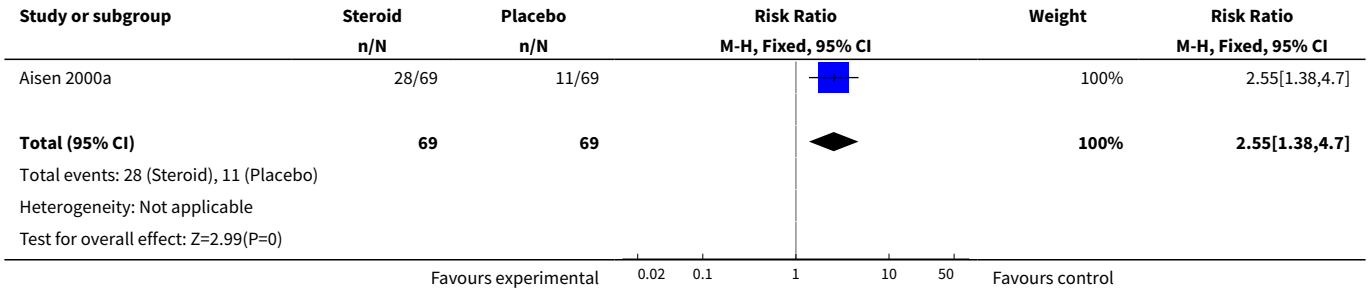
Analysis 2.2. Comparison 2 Steroids vs. placebo, Outcome 2 Confusion.



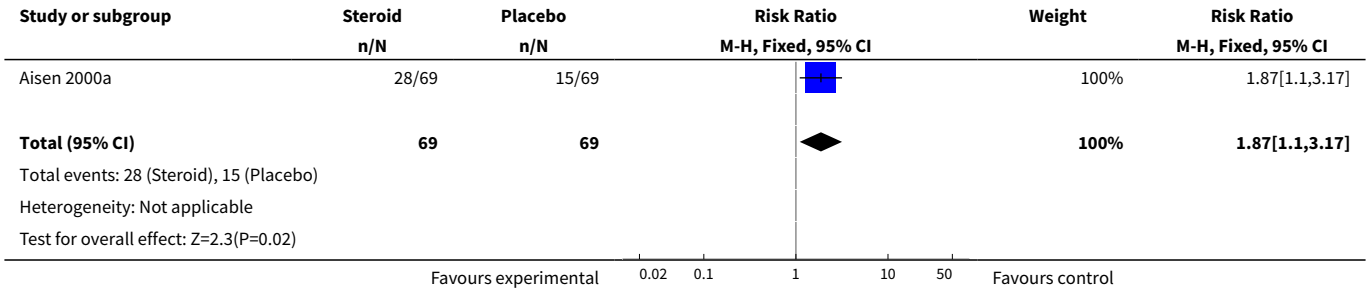
Analysis 2.3. Comparison 2 Steroids vs. placebo, Outcome 3 hyperglycemia.



Analysis 2.4. Comparison 2 Steroids vs. placebo, Outcome 4 Abnormal lab results.



Analysis 2.5. Comparison 2 Steroids vs. placebo, Outcome 5 Face edema.



Comparison 3. NSAIDs vs. placebo

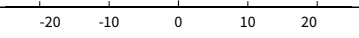
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cognition:ADAScog all studies	9	1745	Mean Difference (IV, Random, 95% CI)	-1.41 [-3.13, 0.32]
1.1 traditional NSAIDs vs placebo	6	411	Mean Difference (IV, Random, 95% CI)	-3.81 [-7.94, 0.33]
1.2 Selective COX-2 inhibitor	4	1334	Mean Difference (IV, Random, 95% CI)	0.30 [-0.99, 1.60]
2 Cognition:MMSE all	6	1268	Mean Difference (IV, Random, 95% CI)	-1.08 [-2.21, 0.04]
2.1 traditional NSAIDs vs placebo	4	234	Mean Difference (IV, Random, 95% CI)	-3.22 [-6.58, 0.14]
2.2 Selective COX-2 inhibitor	2	1034	Mean Difference (IV, Random, 95% CI)	0.34 [-0.07, 0.76]
3 CIBIC+	3	1099	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.09, 0.16]
3.1 traditional NSAIDs vs placebo	1	38	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.58, 0.38]
3.2 Selective COX-2 inhibitor	2	1061	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.08, 0.18]
4 CDR sum score	3	1124	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.25, 0.30]
4.1 traditional NSAIDs vs placebo	1	229	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.50, 0.70]
4.2 Selective COX-2 inhibitor	3	895	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.30, 0.32]
5 NPI	3	632	Mean Difference (IV, Fixed, 95% CI)	0.81 [0.14, 1.49]
5.1 traditional NSAIDs vs placebo	3	399	Mean Difference (IV, Fixed, 95% CI)	0.84 [0.14, 1.54]
5.2 Selective COX-2 inhibitor	1	233	Mean Difference (IV, Fixed, 95% CI)	0.40 [-2.54, 3.34]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Mood/depression	1	40	Std. Mean Difference (IV, Random, 95% CI)	-0.34 [-0.96, 0.29]
6.1 selective COX-2 inhibitor vs placebo	1	40	Std. Mean Difference (IV, Random, 95% CI)	-0.34 [-0.96, 0.29]
7 Clinical global impression: GDS	1	31	Std. Mean Difference (IV, Random, 95% CI)	-0.43 [-1.15, 0.29]
7.1 traditional NSAIDs vs placebo	1	31	Std. Mean Difference (IV, Random, 95% CI)	-0.43 [-1.15, 0.29]
8 Clinical global impression: CGIC and NOSGER 6 months	2	441	Std. Mean Difference (IV, Random, 95% CI)	-0.07 [-0.49, 0.35]
8.1 traditional NSAIDs vs placebo	1	31	Std. Mean Difference (IV, Random, 95% CI)	-0.44 [-1.16, 0.27]
8.2 Selective COX-2 inhibitor	1	410	Std. Mean Difference (IV, Random, 95% CI)	0.05 [-0.16, 0.26]
9 Behavioral disturbance	3	479	Std. Mean Difference (IV, Random, 95% CI)	0.09 [-0.29, 0.46]
9.1 traditional NSAIDs vs placebo	2	69	Std. Mean Difference (IV, Random, 95% CI)	-0.03 [-0.89, 0.82]
9.2 Selective COX-2 inhibitor	1	410	Std. Mean Difference (IV, Random, 95% CI)	0.16 [-0.04, 0.37]
10 Activity of daily living	7	1737	Std. Mean Difference (IV, Random, 95% CI)	-0.22 [-0.48, 0.04]
10.1 traditional NSAIDs vs placebo	4	375	Std. Mean Difference (IV, Random, 95% CI)	-0.48 [-0.97, 0.01]
10.2 Selective COX-2 inhibitor	4	1362	Std. Mean Difference (IV, Random, 95% CI)	-0.03 [-0.22, 0.17]
11 Quality of life	2	382	Std. Mean Difference (IV, Random, 95% CI)	0.08 [-0.14, 0.29]
11.1 traditional NSAIDs vs placebo	2	205	Std. Mean Difference (IV, Random, 95% CI)	0.07 [-0.22, 0.36]
11.2 Selective COX-2 inhibitor	1	177	Std. Mean Difference (IV, Random, 95% CI)	0.09 [-0.23, 0.41]
12 Caregiver burden	3	201	Std. Mean Difference (IV, Random, 95% CI)	-0.35 [-0.63, -0.07]
12.1 traditional NSAIDs vs placebo	3	201	Std. Mean Difference (IV, Random, 95% CI)	-0.35 [-0.63, -0.07]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13 Gastrointestinal side effects	9	1675	Risk Ratio (M-H, Fixed, 95% CI)	1.94 [1.36, 2.77]
14 Elevated creatinine	2	92	Risk Ratio (M-H, Fixed, 95% CI)	4.30 [0.54, 34.30]
15 Elevated liver function test	3	132	Risk Ratio (M-H, Fixed, 95% CI)	4.27 [0.97, 18.76]
16 Headache	4	577	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.34, 3.44]
17 Psychiatric side effects	4	586	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.67, 1.86]
18 Bleeding	1	425	Risk Ratio (M-H, Fixed, 95% CI)	3.45 [0.18, 66.35]
19 Heart disease	2	776	Risk Ratio (M-H, Fixed, 95% CI)	7.58 [1.48, 38.90]
20 Cerebrovascular side effects	4	1555	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.54, 2.02]
21 Hypertension	2	402	Risk Ratio (M-H, Fixed, 95% CI)	5.41 [1.36, 21.60]
22 Hyperglycemia	1	51	Risk Ratio (M-H, Fixed, 95% CI)	1.92 [0.19, 19.90]
23 Rash	2	61	Risk Ratio (M-H, Fixed, 95% CI)	3.47 [1.00, 12.04]
24 Respiratory side effects	1	461	Risk Ratio (M-H, Fixed, 95% CI)	2.73 [0.61, 12.17]
25 Dry mouth	1	351	Risk Ratio (M-H, Fixed, 95% CI)	3.24 [0.40, 26.00]
26 Fatigue	1	351	Risk Ratio (M-H, Fixed, 95% CI)	2.31 [1.06, 5.04]
27 Dizziness	3	423	Risk Ratio (M-H, Fixed, 95% CI)	2.40 [1.10, 5.25]
28 Abnormal labs other than Cr. and LFT	2	466	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.21, 8.69]
29 Withdrawal due to side effects	3	1083	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.89, 1.65]
30 Abdominal pain or dyspepsia	8	994	Risk Ratio (M-H, Fixed, 95% CI)	1.76 [0.97, 3.22]
31 Constipation or diarrhea	3	527	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [0.84, 4.88]
32 Nausea or vomiting	3	112	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [0.39, 7.38]
33 Death	9	1711	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.85, 3.31]

Analysis 3.1. Comparison 3 NSAIDs vs. placebo, Outcome 1 Cognition:ADAScog all studies.

Study or subgroup	NSAIDs N	NSAIDs Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.1.1 traditional NSAIDs vs placebo							
Aisen 2003a	118	5.8 (8)	56	5.7 (8.2)		11.14%	0.1[-2.49,2.69]
De Jong 2008	19	7.8 (7.6)	19	9.3 (10)		5.73%	-1.5[-7.15,4.15]
Hüll 1999	6	1.5 (4.5)	2	10 (8.5)		1.74%	-8.5[-20.8,3.8]
Pasqualetti 2009	66	3 (1.3)	66	3.1 (1.3)		14.72%	-0.1[-0.54,0.34]
Rogers 1993	14	-1.4 (4.9)	14	13.3 (5.6)		8.45%	-14.7[-18.6,-10.8]
Scharf 1999	17	0.3 (4.5)	14	1.9 (5.6)		9.01%	-1.68[-5.29,1.93]
Subtotal ***	**240**		**171**			**50.8%**	**-3.81[-7.94,0.33]**
Heterogeneity: Tau²=20.85; Chi²=55.74, df=5(P<0.0001); I²=91.03%							
Test for overall effect: Z=1.8(P=0.07)							
3.1.2 Selective COX-2 inhibitor							
Aisen 2002a	21	0.9 (4.6)	19	-0.5 (4.4)		10.74%	1.4[-1.37,4.17]
Aisen 2003a	122	7.6 (7.7)	111	5.7 (8.2)		12.29%	1.9[-0.15,3.95]
Reines 2004	321	4.8 (8.6)	327	5.4 (8.6)		13.68%	-0.6[-1.92,0.72]
Soininen 2007	278	4.4 (9.5)	135	5 (9.5)		12.49%	-0.61[-2.56,1.34]
Subtotal ***	**742**		**592**			**49.2%**	**0.3[-0.99,1.6]**
Heterogeneity: Tau²=0.77; Chi²=5.4, df=3(P=0.14); I²=44.45%							
Test for overall effect: Z=0.46(P=0.65)							
Total ***	**982**		**763**			**100%**	**-1.41[-3.13,0.32]**
Heterogeneity: Tau²=5.21; Chi²=61.82, df=9(P<0.0001); I²=85.44%							
Test for overall effect: Z=1.6(P=0.11)							
Test for subgroup differences: Chi²=3.45, df=1 (P=0.06), I²=71.03%							



Analysis 3.2. Comparison 3 NSAIDs vs. placebo, Outcome 2 Cognition:MMSE all.

Study or subgroup	NSAIDs N	NSAIDs Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.2.1 traditional NSAIDs vs placebo							
De Jong 2008	20	2.3 (3.2)	23	2.4 (3.6)		13.23%	-0.1[-2.13,1.93]
Pasqualetti 2009	66	2.1 (0.5)	66	2.7 (0.5)		23.18%	-0.6[-0.77,-0.43]
Rogers 1993	14	0.9 (4.8)	14	13.4 (4.4)		7.42%	-12.5[-15.91,-9.09]
Scharf 1999	17	-0.4 (2.7)	14	0.9 (3.2)		12.79%	-1.27[-3.38,0.84]
Subtotal ***	**117**		**117**			**56.62%**	**-3.22[-6.58,0.14]**
Heterogeneity: Tau²=10.55; Chi²=47.26, df=3(P<0.0001); I²=93.65%							
Test for overall effect: Z=1.88(P=0.06)							
3.2.2 Selective COX-2 inhibitor							
Reines 2004	322	2.6 (4.9)	329	2.1 (4.9)		21.12%	0.44[-0.31,1.19]
Soininen 2007	255	2.3 (2.4)	128	2 (2.4)		22.26%	0.3[-0.21,0.81]
Subtotal ***	**577**		**457**			**43.38%**	**0.34[-0.07,0.76]**
Heterogeneity: Tau²=0; Chi²=0.09, df=1(P=0.76); I²=0%							
Test for overall effect: Z=1.61(P=0.11)							
Total ***	**694**		**574**			**100%**	**-1.08[-2.21,0.04]**
Heterogeneity: Tau²=1.41; Chi²=65.21, df=5(P<0.0001); I²=92.33%							

Study or subgroup	NSAIDs N	NSAIDs Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for overall effect: Z=1.89(P=0.06)							
Test for subgroup differences: Chi²=4.25, df=1 (P=0.04), I²=76.49%							

Favours experimental -100 -50 0 50 100 Favours control

Analysis 3.3. Comparison 3 NSAIDs vs. placebo, Outcome 3 CIBIC+.

Study or subgroup	NSAIDs N	NSAIDs Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.3.1 traditional NSAIDs vs placebo							
De Jong 2008	19	5.6 (0.8)	19	5.7 (0.7)		6.7%	-0.1[-0.58,0.38]
Subtotal ***	**19**		**19**			**6.7%**	**-0.1[-0.58,0.38]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.41(P=0.68)							
3.3.2 Selective COX-2 inhibitor							
Reines 2004	319	0.9 (1)	328	0.9 (1)		64.41%	0.03[-0.12,0.18]
Soininen 2007	279	4.9 (1.1)	135	4.8 (1.1)		28.89%	0.09[-0.14,0.32]
Subtotal ***	**598**		**463**			**93.3%**	**0.05[-0.08,0.18]**
Heterogeneity: Tau²=0; Chi²=0.18, df=1(P=0.67); I²=0%							
Test for overall effect: Z=0.74(P=0.46)							
Total ***	**617**		**482**			**100%**	**0.04[-0.09,0.16]**
Heterogeneity: Tau²=0; Chi²=0.53, df=2(P=0.77); I²=0%							
Test for overall effect: Z=0.61(P=0.54)							
Test for subgroup differences: Chi²=0.35, df=1 (P=0.56), I²=0%							

Favours experimental -100 -50 0 50 100 Favours control

Analysis 3.4. Comparison 3 NSAIDs vs. placebo, Outcome 4 CDR sum score.

Study or subgroup	NSAIDs N	NSAIDs Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.4.1 traditional NSAIDs vs placebo							
Aisen 2003a	118	2.3 (2.3)	111	2.2 (2.3)		21.28%	0.1[-0.5,0.7]
Subtotal ***	**118**		**111**			**21.28%**	**0.1[-0.5,0.7]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=0.33(P=0.74)							
3.4.2 Selective COX-2 inhibitor							
Aisen 2002a	21	0.7 (1.4)	19	0.2 (1.3)		10.94%	0.5[-0.33,1.33]
Aisen 2003a	122	2.2 (2.4)	111	2.2 (2.3)		20.75%	0[-0.6,0.6]
Reines 2004	303	1.7 (2.6)	319	1.8 (2.6)		47.04%	-0.1[-0.5,0.3]
Subtotal ***	**446**		**449**			**78.72%**	**0.01[-0.3,0.32]**
Heterogeneity: Tau²=0; Chi²=1.62, df=2(P=0.44); I²=0%							
Test for overall effect: Z=0.06(P=0.95)							
Total ***	**564**		**560**			**100%**	**0.03[-0.25,0.3]**
Heterogeneity: Tau²=0; Chi²=1.69, df=3(P=0.64); I²=0%							

Favours experimental -100 -50 0 50 100 Favours control

Study or subgroup	NSAIDs N	NSAIDs Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Test for overall effect: Z=0.21(P=0.84)							
Test for subgroup differences: Chi²=0.07, df=1 (P=0.79), I²=0%							

Favours experimental -100 -50 0 50 100 Favours control

Analysis 3.5. Comparison 3 NSAIDs vs. placebo, Outcome 5 NPI.

Study or subgroup	NSAIDs N	NSAIDs Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.5.1 traditional NSAIDs vs placebo							
Aisen 2003a	118	3.7 (12.5)	111	3.4 (11.9)		4.62%	0.3[-2.86,3.46]
De Jong 2008	19	3.2 (18.1)	19	9.4 (14)		0.44%	-6.2[-16.49,4.09]
Pasqualetti 2009	66	2.2 (2)	66	1.3 (2.2)		89.61%	0.9[0.18,1.62]
Subtotal ***	**203**		**196**			**94.66%**	**0.84[0.14,1.54]**
Heterogeneity: Tau²=0; Chi²=1.94, df=2(P=0.38); I²=0%							
Test for overall effect: Z=2.35(P=0.02)							
3.5.2 Selective COX-2 inhibitor							
Aisen 2003a	122	3.8 (10.9)	111	3.4 (11.9)		5.34%	0.4[-2.54,3.34]
Subtotal ***	**122**		**111**			**5.34%**	**0.4[-2.54,3.34]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.27(P=0.79)							
Total ***	**325**		**307**			**100%**	**0.81[0.14,1.49]**
Heterogeneity: Tau²=0; Chi²=2.02, df=3(P=0.57); I²=0%							
Test for overall effect: Z=2.35(P=0.02)							
Test for subgroup differences: Chi²=0.08, df=1 (P=0.78), I²=0%							

Favours experimental -100 -50 0 50 100 Favours control

Analysis 3.6. Comparison 3 NSAIDs vs. placebo, Outcome 6 Mood/depression.

Study or subgroup	NSAIDs N	NSAIDs Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
3.6.1 selective COX-2 inhibitor vs placebo							
Aisen 2002a	21	-0.2 (4.1)	19	1 (2.6)		100%	-0.34[-0.96,0.29]
Subtotal ***	**21**		**19**			**100%**	**-0.34[-0.96,0.29]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.06(P=0.29)							
Total ***	**21**		**19**			**100%**	**-0.34[-0.96,0.29]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.06(P=0.29)							

Favours experimental -100 -50 0 50 100 Favours control

Analysis 3.7. Comparison 3 NSAIDs vs. placebo, Outcome 7 Clinical global impression: GDS.

Study or subgroup	NSAIDs N	NSAIDs Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
3.7.1 traditional NSAIDs vs placebo							
Scharf 1999	17	0.4 (0.5)	14	0.6 (0.5)		100%	-0.43[-1.15,0.29]
Subtotal ***	**17**		**14**			**100%**	**-0.43[-1.15,0.29]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.17(P=0.24)							
Total ***	**17**		**14**			**100%**	**-0.43[-1.15,0.29]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.17(P=0.24)							

Favours experimental -100 -50 0 50 100 Favours control

Analysis 3.8. Comparison 3 NSAIDs vs. placebo, Outcome 8 Clinical global impression: CGIC and NOSGER 6 months.

Study or subgroup	NSAIDs N	NSAIDs Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
3.8.1 traditional NSAIDs vs placebo							
Scharf 1999	17	4.3 (0.7)	14	4.6 (0.5)		24.72%	-0.44[-1.16,0.27]
Subtotal ***	**17**		**14**			**24.72%**	**-0.44[-1.16,0.27]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.21(P=0.23)							
3.8.2 Selective COX-2 inhibitor							
Soininen 2007	275	3.9 (11.6)	135	3.3 (11.6)		75.28%	0.05[-0.16,0.26]
Subtotal ***	**275**		**135**			**75.28%**	**0.05[-0.16,0.26]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%							
Test for overall effect: Z=0.48(P=0.63)							
Total ***	**292**		**149**			**100%**	**-0.07[-0.49,0.35]**
Heterogeneity: Tau^2=0.05; Chi^2=1.68, df=1(P=0.2); I^2=40.35%							
Test for overall effect: Z=0.34(P=0.74)							
Test for subgroup differences: Chi^2=1.68, df=1 (P=0.2), I^2=40.35%							

Favours experimental -100 -50 0 50 100 Favours control

Analysis 3.9. Comparison 3 NSAIDs vs. placebo, Outcome 9 Behavioral disturbance.

Study or subgroup	NSAIDs N	NSAIDs Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
3.9.1 traditional NSAIDs vs placebo							
De Jong 2008	19	3.8 (6.7)	19	1.6 (4.2)		22.73%	0.39[-0.26,1.03]
Scharf 1999	17	-0.6 (3.9)	14	1.4 (3.9)		19.41%	-0.49[-1.21,0.23]
Subtotal ***	**36**		**33**			**42.14%**	**-0.03[-0.89,0.82]**
Heterogeneity: Tau^2=0.26; Chi^2=3.14, df=1(P=0.08); I^2=68.11%							
Test for overall effect: Z=0.08(P=0.94)							
3.9.2 Selective COX-2 inhibitor							

Favours experimental -100 -50 0 50 100 Favours control

Study or subgroup	NSAIDs N	NSAIDs Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Soininen 2007	275	1 (4.5)	135	0.3 (4.5)		57.86%	0.16[-0.04,0.37]
Subtotal ***	**275**		**135**			**57.86%**	**0.16[-0.04,0.37]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.54(P=0.12)							
Total ***	**311**		**168**			**100%**	**0.09[-0.29,0.46]**
Heterogeneity: Tau^2=0.05; Chi^2=3.51, df=2(P=0.17); I^2=43.08%							
Test for overall effect: Z=0.46(P=0.65)							
Test for subgroup differences: Chi^2=0.19, df=1 (P=0.66), I^2=0%							

Favours experimental -100 -50 0 50 100 Favours control

Analysis 3.10. Comparison 3 NSAIDs vs. placebo, Outcome 10 Activity of daily living.

Study or subgroup	NSAIDs N	NSAIDs Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
3.10.1 traditional NSAIDs vs placebo							
Aisen 2003a	118	8.7 (10.5)	56	11.5 (11.2)		13.78%	-0.26[-0.58,0.06]
De Jong 2008	19	19.4 (13.8)	19	18.2 (14.8)		8.42%	0.08[-0.55,0.72]
Pasqualetti 2009	66	0.5 (0.2)	66	0.7 (0.2)		12.98%	-0.99[-1.36,-0.63]
Scharf 1999	17	0.1 (3)	14	1.9 (2)		7.23%	-0.68[-1.41,0.05]
Subtotal ***	**220**		**155**			**42.42%**	**-0.48[-0.97,0.01]**
Heterogeneity: Tau^2=0.18; Chi^2=12.76, df=3(P=0.01); I^2=76.48%							
Test for overall effect: Z=1.93(P=0.05)							
3.10.2 Selective COX-2 inhibitor							
Aisen 2002a	21	-0.2 (1.4)	55	-0.3 (0.9)		10.46%	0.1[-0.41,0.6]
Aisen 2003a	122	8.3 (9.7)	111	11.5 (11.2)		14.88%	-0.31[-0.56,-0.05]
Reines 2004	315	7.9 (11.6)	328	8.1 (11.6)		16.49%	-0.02[-0.18,0.13]
Soininen 2007	275	1 (4.5)	135	0.3 (4.5)		15.75%	0.16[-0.04,0.37]
Subtotal ***	**733**		**629**			**57.58%**	**-0.03[-0.22,0.17]**
Heterogeneity: Tau^2=0.02; Chi^2=7.88, df=3(P=0.05); I^2=61.95%							
Test for overall effect: Z=0.25(P=0.8)							
Total ***	**953**		**784**			**100%**	**-0.22[-0.48,0.04]**
Heterogeneity: Tau^2=0.1; Chi^2=37.11, df=7(P<0.0001); I^2=81.14%							
Test for overall effect: Z=1.69(P=0.09)							
Test for subgroup differences: Chi^2=2.88, df=1 (P=0.09), I^2=65.25%							

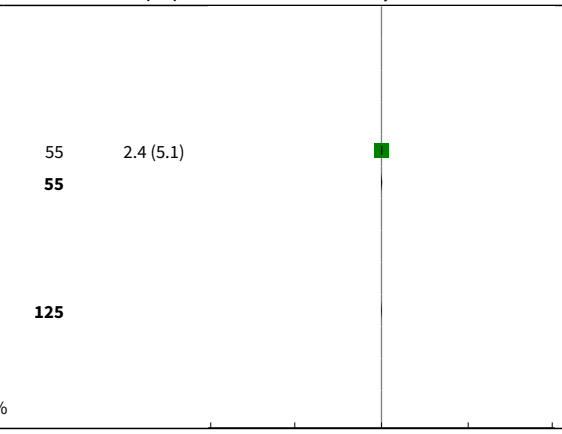
Favours experimental -100 -50 0 50 100 Favours control

Analysis 3.11. Comparison 3 NSAIDs vs. placebo, Outcome 11 Quality of life.

Study or subgroup	NSAIDs N	NSAIDs Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
3.11.1 traditional NSAIDs vs placebo							
Aisen 2003a	118	2.6 (5.5)	56	2.4 (5.1)		45.49%	0.04[-0.28,0.36]
Scharf 1999	17	0.5 (1.8)	14	0.2 (0.9)		9.14%	0.21[-0.5,0.92]
Subtotal ***	**135**		**70**			**54.63%**	**0.07[-0.22,0.36]**

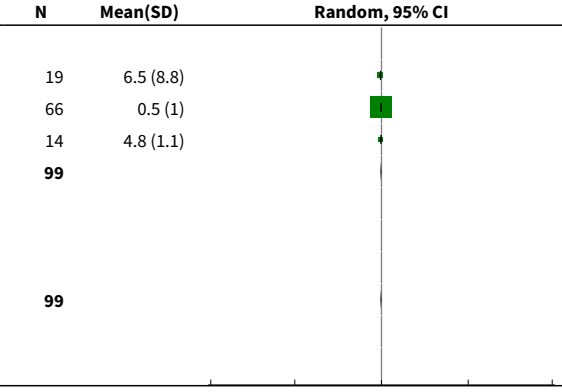
Favours experimental -100 -50 0 50 100 Favours control

Study or subgroup	NSAIDs N	NSAIDs Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Heterogeneity: Tau²=0; Chi²=0.19, df=1(P=0.66); I²=0%							
Test for overall effect: Z=0.44(P=0.66)							
3.11.2 Selective COX-2 inhibitor							
Aisen 2003a	122	2.9 (5.6)	55	2.4 (5.1)		45.37%	0.09[-0.23,0.41]
Subtotal ***	**122**		**55**			**45.37%**	**0.09[-0.23,0.41]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.56(P=0.57)							
Total ***	**257**		**125**			**100%**	**0.08[-0.14,0.29]**
Heterogeneity: Tau²=0; Chi²=0.2, df=2(P=0.9); I²=0%							
Test for overall effect: Z=0.71(P=0.48)							
Test for subgroup differences: Chi²=0.01, df=1 (P=0.91), I²=0%							



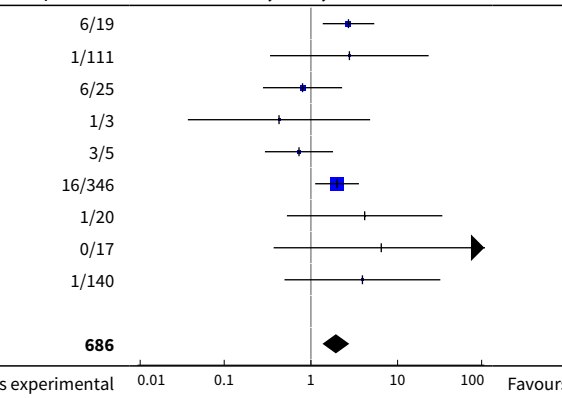
Analysis 3.12. Comparison 3 NSAIDs vs. placebo, Outcome 12 Caregiver burden.

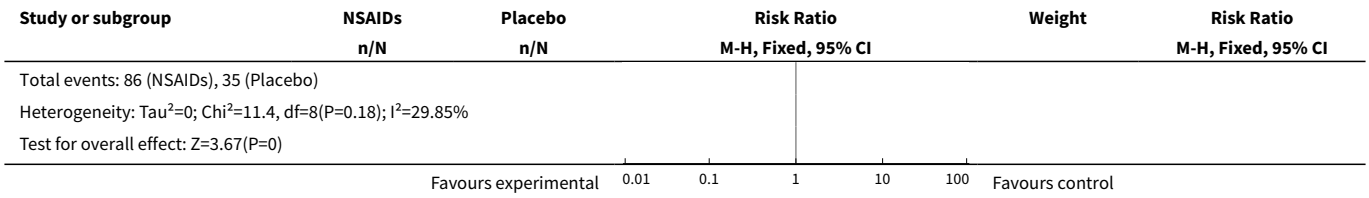
Study or subgroup	NSAIDs N	NSAIDs Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
3.12.1 traditional NSAIDs vs placebo							
De Jong 2008	19	1.4 (8.3)	19	6.5 (8.8)		18.41%	-0.58[-1.23,0.07]
Pasqualetti 2009	66	0.2 (1)	66	0.5 (1)		66.21%	-0.3[-0.64,0.04]
Scharf 1999	17	4.5 (1)	14	4.8 (1.1)		15.38%	-0.3[-1.02,0.41]
Subtotal ***	**102**		**99**			**100%**	**-0.35[-0.63,-0.07]**
Heterogeneity: Tau²=0; Chi²=0.6, df=2(P=0.74); I²=0%							
Test for overall effect: Z=2.47(P=0.01)							
Total ***	**102**		**99**			**100%**	**-0.35[-0.63,-0.07]**
Heterogeneity: Tau²=0; Chi²=0.6, df=2(P=0.74); I²=0%							
Test for overall effect: Z=2.47(P=0.01)							



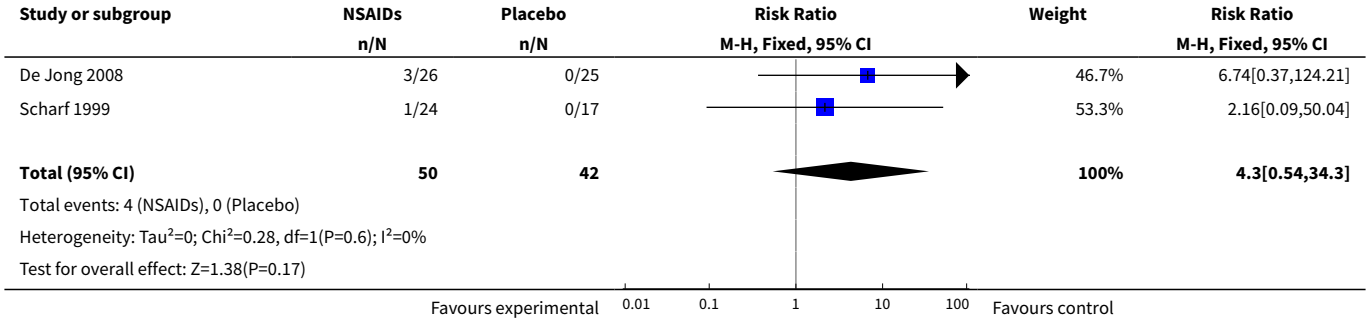
Analysis 3.13. Comparison 3 NSAIDs vs. placebo, Outcome 13 Gastrointestinal side effects.

Study or subgroup	NSAIDs n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aisen 2002a	18/21	6/19		16.25%	2.71[1.37,5.38]
Aisen 2003a	6/240	1/111		3.53%	2.78[0.34,22.78]
De Jong 2008	5/26	6/25		15.78%	0.8[0.28,2.29]
Hüll 1999	1/7	1/3		3.61%	0.43[0.04,4.82]
Jhee 2004	7/16	3/5		11.79%	0.73[0.29,1.8]
Reines 2004	32/346	16/346		41.27%	2[1.12,3.58]
Rogers 1993	5/24	1/20		2.81%	4.17[0.53,32.8]
Scharf 1999	4/24	0/17		1.5%	6.48[0.37,112.95]
Soininen 2007	8/285	1/140		3.46%	3.93[0.5,31.11]
Total (95% CI)	**989**	**686**		**100%**	**1.94[1.36,2.77]**

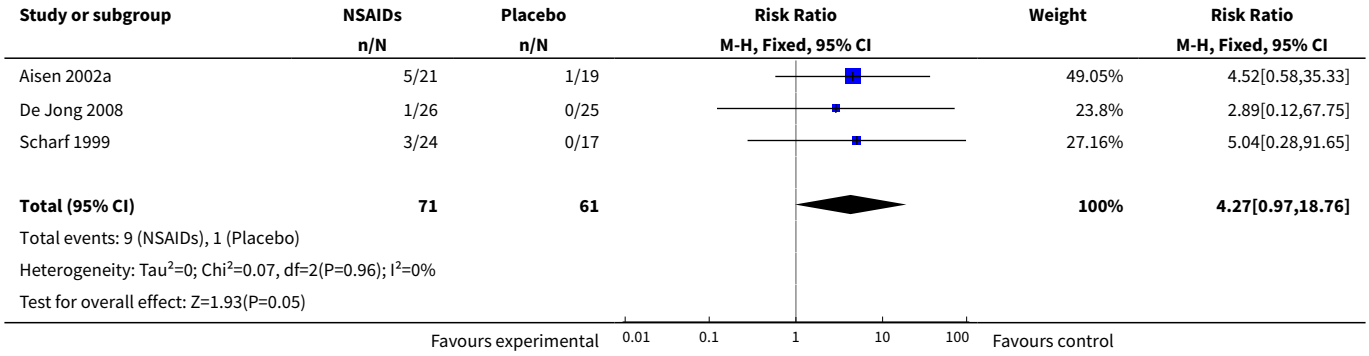




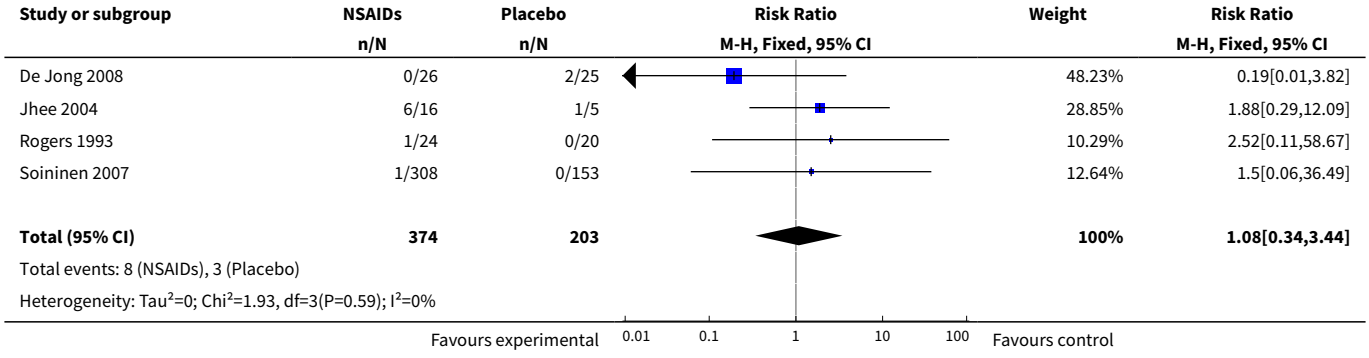
Analysis 3.14. Comparison 3 NSAIDs vs. placebo, Outcome 14 Elevated creatinine.

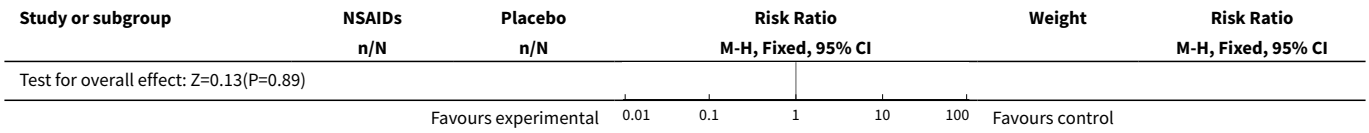


Analysis 3.15. Comparison 3 NSAIDs vs. placebo, Outcome 15 Elevated liver function test.

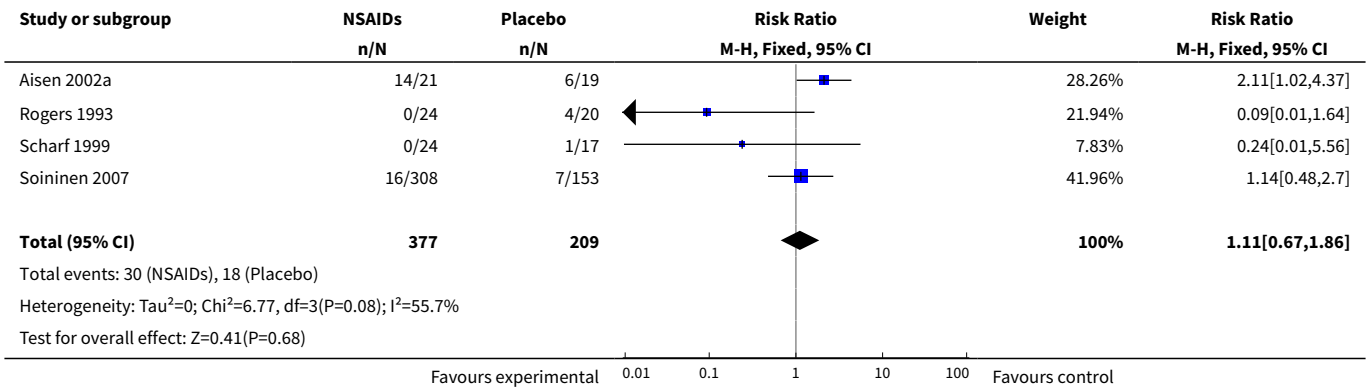


Analysis 3.16. Comparison 3 NSAIDs vs. placebo, Outcome 16 Headache.

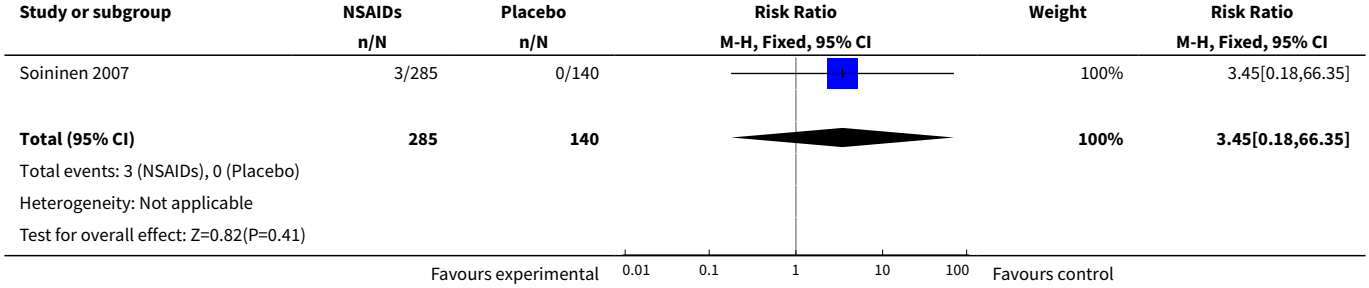




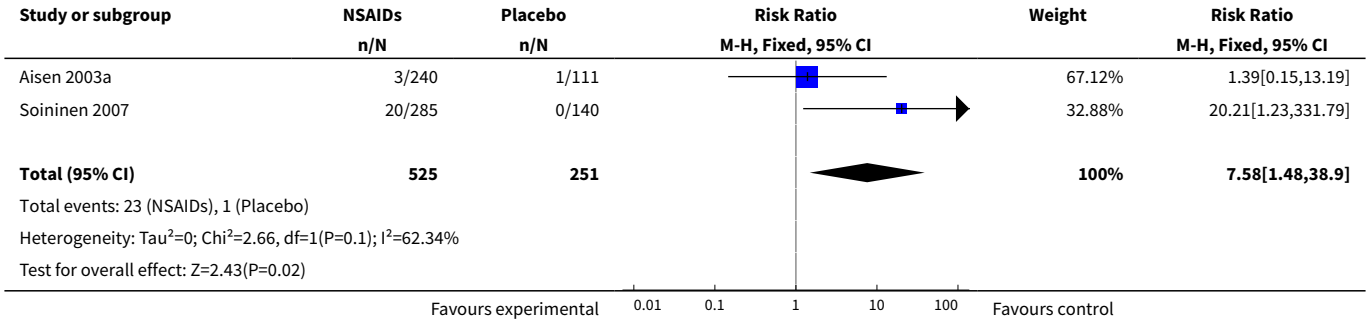
Analysis 3.17. Comparison 3 NSAIDs vs. placebo, Outcome 17 Psychiatric side effects.



Analysis 3.18. Comparison 3 NSAIDs vs. placebo, Outcome 18 Bleeding.



Analysis 3.19. Comparison 3 NSAIDs vs. placebo, Outcome 19 Heart disease.



Analysis 3.20. Comparison 3 NSAIDs vs. placebo, Outcome 20 Cerebrovascular side effects.

Study or subgroup	NSAIDs n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aisen 2003a	9/240	1/111		7.5%	4.16[0.53,32.45]
De Jong 2008	1/26	0/25		2.8%	2.89[0.12,67.75]
Reines 2004	4/346	11/346		60.37%	0.36[0.12,1.13]
Soininen 2007	12/308	4/153		29.33%	1.49[0.49,4.54]
Total (95% CI)	**920**	**635**		**100%**	**1.05[0.54,2.02]**
Total events: 26 (NSAIDs), 16 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=5.86, df=3(P=0.12); I^2=48.78%					
Test for overall effect: Z=0.15(P=0.88)					

Analysis 3.21. Comparison 3 NSAIDs vs. placebo, Outcome 21 Hypertension.

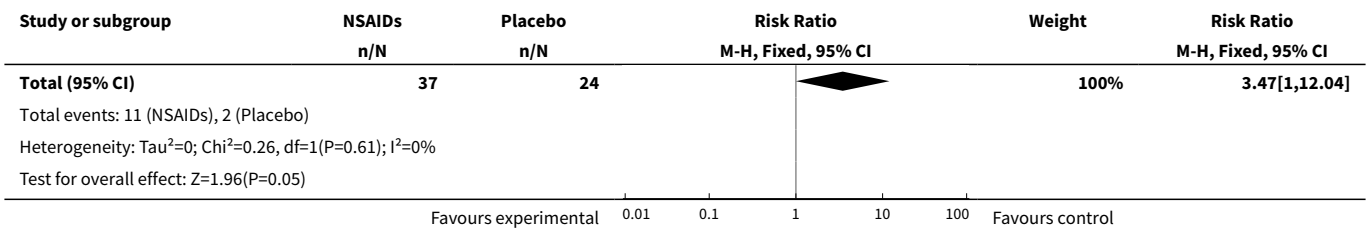
Study or subgroup	NSAIDs n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aisen 2003a	15/240	0/111		25.08%	14.41[0.87,238.63]
De Jong 2008	5/26	2/25		74.92%	2.4[0.51,11.27]
Total (95% CI)	**266**	**136**		**100%**	**5.41[1.36,21.6]**
Total events: 20 (NSAIDs), 2 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.53, df=1(P=0.22); I^2=34.54%					
Test for overall effect: Z=2.39(P=0.02)					

Analysis 3.22. Comparison 3 NSAIDs vs. placebo, Outcome 22 Hyperglycemia.

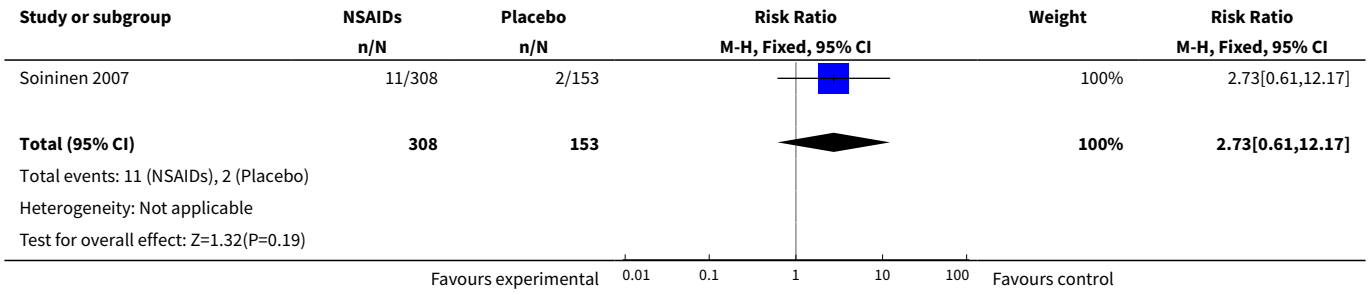
Study or subgroup	NSAIDs n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
De Jong 2008	2/26	1/25		100%	1.92[0.19,19.9]
Total (95% CI)	**26**	**25**		**100%**	**1.92[0.19,19.9]**
Total events: 2 (NSAIDs), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.55(P=0.58)					

Analysis 3.23. Comparison 3 NSAIDs vs. placebo, Outcome 23 Rash.

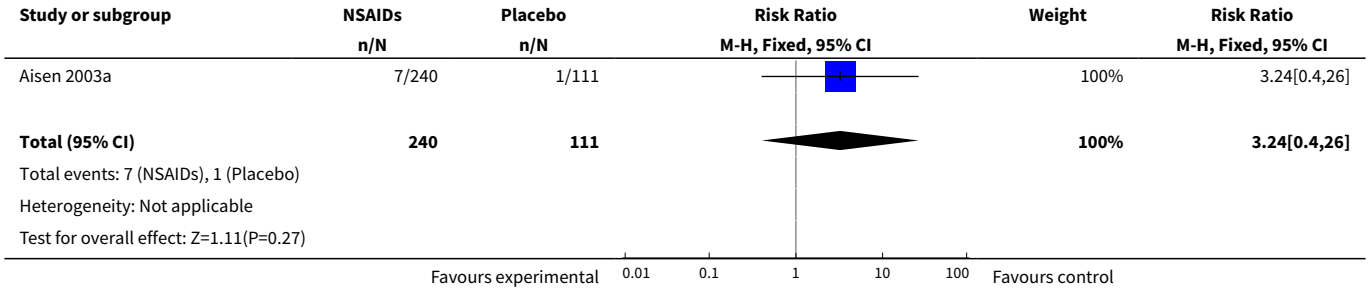
Study or subgroup	NSAIDs n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aisen 2002a	9/21	2/19		73.97%	4.07[1,16.52]
Jhee 2004	2/16	0/5		26.03%	1.76[0.1,31.76]



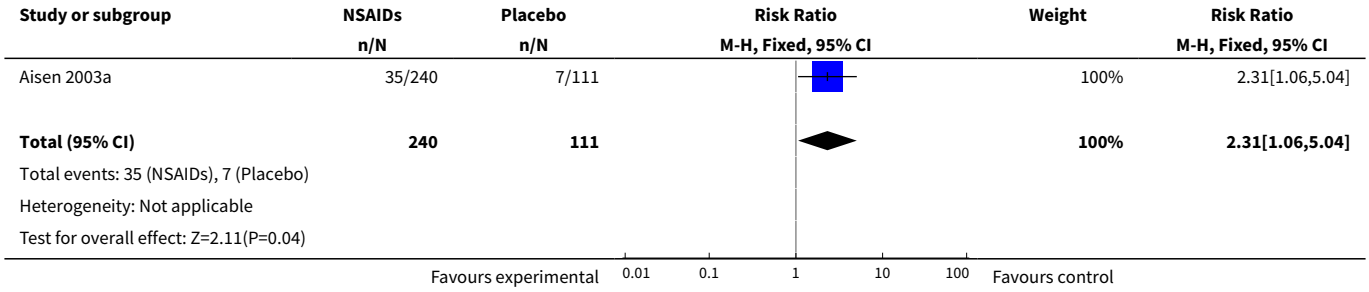
Analysis 3.24. Comparison 3 NSAIDs vs. placebo, Outcome 24 Respiratory side effects.



Analysis 3.25. Comparison 3 NSAIDs vs. placebo, Outcome 25 Dry mouth.



Analysis 3.26. Comparison 3 NSAIDs vs. placebo, Outcome 26 Fatigue.



Analysis 3.27. Comparison 3 NSAIDs vs. placebo, Outcome 27 Dizziness.

Study or subgroup	NSAIDs n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aisen 2003a	28/240	5/111		72.89%	2.59[1.03,6.53]
De Jong 2008	3/26	1/25		10.87%	2.88[0.32,25.92]
Jhee 2004	4/16	1/5		16.24%	1.25[0.18,8.77]
Total (95% CI)	**282**	**141**		**100%**	**2.4[1.1,5.25]**
Total events: 35 (NSAIDs), 7 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.48, df=2(P=0.78); I^2=0%					
Test for overall effect: Z=2.2(P=0.03)					

Favours experimental — Favours control

Analysis 3.28. Comparison 3 NSAIDs vs. placebo, Outcome 28 Abnormal labs other than Cr. and LFT.

Study or subgroup	NSAIDs n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Scharf 1999	1/24	0/17		30.24%	2.16[0.09,50.04]
Soininen 2007	2/285	1/140		69.76%	0.98[0.09,10.74]
Total (95% CI)	**309**	**157**		**100%**	**1.34[0.21,8.69]**
Total events: 3 (NSAIDs), 1 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.15, df=1(P=0.7); I^2=0%					
Test for overall effect: Z=0.31(P=0.76)					

Favours experimental — Favours control

Analysis 3.29. Comparison 3 NSAIDs vs. placebo, Outcome 29 Withdrawal due to side effects.

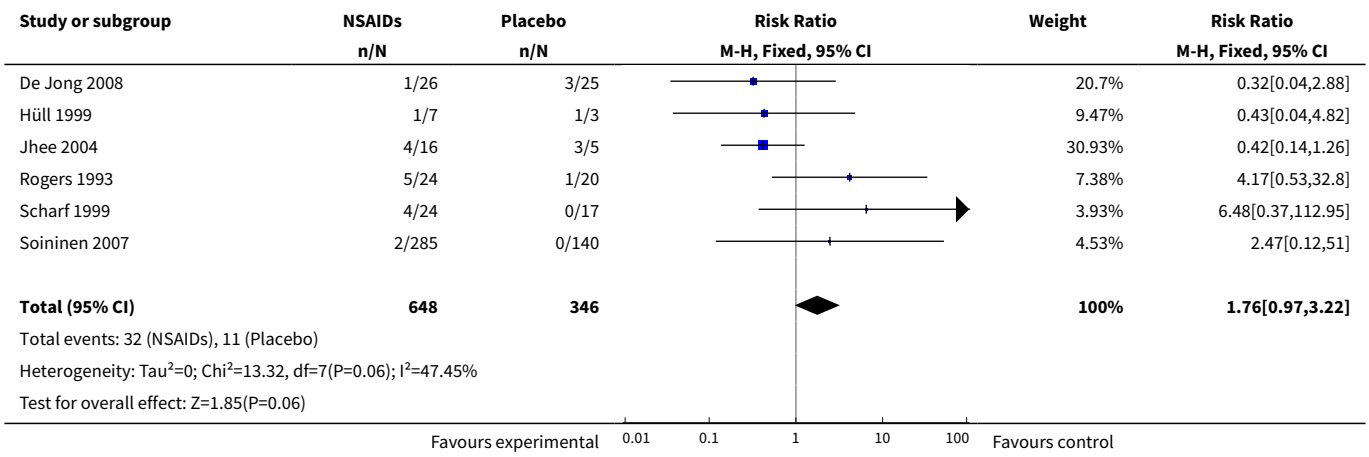
Study or subgroup	NSAIDs n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aisen 2002a	1/21	1/19		1.66%	0.9[0.06,13.48]
Aisen 2003a	46/240	20/111		43.14%	1.06[0.66,1.71]
Reines 2004	47/346	35/346		55.2%	1.34[0.89,2.03]
Total (95% CI)	**607**	**476**		**100%**	**1.22[0.89,1.65]**
Total events: 94 (NSAIDs), 56 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.57, df=2(P=0.75); I^2=0%					
Test for overall effect: Z=1.24(P=0.22)					

Favours experimental — Favours control

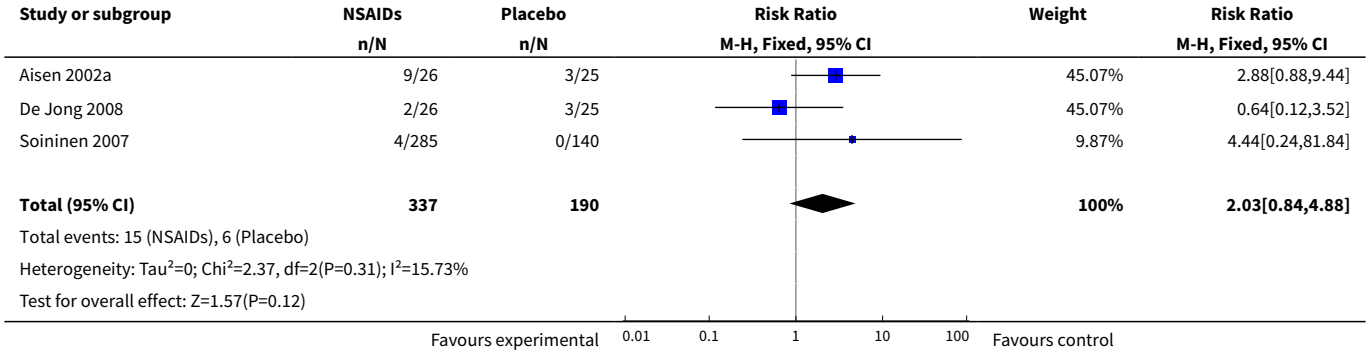
Analysis 3.30. Comparison 3 NSAIDs vs. placebo, Outcome 30 Abdominal pain or dyspepsia.

Study or subgroup	NSAIDs n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aisen 2002a	9/26	2/25		13.8%	4.33[1.04,18.09]
Aisen 2003a	6/240	1/111		9.25%	2.78[0.34,22.78]

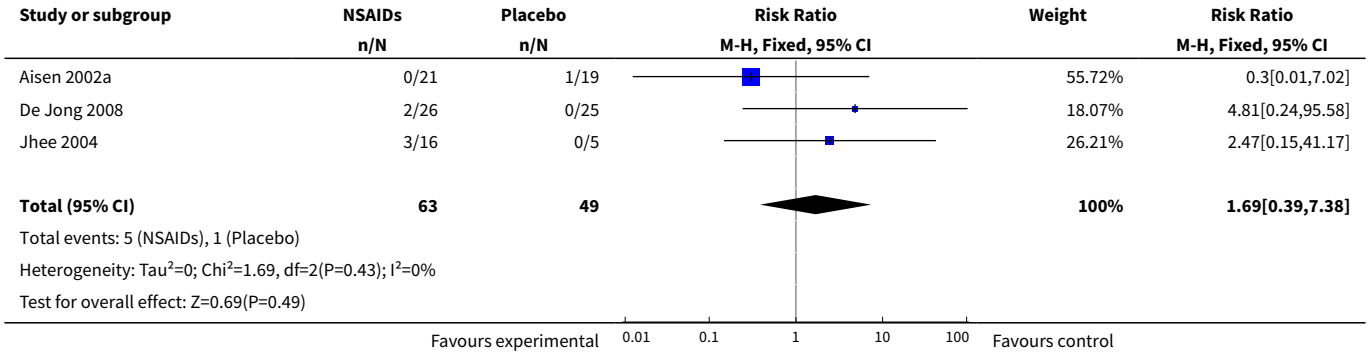
Favours experimental — Favours control



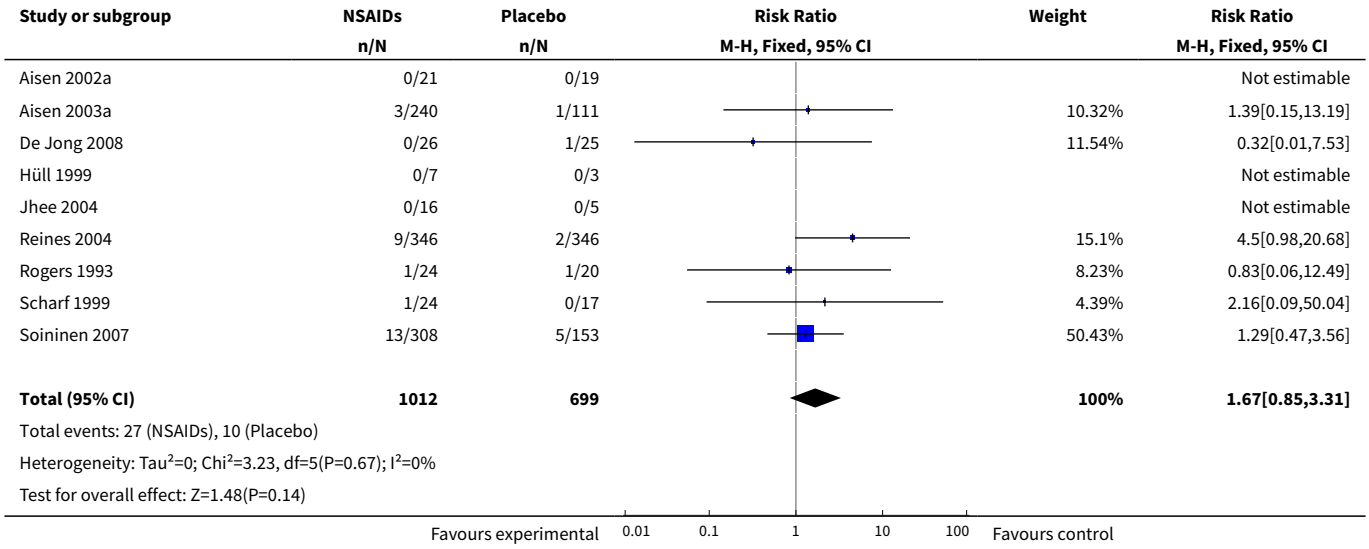
Analysis 3.31. Comparison 3 NSAIDs vs. placebo, Outcome 31 Constipation or diarrhea.



Analysis 3.32. Comparison 3 NSAIDs vs. placebo, Outcome 32 Nausea or vomiting.



Analysis 3.33. Comparison 3 NSAIDs vs. placebo, Outcome 33 Death.

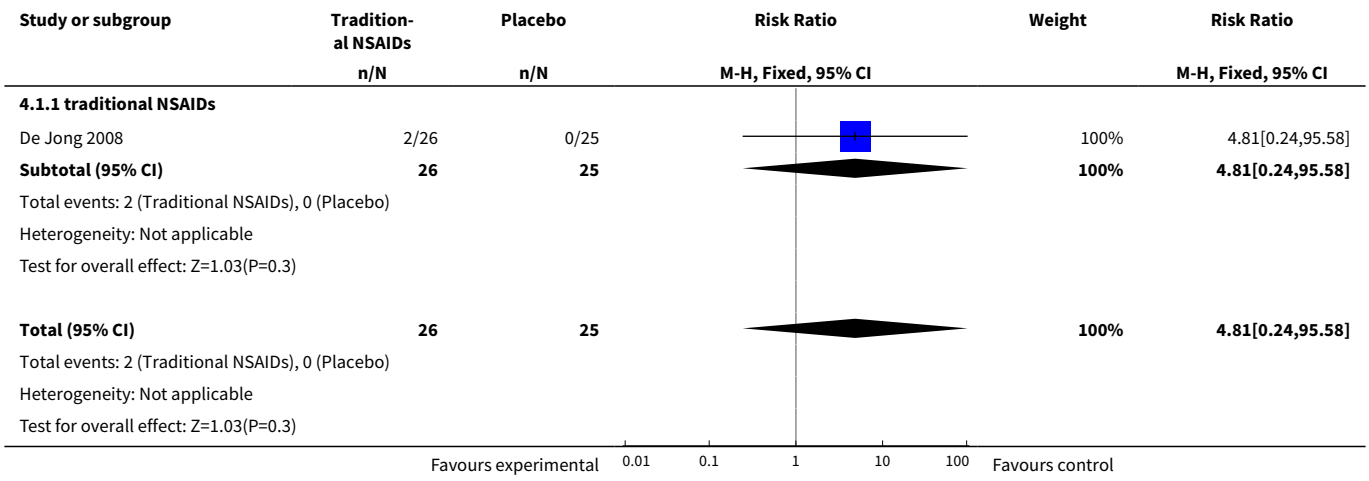


Comparison 4. Traditional NSAIDs vs. placebo

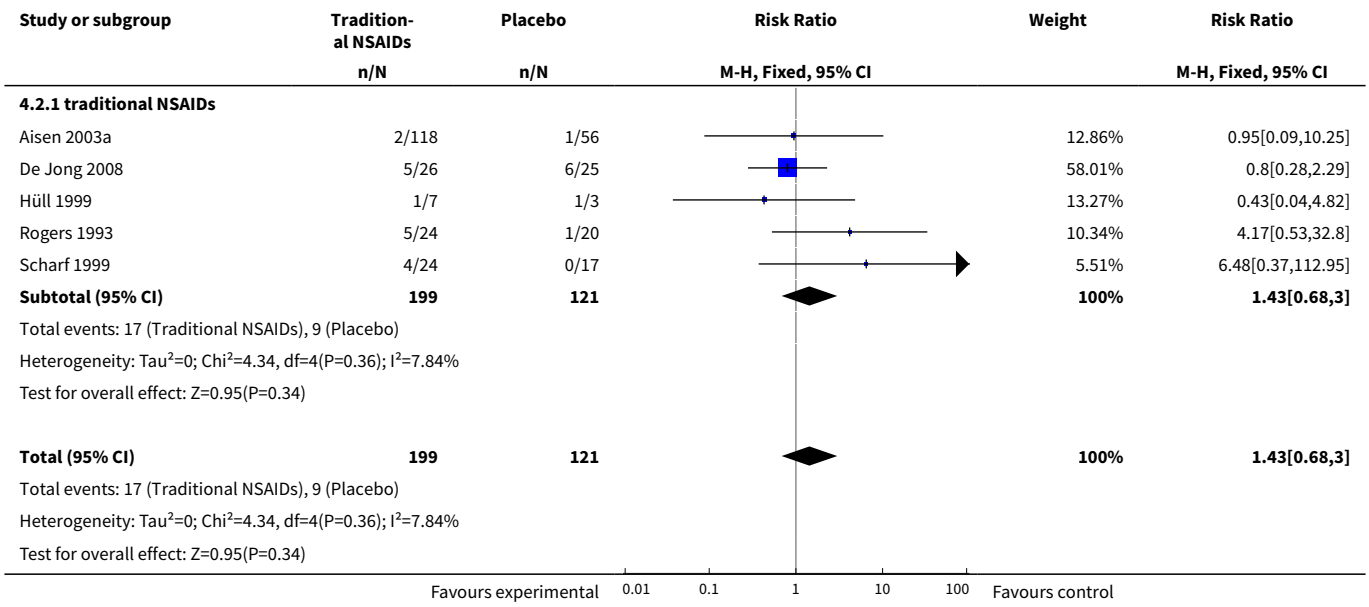
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Nausea or vomiting	1	51	Risk Ratio (M-H, Fixed, 95% CI)	4.81 [0.24, 95.58]
1.1 traditional NSAIDs	1	51	Risk Ratio (M-H, Fixed, 95% CI)	4.81 [0.24, 95.58]
2 Gastrointestinal side effects	5	320	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.68, 3.00]
2.1 traditional NSAIDs	5	320	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.68, 3.00]
3 Elevated creatinine	2	92	Risk Ratio (M-H, Fixed, 95% CI)	4.30 [0.54, 34.30]
3.1 traditional NSAIDs	2	92	Risk Ratio (M-H, Fixed, 95% CI)	4.30 [0.54, 34.30]
4 Elevated liver function test	2	92	Risk Ratio (M-H, Fixed, 95% CI)	4.04 [0.48, 33.98]
4.1 traditional NSAIDs	2	92	Risk Ratio (M-H, Fixed, 95% CI)	4.04 [0.48, 33.98]
5 Hypertension	2	225	Risk Ratio (M-H, Fixed, 95% CI)	3.36 [0.84, 13.34]
5.1 traditional NSAIDs	2	225	Risk Ratio (M-H, Fixed, 95% CI)	3.36 [0.84, 13.34]
6 Headache	2	95	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.10, 3.62]
6.1 traditional NSAIDs	2	95	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.10, 3.62]
7 Psychiatric side effects	2	85	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.02, 1.07]
7.1 traditional NSAIDs	2	85	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.02, 1.07]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Heart disease	1	174	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.01, 3.86]
8.1 traditional NSAIDs	1	174	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.01, 3.86]
9 Cerebrovascular side effects	2	225	Risk Ratio (M-H, Fixed, 95% CI)	2.51 [0.43, 14.63]
9.1 traditional NSAIDs	2	225	Risk Ratio (M-H, Fixed, 95% CI)	2.51 [0.43, 14.63]
10 Hyperglycemia	1	51	Risk Ratio (M-H, Fixed, 95% CI)	1.92 [0.19, 19.90]
10.1 traditional NSAIDs	1	51	Risk Ratio (M-H, Fixed, 95% CI)	1.92 [0.19, 19.90]
11 Dry mouth	1	174	Risk Ratio (M-H, Fixed, 95% CI)	2.85 [0.35, 23.09]
11.1 traditional NSAIDs	1	174	Risk Ratio (M-H, Fixed, 95% CI)	2.85 [0.35, 23.09]
12 Fatigue	1	174	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.51, 2.62]
12.1 traditional NSAIDs	1	174	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.51, 2.62]
13 Dizziness	2	225	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.64, 3.69]
13.1 traditional NSAIDs	2	225	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.64, 3.69]
14 Abnormal labs other than Cr. and LFT	1	41	Risk Ratio (M-H, Fixed, 95% CI)	2.16 [0.09, 50.04]
14.1 traditional NSAIDs	1	41	Risk Ratio (M-H, Fixed, 95% CI)	2.16 [0.09, 50.04]
15 Death	5	320	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.18, 2.87]
15.1 traditional NSAIDs	5	320	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.18, 2.87]
16 Withdrawal due to side effects	1	174	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.30, 0.84]
16.1 traditional NSAIDs	1	174	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.30, 0.84]
17 Abdominal pain or dyspepsia	5	320	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.61, 3.68]
17.1 traditional NSAIDs	5	320	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.61, 3.68]
18 Constipation or diarrhea	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.12, 3.52]
18.1 traditional NSAIDs	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.12, 3.52]

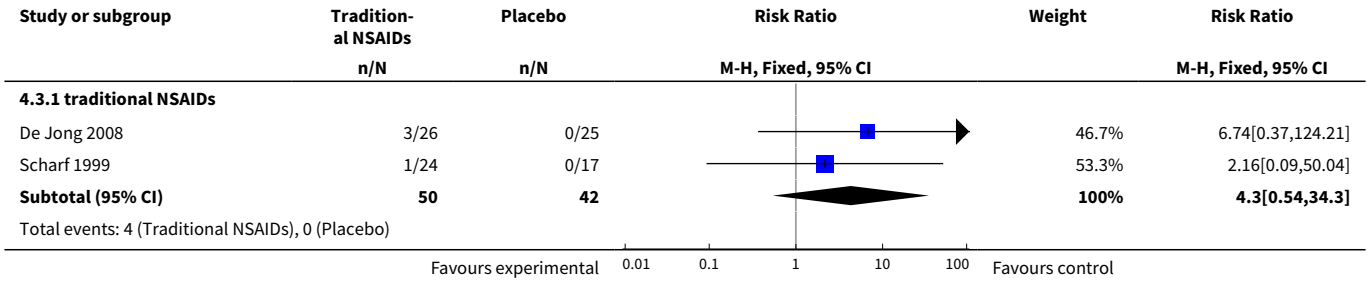
Analysis 4.1. Comparison 4 Traditional NSAIDs vs. placebo, Outcome 1 Nausea or vomiting.

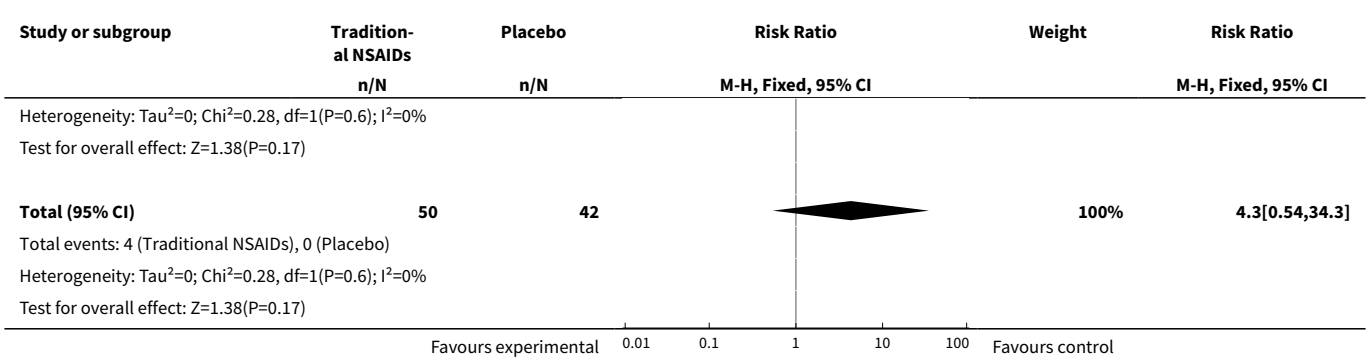


Analysis 4.2. Comparison 4 Traditional NSAIDs vs. placebo, Outcome 2 Gastrointestinal side effects.

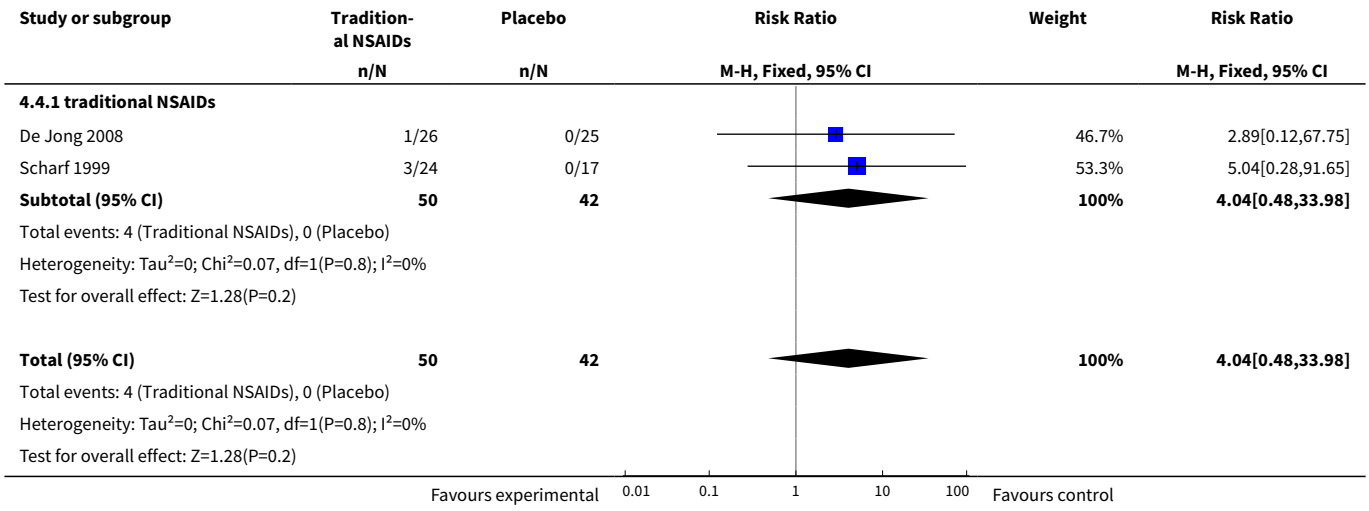


Analysis 4.3. Comparison 4 Traditional NSAIDs vs. placebo, Outcome 3 Elevated creatinine.

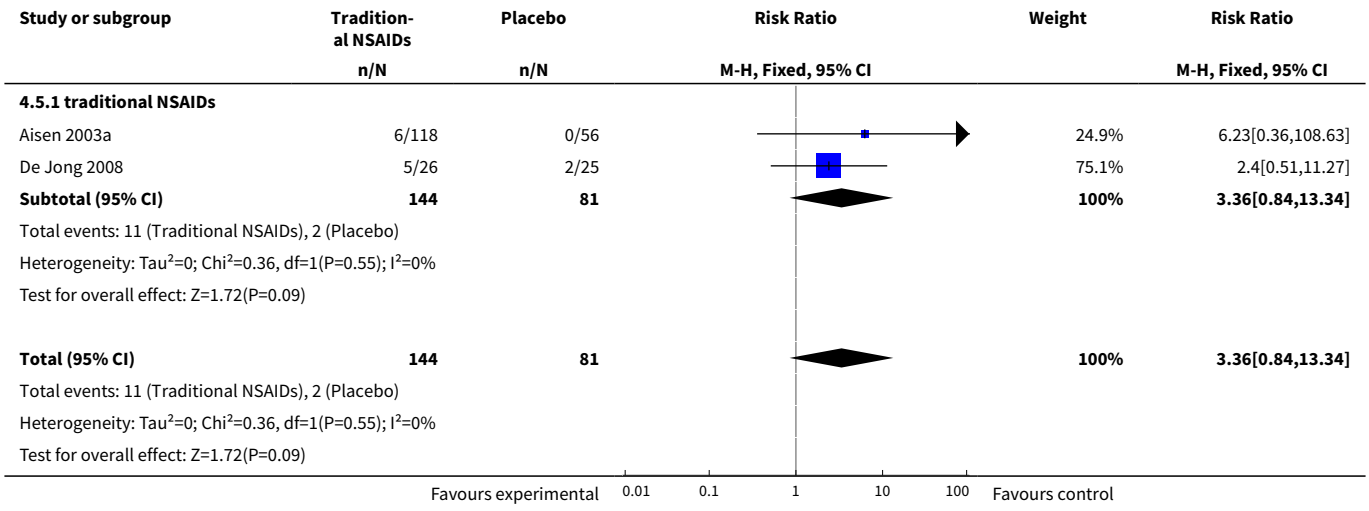




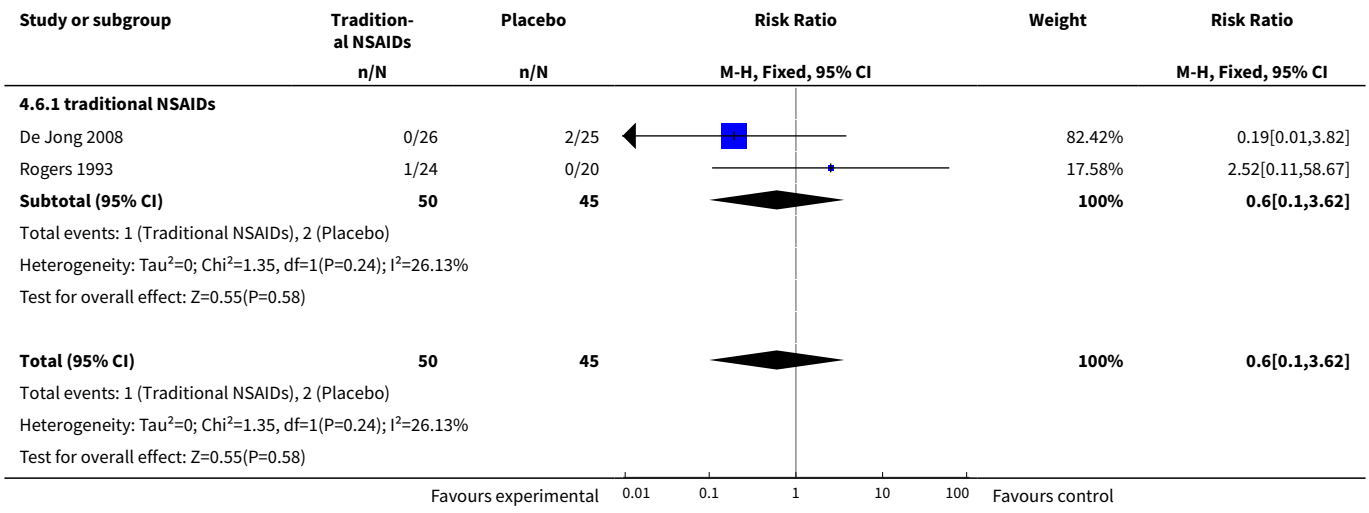
Analysis 4.4. Comparison 4 Traditional NSAIDs vs. placebo, Outcome 4 Elevated liver function test.



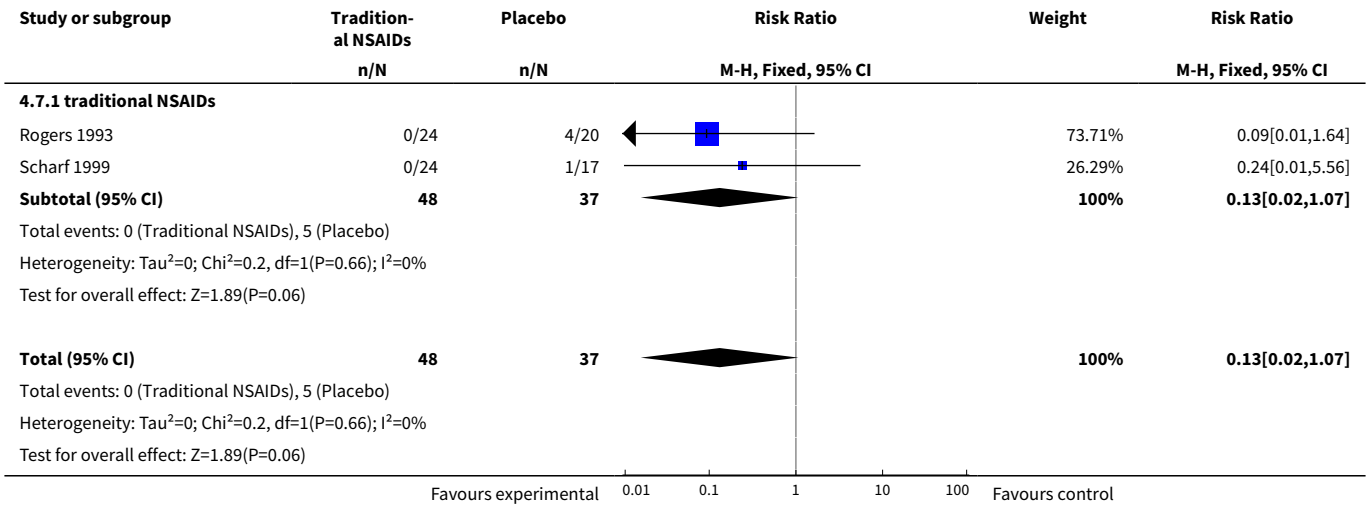
Analysis 4.5. Comparison 4 Traditional NSAIDs vs. placebo, Outcome 5 Hypertension.



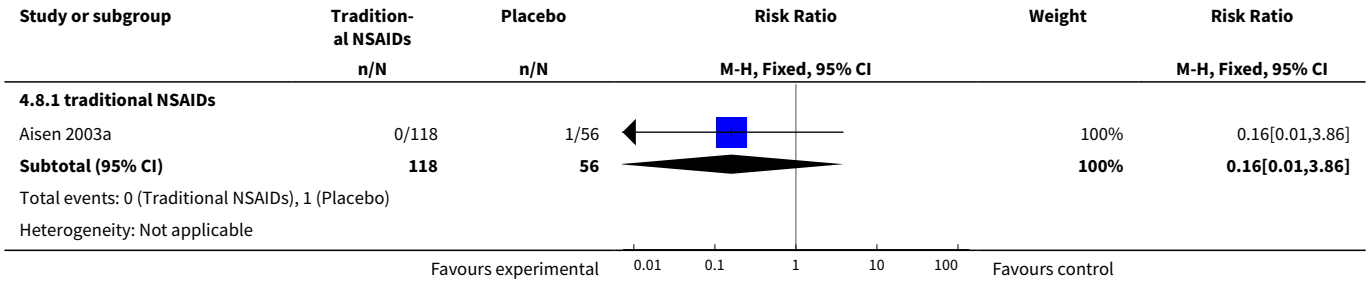
Analysis 4.6. Comparison 4 Traditional NSAIDs vs. placebo, Outcome 6 Headache.

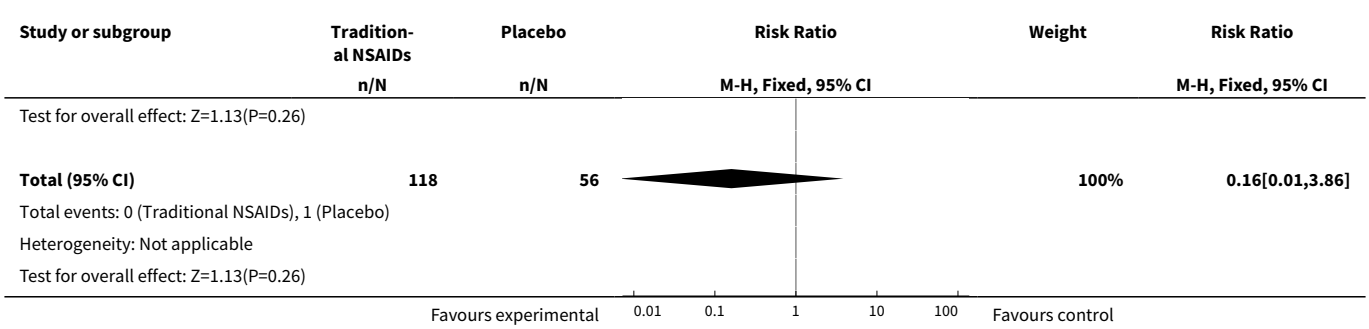


Analysis 4.7. Comparison 4 Traditional NSAIDs vs. placebo, Outcome 7 Psychiatric side effects.

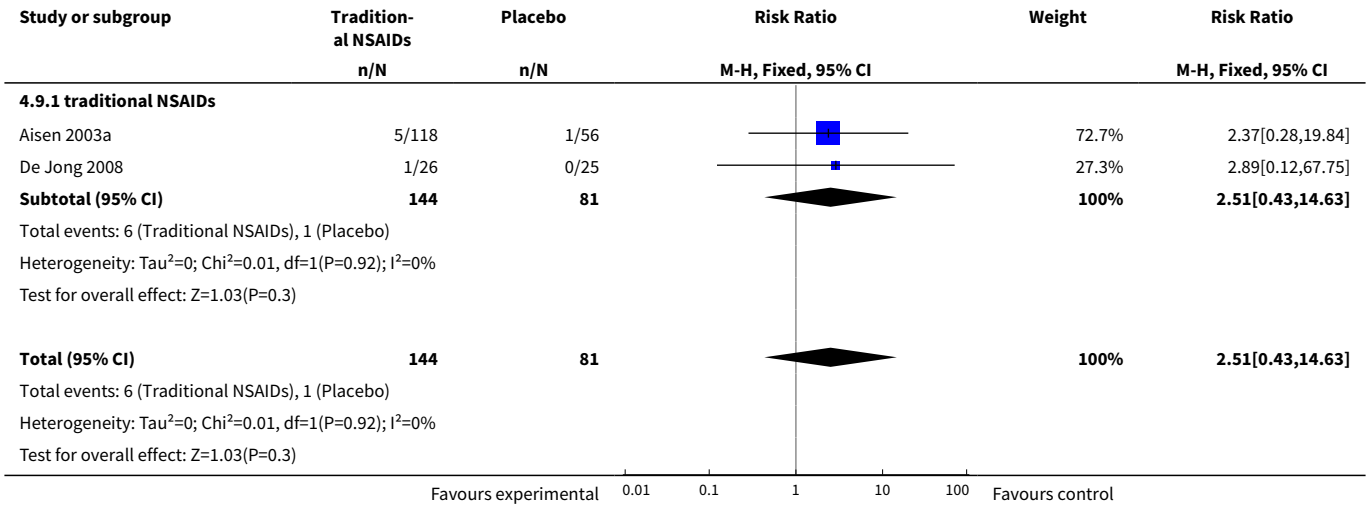


Analysis 4.8. Comparison 4 Traditional NSAIDs vs. placebo, Outcome 8 Heart disease.

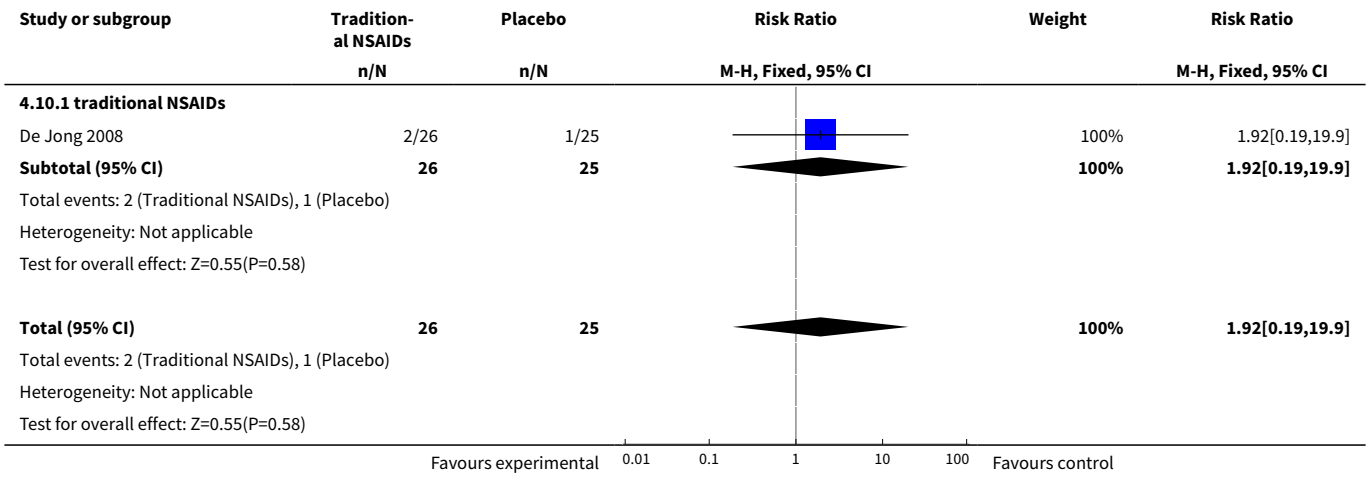




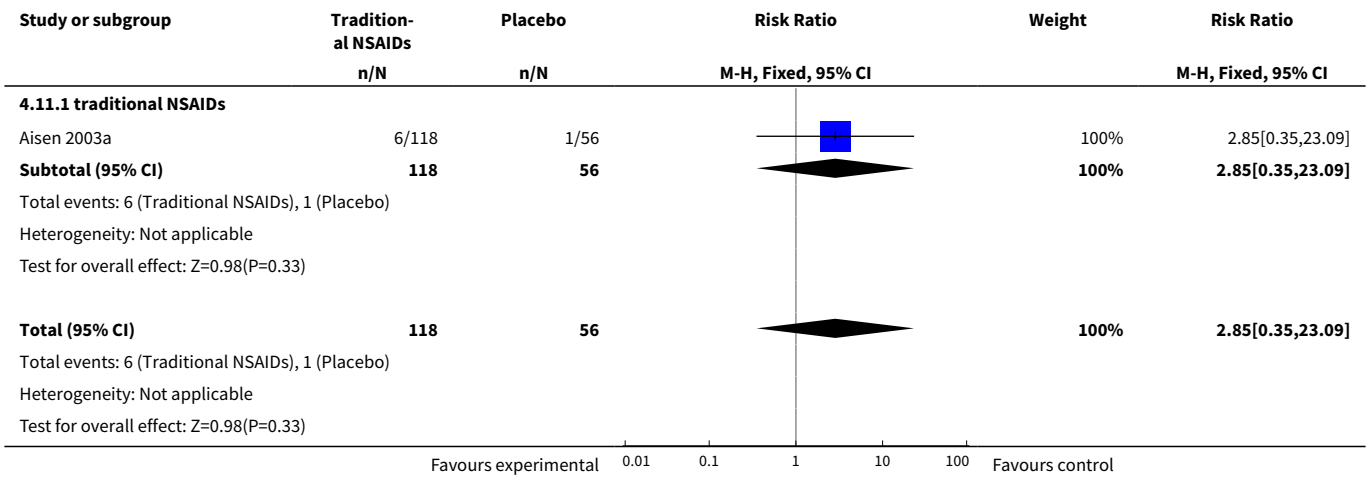
Analysis 4.9. Comparison 4 Traditional NSAIDs vs. placebo, Outcome 9 Cerebrovascular side effects.



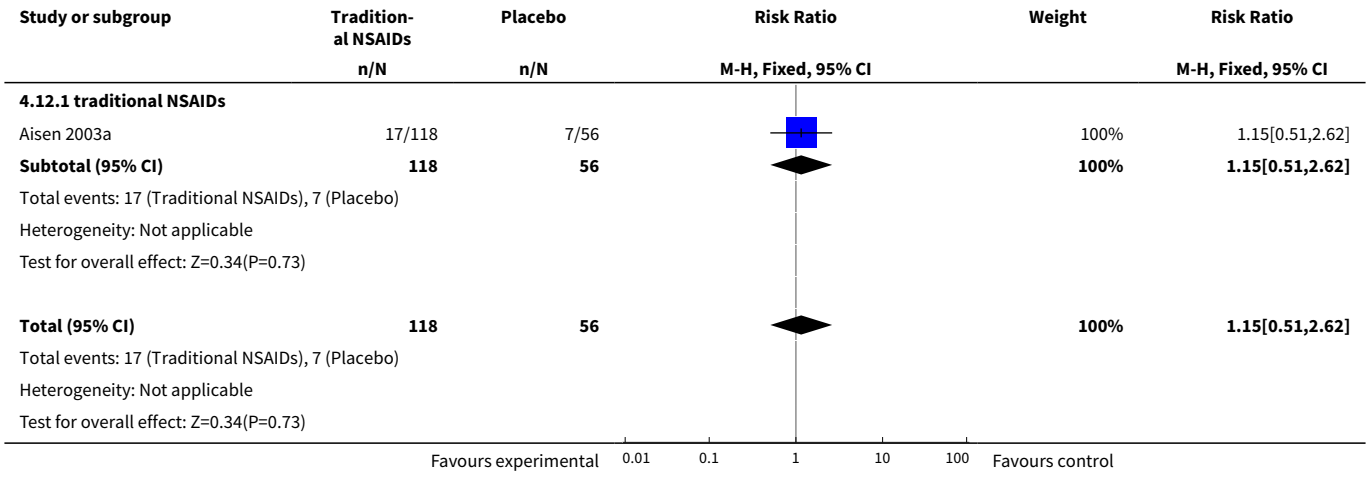
Analysis 4.10. Comparison 4 Traditional NSAIDs vs. placebo, Outcome 10 Hyperglycemia.



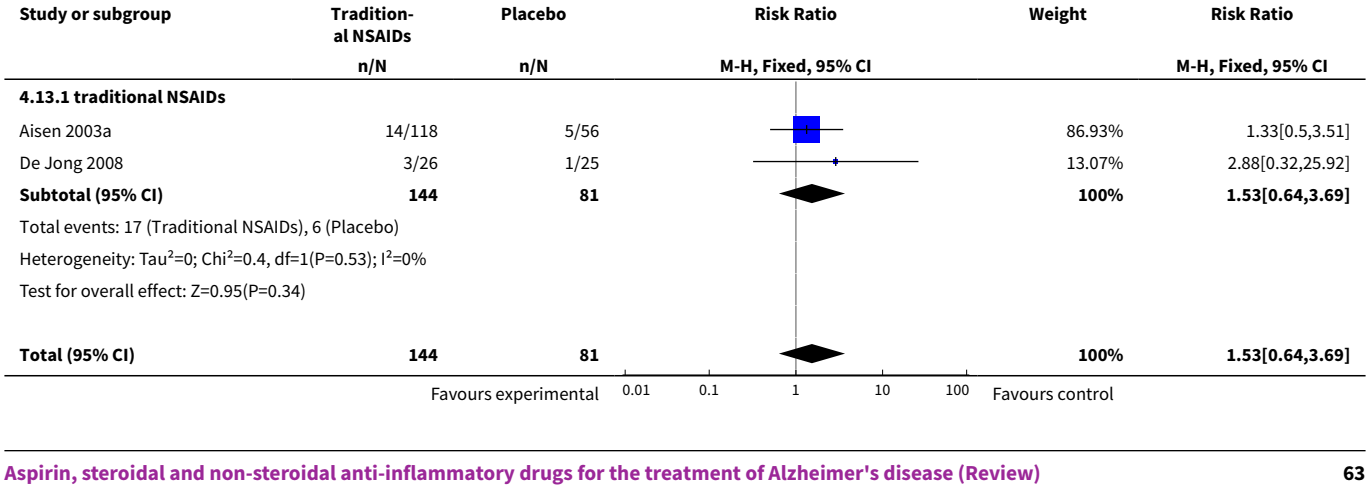
Analysis 4.11. Comparison 4 Traditional NSAIDs vs. placebo, Outcome 11 Dry mouth.

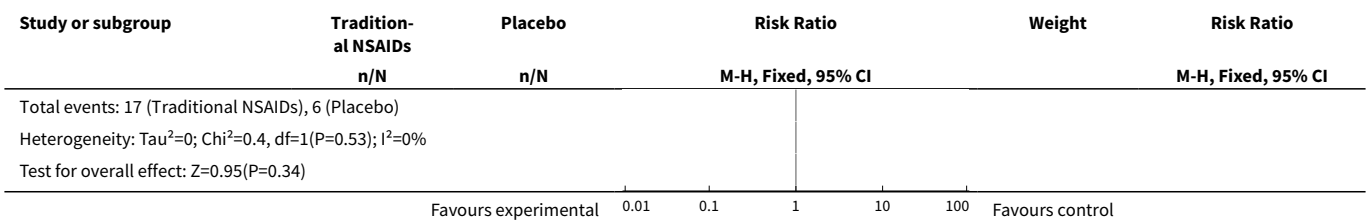


Analysis 4.12. Comparison 4 Traditional NSAIDs vs. placebo, Outcome 12 Fatigue.

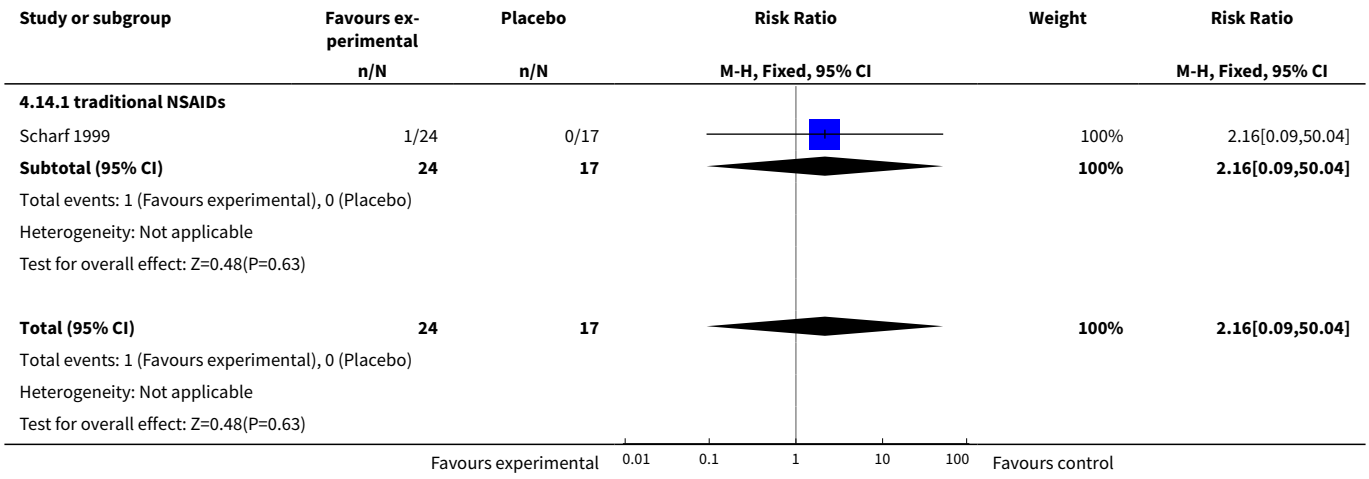


Analysis 4.13. Comparison 4 Traditional NSAIDs vs. placebo, Outcome 13 Dizziness.

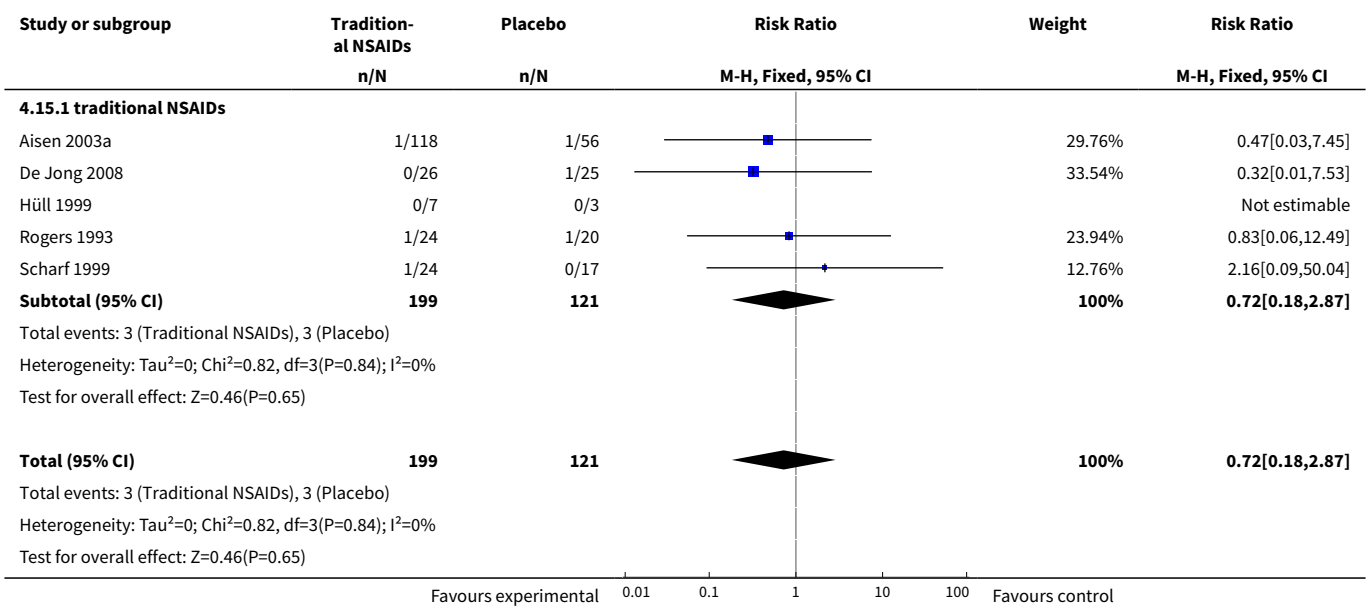




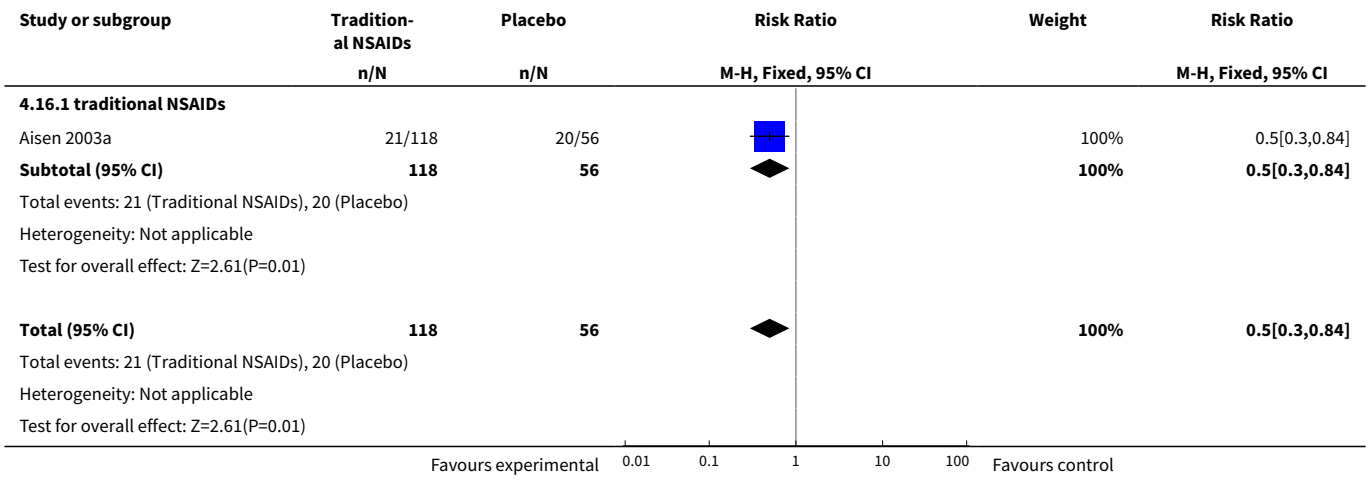
Analysis 4.14. Comparison 4 Traditional NSAIDs vs. placebo, Outcome 14 Abnormal labs other than Cr. and LFT.



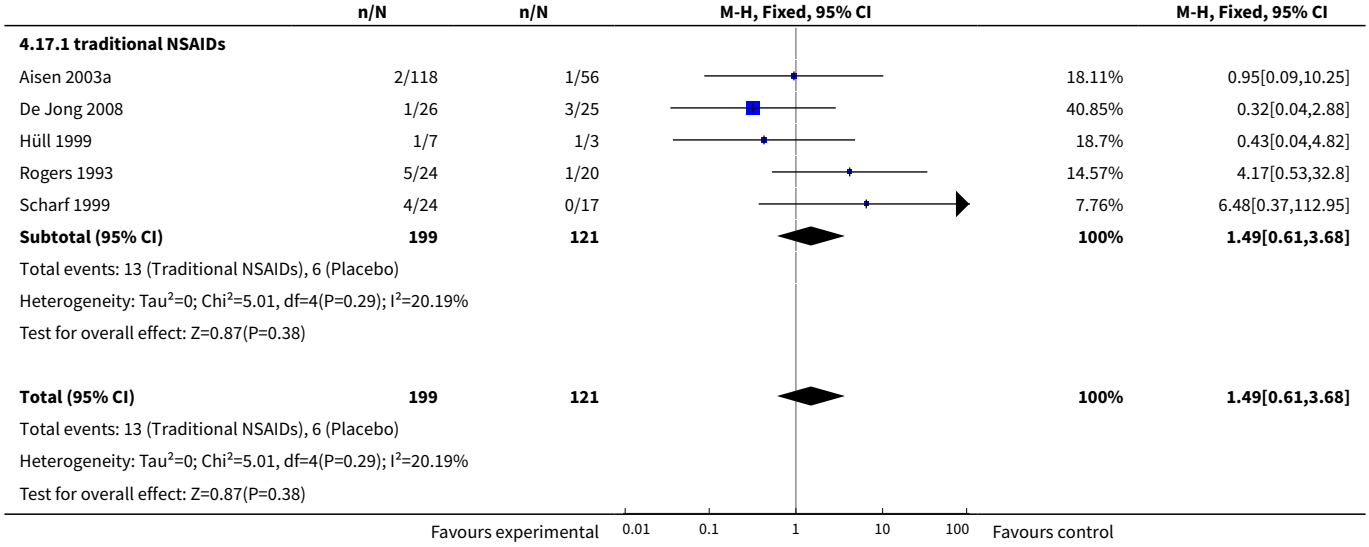
Analysis 4.15. Comparison 4 Traditional NSAIDs vs. placebo, Outcome 15 Death.



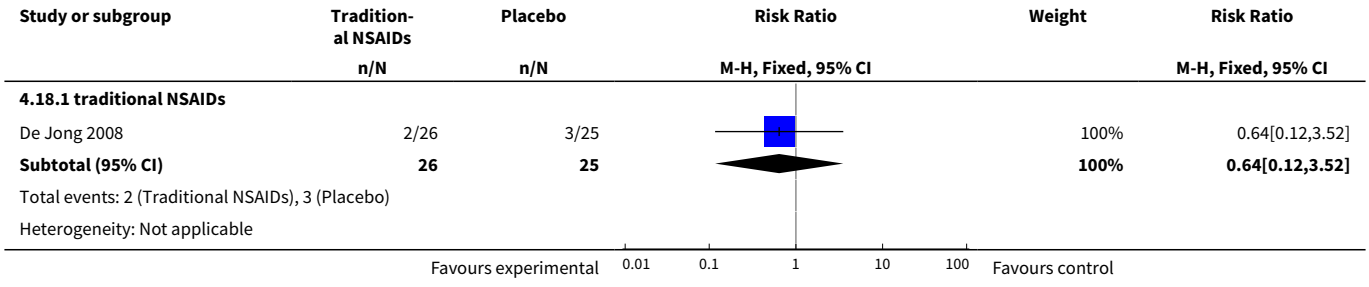
Analysis 4.16. Comparison 4 Traditional NSAIDs vs. placebo, Outcome 16 Withdrawal due to side effects.

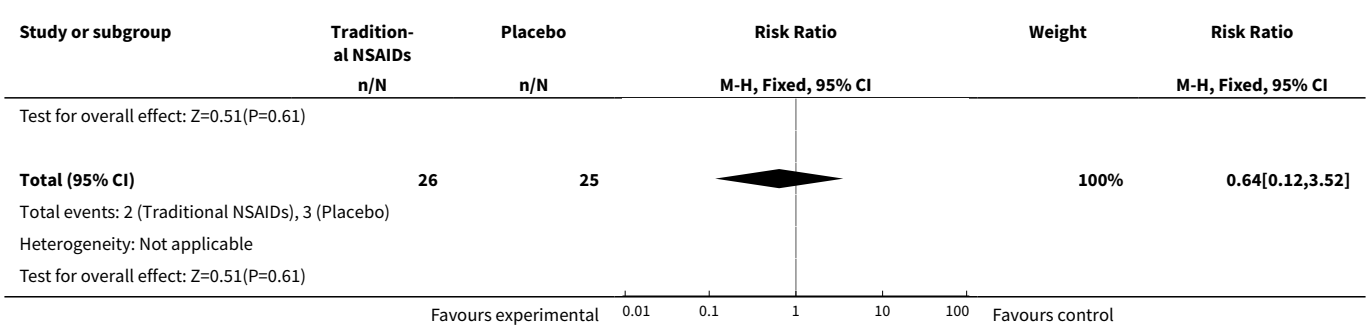


Analysis 4.17. Comparison 4 Traditional NSAIDs vs. placebo, Outcome 17 Abdominal pain or dyspepsia.



Analysis 4.18. Comparison 4 Traditional NSAIDs vs. placebo, Outcome 18 Constipation or diarrhea.





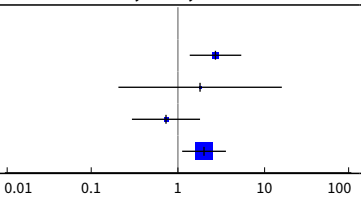
Comparison 5. Selective COX-2 inhibitor vs. placebo

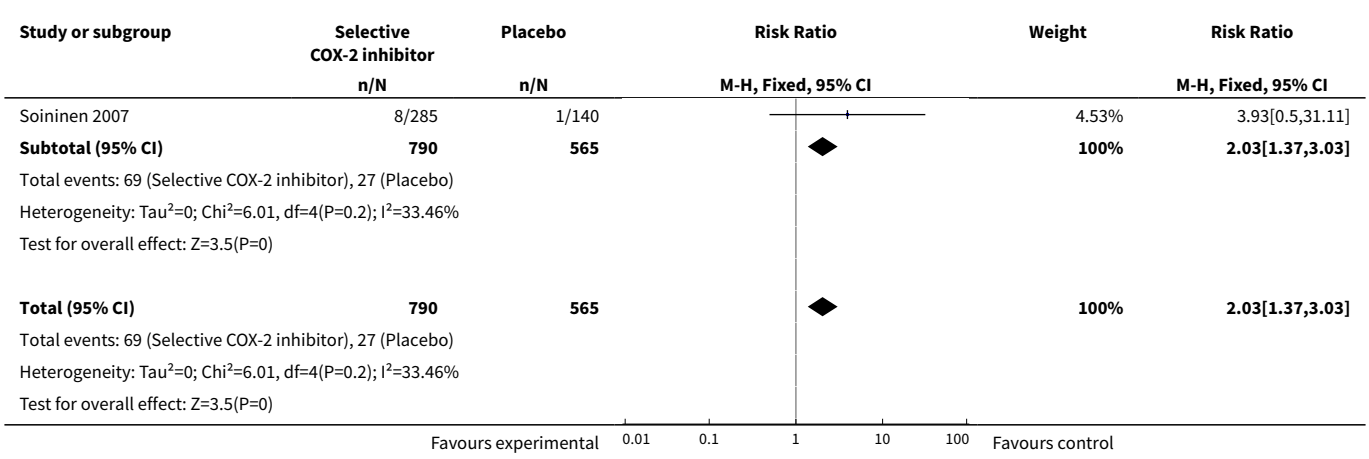
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Gastrointestinal side effects	5	1355	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [1.37, 3.03]
1.1 Selective COX-2 inhibitor	5	1355	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [1.37, 3.03]
2 Hypertension	1	177	Risk Ratio (M-H, Fixed, 95% CI)	8.65 [0.51, 146.03]
2.1 Selective COX-2 inhibitor	1	177	Risk Ratio (M-H, Fixed, 95% CI)	8.65 [0.51, 146.03]
3 Heart disease	2	602	Risk Ratio (M-H, Fixed, 95% CI)	7.52 [1.47, 38.41]
3.1 Selective COX-2 inhibitor	2	602	Risk Ratio (M-H, Fixed, 95% CI)	7.52 [1.47, 38.41]
4 Rash	2	61	Risk Ratio (M-H, Fixed, 95% CI)	3.47 [1.00, 12.04]
4.1 Selective COX-2 inhibitor	2	61	Risk Ratio (M-H, Fixed, 95% CI)	3.47 [1.00, 12.04]
5 Headache	2	482	Risk Ratio (M-H, Fixed, 95% CI)	1.76 [0.35, 8.81]
5.1 Selective COX-2 inhibitor	2	482	Risk Ratio (M-H, Fixed, 95% CI)	1.76 [0.35, 8.81]
6 Psychiatric side effects	2	501	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.87, 2.69]
6.1 Selective COX-2 inhibitor	2	501	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.87, 2.69]
7 Bleeding	1	425	Risk Ratio (M-H, Fixed, 95% CI)	3.45 [0.18, 66.35]
7.1 Selective COX-2 inhibitor	1	425	Risk Ratio (M-H, Fixed, 95% CI)	3.45 [0.18, 66.35]
8 Cerebrovascular side effects	3	1330	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.40, 1.64]
8.1 Selective COX-2 inhibitor	3	1330	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.40, 1.64]
9 Respiratory side effects	1	461	Risk Ratio (M-H, Fixed, 95% CI)	2.73 [0.61, 12.17]
9.1 Selective COX-2 inhibitor	1	461	Risk Ratio (M-H, Fixed, 95% CI)	2.73 [0.61, 12.17]
10 Dry mouth	1	177	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.06, 33.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Selective COX-2 inhibitor	1	177	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.06, 33.01]
11 Fatigue	1	177	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.51, 2.61]
11.1 Selective COX-2 inhibitor	1	177	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.51, 2.61]
12 Dizziness	2	198	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.53, 3.01]
12.1 Selective COX-2 inhibitor	2	198	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.53, 3.01]
13 Abnormal labs other than Cr. and LFT	1	425	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.09, 10.74]
13.1 Selective COX-2 inhibitor	1	425	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.09, 10.74]
14 Death	5	1391	Risk Ratio (M-H, Fixed, 95% CI)	1.88 [0.87, 4.03]
14.1 Selective COX-2 inhibitor	5	1391	Risk Ratio (M-H, Fixed, 95% CI)	1.88 [0.87, 4.03]
15 Withdrawal due to side effects	4	1370	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.71, 1.31]
15.1 Selective COX-2 inhibitor	4	1370	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.71, 1.31]
16 Abdominal pain or dyspepsia	4	663	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.79, 3.55]
16.1 Selective COX-2 inhibitor	4	663	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.79, 3.55]
17 Constipation or diarrhea	2	476	Risk Ratio (M-H, Fixed, 95% CI)	3.16 [1.04, 9.66]
17.1 Selective COX-2 inhibitor	2	476	Risk Ratio (M-H, Fixed, 95% CI)	3.16 [1.04, 9.66]
18 Nausea or vomiting	2	61	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.16, 6.29]
18.1 Selective COX-2 inhibitor	2	61	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.16, 6.29]
19 Abnormal liver function test	1	40	Risk Ratio (M-H, Fixed, 95% CI)	4.52 [0.58, 35.33]

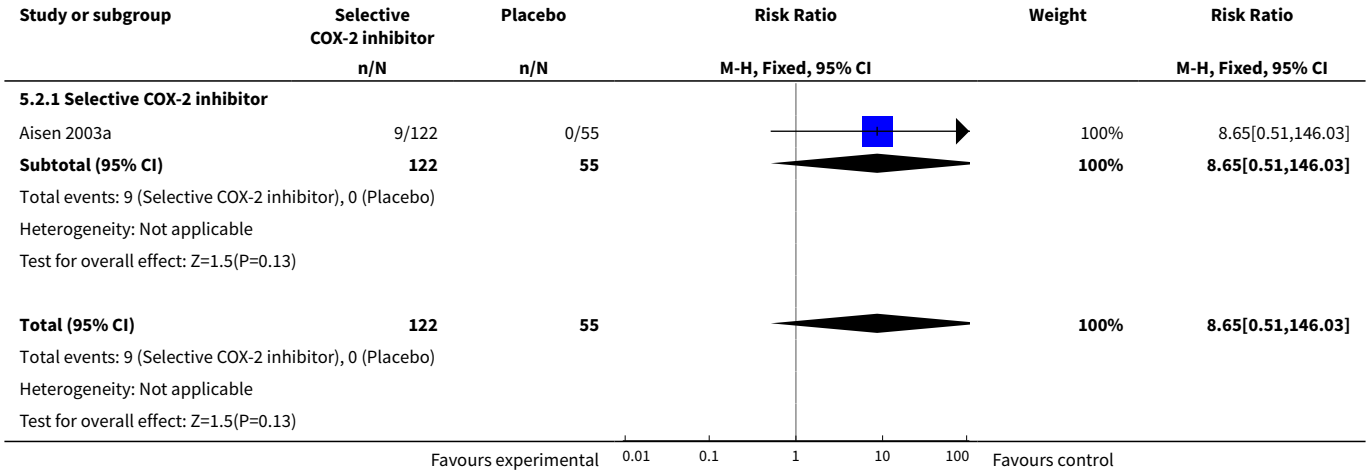
Analysis 5.1. Comparison 5 Selective COX-2 inhibitor vs. placebo, Outcome 1 Gastrointestinal side effects.

Study or subgroup	Selective COX-2 inhibitor n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
5.1.1 Selective COX-2 inhibitor					
Aisen 2002a	18/21	6/19		21.29%	2.71[1.37,5.38]
Aisen 2003a	4/122	1/55		4.66%	1.8[0.21,15.76]
Jhee 2004	7/16	3/5		15.45%	0.73[0.29,1.8]
Reines 2004	32/346	16/346		54.07%	2[1.12,3.58]

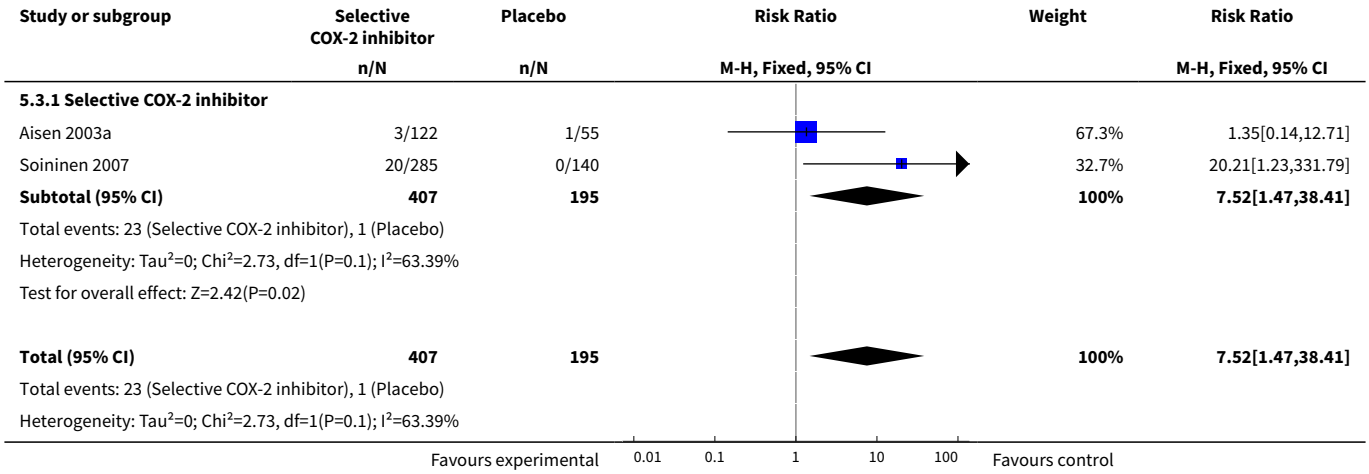


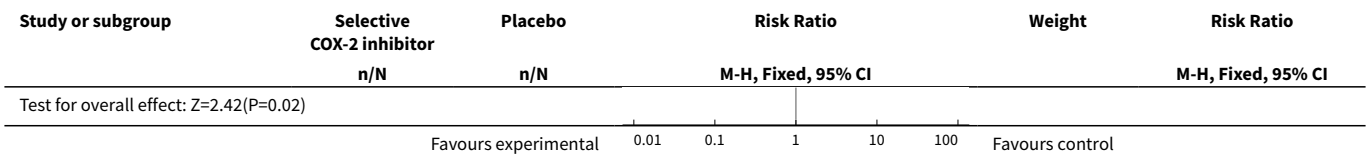


Analysis 5.2. Comparison 5 Selective COX-2 inhibitor vs. placebo, Outcome 2 Hypertension.

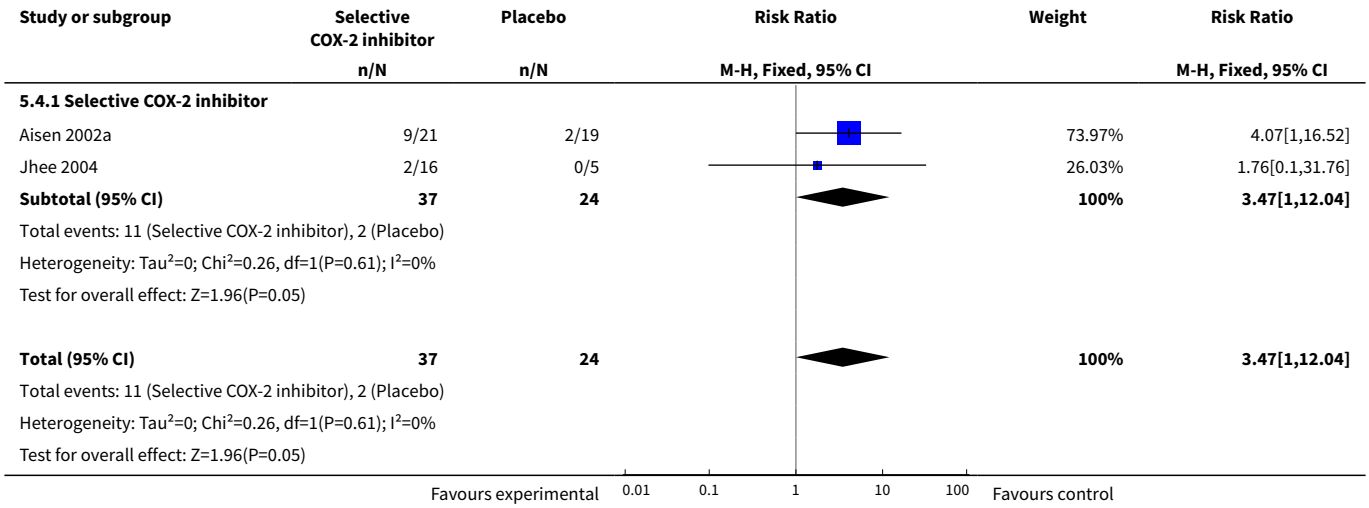


Analysis 5.3. Comparison 5 Selective COX-2 inhibitor vs. placebo, Outcome 3 Heart disease.

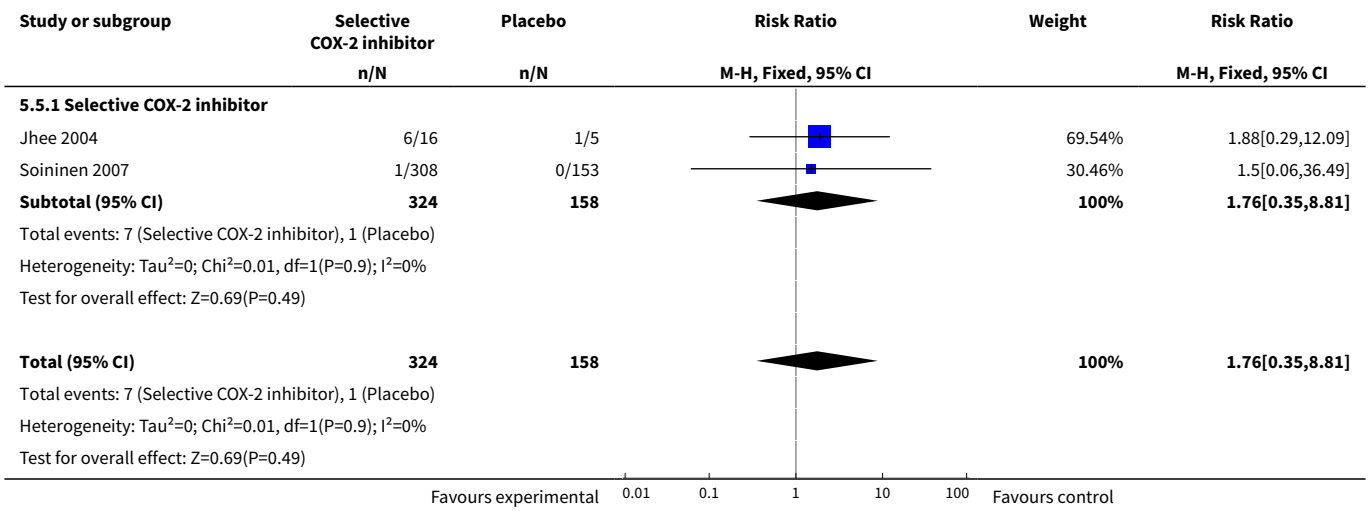




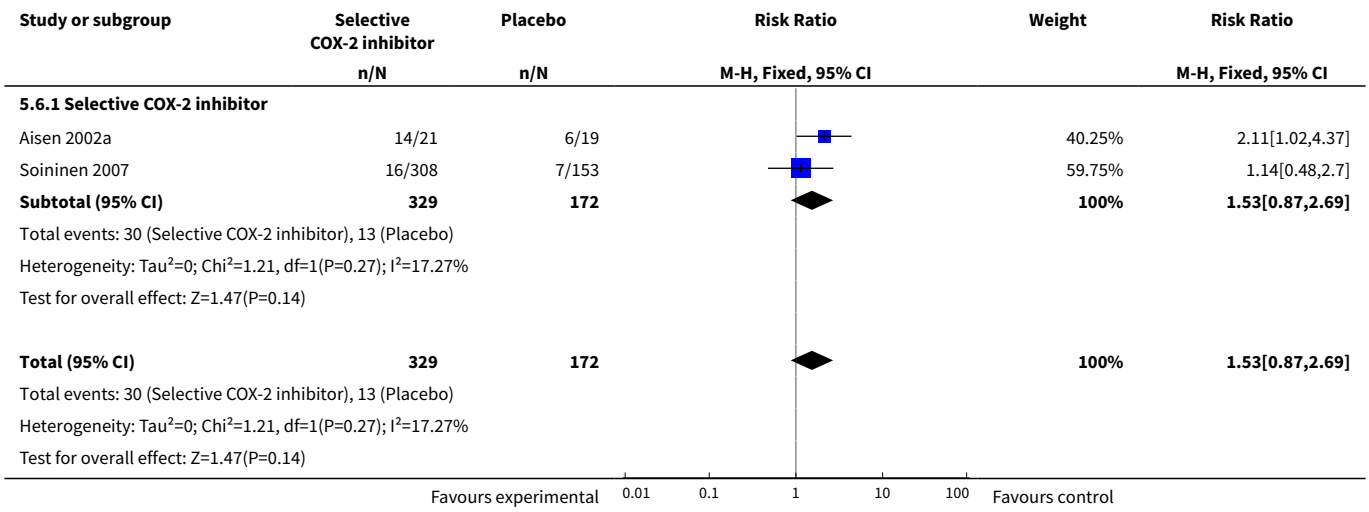
Analysis 5.4. Comparison 5 Selective COX-2 inhibitor vs. placebo, Outcome 4 Rash.



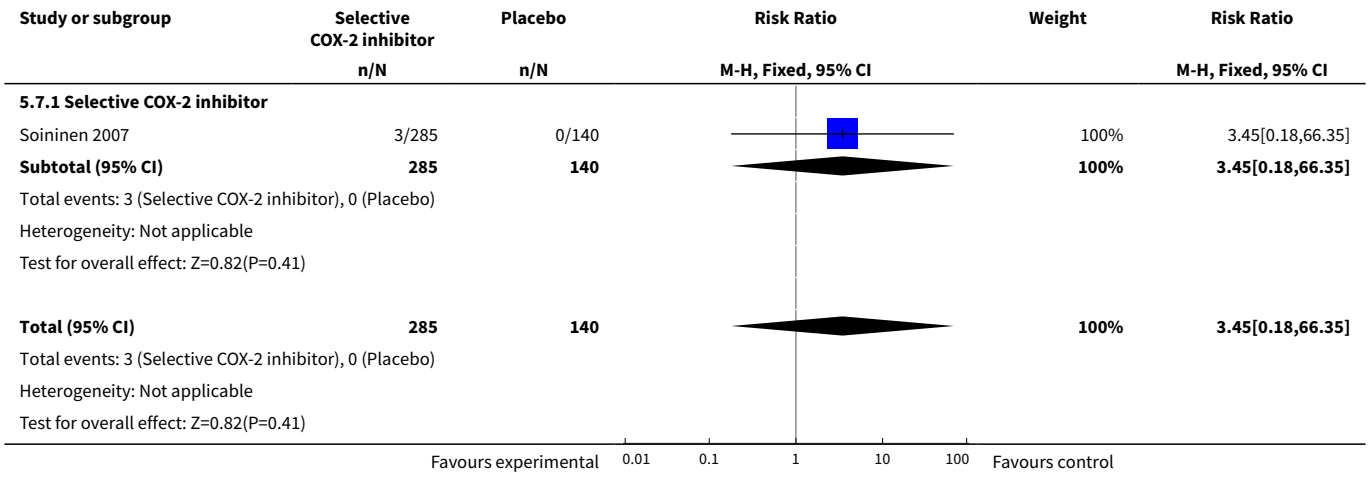
Analysis 5.5. Comparison 5 Selective COX-2 inhibitor vs. placebo, Outcome 5 Headache.



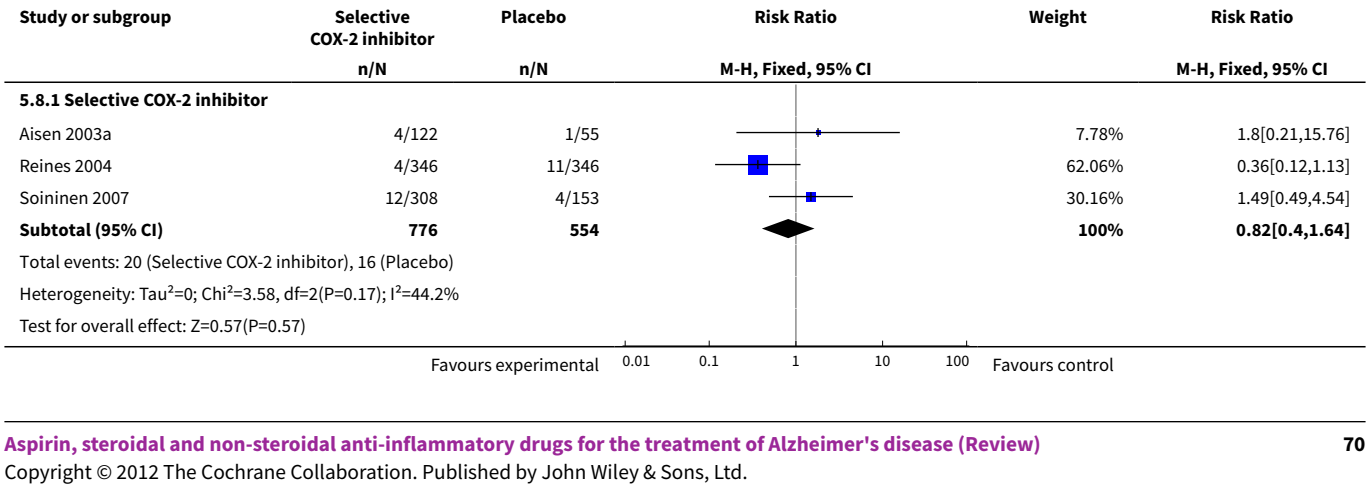
Analysis 5.6. Comparison 5 Selective COX-2 inhibitor vs. placebo, Outcome 6 Psychiatric side effects.

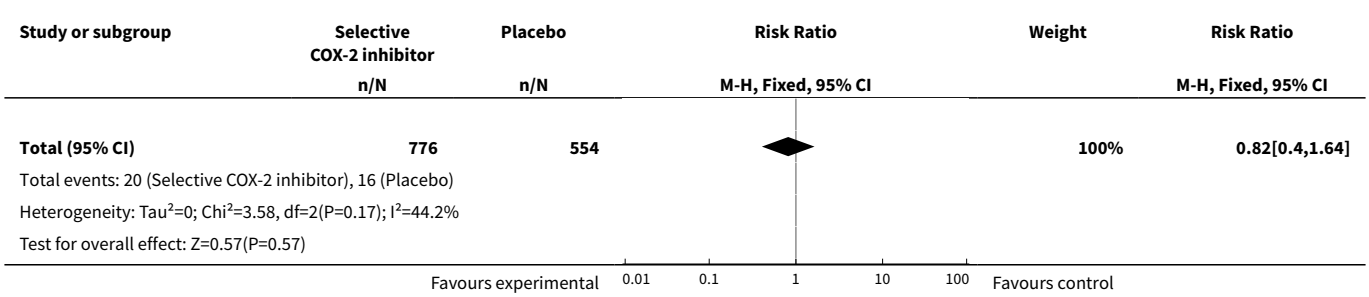


Analysis 5.7. Comparison 5 Selective COX-2 inhibitor vs. placebo, Outcome 7 Bleeding.

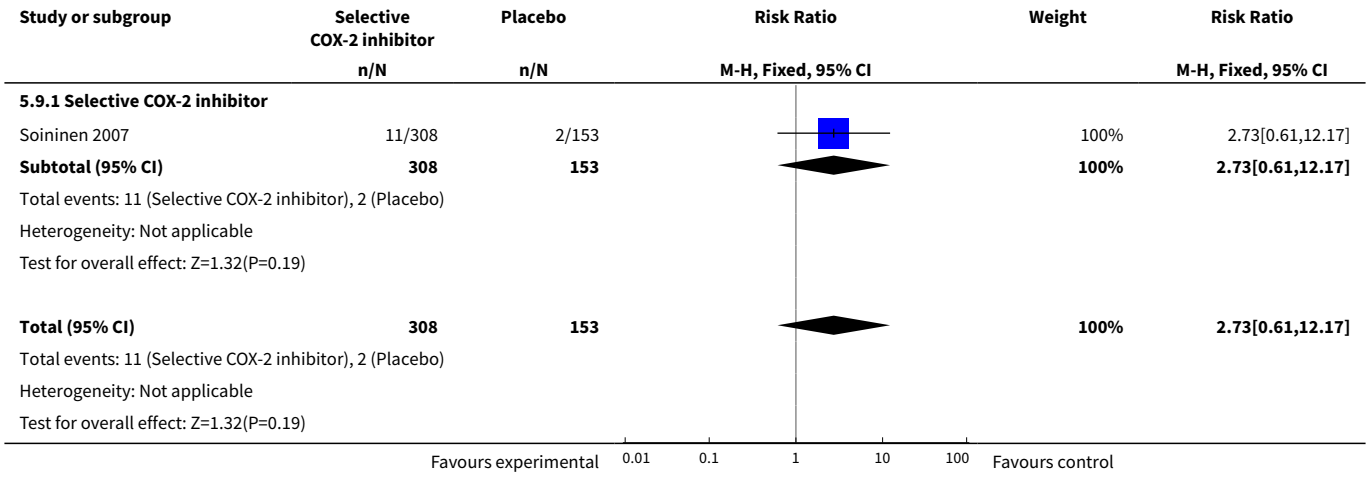


Analysis 5.8. Comparison 5 Selective COX-2 inhibitor vs. placebo, Outcome 8 Cerebrovascular side effects.

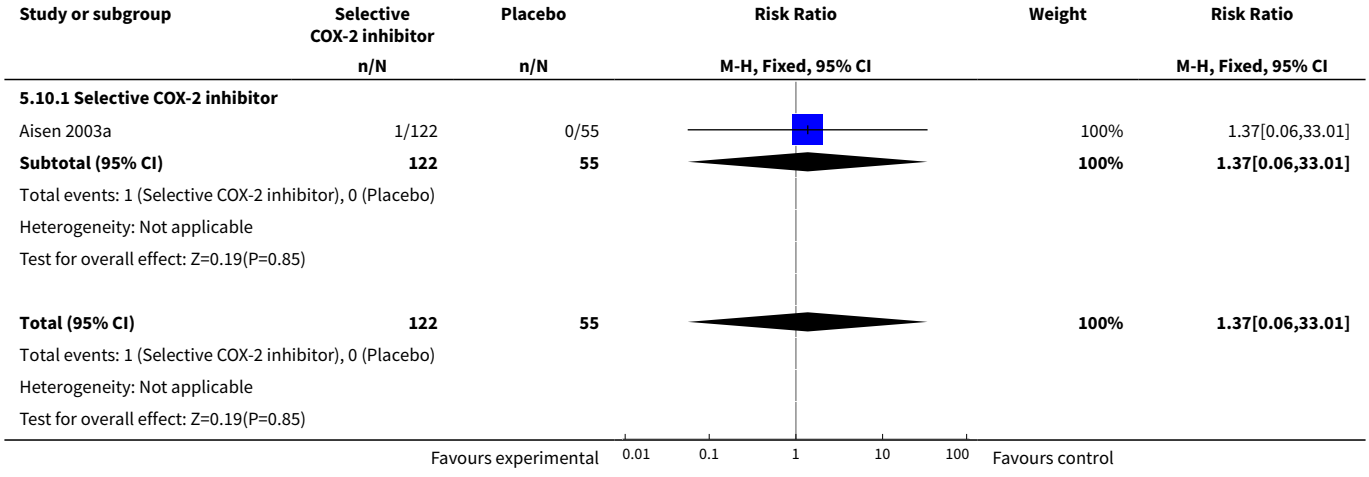




Analysis 5.9. Comparison 5 Selective COX-2 inhibitor vs. placebo, Outcome 9 Respiratory side effects.



Analysis 5.10. Comparison 5 Selective COX-2 inhibitor vs. placebo, Outcome 10 Dry mouth.



Analysis 5.11. Comparison 5 Selective COX-2 inhibitor vs. placebo, Outcome 11 Fatigue.

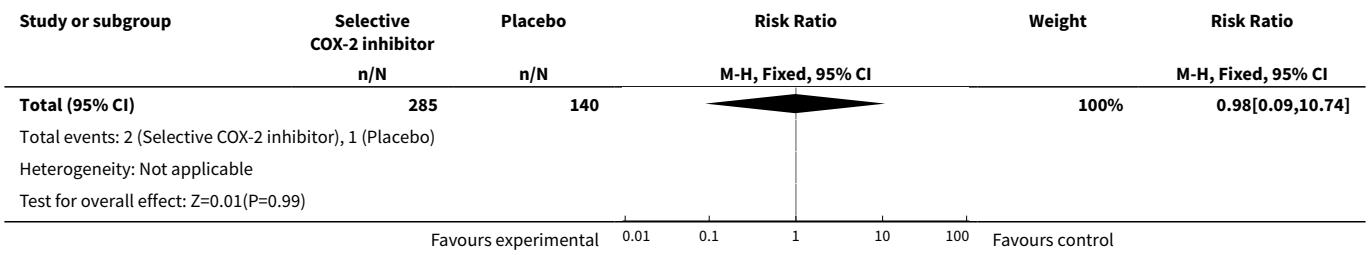
Study or subgroup	Selective COX-2 inhibitor n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
5.11.1 Selective COX-2 inhibitor					
Aisen 2003a	18/122	7/55		100%	1.16[0.51,2.61]
Subtotal (95% CI)	**122**	**55**		**100%**	**1.16[0.51,2.61]**
Total events: 18 (Selective COX-2 inhibitor), 7 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.36(P=0.72)					
Total (95% CI)	**122**	**55**		**100%**	**1.16[0.51,2.61]**
Total events: 18 (Selective COX-2 inhibitor), 7 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.36(P=0.72)					

Analysis 5.12. Comparison 5 Selective COX-2 inhibitor vs. placebo, Outcome 12 Dizziness.

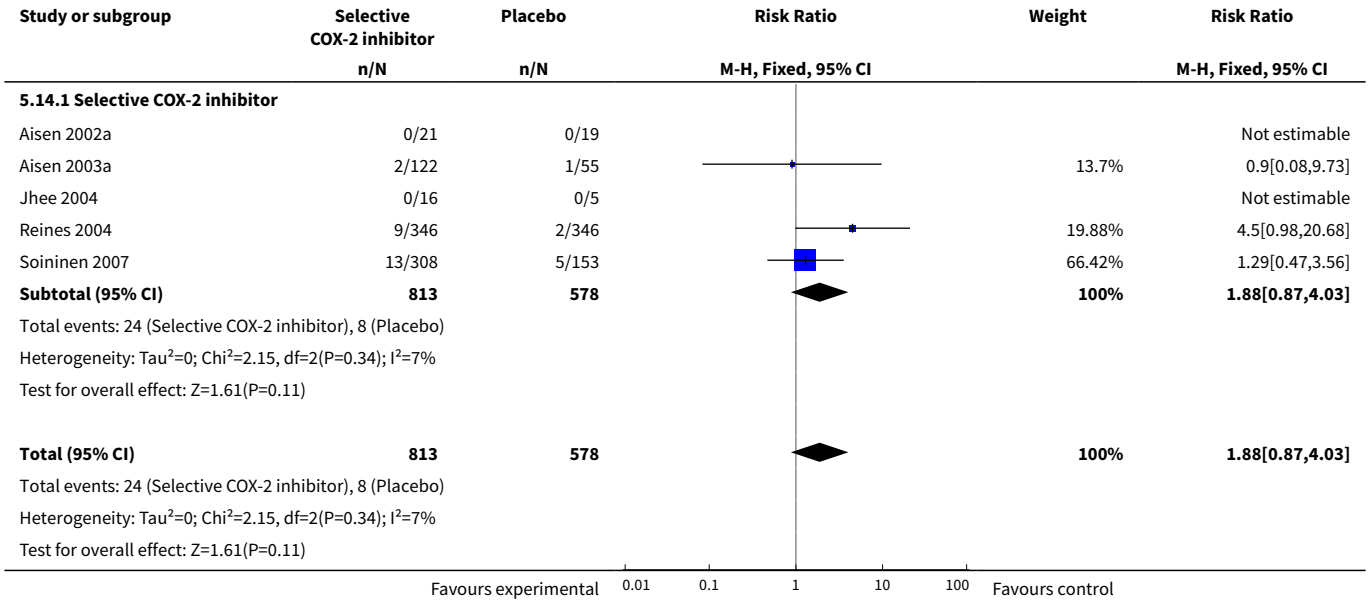
Study or subgroup	Selective COX-2 inhibitor n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
5.12.1 Selective COX-2 inhibitor					
Aisen 2003a	14/122	5/55		81.89%	1.26[0.48,3.33]
Jhee 2004	4/16	1/5		18.11%	1.25[0.18,8.77]
Subtotal (95% CI)	**138**	**60**		**100%**	**1.26[0.53,3.01]**
Total events: 18 (Selective COX-2 inhibitor), 6 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.99); I^2=0%					
Test for overall effect: Z=0.52(P=0.6)					
Total (95% CI)	**138**	**60**		**100%**	**1.26[0.53,3.01]**
Total events: 18 (Selective COX-2 inhibitor), 6 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.99); I^2=0%					
Test for overall effect: Z=0.52(P=0.6)					

Analysis 5.13. Comparison 5 Selective COX-2 inhibitor vs. placebo, Outcome 13 Abnormal labs other than Cr. and LFT.

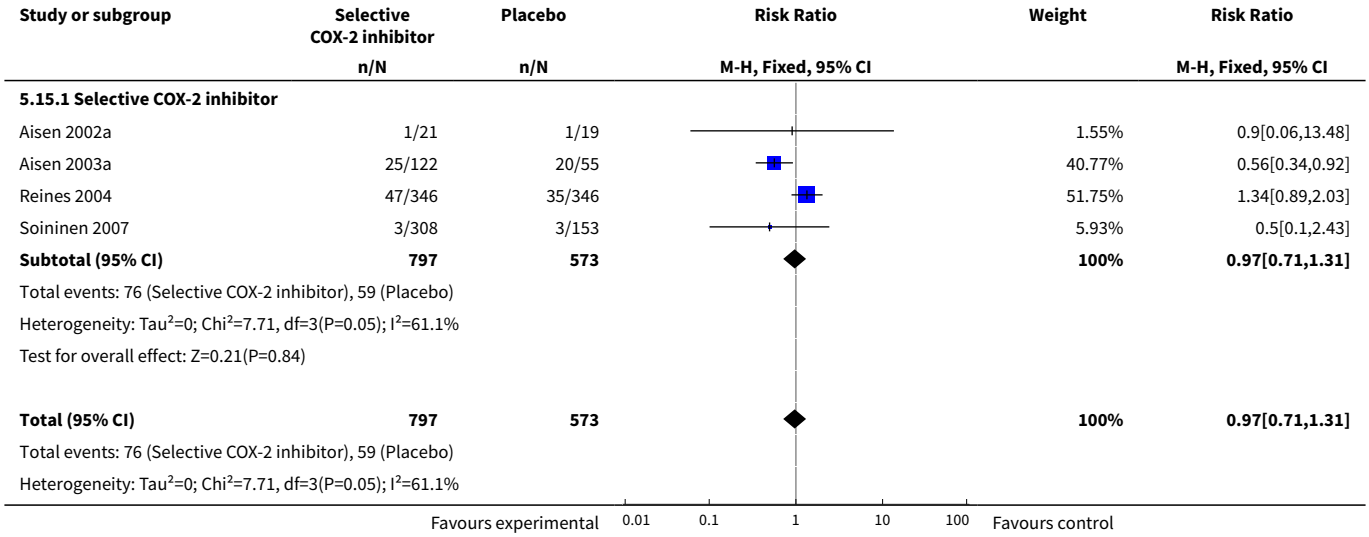
Study or subgroup	Selective COX-2 inhibitor n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
5.13.1 Selective COX-2 inhibitor					
Soininen 2007	2/285	1/140		100%	0.98[0.09,10.74]
Subtotal (95% CI)	**285**	**140**		**100%**	**0.98[0.09,10.74]**
Total events: 2 (Selective COX-2 inhibitor), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.01(P=0.99)					



Analysis 5.14. Comparison 5 Selective COX-2 inhibitor vs. placebo, Outcome 14 Death.



Analysis 5.15. Comparison 5 Selective COX-2 inhibitor vs. placebo, Outcome 15 Withdrawal due to side effects.



Study or subgroup	Selective COX-2 inhibitor n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=0.21(P=0.84)					

Favours experimental 0.01 0.1 1 10 100 Favours control

Analysis 5.16. Comparison 5 Selective COX-2 inhibitor vs. placebo, Outcome 16 Abdominal pain or dyspepsia.

Study or subgroup	Selective COX-2 inhibitor n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
5.16.1 Selective COX-2 inhibitor					
Aisen 2002a	9/21	2/19		24.08%	4.07[1,16.52]
Aisen 2003a	4/122	1/55		15.81%	1.8[0.21,15.76]
Jhee 2004	4/16	3/5		52.43%	0.42[0.14,1.26]
Soininen 2007	2/285	0/140		7.68%	2.47[0.12,51]
Subtotal (95% CI)	**444**	**219**		**100%**	**1.67[0.79,3.55]**
Total events: 19 (Selective COX-2 inhibitor), 6 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=7.64, df=3(P=0.05); I^2=60.73%					
Test for overall effect: Z=1.34(P=0.18)					
Total (95% CI)	**444**	**219**		**100%**	**1.67[0.79,3.55]**
Total events: 19 (Selective COX-2 inhibitor), 6 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=7.64, df=3(P=0.05); I^2=60.73%					
Test for overall effect: Z=1.34(P=0.18)					

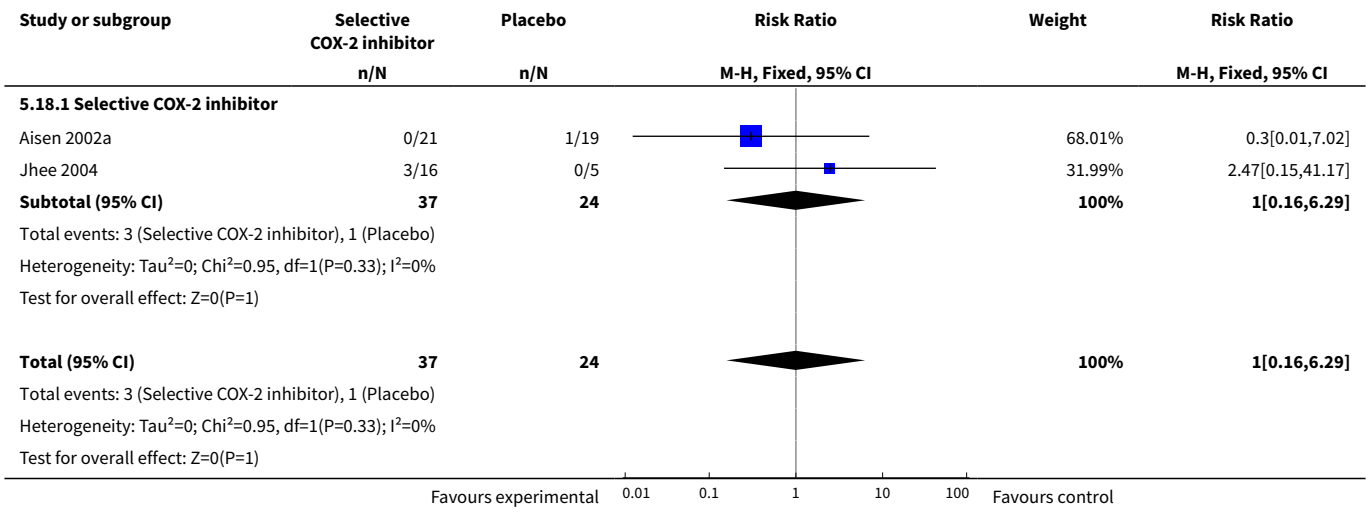
Favours experimental 0.01 0.1 1 10 100 Favours control

Analysis 5.17. Comparison 5 Selective COX-2 inhibitor vs. placebo, Outcome 17 Constipation or diarrhea.

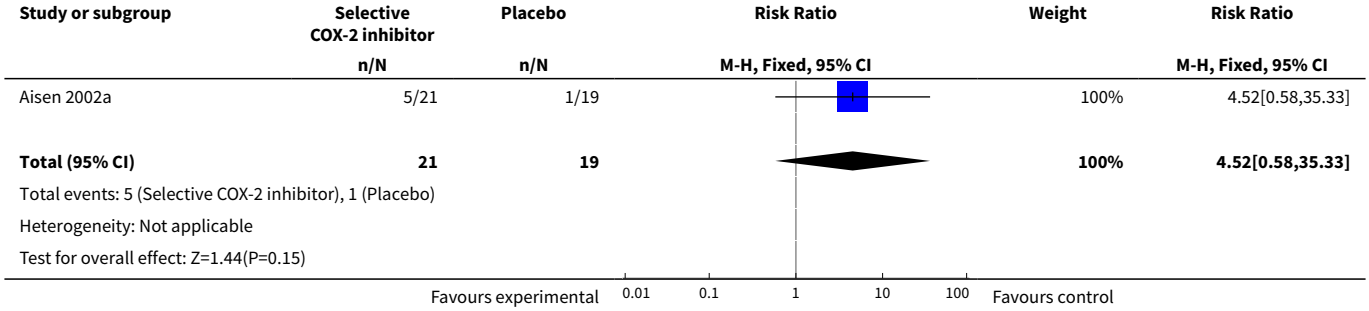
Study or subgroup	Selective COX-2 inhibitor n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
5.17.1 Selective COX-2 inhibitor					
Aisen 2002a	9/26	3/25		82.04%	2.88[0.88,9.44]
Soininen 2007	4/285	0/140		17.96%	4.44[0.24,81.84]
Subtotal (95% CI)	**311**	**165**		**100%**	**3.16[1.04,9.66]**
Total events: 13 (Selective COX-2 inhibitor), 3 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.08, df=1(P=0.78); I^2=0%					
Test for overall effect: Z=2.02(P=0.04)					
Total (95% CI)	**311**	**165**		**100%**	**3.16[1.04,9.66]**
Total events: 13 (Selective COX-2 inhibitor), 3 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.08, df=1(P=0.78); I^2=0%					
Test for overall effect: Z=2.02(P=0.04)					

Favours experimental 0.01 0.1 1 10 100 Favours control

Analysis 5.18. Comparison 5 Selective COX-2 inhibitor vs. placebo, Outcome 18 Nausea or vomiting.



Analysis 5.19. Comparison 5 Selective COX-2 inhibitor vs. placebo, Outcome 19 Abnormal liver function test.



ADDITIONAL TABLES

Table 1. The Cochrane Collaboration's tool for assessing risk of bias

Domain	Description	Review authors' judgment
Sequence generation.	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Was the allocation sequence adequately generated?
Allocation concealment.	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Was allocation adequately concealed?
Blinding of participants, personnel and outcome assessors *Assessments should be made for each main out-*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Was knowledge of the allocated intervention adequately prevented during the study?

Table 1. The Cochrane Collaboration's tool for assessing risk of bias *(Continued)*

come (or class of outcomes).		
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes).*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomised participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Were incomplete outcome data adequately addressed?
Selective outcome reporting.	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Are reports of the study free of suggestion of selective outcome reporting?
Other sources of bias.	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Was the study apparently free of other problems that could put it at a high risk of bias?

Table 2. Risk of bias within a study and across studies

Risk of bias	Interpretation	Within a study	Across studies
Low risk of bias.	Plausible bias unlikely to seriously alter the results.	Low risk of bias for all key domains.	Most information is from studies at low risk of bias.
Unclear risk of bias.	Plausible bias that raises some doubt about the results.	Unclear risk of bias for one or more key domains.	Most information is from studies at low or unclear risk of bias.
High risk of bias.	Plausible bias that seriously weakens confidence in the results.	High risk of bias for one or more key domains.	The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results.

Table 3. Levels of quality of a body of evidence in the GRADE approach for RCT

	Underlying methodology	Quality rating
	Randomised trials	High
	Downgraded randomised trials	Moderate
	Double-downgraded randomised trials	Low
	Triple-downgraded randomised trials	Very low

Table 4. Characteristics of participants from each study

Study	Mean age (SD)	Female (%)	year of education (SD)	Duration of disease, yr (SD)	ApoE (% >/ =1allele)	MMSE (SD)	Hypertension (%)
Bentham 2008 (Aspirin, N=156)	75	63	N/A	N/A	N/A	19	19
Zhou 2004a (Aspirin, N=13)	71.1 (10.6)	57.14	N/A	2.65 (3.15)	N/A	14.65 (5.93)	N/A
Zhou 2004 (Aspirin, N=8)	69.5 (9.8)	37.50	N/A	N/A	N/A	14.5 (6.8)	N/A
Aisen 2000 (Prednisone, N=69)	73.4 (7.2)	49.3	14.1 (3)	3.5 (2.4)	65.6	21.2 (4.4)	N/A
Aisen 2002 (Nimesulide, N=21)	73(2)	38.09	13.1 (11.2)	2 (0.5)	N/A	21.1 (1.1)	N/A
Aisen 2003 (Naproxen, N=118)	74.1 (7.8)	48.3	13.8 (3.2)	4.1 (2.3)	70.4	20.7 (3.6)	N/A
Aisen 2003 (Rofecoxib, N=122)	73.7 (7.2)	54.9	13.8 (3.2)	4.1 (2.3)	68.1	21.2 (3.8)	N/A
de Jong 2008 (Indomethacin, N=26)	72.7 (6.9)	53.85	2.4 (1.3)	2.74 (1.75)	50	19.1 (4.1)	N/A
Pasqualetti 2009 (Ibuprofen, N=66)	73.7 (7.3)	61	7.4 (3.7)	2 (0.5-5.41)	20.4	19.7 (3.0)	N/A
Rogers 1993 (Indoethacin, N=14)	78 (2)	35.71	N/A	N/A	N/A	N/A	N/A
Hull 1999 (Piroxicam, N=6)	range of 55-75	N/A	N/A	N/A	N/A	N/A	N/A
Scharf 1999	71.8 (2.3)	66.67	N/A	N/A	N/A	N/A	18.5 (0.99)

Table 4. Characteristics of participants from each study *(Continued)*

(Diclofenac, N=12)							
Jhee 2004 (Celecoxib, N=15)	71.17	26.67	N/A	N/A	N/A	N/A	N/A
Reines 2004 (Rofecoxib, N=346)	76 (8)	54	N/A	2.17 (1.83)	N/A	N/A	21 (4)
Soininen 2007 (Celecoxib, N=285)	73.7 (8.2)	53	N/A	1.37 (1.7)	N/A	19.8 (4.2)	31.9

APPENDICES

Appendix 1. Pre-publication search: April 2011

Source	Search strategy	Hits retrieved
1. ALOIS (www.medicine.ox.ac.uk/alois)	Keyword search: aspirin OR "cyclooxygenase 2 inhibitor" OR aceclofenac OR acemetacin OR betamethasone OR celecoxib OR cortisone OR deflazacort OR dexamethasone OR dexibruprofen OR dexketoprofen OR diclofenac sodium OR diflunisal OR diflusinal OR etodolac OR etoricoxib OR fenbufen OR fenoprofen OR flurbiprofen OR hydrocortisone OR ibuprofen OR indometacin OR indomethacin OR ketoprofen OR lumiracoxib OR mefenamic OR meloxicam OR methylprednisolone OR nabumetone OR naproxen OR nimesulide OR "anti-inflammatory" OR prednisone OR piroxicam OR sulindac OR tenoxicam OR tiaprofenic acid OR triamcinolone OR NSAIDS OR NSAID	37
2. MEDLINE In-process and other non-indexed citations and MEDLINE 1950-present (Ovid SP)	1. Aspirin/ 2. aspirin*.ti,ab. 3. cyclooxygenase 2 inhibitor*.ti,ab. 4. ("anti-inflammatory agent*" or "antiinflammatory agent" or "antinflammatory agent*").ti,ab. 5. aceclofenac.ti,ab. 6. acemetacin.ti,ab. 7. betamethasone.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* or fenoprofen*).ti,ab. 16. flurbiprofen*.ti,ab. 17. (hydrocortison* or ibuprofen*).ti,ab. 18. (indometacin* or indomethacin*).ti,ab. 19. ketoprofen*.ti,ab. 20. lumiracoxib*.ti,ab. 21. "mefenamic acid".ti,ab. 22. meloxicam*.ti,ab.	193

(Continued)

23. methylprednisolone.ti,ab.
24. nabumeton*.ti,ab.
25. naproxen.ti,ab.
26. nimesulide.ti,ab.
27. "non-steroid* anti-inflammatory agent*".ti,ab.
28. prednisone.ti,ab.
29. piroxicam.ti,ab.
30. sulindac.ti,ab.
31. tenoxicam.ti,ab.
32. "tiaprofenic acid".ti,ab.
33. triamcinolone.ti,ab.
34. Anti-Inflammatory Agents, Non-Steroidal/
35. Anti-Inflammatory Agents/
36. NSAID*.ti,ab.
37. or/1-36
38. Alzheimer Disease/
39. (alzheimer* or AD or dement*).ti,ab.
40. alzheimer*.ti,ab.
41. (AD or dement*).ti,ab.
42. or/38-41
43. 37 and 42
44. randomized controlled trial.pt.
45. controlled clinical trial.pt.
46. randomized.ab.
47. placebo.ab.
48. drug therapy.fs.
49. randomly.ab.
50. trial.ab.
51. groups.ab.
52. or/44-51
53. (animals not (humans and animals)).sh.
54. 52 not 53
55. 43 and 54
56. (2008* or 2009* or 2010* or 2011*).ed.

(Continued)

	57. 55 and 56	
3. EMBASE 1980-2011 week 15 (Ovid SP)	1. Aspirin/ 2. aspirin*.ti,ab. 3. cyclooxygenase 2 inhibitor*.ti,ab. 4. ("anti-inflammatory agent*" or "antiinflammatory agent" or "antinflammatory agent*").ti,ab. 5. aceclofenac.ti,ab. 6. acemetacin.ti,ab. 7. betamethasone.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* or fenoprofen*).ti,ab. 16. flurbiprofen*.ti,ab. 17. (hydrocortison* or ibuprofen*).ti,ab. 18. (indometacin* or indomethacin*).ti,ab. 19. ketoprofen*.ti,ab. 20. lumiracoxib*.ti,ab. 21. "mefenamic acid".ti,ab. 22. meloxicam*.ti,ab. 23. methylprednisolone.ti,ab. 24. nabumeton*.ti,ab. 25. naproxen.ti,ab. 26. nimesulide.ti,ab. 27. "non-steroid* anti-inflammatory agent*".ti,ab. 28. prednisone.ti,ab. 29. piroxicam.ti,ab. 30. sulindac.ti,ab. 31. tenoxicam.ti,ab. 32. "tiaprofenic acid".ti,ab.	460

(Continued)

	33. triamcinolone.ti,ab. 34. NSAID*.ti,ab. 35. nonsteroid antiinflammatory agent/ 36. antiinflammatory agent/ 37. or/1-36 38. ALZHEIMER DISEASE/ 39. (alzheimer* or AD or dement*).ti,ab. 40. or/38-39 41. 37 and 40 42. randomly.ti,ab. 43. trial.ti,ab. 44. placebo.ab. 45. clinical trial/ 46. "double-blind*".ti,ab. 47. (2008* or 2009* or 2010* or 2011*).em. 48. or/42-46 49. 41 and 48 50. 47 and 49	
4. PSYCINFO 1806-April week 2 2011 (Ovid SP)	1. Aspirin/ 2. aspirin*.ti,ab. 3. cyclooxygenase 2 inhibitor*.ti,ab. 4. ("anti-inflammatory agent*" or "antiinflammatory agent" or "antinflammatory agent*").ti,ab. 5. aceclofenac.ti,ab. 6. acemetacin.ti,ab. 7. betamethasone.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.	26

(Continued)

15. (fenbufen* or fenoprofen*).ti,ab.
16. flurbiprofen*.ti,ab.
17. (hydrocortison* or ibuprofen*).ti,ab.
18. (indometacin* or indomethacin*).ti,ab.
19. ketoprofen*.ti,ab.
20. lumiracoxib*.ti,ab.
21. "mefenamic acid".ti,ab.
22. meloxicam*.ti,ab.
23. methylprednisolone.ti,ab.
24. nabumeton*.ti,ab.
25. naproxen.ti,ab.
26. nimesulide.ti,ab.
27. "non-steroid* anti-inflammatory agent*".ti,ab.
28. prednisone.ti,ab.
29. piroxicam.ti,ab.
30. sulindac.ti,ab.
31. tenoxicam.ti,ab.
32. "tiaprofenic acid".ti,ab.
33. triamcinolone.ti,ab.
34. NSAID*.ti,ab.
35. Anti Inflammatory Drugs/
36. or/1-35
37. exp Alzheimer's Disease/
38. (AD or alzheimer* or dement*).ti,ab.
39. or/37-38
40. 36 and 39
41. (random* or trial or placebo or "double-blind*" or "single-blind*").ti,ab.
42. exp Clinical Trials/
43. 41 or 42
44. 40 and 43
45. (2008* or 2009* or 2010* or 2011*).up.
46. 44 and 45

5. CINAHL (EBSCOhost)	S1 (MH "Dementia+")	74

(Continued)

	S2 (MH "Delirium") or (MH "Delirium, Dementia, Amnestic, Cognitive Disorders") S3 (MH "Wernicke's Encephalopathy") S4 TX dement* S5 TX alzheimer* S6 TX lewy* N2 bod* S7 TX deliri* S8 TX chronic N2 cerebrovascular S9 TX "organic brain disease" or "organic brain syndrome" S10 or/S1-S9 S11 MH non-steroidal anti-inflammatory agent S12 MH Aspirin S13 TX aspirin S14TX "cyclooxygenase 2 inhibitor*" OR aceclofenac OR acemetacin OR betamethasone OR celecoxib OR cortisone OR deflazacort OR dexamethasone OR dexibruprofen OR dexketoprofen OR diclofenac sodium OR diflunisal OR diflusinal OR etodolac OR etoricoxib OR fenbufen OR fenoprofen OR flurbiprofen OR hydrocortisone OR ibuprofen OR indometacin OR indomethacin OR ketoprofen OR lumiracoxib OR mefenamic OR meloxicam OR methylprednisolone OR nabumetone OR naproxen OR nimesulide OR "anti-inflammatory" OR prednisone OR piroxicam OR sulindac OR tenoxicam OR tiaprofenic acid OR triamcinolone S15 or/S11-S14 S16 S10 AND S15 S17 TX random* OR placebo* OR trial OR group OR “double-blind*” S18 MH Clinical Trial S19 S17 AND S18 S20 S19 AND S16	
6. ISI Web of Knowledge – all databases [includes: Web of Science (1945-present); BIOSIS Previews (1926-present); MEDLINE (1950-present); Journal Citation Reports]	Topic=(aspirin OR "cyclooxygenase 2 inhibitor*" OR aceclofenac OR acemetacin OR betamethasone OR celecoxib OR cortisone OR deflazacort OR dexamethasone OR dexibruprofen OR dexketoprofen OR diclofenac sodium OR diflunisal OR diflusinal OR etodolac OR etoricoxib OR fenbufen OR fenoprofen OR flurbiprofen OR hydrocortisone OR ibuprofen OR indometacin OR indomethacin OR ketoprofen OR lumiracoxib OR mefenamic OR meloxicam OR methylprednisolone OR nabumetone OR naproxen OR nimesulide OR "anti-inflammatory" OR prednisone OR piroxicam OR sulindac OR tenoxicam OR tiaprofenic acid OR triamcinolone) AND Topic=(Alzheimer* OR AD) AND Topic=(randomized OR randomised OR placebo OR "double-blind*" OR randomly OR RCT OR trial OR CCT) AND Year Published=(2008-2011)	244
7. LILACS (BIREME)	aspirin OR anti-inflammatory [Words] and alzheimer OR AD [Words]	18

(Continued)

8. CENTRAL (*The Cochrane Library*) (Issue 1 of 4, Jan 2011)	#1 aspirin OR aceclofenac OR acemetacin OR betamethasone OR celecoxib OR cortisone OR "cyclooxygenase 2 inhibitor*" OR deflazacort OR dexamethasone OR dexibruprofen OR dexketoprofen OR diclofenac sodium OR diflunisal OR diflusinal OR etodolac OR etoricoxib OR fenbufen OR fenoprofen OR flurbiprofen OR hydrocortisone OR ibuprofen OR indometacin OR indomethacin OR ketoprofen OR lumiracoxib OR mefenamic OR meloxicam OR methylprednisolone OR nabumetone OR naproxen OR nimesulide OR "anti-inflammatory" OR prednisone OR piroxicam OR sulindac OR tenoxicam OR tiaprofenic OR triamcinolone #2 alzheimer* OR AD #3 (#1 AND #2), from 2008 to 2011	88
9. Clinicaltrials.gov (www.clinicaltrials.gov)	alzheimer OR alzheimers OR AD | aspirin OR anti-imflammatory OR celecoxib OR cortisone OR ibuprofen | received from 01/01/2008 to 04/20/2011	6
10. ICTRP Search Portal (http://apps.who.int/trialsearch) [includes: Australian New Zealand Clinical Trials Registry; ClinicalTrilas.gov; ISRCTN; Chinese Clinical Trial Registry; Clinical Trials Registry – India; Clinical Research Information Service – Republic of Korea; German Clinical Trials Register; Iranian Registry of Clinical Trials; Japan Primary Registries Network; Pan African Clinical Trial Registry; Sri Lanka Clinical Trials Registry; The Netherlands National Trial Register]	(aspirin OR anti-inflammatory OR dexamethasone OR dexibruprofen OR dexketoprofen OR diclofenac sodium OR diflunisal OR diflusinal OR etodolac OR etoricoxib OR fenbufen OR fenoprofen OR flurbiprofen OR hydrocortisone OR ibuprofen OR indometacin OR indomethacin OR ketoprofen OR lumiracoxib OR mefenamic OR meloxicam OR methylprednisolone OR nabumetone OR naproxen OR nimesulide OR "anti-inflammatory" OR prednisone OR piroxicam OR sulindac OR tenoxicam OR tiaprofenic OR triamcinolone OR NSAIDS) AND (rec from: 01/01/2008 to 20/04/2011)	77
TOTAL before de-duplication		1223
TOTAL after de-dupe and first-assess		116

Appendix 2. Initial search: September 2008

Source searched	Date of search	Search strategy used
PubMed (MEDLINE)	8 September 2008	(aspirin OR aceclofenac OR acemetacin OR betamethasone OR celecoxib OR cortisone OR deflazacort OR prednisone OR dexamethasone OR dexibruprofen OR dexketoprofen OR diclofenac sodium OR diflusinal OR etodolac OR etoricoxib OR fenbufen OR fenoprofen OR flurbiprofen OR hydrocortisone OR ibuprofen OR indomethacin OR indometacin OR ketoprofen OR lumiracoxib OR mefenamic acid OR meloxicam OR methylprednisolone OR nabumetone OR naproxen OR nimesulide OR piroxicam OR sulindac OR tenoxicam OR tiaprofenic acid OR triamcinolone OR cyclooxygenase 2 inhibitor* OR anti-in-

(Continued)

		flammatory agent*) AND (Alzheimer* OR dementia OR ((cognit* or memory* or mental*) and (declin* or impair* or los* or deteriorat*)) AND (randomized OR randomized OR double blind* OR single blind* OR placebo* OR controlled)
EMBASE (Ovid SP)	9 September 2008	as PubMed
CINAHL (Ovid SP)	9 September 2008	as PubMed
PsycINFO (Ovid SP)	9 September 2008	as PubMed
LILACS (Bireme)	9 September 2008	(aspirin OR aceclofenac OR acemetacin OR betamethasone OR celecoxib OR cortisone OR deflazacort OR prednisone OR dexamethasone OR dexibruprofen OR dexketoprofen OR diclofenac sodium OR diflusinal OR etodolac OR etoricoxib OR fenbufen OR fenoprofen OR flurbiprofen OR hydrocortisone OR ibuprofen OR indomethacin OR indometacin OR ketoprofen OR lumiracoxib OR mefenamic acid OR meloxicam OR methylprednisolone OR nabumetone OR naproxen OR nimesulide OR piroxicam OR sulindac OR tenoxicam OR tiaprofenic acid OR triamcinolone OR cyclooxygenase 2 inhibitor* OR anti-inflammatory agent*) AND (Alzheimer* OR dementia)
CDCIG Specialized Register	8 September 2008	(aspirin OR aceclofenac OR acemetacin OR betamethasone OR celecoxib OR cortisone OR deflazacort OR prednisone OR dexamethasone OR dexibruprofen OR dexketoprofen OR diclofenac sodium OR diflusinal OR etodolac OR etoricoxib OR fenbufen OR fenoprofen OR flurbiprofen OR hydrocortisone OR ibuprofen OR indomethacin OR indometacin OR ketoprofen OR lumiracoxib OR mefenamic acid OR meloxicam OR methylprednisolone OR nabumetone OR naproxen OR nimesulide OR piroxicam OR sulindac OR tenoxicam OR tiaprofenic acid OR triamcinolone OR cyclooxygenase 2 inhibitor* OR anti-inflammatory agent*)
CENTRAL	Issue 3/2008	(aspirin OR aceclofenac OR acemetacin OR betamethasone OR celecoxib OR cortisone OR deflazacort OR prednisone OR dexamethasone OR dexibruprofen OR dexketoprofen OR diclofenac sodium OR diflusinal OR etodolac OR etoricoxib OR fenbufen OR fenoprofen OR flurbiprofen OR hydrocortisone OR ibuprofen OR indomethacin OR indometacin OR ketoprofen OR lumiracoxib OR mefenamic acid OR meloxicam OR methylprednisolone OR nabumetone OR naproxen OR nimesulide OR piroxicam OR sulindac OR tenoxicam OR tiaprofenic acid OR triamcinolone OR cyclooxygenase 2 inhibitor* OR anti-inflammatory agent*) AND (Alzheimer* OR dementia OR ((cognit* or memory* or mental*) and (declin* or impair* or los* or deteriorat*))
ISI Conference Proceedings	10 September 2008	(aspirin OR aceclofenac OR acemetacin OR betamethasone OR celecoxib OR cortisone OR deflazacort OR prednisone OR dexamethasone OR dexibruprofen OR dexketoprofen OR diclofenac sodium OR diflusinal OR etodolac OR etoricoxib OR fenbufen OR fenoprofen OR flurbiprofen OR hydrocortisone OR ibuprofen OR indomethacin OR indometacin OR ketoprofen OR lumiracoxib OR mefenamic acid OR meloxicam OR methylprednisolone OR nabumetone OR naproxen OR nimesulide OR piroxicam OR sulindac OR tenoxicam OR tiaprofenic acid OR triamcinolone OR cyclooxygenase 2 inhibitor* OR anti-inflammatory agent*) AND (Alzheimer* OR dementia)
mRCT including ISRCTN Register, ClinicalTrials.gov	10 September 2008	(aspirin OR aceclofenac OR acemetacin OR betamethasone OR celecoxib OR cortisone OR deflazacort OR prednisone OR dexamethasone OR dexibruprofen OR dexketoprofen OR diclofenac sodium OR diflusinal OR etodolac OR etoricoxib OR fenbufen OR fenoprofen OR flurbiprofen OR hydrocortisone OR ibuprofen OR indomethacin OR indometacin OR ketoprofen OR lumiracoxib OR mefenamic acid OR meloxicam OR methylprednisolone OR nabumetone OR naproxen OR nimesulide OR piroxicam OR sulindac OR tenoxicam OR

(Continued)

		tiaprofenic acid OR triamcinolone OR cyclooxygenase 2 inhibitor* OR anti-inflammatory agent*) AND (Alzheimer* OR dementia)
IFPMA, UMIN Japan trials register, Netherland trials register, Australasian Digital theses, Theses Canada, DATAD	10 September 2008	Alzheimer's disease

Appendix 3. measurement agreement

Kappa statistic was used to measure agreement between 2 authors who make a decision for inclusion and exclusion.From calculation, kappa is 0.782. It should be noted that this calculation is based on the first decision making of both reviewers.

Meaning of kappa statistic

- 0.40-0.59: fair agreement
- 0.60-0.74: good agreement
- 0.75 or more: excellent agreement

From 488 studies, there were 19 studies that we did not agree and required more discussion. Although measuring agreement showed excellent agreement, it should be considered that the discussion is still the main part of the decision making. However, kappa helped us to revisit inclusion criteria again whether it is clear enough for both reviewers in case of poor agreement. Occasionally, we have to revisit and clarify the inclusion and exclusion criteria to assure that all reviewers are on the same page. For example, three reviewers at one point were not sure if we should include all studies of anti-inflammatory. After the discussion, we understood that we will only focus on aspirin, steroidal and non-steroidal anti-inflammatory. This leaded to the change of the review's title.

		Review author 2 (MI)			
			Include	Exclude	Unsure
	Review Author 1 (DJ)	Include	39 (a)	1 (b)	1 (c)
		Exclude	11 (d)	546 (e)	2 (f)
		Unsure	0 (g)	4 (h)	0 (i)
		Total	50 (A2)	551 (E2)	3 (U2)

Po = a+e+i / K Po = 39+546+0 /604 = 0.969

PE = (A1xA2) + (E1+E2) + (U1+U2) / K^2 PE = (41x50) + (559x551) + (4x3) /604^2 = 0.850

Kappa = Po PE/ 1-PE Kappa = 0.969-0.850/ 1-0.850 = 0.793

Appendix 4. Translation sheet

Cochrane Dementia and Cognitive Improvement Group

Translation sheet.

To be completed by the translator.

Please note: full translations of papers are not necessary. The following questions are designed to assist in the extraction of necessary information for the inclusion of randomised controlled trials.

Date of translation:

Translator:

Language of the paper:

1. Publication details

Authors:

Title (in English):

Original title:

Publication details:

(journal, volume, year, page nos)

If details are not reported, please indicate so.

2. Materials and Methods

Is the trial described as RANDOMISED?

(NB - if the paper is not described as randomised, we do not require any further information, but please give a description of the study, ie, a review article, a case controlled trial, a letter to a journal, a double blind trial in which treatment was not randomised etc).

If YES, the following details are necessary:

Was it a parallel or cross-over study?

What were the patients described as suffering from?

Diagnostic criteria

Number of patients involved:

Gender ratio:

Age groups (please give Means and SDs) (+/- values if reported):

Where were the patients recruited from?

Was the treatment double blinded?

Are the allocation of treatment methods described, if so what were they?

What was the treatment compared with (placebo or standard therapies)?

Where did the study take place (city, multi-centre, hospital, community)?

How long did the trial last for?

Was there a follow-up period? If yes, over how long did it take place?

What were the inclusion/exclusion criteria?

What was the dosage involved (if the treatment was pharmacological)?

What were the dosages for the control/placebo group?

3. Results

How were baseline measurements recorded?

What were the outcome measures?

Over what period were values recorded for the outcome measures?

Were there any drop outs reported? If so, how many?

Data:

Were the continuous data reported as Means and SDs/SEMs/Confidence Intervals? Please provide page numbers where results were presented to facilitate double-checking

What outcomes were presented as binary data?

Were the results reported in tables/graphs?

If, so please indicate on the axes of the copy sent to you, what the headings mean in English, and return with this sheet.

What is the value (e.g. % or otherwise) to describe the increase for each of the outcome measures that are reported? Please give +/- values if reported. Please indicate where these values can be found in the original article (this will help to facilitate validation).

Is there any additional information which you consider significant?

HISTORY

Protocol first published: Issue 1, 2007
Review first published: Issue 2, 2012

Date	Event	Description
26 August 2008	Amended	When the full review of "Aspirin and anti-inflammatory drugs for Alzheimer's Disease" is published, it will replace the previously published reviews "Ibuprofen for Alzheimer's Disease", "Indomethacin for Alzheimer's Disease", and the previously published protocol "Naproxen for Alzheimer's Disease". At that time, these ibuprofen and indomethacin reviews and this naproxen protocol will be withdrawn from the Cochrane Library.
26 August 2008	Amended	Converted to new review format.
14 November 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

DJ: Wrote, coordinated, searched and selected trials for inclusion in this review. Also extracted, interpreted and entered data on to RevMan.

MI and NT: contributed to trial searches, obtained copies of trial reports and assessed trials for inclusion/exclusion. They also were involved in data extraction and interpretation, and providing general advice on the review

JMcC: contributed to design of analysis, data interpretation and drafting of review

Contact editors: Leon Flicker and Gordon Wilcock
Consumer editor: Lynne Ramsay

DECLARATIONS OF INTEREST

All authors declare no conflict of interest in this research project.

SOURCES OF SUPPORT

Internal sources

- New Source of support, Not specified.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1) Background about steroidal anti-inflammatory drugs was added in the review.

2) Inclusion criteria was adjusted to include any types of RCT and not only double-blinded

3) Two reviewers (DJ, MI) instead of 3 reviewers independently examined the titles and abstracts of the trials identified in the search and considered them for inclusion according to the pre-determined eligibility criteria. Any disparity was resolved by retrieval of the cited articles and further discussion with the third reviewer (NT).

4) Review topic was changed from aspirin and anti-inflammatory agents for Alzheimer's disease to aspirin, steroidal and non-steroidal anti-inflammatory agents for Alzheimer's disease.

5) Data was not extracted independently by two authors. The first author extracted the data and this was followed by verification by a second author.

INDEX TERMS

Medical Subject Headings (MeSH)

Alzheimer Disease [*drug therapy] [etiology]; Anti-Inflammatory Agents [adverse effects] [*therapeutic use]; Anti-Inflammatory Agents, Non-Steroidal [adverse effects] [*therapeutic use]; Aspirin [adverse effects] [*therapeutic use]; Cyclooxygenase 2 Inhibitors [adverse effects] [therapeutic use]; Glucocorticoids [adverse effects] [therapeutic use]; Inflammation [complications] [drug therapy]; Randomized Controlled Trials as Topic; Treatment Outcome

MeSH check words

Aged; Aged, 80 and over; Humans