Nonsteroidal anti-inflammatory drugs for the prevention of Alzheimer's disease: a systematic review


CRD summary
This review assessed the relationship between exposure to non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) and Alzheimer's disease. The authors concluded that exposure to NSAIDs was associated with a reduced risk of Alzheimer's disease. The review appears to support the authors' conclusions, but the evidence presented came from observational studies and is not sufficient to show a causal relationship.

Authors' objectives
To assess the relationship between exposure to non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) and Alzheimer's disease.

Searching
MEDLINE, Biological Abstracts and the Cochrane Library were searched to July 2003 for studies published in English; the search terms were reported. The reference lists of retrieved articles were also checked.

Study selection
Study designs of evaluations included in the review
Cross-sectional, retrospective and prospective observational studies were eligible for inclusion if they reported original data for cases and controls.

Specific interventions included in the review
Studies that described exposure to NSAIDs were eligible for inclusion. The review focused on non-aspirin NSAIDs. The included studies categorised NSAID exposure as lifetime use (ever or never) or as exposure lasting 2 or more years. Studies used different methods to ascertain NSAID exposure: questionnaires, structured interviews with participants and/or surrogate informers, direct examination of medicine containers, and medical and pharmacy records. Some studies verified the information using medical records or medicine containers.

Participants included in the review
Inclusion criteria were not specified in terms of the participants. Some of the included studies had lower age limits, ranging from 55 to 75 years; other studies placed no age restrictions on the participants.

Outcomes assessed in the review
Studies that assessed Alzheimer's disease diagnosed using formal criteria were eligible for inclusion. Studies using continuous measures of cognitive function as a surrogate measure of Alzheimer's disease were excluded from the meta-analysis.

How were decisions on the relevance of primary studies made?
At least two of four reviewers selected studies for inclusion. Any disagreements were resolved by consensus of all four reviewers.

Assessment of study quality
The authors stated that validity was assessed, but the criteria used were not reported. At least two of four reviewers assessed validity. Any disagreements were resolved by consensus of all four reviewers.
**Data extraction**

At least two of four reviewers extracted the data. Any disagreements were resolved by consensus of all four reviewers. Crude and adjusted risk estimates were extracted and used to calculate odds ratios (ORs) for non-prospective studies and relative risks (RRs) for prospective studies, both with 95% confidence intervals (CIs). For one study that did not report non-aspirin NSAIDs and aspirin separately, the risk estimate was extracted for all patients.

**Methods of synthesis**

How were the studies combined?

Pooled risk estimates for Alzheimer’s disease were calculated separately for prospective studies using RRs and for non-prospective studies using ORs. Both fixed-effect and random-effects models were used but, since the results were similar, the review only reported the results of the fixed-effect model. The studies were weighted using the inverse of the variance. Adjusted risk estimates from all but one of the included studies were used in the meta-analyses.

Publication bias was assessed using Begg’s funnel plot and Egger’s plots.

How were differences between studies investigated?

Statistical heterogeneity was assessed using the Q statistic.

**Results of the review**

Eleven reports of 8 observational studies were included (n=31,366, not all of whom were included in the meta-analyses). There were 4 prospective studies (n=15,899) and 7 non-prospective studies (n=15,467). The non-prospective studies comprised 3 case-control studies and 4 cross-sectional studies.

In all but one of the included studies the analysis was designed to examine the relationship between NSAIDs and Alzheimer’s disease.

All of the included studies controlled for some or all of the following potential confounding factors using matching or multivariate statistical analysis: age, female sex, low education, and genetic factors. The studies varied in their control for other potential confounders.

NSAID exposure was associated with a significantly reduced risk of Alzheimer’s disease in both non-prospective studies (OR 0.51, 95% CI: 0.40, 0.66, P<0.001) and prospective studies (lifetime NSAID use, RR 0.74, 95% CI: 0.62, 0.89, P<0.01; NSAID use for 2 years or more, RR 0.42, 95% CI: 0.26, 0.66, P<0.001, based on 3 studies). No significant heterogeneity was found for any of the analyses (P=0.48, P=0.23 and P=0.56, respectively).

The funnel plot of non-prospective studies showed no obvious publication bias.

**Authors’ conclusions**

Exposure to NSAIDs was associated with a reduced risk of Alzheimer’s disease.

**CRD commentary**

The review addressed a clear question that was defined in terms of the intervention, outcomes and study design. Several relevant sources were searched, but no attempts were made to minimise language bias (by searching for non-English publications) or publication bias (by searching for unpublished material). However, publication bias was assessed using standard methods. Methods were used to minimise reviewer errors and bias in the study selection, validity assessment and data extraction processes. The studies were grouped by study design, statistical heterogeneity was assessed, and the studies were combined using meta-analysis. However, the results were not discussed in relation to study quality. Potential confounding factors were controlled with varying degrees of rigour in the included studies, and were taken into account in the review. The review appears to support the authors’ conclusions, but the evidence presented is only strong enough to show an association and not a causal relationship between NSAID exposure and risk of Alzheimer’s disease.
Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that until the results from a randomised controlled trial on NSAIDs for the prevention of Alzheimer's disease are available (see Other Publications of Related Interest), observational studies should focus on examining the temporal relationship between NSAID exposure and Alzheimer's disease.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.