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## Prevention and treatment of dementia or Alzheimer's disease by statins: a meta-analysis

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### CRD summary

This review concluded that current evidence does not show any beneficial preventive effects of statins on dementia or Alzheimer's disease. Overall, the reviewers' analysis supports their conclusions, but the reliability of the findings is unclear given the poor reporting of the review methods and the absence of any assessment of study quality.

### Authors' objectives

To determine the effects of statins on the prevention and treatment of dementia and Alzheimer's disease (AD).

### Searching

MEDLINE, PsycINFO, CINAHL, Japan Medical Society database and the Cochrane Library were searched to October 2005; the search terms were reported. No restrictions were placed on language or the type of publication used.

### Study selection

#### Study designs of evaluations included in the review

Randomised controlled trials (RCTs) and prospective nested case-control and cohort studies were eligible for inclusion. The follow-up for included studies was between 3 and 9 years for prevention studies, and was 26 weeks and 1 year for treatment studies.

#### Specific interventions included in the review

Studies of any statin were eligible for inclusion. The included prevention studies compared exposure to undefined statins with no exposure; the majority of studies considered any exposure to statins. Treatment studies compared either simvastatin (20 to 80 mg) or atorvastatin (80 mg) with placebo.

#### Participants included in the review

Prevention studies had to include participants with objectively normal cognitive function who were of an age to be at risk of AD, where standardised clinical or pathologic criteria were used to diagnose dementia or AD. Treatment studies had to include participants with a diagnosis of dementia or AD as defined by standardised clinical or pathologic criteria. The majority of prevention studies included both AD and dementia patients; both treatment studies included patients with mild to moderate AD.

#### Outcomes assessed in the review

The primary outcome measure for treatment studies was cognitive function measured using the Alzheimer's Disease Assessment Scale – cognitive (ADAS-cog) subscore. Prevention studies had to record the incidence of dementia or AD according to standardised criteria.

#### How were decisions on the relevance of primary studies made?

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

### 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. Unadjusted and adjusted odds ratios (ORs) or hazard ratios with 95% confidence intervals (CIs) were calculated for the incidence of dementia and AD. Means and standard deviations were calculated for the ADAS-cog scores.

### Methods of synthesis

#### How were the studies combined?

Pooled ORs and relative risks (RRs) with 95% CIs were calculated using both random-effects and fixed-effect models. ADAS-cog scores were reported as pooled mean differences.

#### How were differences between studies investigated?

Statistical heterogeneity was assessed and some clinical differences between the studies were evident from the text and data tables. Subgroup analyses were performed, with studies grouped according to dementia or AD and by study design.

### Results of the review

Nine studies (n=14,027) were included in the review: 7 prevention studies (n=13,920) and 2 treatment studies (n=107). The prevention studies comprised 4 cohort studies and 3 case-control studies; the treatment studies were both RCTs.

#### Prevention.

Unadjusted pooled data (4 cohort and 2 case-control studies) showed a significantly greater incidence of dementia in participants who had not used statins in comparison with those who had (OR 0.67, 95% CI: 0.54, 0.82, p=0.042). When pooled adjusted RRs were calculated, no significant differences were apparent when using either fixed-effect or random-effects models. However, significant heterogeneity was detected in the pooled adjusted RRs. There were no significant differences between statin users and non-users in the incidence of AD, based on unadjusted and adjusted pooled effect sizes using random-effects and fixed-effect models. Statistical tests for heterogeneity were not significant. When studies were grouped according to study design, significant differences in favour of statins were found for case-control studies of dementia (RR 0.28, 95% CI: 0.15, 0.54) and case-control studies of AD (RR 0.61, 95% CI: 0.42, 0.88); no statistically significant differences in the incidence of dementia or AD were observed between statin users and non-users in cohort studies.

#### Treatment.

One RCT of atorvastatin (80 mg) showed a significant difference in ADAS-cog scores at 6 months in favour of the statin, compared with placebo, in patients with mild to moderate dementia (p<0.03); however, no significant differences were present at 12 months (p=0.055). In the second RCT, no significant differences in ADAS-cog scores were found between simvastatin (20 to 80 mg) and placebo after 26 weeks. Overall, the pooled mean difference in ADAS-cog scores was not significantly different between statin and placebo groups.

### Authors' conclusions

The current evidence does not show any beneficial effects of statins on the prevention of dementia or AD.

### CRD commentary

This review answered a clear research question. However, it might not have included all of the relevant studies as there were no apparent attempts to locate unpublished studies. The risk of reviewer error and bias is also unclear since the review methods were not clearly described. The review analysis considered some differences between the studies and statistical tests were performed to assess the level of heterogeneity between studies. The power of these tests, however, is likely to be limited given the small number of included studies. Analyses were also performed to take differences between different study designs into account. However, the authors themselves stated that a number of population characteristics such as age, gender, education and apolipoprotein E can affect the risk of dementia and AD; these factors were not reported in the data tables or considered in the analyses. The apparent lack of an assessment of study quality also makes it difficult to assess the reliability of the review findings, particularly as the majority of the included studies are observational studies which are likely to be at greater risk of bias. The two RCTs that were included in the analysis were also very small and only followed participants for a relatively short period of time given the chronic progressive nature of dementia and AD. Overall, the reviewers' analysis supports their conclusions but, given the aforementioned issues with the review methodology and the absence of any assessment of study quality, the findings may not be reliable.

### Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated 'further study and independent confirmation of the association between statin use and dementia and AD in larger clinical trials is warranted'. They also suggested that in order to counteract the longer length and costs of prevention trials, it may be beneficial to select participants at high risk of developing AD or dementia.

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