Effect of non-steroidal anti-inflammatory drugs on risk of Alzheimer's disease: systematic review and meta-analysis of observational studies
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CRD summary
This review assessed the effect of non-steroidal anti-inflammatory drugs (NSAIDs) on the risk of Alzheimer's disease. The authors concluded that the results support the hypothesis that NSAIDs may protect against the development of Alzheimer's disease. The authors' conclusions appear to follow from the evidence presented.

Authors' objectives
To quantify the risk of Alzheimer's disease (AD) in users of all non-steroidal anti-inflammatory drugs (NSAIDs) and users of aspirin, and to determine any influence of duration of use.

Searching
MEDLINE (1966 to October 2002), EMBASE (1974 to October 2002), International Pharmaceutical Abstracts (1975 to October 2002), and the Cochrane Library (Issue 2, 2002) were searched for English language studies; the search terms were reported. The reference lists of retrieved articles were also checked.

Study selection
Study designs of evaluations included in the review
Observational studies were eligible for inclusion. Both cohort and case-control studies were included.

Specific interventions included in the review
Studies reporting exposure to NSAIDs or aspirin, at any time during the study period, were eligible for inclusion.
Studies classifying NSAID use with respect to exposure duration were classified as short, intermediate or long term.
Studies of other analgesics were excluded. The type of NSAID evaluated in the included studies, and the dose and duration of NSAID exposure in each study, were not reported.

Participants included in the review
There were no inclusion criteria relating to the participants. The participants were aged 55 years or older. No further details of the populations of the included studies were given.

Outcomes assessed in the review
Studies reporting the outcome of AD or dementia were eligible for inclusion. Studies in which vascular dementia was the primary outcome were excluded. The studies had to report relative risks (RR), odds ratios (OR), or sufficient data for these to be calculated. The included studies diagnosed disease by clinical investigation, interviews, Folstein mini-mental state examination, medical records, or autopsy.

How were decisions on the relevance of primary studies made?
Two reviewers assessed studies for relevance, with any disagreements being resolved by consensus with a third reviewer.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.
Methods of synthesis
How were the studies combined?
Pooled RRs and 95% confidence intervals (CIs) were calculated using a random-effects model. Publication bias was investigated using funnel plots.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Q test. When less than 20 studies were in the meta-analysis, heterogeneity was also investigated graphically and quantitatively using the R(I) statistic (reference given). Subgroup analyses were performed to investigate the duration of NSAID use.

Results of the review
Ten studies were included in the review: 6 cohort studies (n=13,211) and 4 case-control studies (n=6,358). Seven studies evaluated the effect of both NSAID and aspirin exposure, two NSAID exposure, and one aspirin exposure.

NSAIDs (9 studies).
The pooled RR for AD among NSAID users was not statistically significant in the cohort studies (RR 0.84, 95% CI: 0.54, 1.05); however, these results were statistically heterogeneous (P=0.04). The pooled RR for AD among NSAID users was statistically significant in the case-controlled studies (RR 0.62, 95% CI: 0.45, 0.82), and when the results for all studies were combined (RR 0.72, 95% CI: 0.56, 0.94).

The RR of short-term exposure to NSAIDs was not statistically significant (RR 0.95, 95% CI: 0.70, 1.29), although this result was based on a single study. The RR of intermediate NSAID exposure was also not statistically significant (RR 0.83, 95% CI: 0.65, 1.06). Long-term exposure resulted in a significant reduction in the RR of AD (RR 0.27, 95% CI: 0.13, 0.58), but the results were heterogeneous (P=0.06).

Aspirin (8 studies).
The pooled RR for AD among aspirin users was not statistically significant (RR 0.87, 95% CI: 0.70, 1.07); no statistical heterogeneity was shown.

The funnel plots did not suggest publication bias.

Authors' conclusions
The results supported the hypothesis that NSAIDs may protect against the development of AD. However, the appropriate dose, duration and ratios of risk to benefit are still unclear.

CRD commentary
The review question was clearly stated. The inclusion criteria for the intervention and outcomes were clear, whereas those for study design were vague and none were reported for the participants. Several relevant electronic databases were searched and reference lists were checked. However, only English language articles were considered, thus introducing the potential for language bias. The possibility of publication bias was investigated. Attempts were made to reduce error and bias by carrying out the study selection process in duplicate; it was unclear whether the data extraction was also carried out in duplicate. The authors did not report a validity assessment of the included studies, although they did highlight the increased potential for bias in observational studies.

The authors provided inadequate study details with regard to the populations and interventions. Appropriate measures of effect were calculated and statistical heterogeneity was assessed. The authors' conclusions appear to follow from the evidence presented, and the authors highlighted the limitations of the data included.
Implications of the review for practice and research
The authors did not state any implications for practice or further research.

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