Statins, cognition, and dementia—systematic review and methodological commentary

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Abstract | Firm conclusions about whether mid-life or long-term statin use has an impact on cognitive decline and dementia remain elusive. Here, our objective was to systematically review, synthesize and critique the epidemiological literature that examines the relationship between statin use and cognition, so as to assess the current state of knowledge, identify gaps in our understanding, and make recommendations for future research. We summarize the findings of randomized controlled trials (RCTs) and observational studies, grouped according to study design. We discuss the methods for each, and consider likely sources of bias, such as reverse causation and confounding. Although observational studies that considered statin use at or near the time of dementia diagnosis suggest a protective effect of statins, these findings could be attributable to reverse causation. RCTs and well-conducted observational studies of baseline statin use and subsequent cognition over several years of follow-up do not support a causal preventative effect of late-life statin use on cognitive decline or dementia. Given that much of the human research on statins and cognition in the future will be observational, careful study design and analysis will be essential.

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Introduction

The American College of Cardiology and American Heart Association guidelines on the management of cholesterol, published in 2013,[1] substantially expanded the proportion of the US population that is eligible to receive statins: an estimated 56 million US adults—49% of those aged 40–75 years—are now eligible to receive statins, even though many do not have overt cardiovascular disease.[2–4] Although the benefits of statins for primary and secondary prevention of cardiovascular outcomes have been demonstrated,[5–7] their effects on cognition and the risk of dementia remain unclear. Case reports link cognitive impairment with statin use[8,9] and, in the USA, the drugs now carry an FDA warning about statin-related reversible cognitive impairment or memory loss,[10] but these effects seem to be unrelated to dementia. Indeed, some evidence suggests that the pleiotropic effects of statins reduce the risk of dementia, for example, by decreasing levels of circulating cholesterol.

Hyperlipidaemia, particularly in mid-life, seems to be associated with an increased risk of dementia,[11–13] potentially by promoting damage to the brain vasculature.[14] Consequently, treatment of hyperlipidaemia would be expected to reduce the risk of dementia. Statins also seem to promote cardiovascular and (by inference) cerebrovascular health through antioxidant and anti-inflammatory effects and improved endothelial function.[15–17] However, they might also confer neuroprotection by other mechanisms. For example, statins—particularly lipophilic statins—might cross the blood–brain barrier and exert antioxidant and anti-inflammatory effects within the CNS, or modulate cholesterol metabolism in the brain.[16,18–23] Experiments in animal and cell models of Alzheimer disease (AD) also suggest that statins modulate amyloid-β; however, little evidence currently supports a similar effect in humans.[16,21,22,24–29] Finally, statins might modulate brain tau metabolism.[22,27,30,31]

Systematic reviews can synthesize data into a coherent evidential framework. However, existing reviews of statins and cognition have focused solely on clinical trials, have not systematically discussed study quality, or have discussed and meta-analysed observational studies as a group, which might be inappropriate when differences in study design or analyses yield noncomparable effect estimates.[32–37] The purpose of this Review is to summarize findings from randomized controlled trials (RCTs) and observational cohort studies; these types of studies are the most useful for evaluating the putative causal effects of statin use on cognition. We group studies by design and statistical approach, and provide specific commentary on study methods and their likely influence on findings. We conclude with a summary of the state of the evidence and recommendations for future research.

Literature search and analysis

We did not register a review protocol; however, our process adhered to the AlzRisk review protocol,[38] albeit with broader inclusion criteria. Briefly, references were identified through title and abstract screening and full-text review of citations identified by systematic searches of the MEDLINE and EMBASE databases (Supplementary Box 1 online) up to 15 June 2014, and

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Competing interests
The authors declare no competing interests.

Key points

- Initiation of statin use in late life does not seem to prevent cognitive decline and dementia over the subsequent few years
- The current literature does not address whether mid-life or long-term statin use has beneficial effects on subsequent cognition
- Many studies that assessed time-updated statin use suggest a protective effect of statin use on cognitive decline, but these findings are probably attributable to reverse causation
- Ethical and feasibility considerations limit randomized controlled trials; carefully designed observational studies that use appropriate analytical methods are our best hope for determining the effects of statin use on cognition
- Future observational work must incorporate study designs and analytical techniques that minimize the potential for bias, especially that which is due to reverse causation and confounding

by reviewing references included in identified eligible articles. No language restrictions were applied. One author (M.P.) was responsible for identifying eligible articles, extracting data, and conducting quality assessments in accordance with our study protocol; a reliability study conducted during protocol development indicated little, if any, benefit of adding a second reviewer.[38] All co-authors reviewed the list of eligible articles to identify any missing studies on the basis of their expert knowledge.

We included all RCTs that reported on statin use in adults and any measure of cognitive status, with the exception of RCTs that exclusively included people with dementia or individuals who were administered statins as secondary prevention therapy (for example, after myocardial infarction or stroke). We also included any observational cohort study that listed statins as a primary exposure of interest if it considered the following: a cohort in which patients were known or assumed to be free of dementia at baseline (based on age or cognitive screening); populations that were not defined by clinical end points, with the exception of deliberate restriction to those with an indication for statin use for primary prevention of cardiovascular disease; and the association between statin use and either a change in neuropsychological test scores (without adjustment for baseline test scores[39]) or incident diagnosis of dementia or AD. We retained multiple articles that reported on the same study population if their outcomes or analytical approaches were unique, or if they reported on overlapping but distinct samples; otherwise, we retained the report that had the longest follow-up period. We excluded conference abstracts and reports in supplements that were not peer-reviewed. These eligibility criteria focused our Review on studies that were the most likely to provide insight into the causal effects of statin use on cognition in the general population.

Ultimately, we identified 14 eligible articles[40–53] that reported on 13 RCTs, and 19 eligible articles[28,54–71] that reported on 17 observational studies (Figure 1). From one article,[69] we excluded analyses of cognitive change that were adjusted for baseline cognitive performance, but included analyses of dementia.

Details of data extraction from the included studies are provided in Supplementary Box 2 online. Each study was assessed for potential confounding, selection or misclassification bias, and reverse causation, as

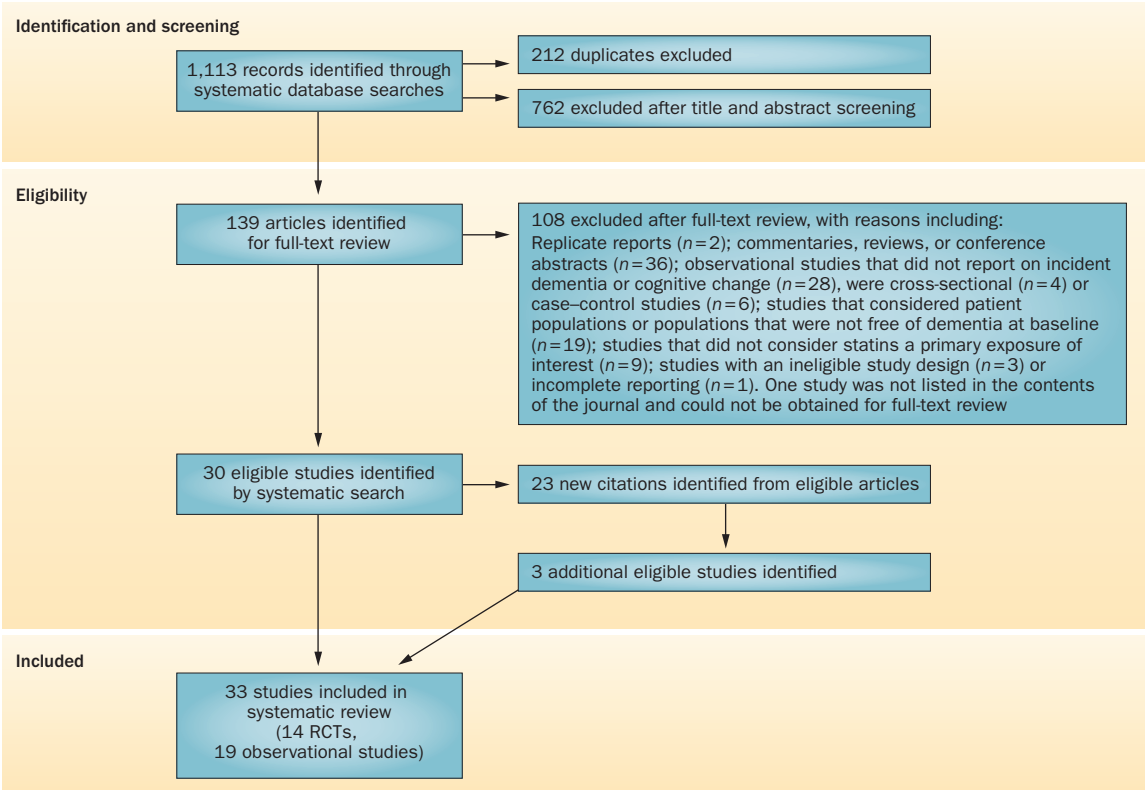

Figure 1 | Flow diagram of the study selection process for the systematic review. Abbreviation: RCTs, randomized controlled trials.

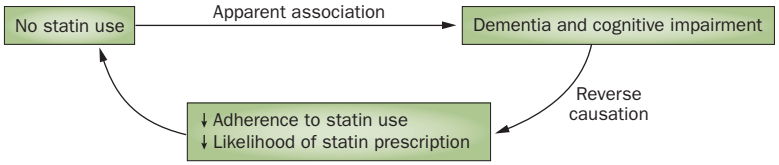

Figure 2 | Reverse causation in analyses that consider statin use and dementia risk. The underlying pathophysiology of dementia produces symptoms of cognitive impairment—including difficulties with memory, other cognitive processes and daily activities—that, once severe enough, lead to a dementia diagnosis. Development of cognitive impairment in study participants who do not use statins suggests that statins protect against cognitive decline, owing to an apparent association between no statin use and cognitive impairment. However, the difficulties caused by cognitive impairment are likely to reduce patient adherence to statin use (for example, if patients forget to take their medication or collect their prescription) and reduce the likelihood that a physician will prescribe statins (for example, if the physician is focused on treating the cognitive impairment or more-acute comorbidities, which might be exacerbated by cognitive impairment and increased inability to care for oneself). Thus, cognitive impairment might influence statin use, leading to reverse causation.

well as the applicability of the findings to other study populations with different characteristics. Studies were grouped by design and analytical approach for discussion. The Review was prepared with reference to published guidelines.[72]

Randomized controlled trials

Summary of published studies

Two large, double-blind, placebo-controlled RCTs of statins, the Heart Protection Study (HPS)[51] and the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial,[46,52] considered cognitive end points (Supplementary Table 1 online). In the HPS, 20,563 participants aged 40–80 years without dementia but with a high risk of vascular disease were randomly allocated to receive either 40 mg simvastatin daily or a placebo, and were followed up for an average of 5 years. Study personnel administered the Telephone Interview for Cognitive Status (TICS) to active study participants at the final follow-up interview. Neither the prevalence of cognitive impairment (indicated by a TICS score <22 or by reported dementia) nor the mean TICS score was associated with treatment assignment.[51] In the PROSPER trial, 5,804 participants aged 70–82 years who had or were at risk of vascular disease were randomly allocated to receive 40 mg pravastatin daily or a placebo, and were followed up for an average of 3 years. Statin treatment was not associated with a change in cognitive test scores.[46,52] Several small RCTs have reported on cognitive outcomes after 1–6 months of statin use,[40–45,47–50,53] with mixed results (Supplementary Table 1 online).

Comment

Collectively, RCTs that evaluated cognitive outcomes after less than 6 months of statin use did not provide strong evidence for short-term effects of statins on cognition, and did not provide any information about the effects of long-term statin use on cognition or the risk of dementia. Thus, we focus our discussion on the HPS and the PROSPER trial.

The key advantage of large, carefully conducted RCTs is the putative absence of confounding (because successful randomization balances characteristics related to both statin use and statin-independent cognitive change across treatment groups) and reverse causation (the situation in which cognition influences statin treatment rather than the reverse; Figure 2). However, other sources of bias remain. Non-adherence—assuming that it is unrelated to cognitive status—would cause an intention-to-treat analysis to underestimate the true aetiological effect of statin use. Although full adherence was not achieved in either the PROSPER trial or the HPS, the small degree of non-adherence that was observed is unlikely to explain the null results unless the size of the true aetiological effect is extremely small.

Likewise, little evidence exists for a strong selection bias that resulted from non-death attrition; loss to follow-up was minimal and did not differ substantially between treatment groups. Theoretically, differential attrition owing to death (for example, 13% mortality among simvastatin-allocated participants versus 15% mortality among placebo-allocated participants in the HPS) might mask a true aetiological protective effect of statins on cognition owing to survival bias (a form of selection bias);[73] in other words, statins might not seem beneficial because they prevent death in people with poor cognition.[5] In this case, the observed association would not necessarily answer the clinical question "does statin use reduce risk of dementia in any individual patient?" but might answer the question "will we observe a difference in the number of dementia cases if we increase use of statins in the population?" However, in this scenario, selective survival would only mask a protective aetiological effect of statin use on cognition if that effect were very small. Supplementary Box 3 online demonstrates that the magnitude of this potential bias is minimal under reasonable assumptions about the relationship between cognitive impairment and survival, and considering the small differences in mortality reported between the treatment groups in the HPS.

The relatively short follow-up times and old age of participants are limitations of both the HPS and the PROSPER trial. Detectable changes in brain structure and function are often present from years to decades before the diagnosis of dementia,[74–76] and associations of other risk factors (for example, blood pressure or cholesterol levels) with cognitive impairment or dementia seem to relate to the time at which these risk factors are measured. Evidence suggests that mid-life or long-term exposure to such risk factors has a greater influence on the risk of dementia than does late-life or short-term exposure.[11,77,78] These observations support the existence of a relevant aetiological window in mid-life or many years before symptoms of cognitive decline develop. Therefore, if statin use prevents or delays disease progression only at early stages of the pathological process or has small cumulative effects over many years, these RCTs would not be expected to demonstrate a benefit. Conversely, we would have expected to observe a benefit despite short follow-up times if statins have a marked and immediate benefit, for example, if they prevent or mitigate concomitant dementia-related

cerebrovascular disease, thereby affecting progression or symptoms of preclinical dementia.[79] Relative to the PROSPER trial, the HPS is further limited, as cognition was measured with a single test just once at the end of the study. However, we do not believe that this limitation is likely to account for the null results.

We conclude that the existing RCTs that assessed the effects of statin use on cognition do not indicate that statin use should be started in late life to prevent cognitive decline or dementia over the subsequent 3–5 years.

Observational studies

Baseline statin use and cognitive decline

Summary of published studies

Several observational studies (conducted almost exclusively in adults aged >65 years) have considered the association between statin use at the baseline study visit and subsequent cognitive decline or incident dementia (Supplementary Table 2 online).

Although statin use at baseline was strongly associated with a lower prevalence of dementia at baseline among participants in the Cache County Study, it was not associated with incident dementia or AD in the 3 years that followed.[65] Similarly, among participants in the Religious Orders Study, no association was observed between statin use and the level or rate of change of global or domain-specific cognitive function or dementia over follow-up periods of up to 12 years.[28] Likewise, no association was observed between baseline statin use and incident dementia in the Three City study, in which the follow-up period was 7 years.[69]

Conversely, in the Indianapolis sample of the Indianapolis–Ibadan Dementia Project, use of statins at baseline was associated with a smaller decline in scores on the Community Screening Instrument for Dementia over 3 years than was non-use of statins at baseline.[61] However, when baseline statin users were further stratified according to statin use at the end of the 3-year follow-up period, only those who discontinued statin use during the 3-year interval exhibited significantly slower cognitive decline than participants who never used statins. Consistent statin users also seemed to exhibit slower cognitive decline than never users, but this association was not as strong as that for discontinuers, and was not statistically significant.

In a study that analysed data from The Health Improvement Network (THIN), a large database of general practice electronic medical records (EMRs), participants who initiated statin use were compared with age-matched and sex-matched control participants who were not receiving statins.[66] Statin initiators were less likely than nonusers to receive a clinical diagnosis of dementia over a median follow-up period of 4.4 years. Similar analyses in the Decision Support System database of the US Veterans Affairs medical system suggested that simvastatin users, but not lovastatin or atorvastatin users, had a reduced risk of incident dementia of the Alzheimer type (as defined by the International Classification of Diseases, 9th Revision codes) compared with users of other cardiovascular medications.[70]

Comment

Bias in observational studies can be minimized or avoided by using appropriate study designs and analyses. For example, methods that have high validity for assessing participants' statin use (such as conducting a drug inventory, or considering prescription records and/or self-reported use[80]) reduce bias caused by misclassification of statin use. Similarly, cohort studies that systematically and prospectively evaluate participants for dementia are unlikely to be biased by differential misclassification of dementia (whereby the error in classification of dementia differs according to statin use) or substantial nondifferential misclassification (that is, random error). By contrast, use of EMRs to classify the dementia status of participants is not ideal:[81–84] random error would simply make a true effect more difficult to detect, but EMR-derived errors in classification of dementia status could differ by statin use. If people with access to good health care are more likely to receive both treatment with statins and a diagnosis of dementia in the course of their normal clinical care, an erroneous adverse association could be obtained. Conversely, if people with comorbidities that lead to statin use are less likely to receive a diagnosis of dementia (because, for example, clinicians focus instead on the comorbidities), we might expect an erroneous protective association.

Observational studies that define statin use at baseline and monitor participants for several years are relatively resistant to reverse causation, provided that the duration of follow-up is sufficient. In the set of studies presented here, the maximum follow-up periods range from 3 to 12 years (Supplementary Table 2 online). If people whose cognition is intact are more likely to be prescribed or to continue taking statins, reverse causation would produce a misleading protective association (Figure 2). Several of the studies discussed here that have relatively short follow-up periods report a protective association,[61,66,70] which could, in theory, be attributable to reverse causation. However, these studies have limitations besides the short follow-up periods—such as the use of EMRs to classify dementia, as discussed above, and confounding by 'healthy user' characteristics or small numbers of cases, as discussed below—that might account for the observed associations. We should also note that in the Indianapolis cohort,[61] those who discontinued statin use during the 3-year follow-up had better cognitive trajectories, a finding opposite to that expected if a decline in cognition led to cessation of statin use in this sample. Cessation of statin use among health-conscious patients in response to the FDA warning[10] could also produce erroneous associations, but this possibility is not relevant to this set of studies, as the warning was introduced after their completion.

Confounding is another concern, and the direction of total confounding bias is difficult to predict. Confounding by indication (for example, when vascular disease leads to both statin use and dementia) is likely to lead to spurious adverse associations, whereas confounding by 'healthy user' characteristics (for example, when preventive care leads to statin use and no dementia)[85]

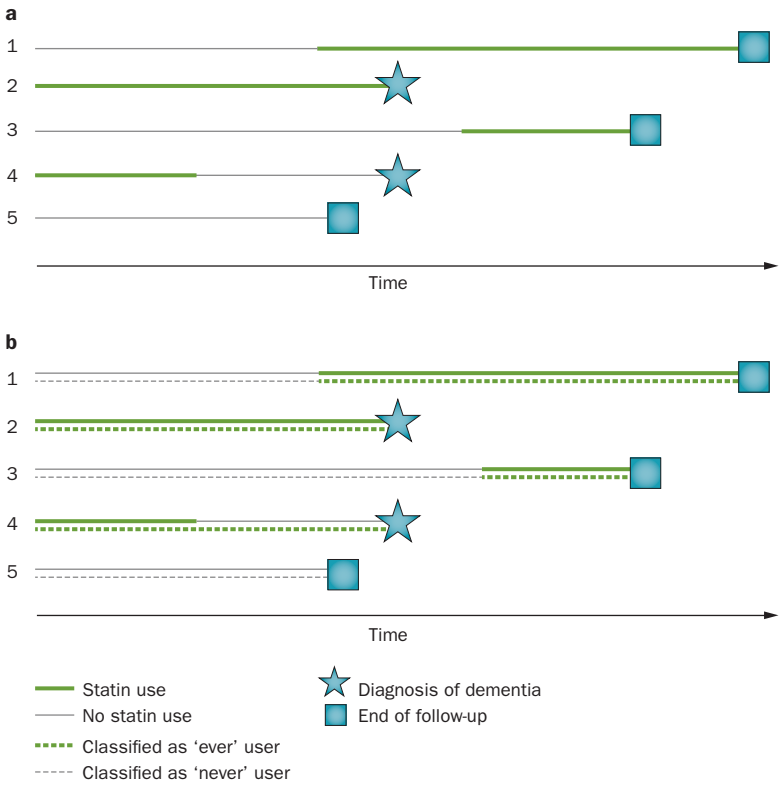

Figure 3 | Interpretation of survival models using time-updated current or never–ever statin use with no lag. A comparison is made each time a participant is diagnosed with dementia. Comparisons at each time point are cross-sectional: statin use at other time points is not considered. **a** | Time-updated current statin use. The model compares the probability of a dementia diagnosis in participants currently using statins versus those not currently using statins. In this example, when patients 2 and 4 are diagnosed, the probability that any participant has a dementia diagnosis is 0.5, regardless of their current statin use, suggesting no benefit of statin use. **b** | Time-updated never–ever statin use. The model compares the probability of a dementia diagnosis in ever versus never statin users. In this example, when participants 2 and 4 are diagnosed, the probability of a dementia diagnosis in an ever user is 0.67, compared with 0 for never users, suggesting that statin use increases the risk of dementia.

would be expected to lead to spurious protective associations. Attempts that have been made to control for confounding by indication have had little impact on results,[28,65,66] thereby arguing against severe uncontrolled confounding by indication, although the possibility cannot be discounted. All studies in which analyses were adjusted for education (one correlate of 'healthy users') reported null results, whereas two studies[66,70] in which analyses were not adjusted for education reported a protective association. These findings would be expected if highly educated participants more readily obtained indicated statin treatments and were less likely to exhibit marked cognitive impairment.

As with the RCTs, bias from selective attrition could influence the findings of observational studies. In the Cache County Study, non-death attrition did not differ according to baseline statin use,[65] suggesting minimal bias from selective loss to follow-up. However, as in the RCTs, deaths might mask a small aetiological benefit of statins, as delayed mortality provides a greater opportunity for dementia to develop.

Two additional characteristics of these studies are worth noting. First, the results from the Indianapolis cohort were based on only 32 participants with dementia, only three of whom were statin users.[61] Similarly, only eight of the 182 participants with dementia in the Cache County Study were baseline statin users.[65] Results based on such small numbers are more likely to be chance findings[86] or to have incomplete control of confounding.[87] Second, the participants in most studies were older adults (≥65 years at baseline; Supplementary Table 2 online), and in THIN[66]—the only study to include adults in mid-life—the follow-up period was too short to capture the risk of late-onset dementia in the younger participants. Therefore, these studies cannot provide information on the effects of mid-life or long-term statin use.

Three of the six observational studies discussed above reported associations that were consistent with a cognitive benefit of statin use;[61,66,70] however, two of these three studies[66,70] used EMRs to define dementia status and did not adjust for education or other socio-demographic factors, and the third[61] was based on very small numbers of participants with dementia. The results of the remaining three studies concur with those of RCTs, and provide no evidence that statin use in late life prevents dementia over the few years following statin initiation.

Time-updated statin use and dementia

Summary of published studies

Several other observational studies (Supplementary Table 3 online) have considered the association between time-updated statin use and incident dementia, typically by reporting on results from a proportional hazards regression model in which statin use status during the follow-up period is entered into the model as a time-dependent covariate (Figure 3). Specifically, many of these analyses consider statin use as a time-updated version of 'ever' versus 'never' statin use; participants who were not using statins at baseline and do not start using statins during follow-up can be classified as 'never' users throughout, whereas participants who were using statins at baseline are classified as 'ever' users throughout (even if they subsequently stop using statins). Participants who initiate statin use during the study are classified as 'never' users until their time of statin initiation, when their status switches to 'ever' user. For example, a participant who begins taking statins in year 3 of follow-up could be considered a 'never' user for years 1 and 2, and an 'ever' user for year 3 and beyond. Studies that use this approach compare the risk of dementia among 'ever' users with that among 'never' users at the time of diagnostic assessment, an approach that is essentially cross-sectional in nature. (Figure 3b) Studies that incorporate a 1-year or 2-year lag compare the risk of dementia among 'never' and 'ever' users according to their statin use status at 1 year or 2 years, respectively, before diagnostic assessment.

Four studies that used this design suggested a strong beneficial effect of statin use on the risk of dementia. Among participants of the Rotterdam Study, time-updated ever statin use was associated with a reduced

risk of AD dementia.[67] Analyses of ever–never statin use with a 2-year lag and current statin use at 1 year before the date of diagnosis produced comparable results. Additional analyses failed to identify differences in this association according to statin lipophilicity (one determinant of whether the drug can cross the blood–brain barrier), dosage or duration of use, or to apolipoprotein E (*APOE*) allele status.

In the Sacramento Area Latino Study on Aging (SALSA), time-updated ever use of statins with a 1-year lag was associated with a reduced risk of dementia or "cognitive impairment without dementia" (a research diagnosis akin to mild cognitive impairment [MCI]).[64] Analyses from the Gingko Evaluation of Memory Study (GEMS)[60] showed that time-updated ever statin use was associated with a reduced risk of dementia in participants without MCI at baseline. Further analyses suggested that this result was primarily due to an association between current statin use at the time of dementia ascertainment and a reduced risk of dementia, as no association with time-updated former use was observed. Similar, but not significant, associations were observed after participants with cardiovascular disease at baseline were excluded, or when AD dementia or dementia with a vascular component was considered; associations were strongest with lipophilic statins and when analyses were restricted to participants who initiated statin use during the follow-up period. Associations observed among participants with MCI at baseline were also protective, though not significant. In addition, the Baltimore Memory Study (BMS) showed that time-updated ever statin use was associated with a reduced risk of dementia and AD dementia, but not with a reduced risk of MCI.[57]

Two articles that we identified evaluated data from the Adult Changes in Thought (ACT) study, but drew slightly different conclusions. In the initial work, no association was observed between time-updated ever statin use and the risk of dementia or AD dementia; analyses that considered dose, duration of use or time-updated ever statin use with a 1-year lag were similarly null.[54] However, in subsequent work that analysed an expanded study population, time-updated ever statin use was associated with a reduced risk of AD in participants younger than 80 years, but not in those aged ≥80 years.[55] *APOE*ε4* allele carrier status did not modify the association.

Data from the Cardiovascular Health Study (CHS) did not suggest a protective effect of statins.[58] Three analyses were reported: time-updated current statin use, time-updated ever statin use with a 1-year lag, and time-updated categories of statin use (current, former, never) with a 1-year lag. Interestingly, analyses of time-updated current statin use that did not incorporate a lag demonstrated protective associations between current statin use and both AD and all-cause dementia. However, neither ever (versus never) nor current (versus never) statin use with a 1-year lag was associated with an increased risk of dementia or dementia subtypes, and time-updated former use of statins (versus never use) was associated with an increased risk of all-cause and AD dementia. The study conclusions were unchanged when the analysis was restricted to people with indications for statin use, or when duration of statin use and statin lipophilicity were considered.

Comment

The interpretation of studies that consider statin use as a time-dependent covariate (with no lag) in a proportional hazards regression model is nearly equivalent to the interpretation of a cross-sectional study (Figure 3). Statin use in incident (rather than prevalent) cases of dementia is compared with statin use in those without dementia at a given point in time. The introduction of a 1-year or 2-year lag to this time-updated approach necessitates an interpretation similar to that of a prospective cohort study with a follow-up period of just 1 or 2 years. Thus, analyses of time-updated statin use and dementia have the same limitations as cross-sectional studies or prospective studies with short follow-up periods.

Analyses of time-updated statin use and dementia are susceptible to reverse causation, in that their findings can easily reflect an effect of declining cognition on statin use (Figure 2).[88] This phenomenon is illustrated by the GEMS[61] and the CHS:[58] the GEMS showed a reduced risk of dementia in current, but not former, statin users, whereas the CHS, which incorporated a 1-year lag in the primary analysis, showed an increased risk of AD dementia in former, but not current, statin users. The apparent lack of a protection against dementia among former users could be explained by discontinuation of statin use as a result of cognitive decline. Similarly, the apparent protective effect of current statin use might reflect the fact that intact cognition affects continued statin use. Lagged exposures can be used to avoid issues of reverse causation. However, if 1-year or 2-year lags were enough to avoid reverse causation, we might expect different results with and without incorporation of lags, but this pattern was not seen consistently. Although the CHS[58] reported an inverse association when no lag was incorporated and null results when a 1-year lag was incorporated, both the ACT[54] and the Rotterdam[67] studies produced similar results regardless of whether a 1-year lag was incorporated. As with observational studies that consider baseline statin use, other sources of bias remain a concern in studies of time-updated statin use; however, given that reverse causation probably accounts for the majority of findings in this group of studies, we will not discuss these biases further.

In summary, although multiple studies that considered the association between time-updated statin use and dementia showed a reduced risk of dementia with statin use, concerns about reverse causation preclude conclusions of a strong beneficial effect.

Alternative study designs

Summary of published studies

Several observational studies have incorporated alternative study designs or analyses to investigate the association between statin use and risk of dementia (Supplementary Table 4 online). Additional analyses in the GEMS[60] used a linear mixed effects regression model

to assess the impact of statin use on scores in cognitive tests; this model included both a time-updated statin use variable and the interaction of this variable with time. In participants without MCI at baseline, this approach demonstrated an association between time-updated statin use and cognitive change, as determined by performance on a battery of cognitive tests.

Several other studies have looked for an association between statin use during follow-up, which was summarized at the end of the follow-up period, and cognitive decline or dementia during this period (Supplementary Table 4 online). In the CHS, for example, participants were classified as consistent statin users (>4 years of continuous use), intermittent users (2–4 years of continuous use or 3–5 years of intermittent use), or untreated (<2 years of use).[59] The untreated group was further classified, according to the 1993 National Cholesterol Education Program guidelines, into three groups: treatment not recommended, diet treatment recommended, and drug treatment recommended. In adjusted analyses, consistent statin users exhibited significantly slower cognitive decline over up to 7 years (as evaluated with the modified Mini-Mental State Examination [MMSE]) compared with untreated users for whom treatment was not recommended, and marginally slower decline compared with untreated users for whom drug treatment was recommended. Other comparisons were not reported.

Another study used data from the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) to classify participants into four groups according to statin use at the end of ~4 years of follow-up: no notable use of lipid-lowering medication, consistent statin use, use of lipid-lowering medication other than statins, and inconsistent statin use.[56] The authors concluded that the incidence of AD dementia was significantly reduced by long-term statin use, although several exposure groups included fewer than five patients with AD.

A similar study considered the Uniform Data Set maintained by the National Alzheimer's Coordinating Centre.[62] In this study, statin use throughout an average follow-up period of 3 years—when compared with no statin use during follow-up—was associated with slower cognitive decline assessed by using the Clinical Dementia Rating Scale Sum of Boxes, and was marginally associated with slower cognitive decline assessed by using the MMSE. Statin use was not associated with a change in cognitive ability assessed by domain-specific cognitive tests. Results were null among participants who had MCI at baseline.

In a follow-up of the 1932 Scottish Mental Health Survey of the Lothian Birth Cohort 1921, participants who were using statins at age 80 years attained, on average, higher age-normalized scores in the Moray House Test of intelligence at age 80 years than at age 11 years. The reverse was true for participants who were not using statins at age 80 years.[68] Notably, a report that analysed primary care EMR data from the QResearch database (England and Wales) found no elevated risk of dementia among new users of statins (who entered the cohort on receipt of their first statin prescription) during follow-up compared with participants who did not use statins during the follow-up period, although the results suggested that the risk of dementia was reduced with simvastatin or atorvastatin use in women.[63] Conversely, new statin use during follow-up was associated with a reduced risk of incident dementia in analyses that used EMR data from the Longitudinal Health Insurance Database 2000 (Taiwan).[71] Associations were stronger with high-potency statins and longer durations of use, but did not differ according to lipophilicity of statins or age of participants. The authors did, however, suggest sex-related differences in the associations. Finally, additional analyses in the Baltimore Longitudinal Study of Aging[58] showed that ever statin use defined at the end of the follow-up period was associated with reduced risks of dementia, AD and MCI.

Comment

Statin use is not a point exposure, so consideration of an individual's history of exposure is desirable. However, existing studies that take this history into account have substantial limitations.

Analyses of cognitive change that use a time-updated exposure (for example, the GEMS analyses[60]) are almost impossible to interpret, and do not clearly answer a clinically relevant question. Analyses that use summaries of statin use defined at the end of the follow-up period are more interpretable, but might not reflect the causal effects of statins on cognition. Existing studies that consider such summaries of statin use have employed variable follow-up periods; participants with shorter follow-up periods are less likely to exhibit variable statin use, although it is unclear whether this factor affects the observed findings. Analyses that incorporate summaries of exposure and concurrent cognition might be biased by reverse causation, because changes in cognitive status can influence statin use.

Confounding is an additional concern. Although several studies included only new users of statins, which might aid identification of and adjustment for relevant confounders, every study that adjusted for confounding seemed to adjust only for baseline characteristics. This approach might be insufficient when using summaries of exposure data collected throughout the follow-up period. In this context, use of time-updated covariates in standard regression models probably also results in bias, given the high probability of time-dependent confounding, which occurs when potential confounders are also mediators of the impact of statins on cognition (Figure 4).[89] Appropriate methods are available to account for this time-dependent confounding.[89–91] Finally, the studies presented here cannot provide information on the effect of mid-life or long-term statin use, given that participants were primarily aged >65 years during follow-up, and the follow-up periods were relatively short (Supplementary Table 4 online).

Legitimate concerns about bias and interpretability in this body of studies preclude the conclusion that statins have a causal protective effect on cognition, despite the relatively consistent reports of protective associations.

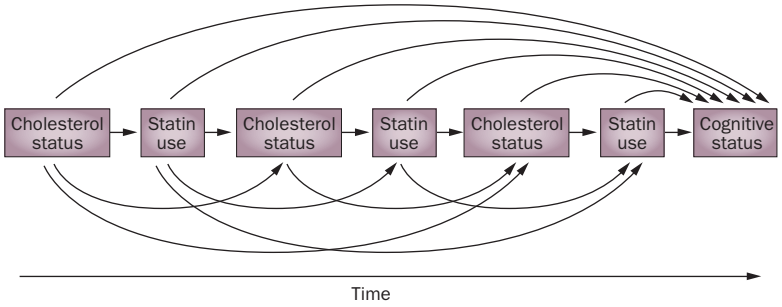

Figure 4 | Time-dependent confounding. Directed acyclic graph that illustrates the potential for time-dependent confounding when studying the influence of statin history on cognition. Arrows between variables denote a causal effect of one variable on the next. Time-dependent confounding occurs when a variable that confounds the effect of interest (in this case, the effect of statins on cognition) also acts as a mediator of that effect. In this example, cholesterol status acts as a confounder, because it is associated with both future cognitive status and future statin use (as it is an indication for statin use). However, it also mediates the effect of statin use on cognition because statin use affects future cholesterol levels, which then affect future cognitive status. Standard regression methods to adjust for confounding (for example, adjusting for time-varying cholesterol status) will produce biased results, so other methods (for example, inverse probability weighting in a marginal structural model) are required.

Overview

Collectively, RCTs and observational studies of the association between statin use at baseline and subsequent cognition do not support the initiation of statin use in late life to prevent cognitive decline and dementia within the subsequent few years. Protective associations demonstrated by observational studies that considered time-updated statin use could be explained by reverse causation. Other existing observational studies, particularly those that defined statin use at the end of the follow-up period, did not sufficiently address potential sources of bias, so cannot be used to comment on the causal relationship between statins and late-life cognitive change or dementia. Whether long-term statin use or the timing of statin use (for example, initiation in mid-life versus late life) affects subsequent cognitive status is unclear. Similarly, questions remain about the impact of the statin dose and treatment duration. Furthermore, the type of statin used might be important, as the hypothesized cognitive benefits might be conferred by only a subset of statins (for example, lipophilic statins); differential associations would provide insight into the mechanisms of any beneficial effects. Such questions can only be answered by use of observational research, as the required RCTs are not feasible given cost, ethical concerns, and participant burden.

Reverse causation, misclassification, confounding by indication or 'healthy user' characteristics, and selection bias can be sufficiently addressed through careful study design and data collection, and appropriate analysis: well-conducted observational studies can generate results that are consistent with high-quality RCTs. Reverse causation can be completely eliminated by the enrolment of participants without overt or preclinical dementia, either by recruiting participants during mid-life, or by using emerging preclinical markers to exclude participants with preclinical dementia. Although existing studies that considered time-updated statin use have significant limitations, fruitful use of time-varying data is possible and of interest. Such efforts must address the issue of time-dependent confounding (Figure 4) by using appropriate analytical approaches.[89,91] The incorporation of exposure lags of at least 3 years is also justified. Adjustment for correlates of adherence to medical recommendations and use of preventative care should allow appropriate control of confounding, but requires thoughtful data collection. Nevertheless, residual confounding could remain. We recommend that future observational research report analyses are restricted to participants with an indication for treatment with statins, so as to aid interpretability.

Finally, future reviews of the relationship between statins and cognition must carefully consider study design and the potential for bias when summarizing the literature. As discussed in this Review, variations in study design and analysis lead to effect estimates that are fundamentally different and should not be pooled for meta-analyses or discussion. Furthermore, meta-analyses must be conducted with caution, as greater numbers (of studies or participants) do not alleviate issues of bias.

Conclusions

Initiation of statin use in late life does not seem to prevent cognitive decline and dementia over the subsequent few years. However, this conclusion in no way undermines existing recommendations regarding statin use for primary and secondary prevention of cardiovascular disease, and does not preclude a beneficial effect of mid-life or long-term statin use on cognition. Given the ethical and feasibility considerations associated with RCTs, carefully designed observational studies that use appropriate analytical methods are our best hope for answering important questions about the relationships between mid-life or long-term statin use and cognitive ability.

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Author contributions

M.C.P. conducted the literature search, determined study eligibility, extracted the data, conducted the quality assessment, and drafted the manuscript. All authors made substantial contributions to the analysis and interpretation of the data and critically revised the manuscript for important intellectual content. All authors gave final approval for publication.

Supplementary information is linked to the online version of the paper at www.nature.com/nrneurol.