Statins and cognitive function: a systematic review
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CRD summary
This review concluded that published data did not suggest an adverse effect of statins on cognition but the strength of available evidence was limited, particularly with regard to high-dose statins. The authors highlighted some limitations in their review. The authors' cautious conclusions reflect the evidence presented and their recommendation for further research seems appropriate.

Authors' objectives
To examine the association between statin therapy and cognitive function.

Searching
PubMed, EMBASE and The Cochrane Library were searched from inception through October 2012 for studies published in English. Bibliographies of included studies were scanned. US Food and Drug Administration (FDA) databases were searched from January 1986 through March 2012 for adverse events relating to statins. Search terms were reported in the supplementary material of the review.

Study selection
Eligible studies were randomised controlled trials (RCTs), cohort, case-control and cross-sectional studies that evaluated cognitive function in adult patients who received statin therapy.

Participant ages ranged from 11 to 89 years. Follow-up ranged from 0.3 to 69 years for cohort and case-control studies and 0.8 to 60 months for RCTs. Various assessment tools were used to test cognitive function.

Two reviewers independently screened studies for inclusion; one reviewer checked the FDA adverse event reporting databases.

Assessment of study quality
The authors assessed risk of bias for individual studies using the Cochrane risk of bias tool for RCTs and the Newcastle-Ottawa Scale for cohort and case-control studies. Evidence quality was assessed using the GRADE approach and graded as high if it included RCTs, low if it included observational studies and very low if it included only descriptive studies.

One reviewer assessed study quality which was then checked by a second reviewer.

Data extraction
Two reviewers independently extracted data to calculate relative risks and related 95% confidence intervals. Incidence of dementia, Alzheimer's disease or mild cognitive impairment were extracted as well as the cognitive performance scores (categories included global cognitive performance, frontal-executive function and working memory, declarative memory, procedural memory, attention, processing speed, visuoperception and motor speed).

Methods of synthesis
Pooled adjusted (if available) relative risks and 95% confidence intervals were calculated using a random-effects model. Where RCTs or observational studies precluded quantitative synthesis, results from individual studies were summarised qualitatively. Sensitivity analysis was performed for studies with lower and higher risk of bias. Adverse event reporting rates were calculated by dividing the number of cognitive-related adverse event cases for statins with the total number of cases of adverse events or the total number of prescriptions dispensed. Adverse event reporting rates were calculated for losartan and clopidogrel.

Results of the review
Fifty-seven studies were included in the review and 27 of these – three RCTs, 16 cohort, four case-control and four cross-sectional studies – were included in the meta-analysis. Four RCTs, four cohort studies and two case-control studies met the criteria for the lowest risk of bias. In most RCTs, insufficient information was available to judge
randomisation or allocation concealment; in cohort and case-control studies, poor representativeness, inadequate follow-up, poor comparability and exposure ascertainment weakened study quality.

Among statin users, low quality evidence suggested no increased incidence of Alzheimer's disease and no difference in cognitive performance in procedural memory, attention or motor speed.

Moderate quality evidence suggested no increased incidence of dementia or mild cognitive impairment and no change in cognitive performance scores, executive function, declarative memory, processing speed and visuoperception.

According to FDA data, adverse event reporting rates were similar among statins, losartan and clopidogrel.

**Authors' conclusions**
Larger and better-designed studies were needed to draw unequivocal conclusions about the relationship between statins and cognition. Published data do not suggest an adverse effect of statins on these outcomes but the strength of available evidence was limited, particularly with regard to high-dose statins.

**CRD commentary**
The review question and inclusion criteria were clear. Relevant sources were searched. The authors searched only for studies published in English so some relevant studies may have been missed. Attempts were made to minimise errors and bias in the review process. Study quality was assessed using appropriate criteria. A reasonable level of information about individual studies was provided. Appropriate methods were used to pool data and although statistical measures of heterogeneity were not reported, the variability in study outcomes was apparent from the presented forest plots and the authors' discussion of the evidence. The authors highlighted some limitations in their review (such as imprecision, inconsistency of some findings and risk of bias limiting the strength of the evidence).

The authors' cautious conclusions reflect the evidence presented. Their recommendation for further research seems appropriate.

**Implications of the review for practice and research**

**Practice:** None stated.

**Research:** The authors stated that larger and better-designed studies were needed to draw unequivocal conclusions about the relationship between statins and cognition.

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