MAYO CLINIC

ORIGINAL ARTICLE

Statins and Cognition: A Systematic Review and Meta-analysis of Short- and Long-term Cognitive Effects

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Abstract

Objective: To evaluate the effect of statins on short-term cognitive function and the long-term incidence of dementia.

Patients and Methods: A systematic search was performed of MEDLINE, EMBASE, and the Cochrane Central Register from their inception to April 25, 2013. Adults with no history of cognitive dysfunction treated with statins were included from high-quality randomized controlled trials and prospective cohort studies after formal bias assessment.

Results: Sixteen studies were included in qualitative synthesis and 11 in quantitative synthesis. Short-term trials did not show a consistent effect of statin therapy on cognitive end points. Digit Symbol Substitution Testing (a well-validated measure of cognitive function) was the most common short-term end point, with no significant differences in the mean change from baseline to follow-up between the statin and placebo groups (mean change, 1.65; 95% CI, −0.03 to 3.32; 296 total exposures in 3 trials). Long-term cognition studies included 23,443 patients with a mean exposure duration of 3 to 24.9 years. Three studies found no association between statin use and incident dementia, and 5 found a favorable effect. Pooled results revealed a 29% reduction in incident dementia in statin-treated patients (hazard ratio, 0.71; 95% CI, 0.61-0.82).

Conclusion: In patients without baseline cognitive dysfunction, short-term data are most compatible with no adverse effect of statins on cognition, and long-term data may support a beneficial role for statins in the prevention of dementia.

 ■ Mayo Clin Proc. 2013;88(11):1213-1221

In February 2012, the US Food and Drug Administration (FDA) released changes in labeling for statins.[1] Specifically, the FDA stated that "ill-defined memory loss" and "confusion" were among the cognitive effects noted in statin users. Citing certain observational studies[2-10] and randomized controlled trials,[11-13] the FDA noted a spectrum of time of onset (typically <1 year) and that these effects could be reversible after medication discontinuation. The FDA noted that these effects were not associated with "fixed or progressive dementias," such as Alzheimer disease.

In a subsequent narrative overview of statin safety literature, it was concluded that there is no increased risk of cognitive decline with statin use and that the FDA label changes should not change clinical practice.[14] Still, the most recent Cochrane Review on statins for the primary prevention of cardiovascular disease indicates a lingering concern for adverse effects of statins on cognition.[15] The FDA label revision and studies therein have been used by some experts as justification for the controversial recommendation to avoid statins in primary prevention.[16] The label revision may have other important public health consequences, such as limiting the use of statins, or doses of statins, in patients with established cardiovascular disease. Indeed, concerns about adverse cognitive effects of statins have been popularized by the media[17,18] and remain an ongoing challenge in the clinic.

In addition to the focus on short-term safety by the FDA, long-term cognitive outcomes, including new diagnoses of dementia, are another important topic of interest to patients and physicians. Statins for the prevention and treatment of dementia first generated attention in 2000 when 2 epidemiologic studies reported a lower risk of dementia in those using statins.[19,20]

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Several publications that followed reported mixed results.[3,21-24] A review published in 2007 found no effect in adjusted analyses,[25] whereas 2 more recently published meta-analyses found a protective effect.[26,27] However, additional studies have become available since their searches in January 2012[26] and July 2011.[27] These 2 meta-analyses[26,27] are also limited by the inclusion of lower-quality studies despite the availability of sufficient evidence from high-quality prospective studies. Therefore, an updated meta-analysis that selects studies based on formal bias assessments is needed.

This systematic review and meta-analysis assesses the hypothesis that statins have short-term and/or long-term cognitive effects in adults with no history of cognitive dysfunction in randomized controlled trials or high-quality prospective cohort studies.

PATIENTS AND METHODS

Data Sources

We performed a systematic, computer-aided search of MEDLINE, EMBASE, and the Cochrane Central Register from their inception to April 25, 2013, and we augmented this search by scrutinizing reference lists of relevant articles and making inquiries among colleagues, collaborators, and experts in the field. An optimal search strategy was devised on the basis of previous literature[28] with the aid of an informationalist (Supplemental Appendix 1 [available online at http://www.mayoclinicproceedings.org]). We did not assign language filters. To assess for publication bias, we sought to identify conference abstracts without an associated manuscript publication and other unpublished research by searching Current Controlled Trials (http://controlled-trials.com) and ClinicalTrials.gov (http://clinicaltrials.gov). The corresponding authors of such articles were contacted.

Study Selection

We registered the eligibility criteria a priori with the Welch Medical Library and the Ciccarone Center for the Prevention of Heart Disease at Johns Hopkins University (Baltimore, MD). Participants were required to have no history of cognitive dysfunction (as evidenced by an explicit statement or formal testing). For short-term cognition, studies were required to be randomized controlled trials of any statin using validated objective measures of cognition as end points. For long-term cognition, studies were required to be either randomized controlled trials or high-quality prospective cohort studies of any statin with an end point of dementia.

Articles were systematically selected for inclusion (Figure 1). Two independent reviewers (K.J.S. and R.J.M.) screened article titles and abstracts to identify potentially eligible articles warranting full-text review. Results were compared (98% raw agreement; Cohen κ, 0.99), and all disagreements were settled by discussion and review of full articles. Full articles of all potentially eligible studies were read by both reviewers, and data were extracted to determine whether they met the eligibility criteria for this study. In the case of duplicate publication, we included only the largest, most complete article. Articles were designated for inclusion in the appropriate domain (short- or long-term cognition, as defined in the Table). The Johns Hopkins Institutional Review Board declared the study exempt.

Outcome Measures and Data Extraction

The taxonomy of outcome measures used in this study is organized in the Table. In qualitative synthesis, this study examined validated tests of cognitive impairment for short-term cognition and an incident diagnosis of dementia for long-term cognition. Quantitative synthesis for short-term cognition was performed for studies incorporating Digit Symbol Substitution Test (DSST) scores because the DSST was the most commonly used objective measure of cognition and has high test-retest reliability. The DSST (visual illustration in Supplemental Appendix 2 [available online at http://www.mayoclinicproceedings.org]) asks patients to match numbers with corresponding symbols as quickly as possible in an allotted period (eg, 90 seconds). It tests a variety of cognitive functions, including incidental short-term memory, perceptual organization, visuomotor coordination, and selective attention.[29] Quantitative synthesis for long-term cognition was similar to qualitative synthesis, although we considered only clinically diagnosed and not *International Classification of Diseases, Ninth Revision* code–diagnosed dementia to limit bias (further discussion below); summary measures included relative risk reduction, absolute risk reduction,

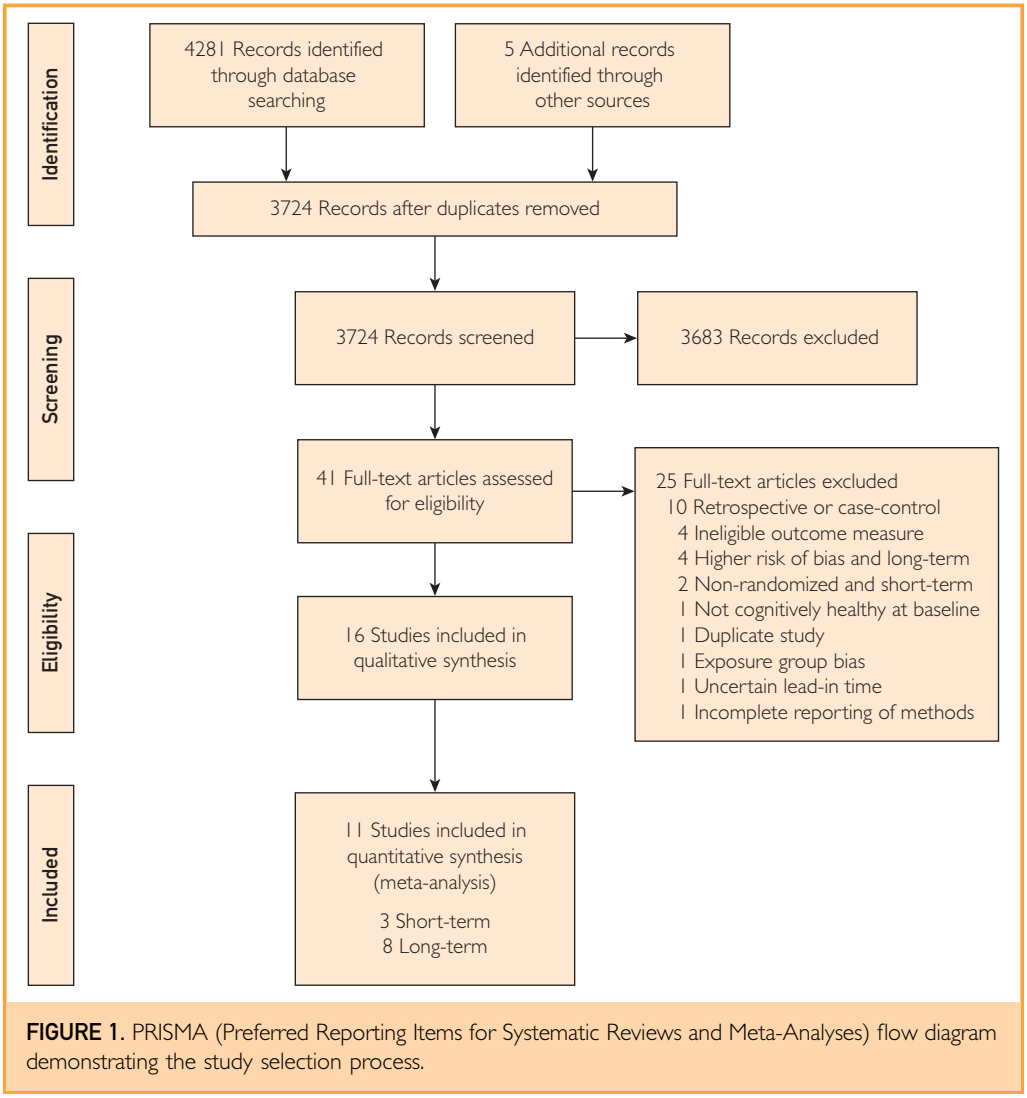


FIGURE 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram demonstrating the study selection process.

and number needed to treat. Data were handled in RevMan version 5.1 software (Cochrane Collaboration), and I^2 was examined as a measure of consistency.

Assessing the Risk of Bias of Selected Articles

For randomized controlled trials, we used the Cochrane Collaboration's tool for assessing risk of bias.[30] Each article was evaluated for 6 domains: sequence generation; allocation concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias. Each domain was assigned low, high, or unclear risk based on the tool's judgment criteria (Supplemental Appendix 3 [available online at http://www.mayoclinicproceedings.org]).

For prospective cohort studies, we used the Newcastle-Ottawa Scale adapted for the exposures and outcomes of interest in this review (Supplemental Figure 4 [available online at http://www.mayoclinicproceedings.org]).[31] The ideal exposed cohort was defined as a representative sampling of the general population at risk for dementia. For the ascertainment of exposure category, self-reported methods were assigned the highest risk of bias; record linkage (generally taken from pharmacy databases on filled prescriptions) was seen as carrying a higher risk of bias compared with in-person clinical assessment of dementia. In addition, studies that did not adjust for known confounders or a propensity score were viewed as higher risk. A sensitivity analysis including higher-risk studies was conducted.

TABLE. Taxonomy of Statin-Related Cognitive Effects[a]

Domain	Time frame	Outcome	Outcome definition	Outcome ascertainment
Short-term cognition	<1 y after drug initiation	Cognitive impairment	Impairment in mental faculty of knowing, including perceiving, recognizing, conceiving, judging, reasoning, and imagining	Validated tests of cognitive impairment, including memory, attention, and problem solving
Long-term cognition	≥1 y after drug initiation	Dementia	*DSM-IV*-TR definition[b] not limited to any particular subtype (eg, Alzheimer disease, vascular dementia) but exclusive of cognitive impairment/decline	*ICD-9* code, interview or questionnaire establishing *DSM-IV*-TR diagnosis

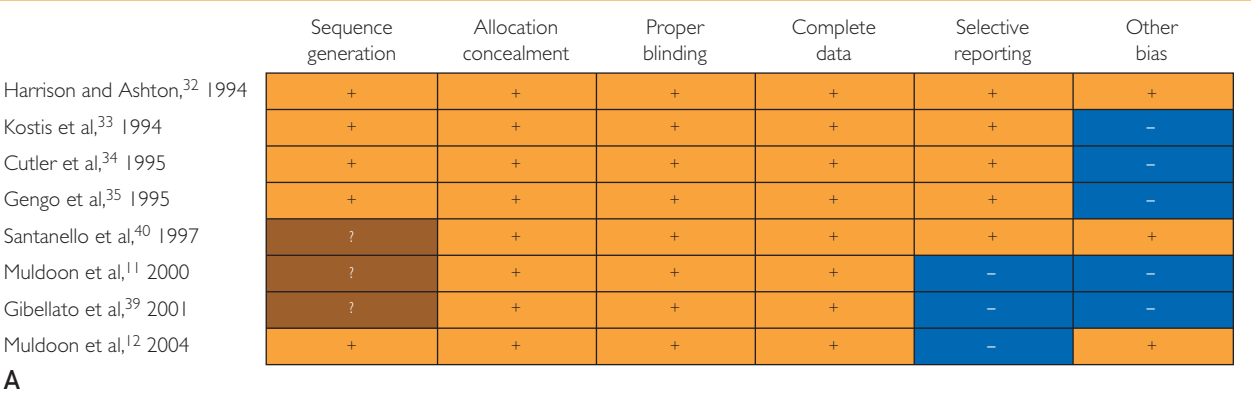
[a]*DSM-IV*-TR = *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision); *ICD-9* = *International Classification of Diseases, Ninth Revision.*
[b]The development of multiple cognitive deficits that include memory impairment and at least 1 of the following cognitive disturbances: aphasia, apraxia, agnosia, or a disturbance in executive functioning. The cognitive deficits must be sufficiently severe to cause impairment in occupational or social functioning and must represent a decline from a previously higher level of functioning.

RESULTS

A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram is shown in Figure 1. The initial search identified 4286 records; after screening, 41 were considered potentially eligible. These 41 full-text articles were assessed for eligibility; 16 met eligibility for qualitative synthesis (8 short-term and 8 long-term cognition studies) and 11 for quantitative synthesis.

Short-term Cognition

Two studies were excluded because they were not randomized,[6,36] one study was excluded due to uncertain lead-in time of treatment relative to cognitive testing,[37] one was excluded



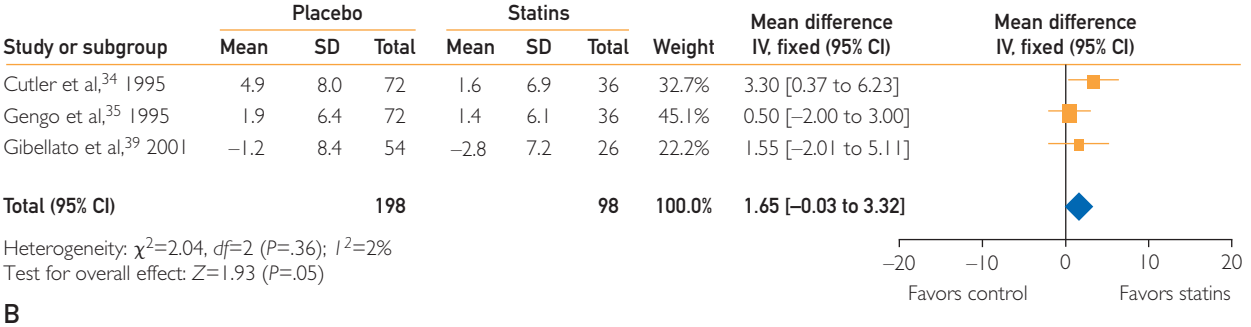


FIGURE 2. A, Bias summary for short-term cognition. + = low risk of bias; ? = unclear risk of bias; − = high risk of bias. B, Forest plot of quantitative synthesis for short-term cognition showing change in mean Digit Symbol Substitution Test scores in the statin vs placebo groups (constructed using Cochrane RevMan version 5.1 software). *df* = degree of freedom; IV = inverse variance.

Mayo Clin Proc. ■ November 2013;88(11):1213-1221 ■ http://dx.doi.org/10.1016/j.mayocp.2013.07.013
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because it was a duplicate of a long-term study,[23] and one was excluded due to incomplete reporting of methods.[38] None of the remaining 8 studies showed excessive bias (Figure 2, A). The characteristics of the studies are summarized in Supplemental Table 1 (available online at http://www.mayoclinicproceedings.org). In total, the studies did not show any consistent effect of statin therapy on cognitive end points.

Of the 8 studies included in qualitative synthesis, 3 provided sufficient DSST data for quantitative synthesis.[34,35,39] Quantitative synthesis of the change in mean DSST score in these 3 studies was consistent with no adverse effect of statin therapy and a trend toward benefit (mean change, 1.65; 95% CI, −0.03 to 3.32; 296 total exposures) (Figure 2, B).

Prevention of Dementia

Twenty-eight studies were considered potentially eligible.[2-5,13,19-22,24,41-58] Ten studies were excluded on the basis of design because they used retrospective data or were nested case-control studies.[2,19,20,24,41-46] Two studies focused on cognitive decline as the primary outcome and not on dementia.[47,48] In one study, participants were not cognitively healthy at baseline.[49] One study added patients and excluded the original cohort (exposure group bias).[50] Two large randomized trials that analyzed cognitive decline or dementia as a secondary outcome were also excluded.[13,22] The Heart Protection Study did not assess baseline cognition and recorded a new diagnosis of dementia in 31 patients in both treatment arms.[22] The Prospective Study of Pravastatin in the Elderly at Risk study assessed cognitive function 6 times throughout the study using 4 neuropsychological performance tests but did not include dementia as an end point.[13]

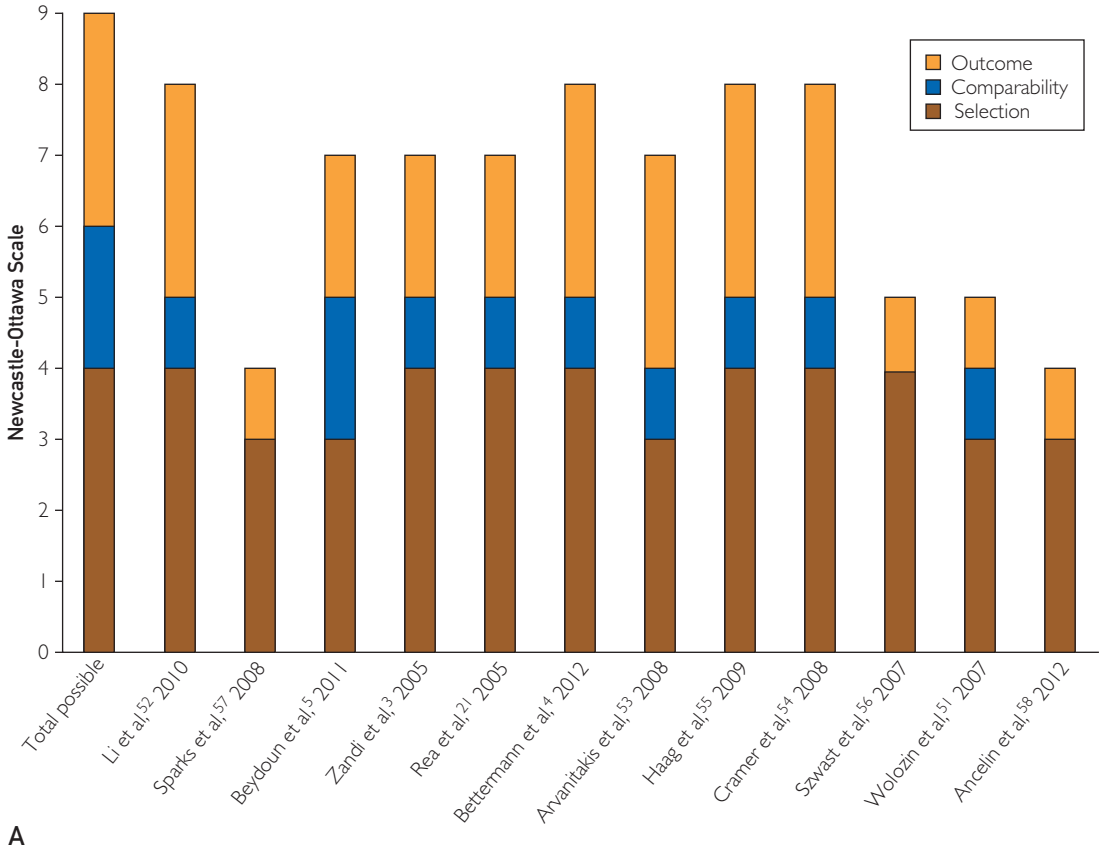
The 12 remaining studies underwent bias assessment.[3-5,21,51-58] Four were excluded as their risk of bias was higher than that of the remaining group (Figure 3, A), primarily due to outcome measurement and appropriate consideration of confounders.[51,56-58] Three of the 4 excluded trials reported a reduction in incident dementia with statin use (additional details on the characteristics of these excluded trials are provided in Supplemental Table 2 [available online at http://www.mayoclinicproceedings.org]).

The 8 remaining studies were included in quantitative synthesis, encompassing 23,443 patients with a mean exposure duration of 3 to 24.9 years (Supplemental Table 3 [available online at http://www.mayoclinicproceedings.org]).[3-5,21,52-55] The outcome was dementia in 5 studies and specifically Alzheimer dementia in 3. Three studies found no association between statin use and incident dementia, and 5 found a favorable effect. We found no difference in the risk of bias based on the modified Newcastle-Ottawa Scale between the significant and nonsignificant studies. Quantitative synthesis (Figure 3, B) showed a 29% reduction in incident dementia in statin-treated patients (hazard ratio, 0.71; 95% CI, 0.61-0.82). A sensitivity analysis including the 4 studies with a higher risk of bias provided a similar result (hazard ratio, 0.71; 95% CI, 0.68-0.74). Five studies[3,4,21,53,54] with mean follow-up of 6.2 years provided sufficient data to calculate an absolute risk reduction of 2% (95% CI, 1%-3%) and a number needed to treat of 50 (95% CI, 33-100).

DISCUSSION

In this systematic review and meta-analysis of adults without a history of cognitive dysfunction, randomized controlled trials of statin effects on short-term cognition were most compatible with no adverse effects; the studies included relatively small numbers of participants. In the long-term studies, results were consistent with a protective statin effect on dementia, with a 29% relative reduction and a 2% absolute risk reduction (number needed to treat for 6.2 years was 50).

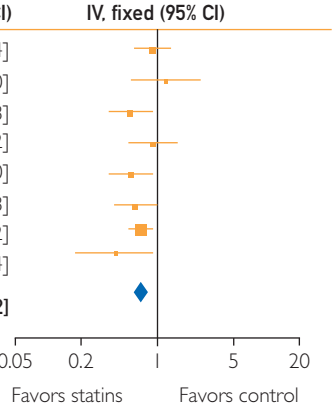
The strengths of the present study include a clear taxonomy for short- vs long-term effects of statin therapy, use of a priori eligibility criteria, focus on objective outcome measures, formal assessment of bias, and quantitative synthesis. Regarding statins and short-term cognition, studies were small, and this review provides the first quantitative synthesis of DSST scores. This was the most common outcome measure used in short-term studies, is well validated, and integrates multiple cognitive functions, including short-term memory. Nevertheless, certain cognitive domains may be better evaluated by other outcome measures. We considered all statins together as a class effect; although another review[26] found no difference in the prevention of dementia by lipophilicity, there is a paucity of head-to-head comparisons between lipophilic and hydrophilic statins. We cannot exclude differential effects of a particular statin



A

Study or subgroup	Log [hazard ratio]	Statins SE	Statins Total		Control Total	Control Weight	Hazard ratio IV, fixed (95% CI)
Rea et al,[21] 2005	–0.11	0.2	238		2560	14.9%	0.90 [0.61-1.34]
Zandi et al,[3] 2005	0.17	0.38	198		3110	4.1%	1.19 [0.56-2.50]
Cramer et al,[54] 2008	–0.58	0.23	452		1222	11.2%	0.56 [0.36-0.88]
Arvanitakis et al,[53] 2008	–0.09	0.26	119		810	8.8%	0.91 [0.55-1.52]
Haag et al,[55] 2009	–0.56	0.23		6992		11.2%	0.57 [0.36-0.90]
Li et al,[52] 2010	–0.47	0.23	775		2324	11.2%	0.63 [0.40-0.98]
Bettermann et al,[4] 2012	–0.34	0.13	776		2293	35.2%	0.71 [0.55-0.92]
Beydoun et al,[5] 2011	–0.89	0.42	109		1465	3.4%	0.41 [0.18-0.94]
Total (95% CI)			**2667**	**23,443**	**13,784**	**100.0%**	**0.71 [0.61-0.82]**

Heterogeneity: χ^2=8.20, *df*=7 (*P*=.32); I^2=15%
Test for overall effect: *Z*=4.49 (*P*<.00001)



B

FIGURE 3. A, Bias summary for long-term cognition, rated by the Newcastle-Ottawa Scale, with 9 total possible points (4 for selection, 2 for comparability, and 3 for outcome). More points indicate a higher-quality study. B, Forest plot of quantitative synthesis for long-term cognition showing incidence of dementia in the statin vs placebo groups (constructed using Cochrane RevMan version 5.1 software). The total N (6992) for the study of Haag et al is presented; it is not differentiated between statins and control because the analysis was performed at the drug exposure level rather than patient level. Combined with the Ns in the Statins and Control columns, the total N for analysis was 23,443. *df* = degree of freedom.

Mayo Clin Proc. ■ November 2013;88(11):1213-1221 ■ http://dx.doi.org/10.1016/j.mayocp.2013.07.013
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on cognition in this review. Moreover, we focused on adults without a history of cognitive dysfunction; it is uncertain how the results might apply to those with baseline cognitive dysfunction or other patient subgroups.

Regarding statins and long-term cognition, this review strengthens the findings of 2 recent meta-analyses in incorporating several additional publications and focusing solely on high-quality prospective studies defined by formal risk of bias assessment.[26,27] Applying greater scrutiny to the design and quality of included studies, this report should provide the most reliable synthesis to date. The results of this study suggest a risk reduction for the incidence of dementia in statin users. This pooled result must be interpreted cautiously given the heterogeneity in study design, exposure, outcome, and comparability. In addition, observational studies can never truly control for confounding factors, especially when they are unknown. In this case, bias by indication is possible away from the null, with the effect that cardiovascular disease has on dementia risk, and toward the null, with personal characteristics such as education and self-rated health associated with statin use. Given the duration of exposure theoretically necessary to prevent dementia and the widespread use of statin therapy, it will be difficult to adequately fund and ethically randomize a well-designed trial.

It is important to consider this study's results, strengths, and limitations in the context of other studies. This study confirms and extends a recent narrative review supporting the neurocognitive safety of statin therapy.[14] However, a review of the MedWatch database yielded 60 heterogeneous reports of statin-associated memory loss occurring mostly within a few months of statin initiation or dose increases with simvastatin, pravastatin, or atorvastatin.[8] Potential confounding factors, including medical comorbidities, neurologic conditions, and other medication therapies, varied widely. The nature of the memory loss was based almost completely on patient report; no objective measures were reported. The reversibility of these impairments was also variable. Therefore, it is difficult to draw any firm conclusions from this case series.

Analyzing survey data taken from 171 participants in the University of California at San Diego Statin Effects Study, the authors noted a strong association between the potency of the statin and amnesia or "cognitive symptoms."[6] Median time to symptom onset was 5 months, with recovery after cessation taking days to years. However, the study did not use objective measures of memory or cognitive impairment. Moreover, this group of investigators conducted a randomized trial on the effects of statins on cognition and other outcomes, with results available in 2004 (clinicaltrials.gov Identifier: NCT00330980), but have not published an article on the trial's primary results, including cognitive outcomes. Publication bias, whereby studies that support the null hypothesis are preferentially excluded from publication, is an important consideration.

In 2000, 2 epidemiologic studies first found a 60% lower prevalence of dementia in statin users.[19,20] Multiple cross-sectional and case-control studies furthered this claim.[2,24,43] However, these studies may have experienced indication bias, and one study that attempted to control for such bias was the only epidemiologic study to report no risk reduction.[3] A review undertaken in 2005 that included nested case controls showed a significance by crude odds ratios that disappeared after adjustment in random-effects modeling.[25] Since that time, 10 prospective cohorts have been described, and they were considered for this review.[4,5,42,51-57] Compared with earlier work, more recent studies used statin exposure as a time-dependent variable, had a greater percentage of participants taking statins, had longer follow-up, and reported higher numbers of incident dementia, which may account for the differences in outcome.

Several large clinical trials did not meet eligibility criteria for this study but warrant mentioning. Among these is PROSPER (Prospective Study of Pravastatin in the Elderly at Risk),[13,23] which reported a reduction in major vascular events with pravastatin use in 5804 elderly men and women treated for 3 years. A secondary end point of the study was cognitive function measured via the Mini-Mental State Examination, letter-digit coding test, the picture-word learning test, and the Stroop test; no differences in the rate of decline were noted between the experimental and control groups. In the somewhat younger population captured in the Heart Protection Study (72% younger than 70 years), statins also provided protection from cardiovascular disease in 20,536 individuals.[22] As a secondary analysis, the study incorporated the modified Telephone Interview for Cognitive Status at final follow-up after a mean of 5.3 years

of statin treatment. No significant differences were found between the treatment and control groups. The Lipid Lowering and Onset of Renal Disease trial was a randomized, placebo-controlled study that investigated the effects of atorvastatin on progression of renal disease in patients with chronic kidney disease.[37] A substudy to assess cognitive function was performed in 60 participants via objective psychological measures. No statistically significant differences were found. In a strictly primary prevention setup, JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) also did not detect memory impairment or adverse cognitive effects of statin therapy.[59]

CONCLUSION

In patients without baseline cognitive dysfunction, the results of the available studies are most compatible with no significant short-term cognitive detriments related to statin therapy, whereas long-term data suggest a beneficial role in the prevention of dementia. At present, patients and physicians can be reassured about concerns related to neurocognitive effects of statin therapy, and the evidence does not support a change to practice guidelines. Future studies investigating statins and cognition should use a clear taxonomy as proposed in this study, establish protocols a priori, and focus on objective outcome measures.

ACKNOWLEDGMENTS

We acknowledge Jaime Blanck from the Johns Hopkins Welch Medical Library for contributing to the search strategy for this study.

Drs Swiger and Manalac contributed equally to this work.

Dr Martin is supported by the Pollin Fellowship in Preventive Cardiology, as well as the Marie-Josée and Henry R. Kravis endowed fellowship.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org.

Abbreviations and Acronyms: **FDA** = Food and Drug Administration; **DSST** = Digit Symbol Substitution Test

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