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Statins for the prevention of dementia (Review)

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[Intervention Review]

Statins for the prevention of dementia

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ABSTRACT

Background

This is an update of a Cochrane review first published in 2001 and then updated in 2009. Vascular risk factors including high cholesterol levels increase the risk of dementia due to Alzheimer's disease and of vascular dementia. Some observational studies have suggested an association between statin use and lowered incidence of dementia.

Objectives

To evaluate the efficacy and safety of statins for the prevention of dementia in people at risk of dementia due to their age and to determine whether the efficacy and safety of statins for this purpose depends on cholesterol level, apolipoprotein E (ApoE) genotype or cognitive level.

Search methods

We searched ALOIS (the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group), *The Cochrane Library*, MEDLINE, EMBASE, PsycINFO, CINAHL, LILACS, ClinicalTrials.gov and the World Health Organization (WHO) Portal on 11 November 2015.

Selection criteria

We included double-blind, randomised, placebo-controlled trials in which statins were administered for at least 12 months to people at risk of dementia.

Data collection and analysis

We used standard methodological procedures expected by Cochrane.

Main results

We included two trials with 26,340 participants aged 40 to 82 years of whom 11,610 were aged 70 or older. All participants had a history of, or risk factors for, vascular disease. The studies used different statins (simvastatin and pravastatin). Mean follow-up was 3.2 years in one study and five years in one study. The risk of bias was low. Only one study reported on the incidence of dementia (20,536 participants, 31 cases in each group; odds ratio (OR) 1.00, 95% confidence interval (CI) 0.61 to 1.65, moderate quality evidence, downgraded due to imprecision). Both studies assessed cognitive function, but at different times using different scales, so we judged the results unsuitable for a meta-analysis. There were no differences between statin and placebo groups on five different cognitive tests

(high quality evidence). Rates of treatment discontinuation due to non-fatal adverse events were less than 5% in both studies and there was no difference between statin and placebo groups in the risk of withdrawal due to adverse events (26,340 participants, 2 studies, OR 0.94, 95% CI 0.83 to 1.05).

Authors' conclusions

There is good evidence that statins given in late life to people at risk of vascular disease do not prevent cognitive decline or dementia. Biologically, it seems feasible that statins could prevent dementia due to their role in cholesterol reduction and initial evidence from observational studies was very promising. However, indication bias may have been a factor in these studies and the evidence from subsequent RCTs has been negative. There were limitations in the included studies involving the cognitive assessments used and the inclusion of participants at moderate to high vascular risk only.

PLAIN LANGUAGE SUMMARY

Statins for the prevention of dementia

Background

Dementia (including Alzheimer's disease) is a global healthcare concern; the number of people affected worldwide is predicted to double every 20 years, reaching 74.7 million in 2010 and 131.5 million in 2050. Therefore, it is important to find means of preventing dementia. It has been suggested that high levels of cholesterol in the serum (part of the blood) may increase the risk of dementia and that treatment with cholesterol-lowering medicines such as statins may reduce the risk of dementia.

Study characteristics

We searched medical databases for clinical trials comparing giving a statin to giving a placebo (pretend medicine) to people with normal cognitive function (which is brain activities that allow us to gain and use knowledge) and of sufficient age to be at risk of Alzheimer's disease.

Key results

We found two suitable randomised trials for inclusion in this review with 26,340 participants; neither showed any reduction in occurrence of Alzheimer's disease or dementia in people treated with statins compared to people given placebo. Side effects were low in both statin and placebo groups with no difference between groups in the risk of dropping out of the trial due to side effects.

Quality of the evidence

There were limitations in the included studies involving the methods of assessment of cognition and the inclusion only of participants deemed to be of moderate to high risk of a problem with their blood (vascular) system. Nevertheless, there was good evidence that statins given in late life to people at risk of vascular disease do not prevent cognitive decline or dementia.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Statins compared with placebo for prevention of dementia

Patient or population: older people with normal cognition[a]
Setting: community
Intervention: any statin
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Statin				
Incidence of dementia Range of scale yes/no Follow-up 5 years	Number developing dementia 31/10,267 (0.3%)	Number developing dementia 31/10,269 (0.3%)	OR 1.0 (0.61 to 1.65)	20,536 participants (1 study) HPS 2002 only	Moderate[b]	-
Mini Mental State Examination Score Score out of 30 (higher score better) Measures global cognitive function Follow-up 42 months	-	-	MD 0.06 (-0.04 to 0.16)	5804 participants (1 study) PROSPER only	High	2 points of difference may be considered clinically relevant (Lopez 2005)
Stroop Colour Word Test Total number of seconds required to complete the third Stroop card containing 40 items Measures attention Follow-up 42 months	-	-	MD 0.8 (-0.4 to 2.0)	5804 participants (1 study) PROSPER only	High	-

Picture-Word Learning Test 15 Picture Learning Test Measures immediate and delayed recall Follow-up 42 months	-	-	MD 0.02 (-0.12 to 0.16)	5804 participants (1 study) PROSPER only	High	-
Letter Digit Coding Test Total number of correct entries completed in 60 seconds Measures processing speed Follow-up 42 months	-	-	MD -0.01 (-0.24 to 0.23)	5804 participants (1 study) PROSPER only	High	-
Mean Modified Telephone Interview for Cognitive Status Score Score out of 39	-	-	MD 0.02 (-0.12 to 0.16)	20,536 (1 study) HPS 2002 only	High	Score $\leq$ 35 clinically relevant (Abner 2015)
Adverse events leading to discontinuation of therapy	641/13,180 (4.8%)	600/13,160 (4.5%)	OR 0.94 (0.83 to 1.05)	26,340 participants (2 studies)	High	-

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.
If evidence was downgraded it was because of imprecision.

a All participants had a history of, or risk factors for, vascular disease.
b Downgraded due to imprecision.

BACKGROUND

This is an update of the review published in 2009 (Other published versions of this review), which concluded that statins given in late life to people at risk of vascular disease have no effect in preventing Alzheimer's disease (AD) or dementia. Biologically, it seemed feasible that statins could prevent dementia by lowering cholesterol and initial evidence from observational studies was very promising. However, indication bias may have been a factor in these studies and the evidence from the two included randomised controlled trials (RCTs) was negative. This updated review aimed to re-assess the evidence.

Description of the condition

Dementia is defined as "a progressive and largely irreversible clinical syndrome that is characterised by a widespread impairment of mental function" (NICE 2006). It is characterised by a cluster of symptoms and signs including difficulties in memory, disturbances in language, psychosocial and psychiatric changes, and impairments in activities of daily living (ADL) (Burns 2009). The intellectual decline is usually progressive and spares the level of consciousness until the very late stages of the illness. Alzheimer's Disease International estimates that in 2015 there are 46.8 million people with dementia in the world, the number is predicted to double every 20 years, reaching 74.7 million in 2030 and 131.5 million in 2050 (World Alzheimer Report 2015). These estimates are 12% to 13% higher than those made for the World Alzheimer Report 2009. Therefore, it is a major health concern and any intervention that may reduce risk would have a major public health impact.

There are different subtypes of dementia associated with differing underlying brain pathologies (World Alzheimer Report 2009; Burns 2009). The most common subtypes in older people are AD, vascular dementia (VaD) and mixed dementia (a mixture of AD and VaD pathology). AD is the most common subtype accounting for 60% to 70% of all cases; it has a prevalence of approximately 1% among 60- to 64-year olds rising to 40% in people aged 85 years and older. Although AD occurs later in life there is a long preclinical stage characterised by progressive neuropathological changes. These include amyloid plaques composed primarily of β-amyloid peptide (Aβ), neurofibrillary tangles (NFTs), neuroinflammation, neuronal dysfunction and cell death (Cole 2007). According to the influential amyloid cascade hypothesis, Aβ accumulation is a critical first step in the sequence of pathological changes that ultimately lead to cognitive dysfunction (Glenner 1984).

VaD is characterised by both large- and small-vessel lesions. Subcortical ischaemic vascular disease is now thought to be more prevalent than multi-infarct dementia caused by large-vessel lesions (Ballard 2000; Esiri 1997). VaD accounts for approximately 17% of cases of dementia; prevalence estimates are 1.6% in Europe in people over 65 years of age (Rizzi 2014), and correspondingly 1.7% in China (Ji 2015).

Cholesterol and Alzheimer's disease

There is a close relationship between AD and cardiovascular disease with coronary heart disease and hypertension being significant risk factors for AD (Kivipelto 2002; Skoog 1998). Several epidemiological studies have shown an association between high serum cholesterol levels and an increased susceptibility to AD (Hayden 2006; Jarvik 1995; Kalmijn 2000; Kivipelto 2002; Kivipelto 2005; Notkola 1998; Solomon 2009; Whitmer 2005), while other studies have shown no association (Mainous 2005; Mielke 2010; Romas 1999; Tan 2003), or a negative association (Mielke 2005; Moroney 1999; Reitz 2004). There have been inconsistencies between studies, for example, in study design and follow-up period, making it difficult to compare studies directly.

The best established genetic risk factor for sporadic and late-onset AD is the $\epsilon 4$ allele of apolipoprotein E (ApoE); this is a protein that is involved in cholesterol transport in the brain and that also binds directly to the Aβ peptide and influences its aggregation and clearance in vitro (Strittmatter 1993) and in vivo (Naslund 1995; Wisniewski 1995). Meta-analysis has shown that the ApoE $\epsilon 4$ allele increases the risk of the disease by three times in heterozygotes and by 15 times in homozygotes (Farrer 1997). Each copy of the allele lowers the age of onset of AD by almost 10 years (Corder 1993). The $\epsilon 4$ allele is associated with higher plasma concentrations of total and low-density lipoprotein (LDL) cholesterol as well as a higher risk of atherosclerosis. Other genes involved in cholesterol metabolism have been found to be associated with AD through Genome Wide Association Studies (GWAS): Apo J or clusterin (Harold 2009), adenosine triphosphate (ATP)-binding cassette subfamily A member 7 (ABCA7) (Beecham 2014), and sortilin-related receptor (SORL1) (Meng 2007).

Generation of cerebral Aβ in vitro (Mizuno 1999; Simons 1998) and in vivo is cholesterol dependent (Burns 2003; Refolo 2000; Sparks 1994). Aβ is a cleavage product of amyloid precursor protein (APP). APP can be cleaved in several ways but Aβ derives from the sequential proteolytic activities of beta and gamma secretase (the amyloidogenic processing pathway) (Marks 2003). Both beta and gamma secretases are active in lipid rafts-specialised cell membrane microdomains rich in cholesterol and sphingolipids, and it appears that APP processing within these lipid rafts determines the level of Aβ production (Ehehalt 2003; Vetrivel 2004).

Cholesterol and vascular dementia

Risk factors for VaD are similar to risk factors for all types of vascular disease, namely hypertension, diabetes, smoking and hypercholesterolaemia (Ott 1998; Posner 2002; Stewart 1999). Several studies have found an association of VaD with decreased levels of high-density lipoprotein (HDL) cholesterol (Kuriyama 1994; Muckle 1985; Reitz 2004; Zuliani 2001). The role of LDL

cholesterol remains controversial, with some studies finding an association between increased LDL cholesterol and risk of VaD (Klich-Raczka 2002; Moroney 1999; Paragh 2002; Reitz 2004), and other studies reporting a negative association (van Exel 2002; Yoshitake 1995). Plasma lipids could be associated with the risk of VaD through several mechanisms. High levels of LDL cholesterol and low levels of HDL cholesterol are established risk factors for coronary heart disease (Moroney 1999) and carotid artery atherosclerosis (Sharrett 1994). These may lead to cognitive impairment through cerebral hypoperfusion or embolism (Breteler 1994). HDL cholesterol may interact with ApoE to cause small-vessel disease (Dantoine 2002).

Stroke is also a major risk factor for VaD. Lowering of cholesterol concentrations using statins reduces the risk of stroke in high-risk populations and in people with non-cardioembolic stroke or transient ischaemic attack. Each 1 mmol/L decrease in LDL cholesterol equates to a reduction in risk ratio for stroke of 21.1% (Amarenco 2009). By reducing the risk of stroke, statins may also act to reduce the incidence of post-stroke dementia.

Description of the intervention

Statins are a class of drugs that inhibit the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. HMG-CoA reductase catalyses the rate-limiting step in cholesterol synthesis. Statins thereby reduce formation and entry of LDL cholesterol into the circulation and upregulate LDL receptor activity, which in turn lowers LDL cholesterol and triglycerides and increases HDL cholesterol. They have also been shown to lower serum fatty acid concentrations and to alter the relative percentages of important polyunsaturated fatty acids (Harris 2004). Statins also have multiple other cholesterol-independent effects since they:

- improve the endothelial function of atherosclerotic vessels (Wassmann 2001);
- have antithrombotic and anti-inflammatory effects (Reitz 2004);
- may reduce apoptosis and cell death (Ruocco 2002).

Statins are widely prescribed for the treatment of hypercholesterolaemia and for the secondary prevention of cardiovascular and cerebrovascular disease. There has been controversy about the level of cardiovascular risk that justifies treatment. Some guidelines advocate treatment for primary prevention in people with a high 10-year cardiovascular disease risk and in people with a high lifetime cardiovascular disease risk estimated from heart age and other JBS3 calculator metrics, and in whom lifestyle changes alone are considered insufficient by the physician and person concerned (Heart 2014). Statins are taken once a day by mouth. Most are available generically, decreasing their cost. They are classified according to their solubility in lipids (lipophilic) or water (hydrophilic). Lipophilic statins (lovastatin, simvastatin, cervistatin) cross the blood-brain barrier (BBB) and penetrate cell membranes more effectively than the hydrophilic statins (atorvastatin, pravastatin, fluvastatin).

Statins and dementia: observational studies

When the first version of this review was written in 2001, two clinical reports had been published describing an association between statin therapy and a reduction in the occurrence of AD by as much as 70% (Jick 2000; Wolozin 2000). Since then, several more observational studies (cross-sectional and longitudinal) assessing the relationship between statin therapy and dementia have been conducted. These have been systematically reviewed by several groups. Wong 2013 performed a meta-analysis of observational studies and concluded that statins may provide a slight benefit in the prevention of AD and all-type dementia but that the studies were subject to bias and so should be interpreted with caution. Swiger 2013 evaluated the effects of statins on short-term cognitive function and long-term incidence of dementia in RCTs or high-quality prospective cohort studies. There was no consistent effect of statin therapy on cognitive end points in the short term. Pooled results assessing long-term cognitive effects revealed a 29% reduction in incident dementia in people treated with statins with the caveat of heterogeneity in study design, exposure and outcomes. Song 2013 carried out a meta-analysis of eight prospective cohort studies; the risk ratio of dementia was reduced in the statin users but again the authors commented on significant heterogeneity.

Adverse effects of statins

Statins have known adverse effects; headache; altered liver-function tests; paraesthesia and gastrointestinal effects including abdominal pain, flatulence, constipation, diarrhoea, nausea and vomiting, are the most commonly reported. Reversible myositis is a rare but significant adverse effect of statins; myalgia and myopathy have also been reported. There has also been controversy about the level of cardiovascular risk that justifies treatment. Some guidelines advocate treatment for primary prevention in people with a high 10-year cardiovascular disease risk and in people with a high lifetime cardiovascular disease risk estimated from heart age and other JBS3 calculator metrics, in whom lifestyle changes alone are considered insufficient by the physician and person concerned (Heart 2014).

It is also possible that treatment with statins may *cause* neurocognitive deficits. Cognitive impairment has been cited on post-marketing surveillance reports, case reports, observational studies and RCTs (Bettermann 2012; Evans 2009; Orsi 2001; Wagstaff 2003; Zamrini 2004; Zandi 2005), and following a review, the US Food and Drug Administration (FDA) issued a new warning for the labelling of statin drugs regarding potential adverse effects on cognition in 2012. The FDA advised the reports about memory loss, forgetfulness and confusion spanned all statin products and all age groups. In general, the symptoms were not serious and were reversible within a few weeks after the person stopped taking the

medication; people affected may have been taking the medication for a few days; others affected had been taking it for years. Other groups have systematically assessed the evidence available in an effort to address the question 'do statins impair cognition?'; they concluded there is no significant evidence that statins cause or contribute towards cognitive decline (Kelley 2014; Ott 2015; Richardson 2013).

How the intervention might work

Lack of understanding as to the true pathophysiology of AD limits our understanding of the role of statins in the possible prevention of AD. In vitro and in vivo studies have been carried out that have resulted in a number of proposed mechanisms of action including: action on APP metabolism, reduction of chronic neuroinflammation, reductions in brain oxidative stress, gamma-secretase relocation in lipid rafts, and reduced amyloid plaques and phosphorylated tau-positive dystrophic neuritis (McFarland 2014).

The range of cholesterol-dependent and cholesterol-independent actions described above may all be relevant to an effect of statins on the incidence of VaD. They could also reduce the incidence of post-stroke dementia through efficacy in the primary and secondary prevention of stroke and other pleiotropic effects. Clinical trials indicate that statins significantly decrease stroke risk. The meta-analysis carried out by The Cholesterol Treatment Trialists' Collaborators including 90,056 participants found that the use of statins caused a significant 17% proportional reduction in the incidence of first-ever stroke of any type per 1 mmol/l LDL cholesterol reduction (CTTC 2005). In secondary prevention of stroke, the Stroke Prevention by Aggressive Reduction in Cholesterol Levels study showed that treatment with atorvastatin reduced the risk of recurrent cerebrovascular events in people with recent stroke or transient ischaemic attack but no history of heart disease (SPARCL Investigators 2006). A more recent meta-analysis included 18 RCTs and concluded that statins may be beneficial in reducing the overall incidence of stroke (Wang 2014).

Why it is important to do this review

In 2015 over 46 million people live with dementia worldwide. This number is estimated to increase to 131.5 million by 2050. Dementia also has a huge economic impact. In 2015 the total estimated worldwide cost of dementia is USD 818 billion, and it will become a trillion dollar disease by 2018 (World Alzheimer Report 2015). Therefore, any medication that may have an impact in preventing onset of the disease will be of immense interest to the public, healthcare workers and policy makers. Debate continues about risks and benefits of widespread statin use with controversy concerning primary prevention of vascular disease in particular. This review will add to the knowledge base concerning primary prevention of dementia.

OBJECTIVES

To evaluate the efficacy and safety of statins for the prevention of dementia in people at risk of dementia due to their age and to determine whether the efficacy and safety of statins for this purpose depends on cholesterol level, ApoE genotype or cognitive level.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised, double-blind, placebo-controlled trials in which a statin was given for at least 12 months. We considered it unlikely that any preventive effect on dementia incidence could be detected in trials with shorter treatment periods.

We excluded trials comparing two different statins without a placebo.

Types of participants

People with objectively normal cognitive function and of sufficient age to be at risk of AD (mean age 65 years or over). We also included people with evidence of cerebrovascular disease or at high risk of cerebrovascular disease.

Types of interventions

Any member of the statin family given within the licensed dose range with parallel concomitant placebo.

Types of outcome measures

Primary outcomes

- Objective diagnosis of dementia.
- Objective diagnosis of AD according to standard criteria.
- Objective diagnosis of VaD according to standard criteria.
- Change in Mini Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale - Cognition (ADAS-Cog) or other accepted objective and standardised tests of cognitive performance in people at risk of AD/VaD on treatment with statins.
- Incidence and severity of adverse effects.

Secondary outcomes

- Change in cognitive status accounting for prior cholesterol level, ApoE genotype and cognitive level.
- Participant-perceived quality of life.
- Change in ADLs.
- Change in behaviour.

Search methods for identification of studies

Electronic searches

We searched ALOIS - the Cochrane Dementia and Cognitive Improvement Group's (CDCIG) specialised register on 11 November 2015 (www.medicine.ox.ac.uk/alois). We used the following search terms: statin*, simvastatin*, lovastatin*, pravastatin*, fluvastatin*, atorvastatin* and rosuvastatin*.
The Trials Search Co-ordinator for the CDCIG maintains ALOIS, which contains studies that fall within the areas of dementia prevention, dementia treatment and management, and cognitive enhancement in healthy elderly populations. The studies are identified through:

- monthly searches of a number of major healthcare databases: MEDLINE, EMBASE, CINAHL, PsycINFO and Lilacs;
- monthly searches of a number of trial registers: ISRCTN; UMIN (Japan's Trial Register); the World Health Organization (WHO) portal (which covers ClinicalTrials.gov; ISRCTN; the Chinese Clinical Trials Register; the German Clinical Trials Register; the Iranian Registry of Clinical Trials and the Netherlands National Trials Register, plus others);
- quarterly searches of the Central Register of Controlled Trials (CENTRAL);
- six-monthly searches of a number of grey literature sources: ISI Web of Knowledge Conference Proceedings; Index to Theses and Australasian Digital Theses.

To view a list of all sources searched for ALOIS see About ALOIS on the ALOIS website (www.medicine.ox.ac.uk/alois).
We ran additional searches in MEDLINE, EMBASE, PsycINFO, CINAHL, ClinicalTrials.gov and WHO Portal/ICTRP to ensure that the search was as comprehensive and as up-to-date as possible. Appendix 1 shows the search strategies used for the retrieval of reports of trials.

Data collection and analysis

Selection of studies

Two authors (BMcG and PP) independently undertook searching and screening of publications.

Two authors (BMcG and PP) agreed upon and tested the MeSH terms and search strategy. The other authors (DC and RB) acted as adjudicators and reviewed the process. BMcG and PP screened the citations and independently selected trials for relevance against the defined inclusion criteria. We resolved any disagreements in the independent selection by discussion. We excluded those trials that did not fulfil the criteria from further analysis. We referred to excluded studies in the Discussion and Characteristics of excluded studies table.

Data extraction and management

We extracted data from the published reports using a data collection form that was piloted by the team. We extracted available data on demographics of participants (age, gender, lipid values at baseline), statin regimen (type of statin, daily dosage, starting time, duration) and follow-up duration. For continuous outcomes, neither the mean scores nor the mean changes from baseline in the individual treatment groups were reported. Therefore, we extracted the mean difference (MD) between groups and the standard error of the MD. For dichotomous data, we extracted the number of participants in each treatment group and the number of participants experiencing the outcome of interest.

Assessment of risk of bias in included studies

We assessed methodological quality of the included trials using Cochrane's tool for assessing risk of bias. We assessed the following domains: selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias.

Measures of treatment effect

Continuous data

We used the MD to measure the treatment effect. If the same outcome was assessed using different scales, then we used the standardised mean difference (SMD). We reported 95% confidence intervals (CI).

Dichotomous data

We reported results of dichotomous outcomes as an odds ratio (OR) with 95% CI.

Dealing with missing data

For each outcome measure, we sought data on every participant assessed. To allow an intention-to-treat analysis, we sought the data irrespective of compliance, whether or not the participant was subsequently deemed ineligible, or otherwise excluded from treatment or follow-up. If intention-to-treat data were not available in the publications, we sought 'on-treatment' or the data of

participants who completed the trial and indicated as such. We did not use data from titration phases prior to the randomised phase to assess safety or efficacy.

Assessment of heterogeneity

We considered clinical heterogeneity between trials (participants, interventions and outcomes) when deciding whether or not to synthesise data. Where we performed a meta-analysis, we used a standard Chi^2 test to check for heterogeneity. We also assessed the impact of heterogeneity on the meta-analysis using the I^2 statistic. If heterogeneity still existed with any model, we carried out a sensitivity analysis (excluding studies with conflicting results from the rest) thereby assessing the robustness of the results of fixed-effect versus random-effects models.

Data synthesis

Where data were suitable for a meta-analysis, we presented the overall estimate from a fixed-effect model. If we found substantial heterogeneity (I^2 greater than 30%), we also presented results from a random-effects model and reported this as the main result.

Presentation of results - 'Summary of findings' table

We used the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach to assess the quality of the supporting evidence behind each estimate of treatment effect. We presented primary outcomes of the review in a 'Summary of findings' table including, for each outcome, a summary of the amount of data, the magnitude of the effect size and the overall quality of the evidence (Schunemann 2011).

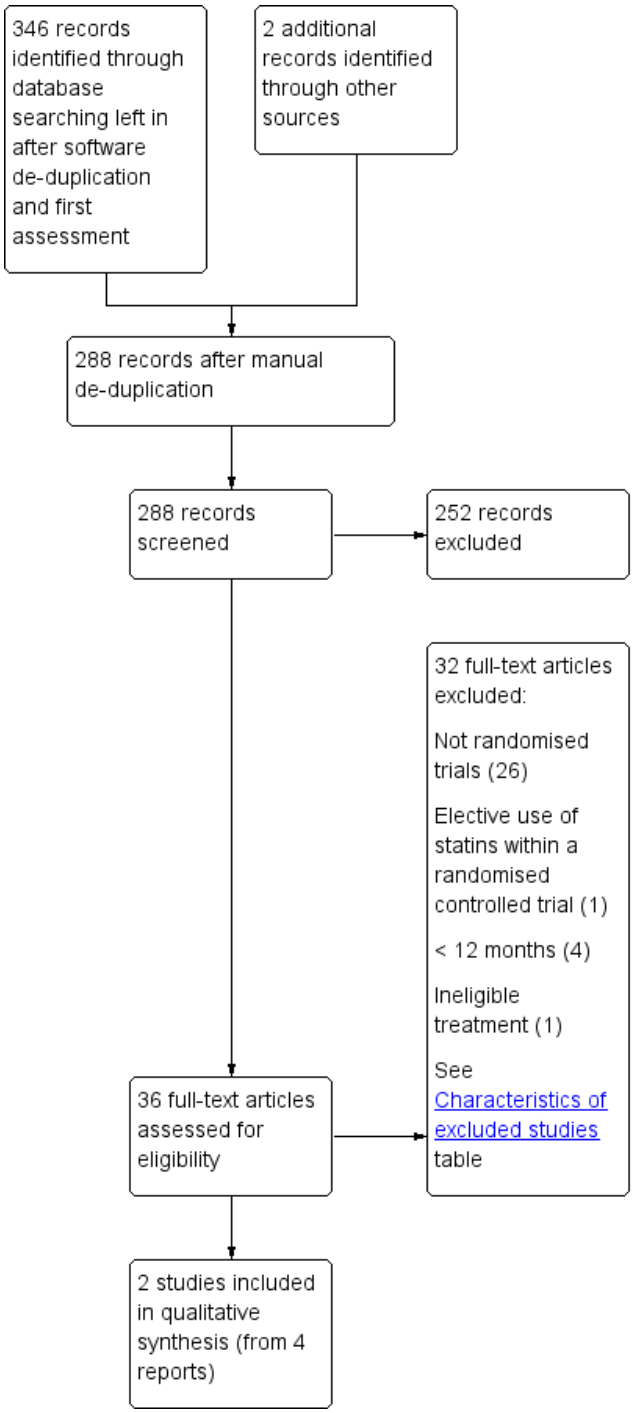
RESULTS

Description of studies

Results of the search

For this update, the electronic searches retrieved 346 references. We obtained 36 papers in full-test form and considered eight studies potentially eligible after screening (Figure 1).

Figure 1. Study flow diagram.



Included studies

We identified two RCTs with 26,340 participants (HPS 2002; PROSPER 2002). For full details, see Characteristics of included studies table.

Participants

The HPS 2002 trial included adults aged 40 to 80 years at high risk of vascular events (past medical history of coronary heart disease, other occlusive arterial disease, diabetes or hypertension (if also male and aged at least 65 years, in order to be at similar risk to the other disease categories)). A total of 20,536 people were randomised, with 5806 (28.3%) participants aged at least 70 years at study entry. A total of 1820 participants had cerebrovascular disease defined by past history of non-disabling stroke not thought to be haemorrhagic or transient cerebral ischaemia.

The PROSPER study included 5804 adults aged 70 to 82 years (mean age 75.4 years) with a history of, or risk factors for, vascular disease. A total of 649 had a history of stroke or transient Ischaemic attack.

Participants were recruited from industrialised countries. HPS 2002 recruited participants from the UK and PROSPER 2002 recruited participants from Scotland, Ireland and the Netherlands. Study participants predominantly consisted of ambulatory participants recruited from the community or primary care facilities. HPS 2002 did not assess cognition at baseline but excluded people with dementia or any other condition that might limit long-term compliance (e.g. severely disabling stroke, psychiatric disorder). PROSPER 2002 excluded participants with poor cognitive function (MMSE less than 24) at baseline.

Mean non-fasting blood concentration of total cholesterol in HPS 2002 was 5.9 mmol/L (standard deviation (SD) 1.0), directly measured LDL cholesterol of 3.4 mmol/L (SD 0.8), HDL cholesterol of 1.06 mmol/L (SD 0.33) and triglycerides of 2.1 mmol/L (SD 1.4).

For inclusion in the PROSPER 2002 trial, plasma total cholesterol was required to be 4.0 to 9.0 mmol/L and triglycerides concentrations less than 6.0 mmol/L. Mean cholesterol at entry in both groups was 5.7 mmol/L (SD 0.9), LDL cholesterol 3.8 mmol/L (SD 0.8), HDL cholesterol 1.3 mmol/L (SD 0.35) and triglycerides 1.5 mmol/L (SD 0.7).

Interventions

Treatment in HPS 2002 consisted of simvastatin 40 mg daily or matching placebo. Mean compliance with simvastatin was 85%. Mean non-study statin use in the placebo group was 17%. Mean duration of follow-up was five years for all randomised participants. There was a mean difference in LDL cholesterol of 1.0 mmol/L between participants allocated simvastatin and participants allocated placebo during the study. The proportional reduction in LDL cholesterol produced by actual use of simvastatin 40 mg daily was approximately independent of the presenting cholesterol concentration.

Treatment in PROSPER 2002 consisted of pravastatin 40 mg or matching placebo. Adherence was 94% in both the placebo and pravastatin groups. About 10% of the placebo group and 5% of the pravastatin group initiated non-study statin therapy. Mean duration of follow-up was 3.2 years (range 2.8 to 4.0) for participants who did not die or withdraw consent. At the second annual visit post-randomisation, the pravastatin-induced decrease in LDL cholesterol was 33% in compliant participants and 27% in the entire cohort.

Outcomes - primary

Incidence of dementia was an outcome in HPS 2002 although it was not clear from the study results or the protocol what criteria were used to diagnose dementia.

Cognition: HPS 2002 assessed cognitive outcomes using the modified Telephone Interview for Cognitive Status (TICS-m) questionnaire, administered to participants at final follow-up, either face-to-face in the clinic or over the telephone. A TICS-m score below 22 out of 39 was pre-specified as indicative of some cognitive impairment.

Cognition was a tertiary outcome in PROSPER 2002. The difference was reported between last-on-treatment and second baseline values for a number of cognitive tests: MMSE, number of correct letter digit codes, number of words remembered in the Picture-Word Learning Test (immediate and delayed) and time needed to complete the Stroop test. The first baseline measure was used as a practice measurement to reduce possible learning effects. Cognitive function was measured after nine, 18 and 30 months and at the end of the study (mean 42 months). A cognitive re-analysis was published in 2010 (PROSPER 2010).

Adverse effects that were serious were reported by both studies (HPS 2002; PROSPER 2002). HPS 2002 reported on development of psychiatric disorders and attempted suicide.

Outcomes - secondary

PROSPER 2002 measured function in ADLs using the Barthel Index and the Instrumental Activities of Daily Living (IADL) scale. Neither study provided data on quality of life or behaviour.

Change in cognition accounting for prior cholesterol level, ApoE genotype and cognitive function provided by PROSPER 2007.

Excluded studies

We excluded three new studies from this updated review. For full details see Characteristics of excluded studies table. We excluded 26 non-randomised trials from the outset as per Figure 1.

Sparks 2010 assessed cognitive outcomes following the elective use of statins in people diagnosed with mild cognitive impairment after enrolment in the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT). This was a pilot study in which use of statin was not randomly assigned.

Tendolkar 2012 was an exploratory hypothesis-generating trial in which 34 stroke-free elderly participants with atrial fibrillation were randomly assigned to treatment with both atorvastatin and ezetimibe (inhibits the intestinal absorption of cholesterol) or placebo for one year on top of normal anticoagulation. We excluded the study as it was not possible to assess the effect attributable to statin treatment.

Summers 2007 was a cognitive sub-study within the Lipid Lowering and Onset of Renal Disease (LORD) randomised double-blind placebo-controlled trial. Participants were randomly assigned to atorvastatin 10 mg/day or matching placebo and all had chronic kidney disease. We excluded the trial due to its short duration.

Three studies were excluded from the 2009 review and this update (Muldoon 2000; Muldoon 2004; Santanello 1997). All three studies followed participants for only six months and so failed to meet our duration criteria. In addition, participants in Muldoon 2000 had a mean age of 46 years and Muldoon 2004 had a mean age of 53 years and so were not considered to be at risk of dementia over the follow-up period.

Ongoing studies

Two further studies are ongoing: PODCAST 2013 (Prevention of Decline in Cognition after Stroke Trial) and The European Society of Hypertension - Chinese Hypertension League Stroke in Hypertension Optimal Treatment (ESH-CHL-SHOT 2014) randomised trial.

PODCAST 2013 is a multi-centre, prospective, randomised, open-label, blinded-endpoint, controlled partial-factorial phase IV trial in secondary and primary care aiming to recruit 100 participants who are post-ischaemic stroke by three to seven months from 30 UK Stroke Research Network sites. Participants with ischaemic stroke are randomised to intensive versus guideline lipid lowering with ezetimibe and a resin. The primary outcome is cognitive function measured by the Addenbrooke's Cognitive Examination-Revised (ACE-R), which includes the MMSE. There are also other cognitive secondary outcomes: MoCA (Montreal Cognitive Assessment), TICS, Stroop test and Trail Making A & B; there is also a blood pressure lowering arm of the trial. As there is no placebo arm, it will not be suitable for inclusion in this review.

ESH-CHL-SHOT 2014 is a prospective multi-national RCT with a 3 x 2 factorial design comparing three different systolic blood pressure targets and two different LDL cholesterol targets in participants with hypertension and a stroke or transient Ischaemic attack one to six months before randomisation. Cognitive decline as measured by the Montreal Cognitive Assessment (MoCA) and dementia are secondary outcomes. The study aims to recruit 925 participants with four years of follow-up. Investigators are free to choose the statin (among those approved in each country). As there is no placebo arm, it will not be suitable for inclusion in this review.

Risk of bias in included studies

For full details, see 'Risk of bias' tables and Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

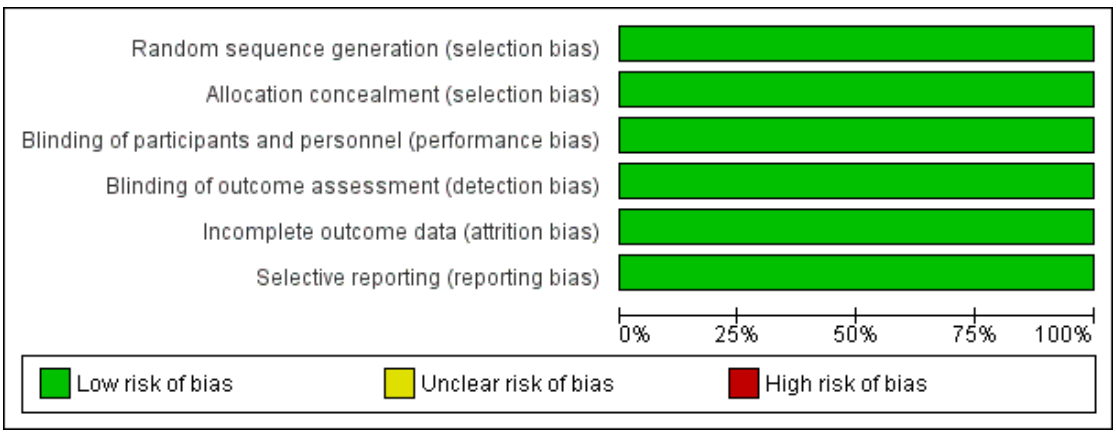
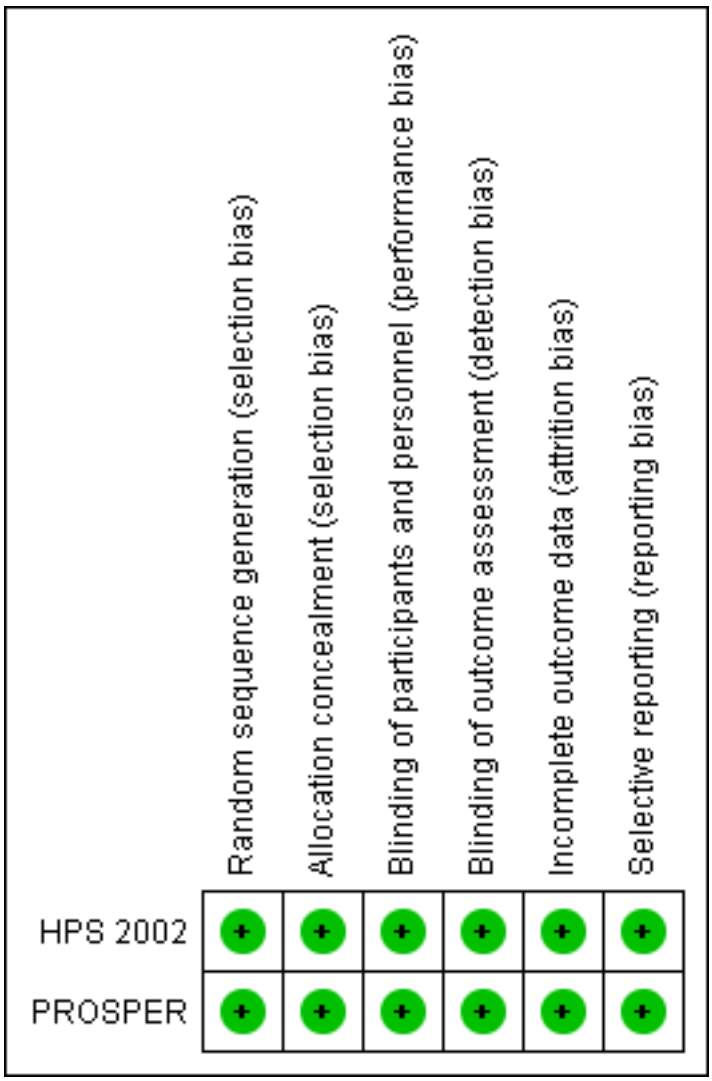


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation (selection bias)

In HPS 2002, potentially eligible people entered a pre randomisation 'run-in' phase, which was intended chiefly to limit subsequent randomisation to people likely to take the randomly allocated study medication for at least five years. A central telephone randomisation system using a minimisation algorithm was used to balance the treatment groups; this appeared adequate.

PROSPER 2002 used a computerised pseudo-random number generator, which consisted of balanced blocks of size 4. Randomisation was done by telephone call or through fax exchange with the study data centre. This appeared satisfactory.

Blinding (performance bias and detection bias)

In HPS 2002, blinding of participants and key study personnel occurred and it was unlikely that the blinding could have been broken except in a medical emergency. Comment: probably done. In PROSPER 2000, all study personnel, including the endpoint adjudication committee, remained unaware of the allocated study medication status of the participants throughout the study. Emergency unblinding was available via an interactive voice response telephone system. There were only two requests for emergency unblinding. Comment: appeared adequate.

Incomplete outcome data (attrition bias)

In HPS 2002, small numbers in both groups were lost to follow-up; 37 in the simvastatin group: three due to death, 34 due to morbidity and 30 in the placebo group: four due to death, 26 due to morbidity. In total, there were 1328 (12.9%) deaths in the simvastatin group and 1507 (14.7%) deaths in the placebo group during the scheduled treatment period.

In PROSPER 2000, similar numbers in both groups discontinued with similar reasons, with approximately 25% in each group over the 3.2-year follow-up. A total of 725 participants discontinued in the placebo group: 116 due to a non-fatal adverse event, 240 died, 311 refused to participate or did not attend, 58 other reasons. In addition seven withdrew consent. A total of 724 discontinued in the pravastatin group: 107 due to non-fatal adverse events, 219 died, 346 refused to participate or did not attend, 52 other reasons. In addition five withdrew consent. In total, there were 298 (10.3%) deaths in the pravastatin group and 306 (10.5%) deaths in the placebo group over the mean follow-up of 3.2 years.

Selective reporting (reporting bias)

There was no evidence of selective reporting.

Other potential sources of bias

We identified no other potential sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Statins compared with placebo for prevention of dementia

We judged that efficacy data could not be combined from the two studies as they measured different cognitive outcomes at different time points. We synthesised adverse events data. Please refer to Summary of findings for the main comparison.

Incidence of dementia: there was no evidence of a difference in the incidence of dementia between the statin group (31 cases, 0.3%) and the placebo group (31 cases, 0.3%), but the result was imprecise and we downgraded the evidence to moderate (OR 1.00, 98% CI 0.61 to 1.65, 20,536 participants, moderate quality evidence) (HPS 2002).

Cognitive change from baseline: the MD between groups (pravastatin-placebo) in change from baseline to last on-treatment visit for various cognitive tests was as follows: change in MMSE MD 0.06 (95% CI -0.04 to 0.16, 5804 participants, high quality evidence), number of correct letter digit codes MD -0.01 (95% CI -0.25 to 0.23, 5804 participants, high quality evidence), number of words remembered in the Picture-Word Learning Test MD 0.02 (95% CI -0.12 to 0.16, 5804 participants, high quality evidence), time needed to complete the Stroop test MD 0.8 seconds (95% CI -0.4 to 2.0, 5804 participants, high quality evidence) (PROSPER 2002).

Difference in mean TICS-m score: between the two treatment groups at final visit (MD 0.02, 95% CI -0.12, to 0.16, 20,536 participants, high quality evidence). A TICS-m score below 22 out of 39 was pre-specified as indicative of some cognitive impairment. No significant difference observed between the treatment groups in percentage of participants classified as cognitively impaired either overall (OR 0.97, 95% CI 0.91 to 1.04, 20,536 participants, high quality evidence) or in subgroups defined with respect to their age at study entry (under 65 years: OR 0.95, 95% CI 0.85 to 1.05, 9839 participants; 65 to 69 years: OR 1.02, 95% CI 0.90 to 1.16, 4891 participants; 70 to 80 years: OR 0.93, 95% CI 0.84 to 1.04, 2045 participants, high quality evidence) (HPS 2002).

Incidence and severity of adverse events: in HPS 2002, discontinuation of allocated treatment was attributed to adverse events for similar numbers of participants in the two groups (4.8% with simvastatin-allocated versus 5.1% with placebo-allocated). In PROSPER 2002, 107 (3.7%) pravastatin-allocated participants and 116 (3.98%) placebo-allocated participants withdrew due to a non-fatal adverse event. When data were combined in a meta-analysis, there was no evidence of a difference in withdrawal rates between groups (OR 0.94, 95% CI 0.83 to 1.05, 26,340 participant, high quality of evidence). In PROSPER 2002, there was an increased incidence of newly diagnosed cancers in the pravastatin group (25% more frequent compared to placebo) (see Agreements and disagreements with other studies or reviews).

PROSPER 2002 reported serious adverse events. One or more events were reported by 1604 (55%) participants allocated to placebo and by 1608 (56%) participants allocated to pravastatin (OR 1.02, 95% CI 0.92 to 1.13, 5804 participants, high quality evidence).

Effect on liver and muscle enzymes: in PROSPER 2002 there were no reported cases of rhabdomyolysis; in HPS 2002, rhabdomyolysis developed in five simvastatin-allocated and three placebo-allocated participants (combined analysis OR 1.67, 95% CI 0.40 to 6.98, 26,340 participants, moderate quality of evidence, downgraded due to imprecision). In PROSPER 2002, there were 36 instances of reported myalgia in the pravastatin group and 32 in the placebo group (OR 1.14, 95% CI 0.70 to 1.83, 5804 participants, moderate quality evidence, downgraded due to imprecision); in HPS 2002, myopathy developed in five simvastatin-

allocated and one placebo-allocated participants (OR 5.00, 95% CI 0.58 to 42.81, 20,536 participants).

In PROSPER 2002, the three month visit was the only formal safety laboratory assessment and there were no participants in either group with creatine kinase concentrations higher than 10 times the upper limit of normal (ULN). There was one participant in each group with greater than three times ULN plasma concentrations of alanine and aspartate transaminases. In HPS 2002, 19 simvastatin-allocated and 13 placebo-allocated participants had creatine kinase four to 10 times ULN and 11 simvastatin-allocated versus six placebo-allocated participants had creatine kinase greater than 10 times ULN.

HPS 2002 measured blood concentrations of alanine aminotransferase at each follow-up visit. There was no significant difference between the groups in the numbers of participants whose study treatment was stopped because of elevated liver enzymes (OR 1.39, 95% CI 0.90 to 2.15, 5804 participants, moderate quality of evidence, downgraded due to imprecision). In PROSPER 2002, one participant in each group (pravastatin and placebo) had increased plasma concentrations of alanine and aspartate transaminases (greater than three times ULN).

In HPS 2002, 14 simvastatin-allocated and 11 placebo-allocated participants had attempted suicide; 67 simvastatin-allocated and 60 placebo-allocated participants had developed some other psychiatric disorder.

In PROSPER 2002, there were no significant differences between the groups in function over time as measured by the Barthel index (MD 0.06, 95% CI -0.03 to 0.15, 5804 participants, high quality of evidence) or in the IADL questionnaire (MD 0.03, 95% CI -0.08 to 0.14, 5804 participants, high quality of evidence).

Subgroups

Effect of ApoE genotype: one follow-up prospective study from PROSPER assessed the association between ApoE4 and cognitive decline in elderly adults. Of the 5804 participants recruited into the study, ApoE genotyping was available for 95.5%; 4155 were classified as E4- and 1389 as E4+. At baseline, participants in the E4+ group performed significantly less well on the Stroop test and Picture-Word Recall (immediate and delayed) than participants in the E4- group and had marginally, but significantly, poorer scores on the MMSE. Over the mean 3.2 years of follow-up, ApoE4 status significantly influenced change in scores on the cognitive tests associated with memory (immediate and delayed Picture-Word Recall) but not those for attention and information processing (Stroop, Letter-Digit Coding). Participants in the E4+ group had significantly greater decrements than participants in the E4- group on MMSE, Barthel Index, and IADL scores. Treatment assignment (i.e. to placebo or pravastatin) was included in the multi-variate models and there was no significant interaction between ApoE4 genotype, treatment and cognition. There were no significant associations with any of the tests, confirming the lack of effect of statin therapy on cognition.

From the further analysis published in PROSPER 2010, there was no difference in pravastatin and placebo groups in cognitive decline in men or women, people with or without a history of vascular disease or history of diabetes, with low or high HDL and total cholesterol levels (all P value > 0.05). There was an effect of pravastatin on processing speed within the ApoE2 carriers and within the low cholesterol group but this finding lost statistical significance after correction for multiple testing, and there was no consistent parallel change in other cognitive performance tests.

In HPS 2002, age at study entry was not associated with any significant difference between the treatment groups in percentage of participants defined as cognitively impaired, that is, in participants aged under 65 years, statin users were no less likely to develop dementia than participants in the placebo group, likewise for participants in the 65- to 69-years age group and the 70- to 80-years age group.

DISCUSSION

Summary of main results

Two studies including 26,340 people contributed data relevant to the primary outcomes of this review. The evidence showed that statins given in late life to people at risk of vascular disease have no effect on the incidence of dementia or on cognitive decline.

HPS 2002 evaluated simvastatin in the prevention of heart disease among 20,536 older adults, including 5806 people aged 70 to 80 years at baseline. Despite significantly reduced rates of myocardial infarction, stroke and revascularisation procedures, there was no significant difference between treatment groups in the percentages of participants classified as cognitively impaired either in the whole study population or in subgroups classified by their age at study entry, or their previous history of cerebrovascular disease. The same numbers of participants in each treatment group were reported to have developed dementia during follow-up (31 in each group).

In PROSPER 2002, 5804 people aged 70 to 82 years were randomised to either pravastatin or placebo. These participants were considered to be at moderate risk of developing dementia over the mean 3.2 years of follow-up. Despite a 34% reduction in LDL cholesterol and a significant reduction in the primary endpoint of composite coronary death, non-fatal myocardial infarction and fatal or non-fatal stroke in the pravastatin group, there was no significant effect on cognitive function measured using several cognitive tests.

Rates of treatment discontinuation due to non-fatal adverse events were less than 5% in both studies. There was no difference between statin and placebo groups in the risk of withdrawal due to adverse events. PROSPER reported serious adverse events separately and, again, these did not differ between treatment groups.

Overall completeness and applicability of evidence

This review provided some evidence towards the answer to the review question. However, the studies identified were not sufficient to answer all of the objectives of the review. Our primary interest was in the prevention of dementia. Neither study systematically ascertained dementia at baseline although both attempted to exclude people with pre-existing dementia or significant cognitive impairment. Only HPS 2002 included incidence of dementia as an outcome, but the criteria used to identify dementia were not clear.

Cognition was a tertiary endpoint in both included studies and neither included a comprehensive cognitive assessment although PROSPER 2002, which used the MMSE and several neuropsychological tests, was more informative in cognitive terms than the HPS 2002 study, which used a telephone interview only. Decline in cognition was very low in both studies and this may relate to careful control of cardiovascular risk factors. This parallels the absence of decline in two VaD clinical trials; the control of cardiovascular risk factors is common in both (Black 2003; Wilkinson 2003).

Both studies included a large number of participants at risk of cognitive decline, follow-up was sufficient, one study included the lipophilic statin simvastatin (HPS 2002), and one study included the hydrophilic statin pravastatin (PROSPER 2002). There were adequate data on adverse effects in both studies. There were data on function in ADL and on change in cognition accounting for prior cholesterol level, ApoE genotype and cognitive level along with functional performance from PROSPER 2002 only. There were no data on quality of life or behaviour.

Both studies included participants at moderate to high risk of vascular events; therefore, the results may not apply to people at low vascular risk.

Quality of the evidence

Both studies were at low risk of bias. However, there were key methodological limitations concerning cognitive outcomes as cognition was a tertiary endpoint in both studies. HPS 2002 had no baseline cognitive data and included only one cognitive test (TICS-m), it recorded incidence of dementia but event rates were very low. Our estimate for the effect of statin treatment on dementia incidence was imprecise (OR 1.00, 95% CI 0.61 to 1.65), so we downgraded the quality of the evidence for this outcome to moderate. PROSPER 2002 used different cognitive tests at different time points and incidence of dementia was not an outcome. Loss to follow-up was low in HPS 2002, but most cases of mortality were not included in this statistic (three participants in the simvastatin group lost to follow-up due to mortality, 1328 participants died in total in the simvastatin group; four participants in the placebo group lost to follow-up due to mortality, 1507 participants died in total in the placebo group). In PROSPER 2002, 724 participants in the pravastatin group and 725 participants in the placebo group withdrew due to various reasons; 219 participants died in the pravastatin group and 240 participants died in the placebo group. All analyses were by intention to treat.

Potential biases in the review process

It is likely that we identified all relevant studies and obtained all relevant data due to the strengths of the search strategy and review process. We do not believe that we introduced bias using our review methods.

Agreements and disagreements with other studies or reviews

The question of whether statins were of benefit in the prevention of dementia stemmed from cross-sectional studies in the early 2000s; initial evidence was very promising with some estimates of risk reduction of more than two-thirds (Jick 2000; Wolozin 2000). However, these studies were subject to important limitations. How representative people in these databases were of the general population was unclear and information on important confounding factors, such as education, was unavailable. Cross-sectional studies are subject to indication bias, which occurs when a drug is prescribed for a reason that itself is associated with an outcome of interest. Of note from the Wolozin 2000 study, while the data were being collected (1996 to 1998), physicians were more likely to have prescribed statins to people who were 'more highly educated, attentive, inquisitive and concerned about their future health' (Haley 2000), than people at higher risk of dementia. This may also explain why an effect was seen for pravastatin and lovastatin but not simvastatin, sales of which lagged behind the former two.

Subsequent systematic reviews have been carried out. Wong 2013 identified 20 relevant studies, comprising 16 cohort studies, three case-control studies and one RCT. In one meta-analysis, there were modest protective effects of statin use for any dementia (random effects pooled RR 0.82, 95% CI 0.69 to 0.97) and AD (random effects pooled RR 0.70, 95% CI 0.60 to 0.80). There was substantial heterogeneity in the effect sizes for any dementia, but not for AD. Of note, effect sizes were smaller and closer to the null in studies that had controlled for more confounders, and where a clinical diagnosis as opposed to linkage to health records was used to establish dementia incidence. Song 2013 performed a meta-analysis of prospective cohort studies but was much less comprehensive and several studies were missed. They found a reduced incidence of dementia in statin users but there was considerable heterogeneity (RR 0.62, 95% CI 0.43 to 0.81, I^2 = 70.8%).

When considering the increased cancer incidence in PROSPER 2002 in the pravastatin group compared to the placebo group,

a meta-analysis carried out by the study authors of cancer rates in previous randomised placebo-controlled studies lasting more than three years revealed no increased incidence in pravastatin or all statin users, which is reassuring, but this outcome should be included in future RCTs of statins. There was no increased incidence of newly diagnosed cancer in HPS 2002 in the simvastatin group compared to the placebo group (814 simvastatin-allocated participants versus 803 placebo-allocated participants; RR 1.0, 95% CI 0.91 to 1.11). Subsequently, one systematic review found six meta-analyses of RCTs and two meta-analyses of RCTs and observational studies found no association between statin use and overall incident cancer risk (Bondreau 2010).

Overall, it is still unclear how dyslipidaemia exerts its effects on dementia risk; the association may vary depending upon the age at which cholesterol level is assessed and the follow-up interval. The World Alzheimer Report found studies where the exposure was assessed in mid-life were more likely to report a positive association than short latency studies where exposure was assessed in late-life shortly before the onset of dementia (Prince 2014). It is postulated that cholesterol levels may decline more rapidly from mid-life to late-life in people who go on to develop dementia, particularly AD. Of note in the Honolulu Asia Aging Study (HASS) (Stewart 2007), the Baltimore Longitudinal Study of Aging in the USA (Beydoun 2011), the Prospective Population Study of Women in Sweden (Mielke 2010), and Cardiovascular Risk Factors, Aging and Dementia (CAIDE) in Finland (Solomon 2007), a more rapid decline in total cholesterol from mid to late life was predictive of the onset of AD. The only study which did not replicate this finding was the Framingham Heart Study (Tan 2003). This decline in total cholesterol could be causal, could reflect reverse causality or could be accounted for by confounding. In order to address this question, ideally large RCTs would run for many years assessing cognitive decline in statin users compared to non-users but these would be extremely expensive and labour intensive. It is also unfeasible, as many people at risk of dementia will be prescribed statins for other reasons.

Limitations

This review is limited primarily by the lack of evidence from well-designed RCTs in which cognition is a primary outcome. Ideally, large RCTs would run for many years in order to assess cognitive decline in statin users compared to non-users but this is not feasible due to costs involved and as many participants at risk of dementia will be prescribed statins for other reasons.

AUTHORS' CONCLUSIONS

Implications for practice

There is good evidence that statins given in late life to people at risk of vascular disease have no effect in preventing cognitive decline or dementia. Inclusion of statins for this indication on national or local formularies is not currently warranted.

Implications for research

Statins to date have not been shown to be beneficial in the prevention of dementia in randomised controlled trials (RCTs), the gold standard of clinical research. However, there remain unanswered questions, as there were insufficient data in the current trials to address the following questions.

- Whether there is a relationship between the occurrence of disease and the level of cholesterol - as one's cholesterol rises does the risk of disease rise in some graded fashion or does a rapid decline in total cholesterol from mid to late life predict onset of Alzheimer's disease (AD)?
- Whether lowering of cholesterol levels judged normal in the developed parts of the world might influence the onset of disease.
- Whether people with a family history of AD might preferentially benefit from therapy compared to people without a family history.
- Whether therapy started in middle life has an advantage over therapy started people in their 60s or early 70s.

Further RCTs may address these questions but costs and logistics make this difficult.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

HPS 2002

Methods	Randomised controlled trial
Participants	20,536 participants (10,269 in intervention group, 10,267 in control group) with coronary heart disease, other occlusive arterial disease, diabetes or hypertension Aged 40-80 years, 5806 participants > 70 years of age Baseline total cholesterol at least 3.5 mmol/L, mean total cholesterol 5.9 mmol/L, LDL cholesterol 3.4 mmol/L
Interventions	Intervention: simvastatin 40 mg Control: matching placebo
Outcomes	Those analysed in review: Telephone Interview for Cognitive Status (TICS-m) score (mean); presence of cognitive impairment overall, presence of cognitive impairment with respect to age or previous history of cerebrovascular disease; incidence of dementia; adverse events; cholesterol level Those not analysed in review: all-cause mortality, major vascular event (first major coronary event, stroke, revascularisation), first stroke, first ever vascular event
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation system using a minimisation algorithm. Comment: probably done
Allocation concealment (selection bias)	Low risk	Central telephone allocation. Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured and unlikely that the blinding could have been broken except in a medical emergency. Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The Steering Committee, the collaborators, the funding agencies, and the coordinating centre staff (except those supplying the confidential analyses) remained unaware of the results on mortality and morbidity until completion of the scheduled treatment period." Comment: probably done

Incomplete outcome data (attrition bias) All outcomes	Low risk	Small numbers in both groups lost to follow-up. 37 in simvastatin group lost to follow-up: 3 due to death, 34 due to morbidity; 30 in placebo group lost to follow-up: 4 due to death, 26 due to morbidity
Selective reporting (reporting bias)	Low risk	Study protocol was available and all of the study's pre-specified outcomes were reported

PROSPER

Methods	Randomised controlled trial
Participants	5804 participants (2804 men and 3000 women; 2891 in intervention group, 2913 in placebo group) with history of, or risk factors for, vascular disease Aged 70-82 years Baseline cholesterol 4.0-9.0 mmol/L, mean total cholesterol 5.7 mmol/L, LDL cholesterol 3.8 mmol/L Mean follow-up 3.2 years (range 2.8-4.0 years)
Interventions	Intervention: pravastatin 40 mg Control: placebo
Outcomes	Those analysed in review: difference between the last 'on-treatment' and the second baseline value in MMSE score, correct letter digit codes, number of words remembered in Picture-Word Learning Test, time needed to complete Stroop test; difference between the last 'on-treatment' and second baseline value in Barthel Index and instrumental ADL score; serious adverse events; serum lipid concentrations Those not analysed in review: coronary heart disease death or non-fatal myocardial infarction, or fatal or non-fatal stroke; transient ischaemic attack; coronary angioplasty and coronary artery bypass graft; peripheral arterial surgery/angioplasty; heart failure hospitalisation; deaths due to coronary heart disease, stroke, vascular and non-vascular causes, cancer, trauma or suicide; all-cause mortality
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computerised pseudo-random number generator, balanced blocks of size 4. Comment: probably done
Allocation concealment (selection bias)	Low risk	Telephone call or fax exchange with the study data centre. Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All study personnel remained unaware of the allocated study medication status of the participants throughout the study. Only 2 requests for emergency unblinding were

PROSPER (*Continued*)

		implemented - emergency unblinding was available via an interactive voice response telephone system
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All study personnel, including the endpoint adjudication committee, remained unaware of the allocated study medication status of the participants throughout the study. Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar numbers in both groups discontinued with similar reasons, approximately 25% in each group over the 3.2-year follow-up. 725 discontinued in placebo group: 116 due to a non-fatal adverse event, 240 died, 311 refused to participate or did not attend, 58 other reasons. In addition 7 withdrew consent. 724 discontinued in the pravastatin group: 107 due to non-fatal adverse events, 219 died, 346 refused to participate or did not attend, 52 other reasons. In addition 5 withdrew consent
Selective reporting (reporting bias)	Low risk	Study protocol was available and all of the study's pre-specified outcomes (primary, secondary and tertiary) were reported in the pre-specified way

ADL: activities of daily living; LDL: low-density lipoprotein; MMSE: Mini Mental State Examination.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Muldoon 2000	Participants not of sufficient age to be at risk of dementia (aged 24-60 years, mean age 46 years); participants only followed for 6 months so insufficient follow-up
Muldoon 2004	Participants not of sufficient age to be of risk of dementia (aged 35-70 years, mean 54 years); participants only followed for 6 months so insufficient follow-up
Santanello 1997	Pilot study and funding ended before all participants could complete their 12-month visit. Data provided for 6-month follow-up only so of insufficient duration
Sparks 2010	Use of statin not randomly assigned
Summers 2007	Cognitive follow-up only 12 weeks so of insufficient duration for inclusion
Tendolkar 2012	Exploratory hypothesis-generating trial. All participants in treatment group received statin and ezetimibe so not possible to ascertain what treatment effect due to

Characteristics of ongoing studies *[ordered by study ID]*

ESH-CHL-SHOT 2014

Trial name or title	ESH-CHL-SHOT
Methods	Prospective multinational randomised trial with a 3 x 2 factorial design comparing 3 different systolic BP targets and 2 different LDL cholesterol targets
Participants	7500 participants (2500 in Europe and 5000 in China) at least 65 years old with hypertension and a stroke or transient ischaemic attack 1-6 months before randomisation
Interventions	Antihypertensive and statin treatments modified using suitable registered agents chosen by the investigator in order to maintain participants within the randomised SBP and LDL cholesterol windows
Outcomes	Primary: time to stroke (fatal and non-fatal) Secondary: time to first major cardiovascular event; cognitive decline and dementia
Starting date	2014
Contact information	alberto.zanchetti@auxologico.it
Notes	

PODCAST 2013

Trial name or title	PODCAST
Methods	Multi-centre prospective randomised open-label blinded endpoint controlled partial-factorial phase IV trial
Participants	100 participants from 30 UK Stroke Research Network sites who were post ischaemic stroke by 3-7 months
Interventions	Intensive vs. guideline BP lowering (target systolic < 125 mmHg vs. < 140 mmHg); intensive vs. guideline lipid lowering (target LDL cholesterol < 1.4 mmol/L vs. < 3 mmol/L)
Outcomes	Primary: cognitive decline as measured by the Addenbrooke's Cognitive Examination - Revised Secondary: feasibility of recruitment and retention of participants, tolerability and safety of the interventions, achieving and maintaining the BP and lipid targets, maintaining differences in SBP (> 10 mmHg) and LDL cholesterol (> 1 mmol/L) between the treatment groups, and performing clinic and telephone follow-up of cognition measures
Starting date	2013
Contact information	philip.bath@nottingham.ac.uk
Notes	

BP: blood pressure; LDL: low-density lipoprotein; SBP: systolic blood pressure.

DATA AND ANALYSES

Comparison 1. Incidence of dementia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of cases of dementia	1	20536	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.61, 1.65]

Comparison 2. Cognitive change from baseline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in Mini Mental State Examination	1	5804	Mean Difference (Fixed, 95% CI)	0.06 [-0.04, 0.16]
2 Stroop test (seconds)	1	5804	Mean Difference (Fixed, 95% CI)	0.8 [-0.38, 1.98]
3 Picture-Word Learning Task	1	5804	Mean Difference (Fixed, 95% CI)	0.02 [-0.12, 0.16]
4 Letter Digit	1	5804	Mean Difference (Fixed, 95% CI)	-0.01 [-0.25, 0.23]

Comparison 3. Modified Telephone Interview for Cognitive Status (TICS-m) at final visit

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean TICS-m Score	1	20536	Mean Difference (Fixed, 95% CI)	0.02 [-0.12, 0.16]
2 Aged < 65 years at study entry	1	9839	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.85, 1.05]
3 Aged 65-69 years at study entry	1	4891	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.90, 1.16]
4 Aged 70-80 years at study entry	1	5806	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.84, 1.04]
5 Cognitive impairment	1	20536	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.91, 1.04]

Comparison 4. Incidence and severity of adverse effects

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse effects requiring discontinuation of treatment	2	26340	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.83, 1.05]
2 Serious adverse event	1	5804	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.92, 1.13]
3 Myalgia incidence	1	5804	Odds Ratio (M-H, Fixed, 95% CI)	1.14 [0.70, 1.83]
4 Rhabdomyolysis	2	26340	Odds Ratio (M-H, Fixed, 95% CI)	1.67 [0.40, 6.98]
5 Myopathy incidence	1	20536	Odds Ratio (M-H, Fixed, 95% CI)	5.00 [0.58, 42.81]

6 Elevated liver enzymes causing discontinuation of treatment	1	5804	Odds Ratio (M-H, Fixed, 95% CI)	1.39 [0.90, 2.15]

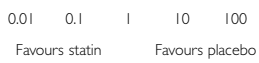
Analysis 1.1. Comparison 1 Incidence of dementia, Outcome 1 Number of cases of dementia.

Review: Statins for the prevention of dementia

Comparison: 1 Incidence of dementia

Outcome: 1 Number of cases of dementia

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
HPS 2002	31/10269	31/10267		100.0 %	1.00 [0.61, 1.65]
Total (95% CI)	**10269**	**10267**		**100.0 %**	**1.00 [0.61, 1.65]**
Total events: 31 (Experimental), 31 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.00 (P = 1.0)					
Test for subgroup differences: Not applicable					



Analysis 2.1. Comparison 2 Cognitive change from baseline, Outcome 1 Change in Mini Mental State Examination.

Review: Statins for the prevention of dementia

Comparison: 2 Cognitive change from baseline

Outcome: 1 Change in Mini Mental State Examination

Study or subgroup	Statin N	Placebo N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
PROSPER	2891	2913	0.06 (0.05)		100.0 %	0.06 [-0.04, 0.16]
Total (95% CI)	**2891**	**2913**			**100.0 %**	**0.06 [-0.04, 0.16]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.20 (P = 0.23)

Test for subgroup differences: Not applicable

Analysis 2.2. Comparison 2 Cognitive change from baseline, Outcome 2 Stroop test (seconds).

Review: Statins for the prevention of dementia

Comparison: 2 Cognitive change from baseline

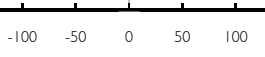
Outcome: 2 Stroop test (seconds)

Study or subgroup	Statin N	Placebo N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
PROSPER	2891	2913	0.8 (0.6)		100.0 %	0.80 [-0.38, 1.98]
Total (95% CI)	**2891**	**2913**			**100.0 %**	**0.80 [-0.38, 1.98]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.33 (P = 0.18)

Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2 Cognitive change from baseline, Outcome 3 Picture-Word Learning Task.

Review: Statins for the prevention of dementia

Comparison: 2 Cognitive change from baseline

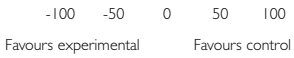
Outcome: 3 Picture-Word Learning Task

Study or subgroup	Statin N	Placebo N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
PROSPER	2891	2913	0.02 (0.07)		100.0 %	0.02 [-0.12, 0.16]
Total (95% CI)	**2891**	**2913**			**100.0 %**	**0.02 [-0.12, 0.16]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.29 (P = 0.78)

Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2 Cognitive change from baseline, Outcome 4 Letter Digit.

Review: Statins for the prevention of dementia

Comparison: 2 Cognitive change from baseline

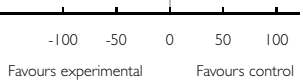
Outcome: 4 Letter Digit

Study or subgroup	Statin N	Placebo N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
PROSPER	2891	2913	-0.01 (0.12)		100.0 %	-0.01 [-0.25, 0.23]
Total (95% CI)	**2891**	**2913**			**100.0 %**	**-0.01 [-0.25, 0.23]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.08 (P = 0.93)

Test for subgroup differences: Not applicable



Analysis 3.1. Comparison 3 Modified Telephone Interview for Cognitive Status (TICS-m) at final visit, Outcome 1 Mean TICS-m Score.

Review: Statins for the prevention of dementia

Comparison: 3 Modified Telephone Interview for Cognitive Status (TICS-m) at final visit

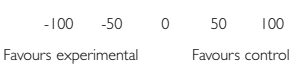
Outcome: 1 Mean TICS-m Score

Study or subgroup	Simvastatin N	Placebo N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
HPS 2002	10269	10267	0.02 (0.07)		100.0 %	0.02 [-0.12, 0.16]
Total (95% CI)	**10269**	**10267**			**100.0 %**	**0.02 [-0.12, 0.16]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.29 (P = 0.78)

Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3 Modified Telephone Interview for Cognitive Status (TICS-m) at final visit, Outcome 2 Aged < 65 years at study entry.

Review: Statins for the prevention of dementia

Comparison: 3 Modified Telephone Interview for Cognitive Status (TICS-m) at final visit

Outcome: 2 Aged < 65 years at study entry

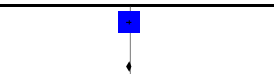
Study or subgroup	Simvastatin n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
HPS 2002	834/4903	879/4936		100.0 %	0.95 [0.85, 1.05]
Total (95% CI)	**4903**	**4936**		**100.0 %**	**0.95 [0.85, 1.05]**

Total events: 834 (Simvastatin), 879 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 1.04 (P = 0.30)

Test for subgroup differences: Not applicable



Analysis 3.3. Comparison 3 Modified Telephone Interview for Cognitive Status (TICS-m) at final visit, Outcome 3 Aged 65-69 years at study entry.

Review: Statins for the prevention of dementia

Comparison: 3 Modified Telephone Interview for Cognitive Status (TICS-m) at final visit

Outcome: 3 Aged 65-69 years at study entry

Study or subgroup	Simvastatin n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
HPS 2002	631/2447	621/2444		100.0 %	1.02 [0.90, 1.16]
Total (95% CI)	**2447**	**2444**		**100.0 %**	**1.02 [0.90, 1.16]**
Total events: 631 (Simvastatin), 621 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.30 (P = 0.76)					
Test for subgroup differences: Not applicable					

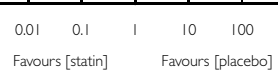
Analysis 3.4. Comparison 3 Modified Telephone Interview for Cognitive Status (TICS-m) at final visit, Outcome 4 Aged 70-80 years at study entry.

Review: Statins for the prevention of dementia

Comparison: 3 Modified Telephone Interview for Cognitive Status (TICS-m) at final visit

Outcome: 4 Aged 70-80 years at study entry

Study or subgroup	Simvastatin n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
HPS 2002	1010/2919	1045/2887		100.0 %	0.93 [0.84, 1.04]
Total (95% CI)	**2919**	**2887**		**100.0 %**	**0.93 [0.84, 1.04]**
Total events: 1010 (Simvastatin), 1045 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.27 (P = 0.20)					
Test for subgroup differences: Not applicable					



Analysis 3.5. Comparison 3 Modified Telephone Interview for Cognitive Status (TICS-m) at final visit, Outcome 5 Cognitive impairment.

Review: Statins for the prevention of dementia

Comparison: 3 Modified Telephone Interview for Cognitive Status (TICS-m) at final visit

Outcome: 5 Cognitive impairment

Study or subgroup	Simvastatin n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
HPS 2002	2433/10269	2485/10267		100.0 %	0.97 [0.91, 1.04]
Total (95% CI)	**10269**	**10267**		**100.0 %**	**0.97 [0.91, 1.04]**

Total events: 2433 (Simvastatin), 2485 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 0.86 (P = 0.39)
Test for subgroup differences: Not applicable

Analysis 4.1. Comparison 4 Incidence and severity of adverse effects, Outcome 1 Adverse effects requiring discontinuation of treatment.

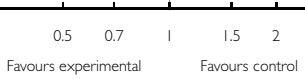
Review: Statins for the prevention of dementia

Comparison: 4 Incidence and severity of adverse effects

Outcome: 1 Adverse effects requiring discontinuation of treatment

Study or subgroup	Statin n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
HPS 2002	493/10269	524/10267		81.8 %	0.94 [0.83, 1.06]
PROSPER	107/2891	116/2913		18.2 %	0.93 [0.71, 1.21]
Total (95% CI)	**13160**	**13180**		**100.0 %**	**0.94 [0.83, 1.05]**

Total events: 600 (Statin), 640 (Placebo)
Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.94); I^2 =0.0%
Test for overall effect: Z = 1.14 (P = 0.25)
Test for subgroup differences: Not applicable



Analysis 4.2. Comparison 4 Incidence and severity of adverse effects, Outcome 2 Serious adverse event.

Review: Statins for the prevention of dementia

Comparison: 4 Incidence and severity of adverse effects

Outcome: 2 Serious adverse event

Study or subgroup	Statin n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
PROSPER	1608/2891	1604/2913		100.0 %	1.02 [0.92, 1.13]
Total (95% CI)	**2891**	**2913**		**100.0 %**	**1.02 [0.92, 1.13]**

Total events: 1608 (Statin), 1604 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 0.43 (P = 0.67)
Test for subgroup differences: Not applicable

Analysis 4.3. Comparison 4 Incidence and severity of adverse effects, Outcome 3 Myalgia incidence.

Review: Statins for the prevention of dementia

Comparison: 4 Incidence and severity of adverse effects

Outcome: 3 Myalgia incidence

Study or subgroup	Statin n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
PROSPER	36/2891	32/2913		100.0 %	1.14 [0.70, 1.83]
Total (95% CI)	**2891**	**2913**		**100.0 %**	**1.14 [0.70, 1.83]**

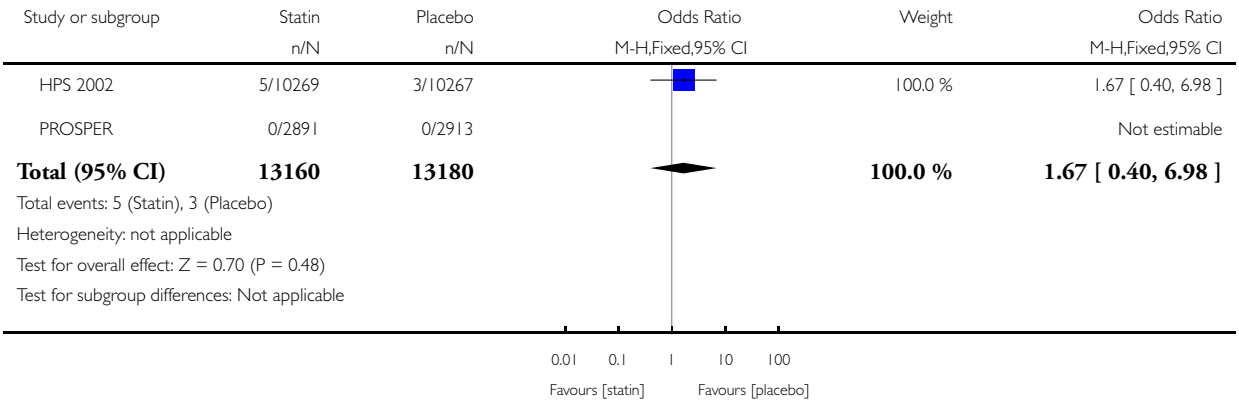
Total events: 36 (Statin), 32 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 0.52 (P = 0.60)
Test for subgroup differences: Not applicable

Analysis 4.4. Comparison 4 Incidence and severity of adverse effects, Outcome 4 Rhabdomyolysis.

Review: Statins for the prevention of dementia

Comparison: 4 Incidence and severity of adverse effects

Outcome: 4 Rhabdomyolysis

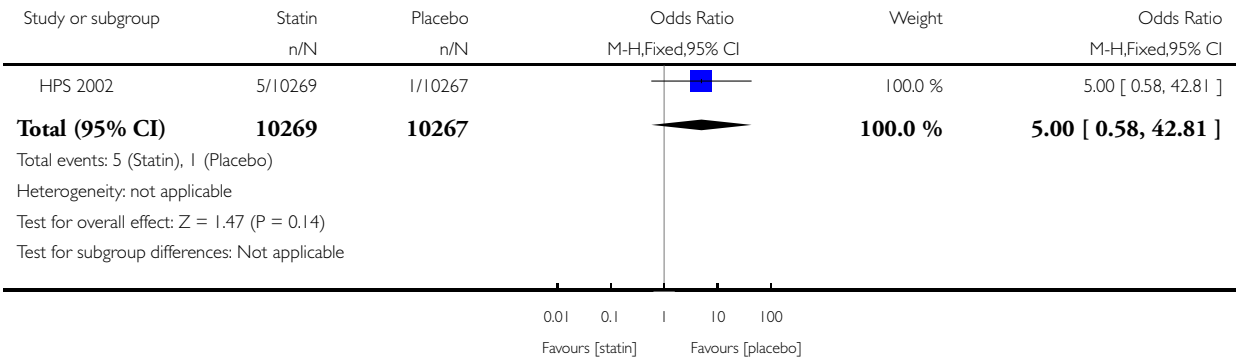


Analysis 4.5. Comparison 4 Incidence and severity of adverse effects, Outcome 5 Myopathy incidence.

Review: Statins for the prevention of dementia

Comparison: 4 Incidence and severity of adverse effects

Outcome: 5 Myopathy incidence

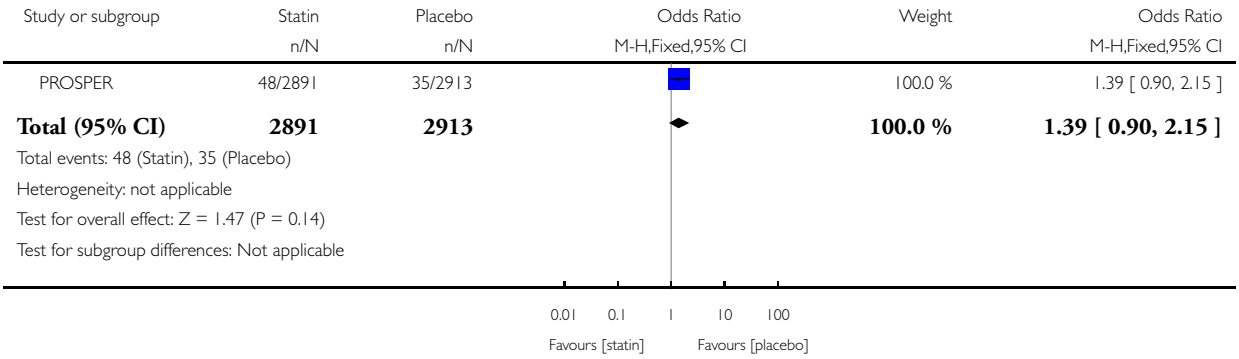


Analysis 4.6. Comparison 4 Incidence and severity of adverse effects, Outcome 6 Elevated liver enzymes causing discontinuation of treatment.

Review: Statins for the prevention of dementia

Comparison: 4 Incidence and severity of adverse effects

Outcome: 6 Elevated liver enzymes causing discontinuation of treatment



APPENDICES

Appendix 1. Sources searched and search strategies

Source	Search strategy	Hits retrieved
1. ALOIS (www.medicine.ox.ac.uk/alois)	statins OR statin OR simvastatin OR lovastatin OR pravastatin OR fluvastatin OR atorvastatin OR rosuvastatin	Dec 2014: 60 Nov 2015: 3
2. MEDLINE In-process and other non-indexed citations and MEDLINE 1950-present (Ovid SP)	1. exp Dementia/ 2. Delirium/ 3. Wernicke Encephalopathy/ 4. Delirium, Dementia, Amnestic, Cognitive Disorders/ 5. dement*.mp. 6. alzheimer*.mp. 7. (lewy* adj2 bod*).mp. 8. deliri*.mp. 9. (chronic adj2 cerebrovascular).mp. 10. ("organic brain disease" or "organic	Dec 2014: 2001 Nov 2015: 310

(*Continued*)

	brain syndrome").mp 11. ("normal pressure hydrocephalus" and "shunt*").mp. 12. "benign senescent forgetfulness".mp. 13. (cerebr* adj2 deteriorat*).mp. 14. (cerebral* adj2 insufficient*).mp. 15. (pick* adj2 disease).mp. 16. (creutzfeldt or jcd or cjd).mp. 17. huntington*.mp. 18. binswanger*.mp. 19. korsako*.mp. 20. or/1-19 21. (statin or statins).ti,ab. 22. atorvastatin.ti,ab. 23. cerivastatin.ti,ab. 24. fluvastatin.ti,ab. 25. lovastatin.ti,ab. 26. pravastatin.ti,ab. 27. simvastatin.ti,ab. 28. lipitor.ti,ab. 29. baycol.ti,ab. 30. lescol.ti,ab. 31. mevacor.ti,ab. 32. altocor.ti,ab. 33. pravachol.ti,ab. 34. lipostat.ti,ab. 35. zocor.ti,ab. 36. mevinolin.ti,ab. 37. compactin.ti,ab. 38. fluindostatin.ti,ab. 39. rosuvastatin.ti,ab. 40. Hydroxymethylglutaryl-CoA Reductase Inhibitors/ or Lovastatin/ 41. Simvastatin/ 42. or/21-41 43. 20 and 42 44. randomized controlled trial.pt. 45. controlled clinical trial.pt. 46. controlled clinical trial.pt. 47. randomized.ab. 48. placebo.ab. 49. drug therapy.fs. 50. randomly.ab. 51. trial.ab. 52. groups.ab. 53. or/44-52 54. (animals not (humans and animals)).sh.	

(*Continued*)

	55. 53 not 54 56. 43 and 55 57. exp *Secondary Prevention/ or exp *Primary Prevention/ 58. (prevent or prevention).ti,ab. 59. "delay onset".ti,ab. 60. exp *Cognition/ 61. ((cognit* or cognition or memory or mental or brain) adj3 (impair* or decline* or deficit* or los* or stop* or reduc*)).ti,ab 62. (dementia or alzheimer*).ti,ab. 63. Dementia/ 64. or/57-63 65. 42 and 64 66. 55 and 65	
3. EMBASE 1974-2012 September 05 (Ovid SP)	1. (statin or statins).ti,ab. 2. atorvastatin.ti,ab. 3. cerivastatin.ti,ab. 4. fluvastatin.ti,ab. 5. lovastatin.ti,ab. 6. pravastatin.ti,ab. 7. simvastatin.ti,ab. 8. lipitor.ti,ab. 9. baycol.ti,ab. 10. lescol.ti,ab. 11. mevacor.ti,ab. 12. altocor.ti,ab. 13. altocor.ti,ab. 14. pravachol.ti,ab. 15. lipostat.ti,ab. 16. zocor.ti,ab. 17. mevinolin.ti,ab. 18. compactin.ti,ab. 19. fluindostatin.ti,ab. 20. rosuvastatin.ti,ab. 21. hydroxymethylglutaryl coenzyme A reductase inhibitor/ 22. simvastatin/ 23. mevinolin/ 24. fluindostatin/ 25. rosuvastatin/ 26. pravastatin/ 27. atorvastatin/ or cerivastatin/ 28. or/1-27 29. randomized controlled trial/ 30. controlled clinical trial/ 31. (RCT or CCT).ti,ab. 32. randomly.ab.	Dec 2014: 2872 Nov 2015: 397

(*Continued*)

	33. placebo.ab. 34. trial.ab. 35. randomized.ab. 36. or/29-35 37. 28 and 36 38. primary prevention/ or prevention/ or secondary prevention/ or prevention study/ 39. dementia/ 40. ((prevent* or delay*) adj3 (dement* or alzheimer* or cognit*)).ti,ab 41. or/48-40 42. 41 and 37	
4. PsycINFO 1806-July week 1 2015 (Ovid SP)	1. (statin or statins).ti,ab. 2. atorvastatin.ti,ab. 3. cerivastatin.ti,ab. 4. fluvastatin.ti,ab. 5. lovastatin.ti,ab. 6. pravastatin.ti,ab. 7. simvastatin.ti,ab. 8. lipitor.ti,ab. 9. baycol.ti,ab. 10. lescol.ti,ab. 11. mevacor.ti,ab. 12. altocor.ti,ab. 13. altocor.ti,ab. 14. pravachol.ti,ab. 15. lipostat.ti,ab. 16. zocor.ti,ab. 17. mevinolin.ti,ab. 18. compactin.ti,ab. 19. fluindostatin.ti,ab. 20. rosuvastatin.ti,ab. 21. hydroxymethylglutaryl coenzyme A reductase inhibitor/ 22. simvastatin/ 23. mevinolin/ 24. fluindostatin/ 25. rosuvastatin/ 26. pravastatin/ 27. atorvastatin/ or cerivastatin/ 28. or/1-27 29. randomized controlled trial/ 30. controlled clinical trial/ 31. (RCT or CCT).ti,ab. 32. randomly.ab. 33. placebo.ab. 34. trial.ab. 35. randomized.ab.	Dec 2014: 253 Nov 2015: 14

(*Continued*)

	36. or/29-35 37. 28 and 36 38. primary prevention/ or prevention/ or secondary prevention/ or prevention study/ 39. dementia/	
5. CINAHL (EBSCOhost)	S1 (MH "Dementia+") S2 (MH "Delirium") or (MH "Delirium, Dementia, Amnestic, Cognitive Disorders") S3 (MH "Wernicke's Encephalopathy") S4 TX dement* S5 TX alzheimer* S6 TX lewy* N2 bod* S7 TX deliri* S8 TX chronic N2 cerebrovascular S9 TX "organic brain disease" or "organic brain syndrome" S10 TX "normal pressure hydrocephalus" and "shunt*" S11 TX "benign senescent forgetfulness" S12 TX cerebr* N2 deteriorat* S13 TX cerebral* N2 insufficient* S14 TX pick* N2 disease S15 TX creutzfeldt or jcd or cjd S16 TX huntington* S17 TX binswanger* S18 TX korsako* S19 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 S20 TX statin OR statins S21 TX atorvastatin S22 TX cerivastatin S23 TX fluvastatin S24 TX lovastatin S25 TX pravastatin S26 TX simvastatin S27 TX Lipitor S28 TX baycol S29 TX lescol S30 TX mevacor S31 TX altocor S32 TX pravachol S33 TX lipostat S34 TX Zocor S35 TX mevinolin S36 TX compactin S37 TX fluindostatin	Dec 2014: 286 Nov 2015: 72

(*Continued*)

	S38 TX rosuvastatin S39 (MH "Statins") OR (MH "Rosuvastatin") S40 (MH "Simvastatin") S41 (MH "Atorvastatin") S42 (MH "Fluvastatin") S43 (MH "Pravastatin") S44 S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 S45 S19 AND S44 S46 (MH "Preventive Trials") OR (MH "Preventive Health Care") S47 TX prevention S48 TX prevent or preventing or delay or delaying S49 S46 or S47 or S48 S50 S49 and S45	
6. Web of Science and conference proceedings	(dement* OR alzheimer* OR AD OR VCI OR VaD OR "vascular cognitive impairment" OR "lew* bod*" OR CADASIL OR cognit*) *AND* **TOPIC:** (prevent* OR delay* OR stop*) *AND* **TOPIC:** (statin* OR atorvastatin OR cerivastatin OR fluvastatin OR lovastatin OR pravastatin OR simvastatin OR lipitor OR baycol OR lescol OR mevacor OR altocor OR pravachol OR lipostat OR zocor OR mevinolin OR compactin OR fluindostatin OR rosuvastatin) *AND* **TOPIC:** (random* OR trial OR placebo OR "double-blind*" OR "single-blind*" OR RCT OR "control group*") **Timespan:** 2014-2015. Search language=Auto	Dec 2014: 410 Nov 2015: 59
7. LILACS (BIREME)	statins OR statin OR simvastatin OR lovastatin OR pravastatin OR fluvastatin OR atorvastatin OR rosuvastatin [Words] and elderly OR cognition OR cognitive OR dementia OR alzheimer OR alzheimers [Words] and randomly OR randomised OR randomized OR RCT OR "controlled trial" OR "double blind$" OR placebo [Words]	Nov 2015: 19 (all dates)

(*Continued*)

8. CENTRAL (*The Cochrane Library*) (Issue 10, 2015)	#1 MeSH descriptor: [Dementia] explode all trees #2 MeSH descriptor: [Delirium] this term only #3 MeSH descriptor: [Wernicke Encephalopathy] this term only #4 MeSH descriptor: [Delirium, Dementia, Amnestic, Cognitive Disorders] this term only #5 dement* #6 alzheimer* #7 "lewy* bod*" #8 deliri* #9 "chronic cerebrovascular" #10 "organic brain disease" or "organic brain syndrome" #11 "normal pressure hydrocephalus" and "shunt*" #12 "benign senescent forgetfulness" #13 "cerebr* deteriorat*" #14 "cerebral* insufficient*" #15 "pick* disease" #16 creutzfeldt or jcd or cjd #17 huntington* #18 binswanger* #19 korsako* #20 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 #21 statin or statins #22 atorvastatin or cerivastatin or fluvastatin or lovastatin or pravastatin or simvastatin or lipitor or baycol or lescol or mevacor or altocor or pravachol or lipostat or zocor or mevinolin or compactin or fluindostatin or rosuvastatin #23 #21 or #22 #24 MeSH descriptor: [Hydroxymethylglutaryl-CoA Reductase Inhibitors] explode all trees #25 #23 or #24 #26 #25 and #20	Dec 2014: 62 Nov 2015: 2
9. Clinicaltrials.gov (www.clinicaltrials.gov)	(statins OR statin OR simvastatin OR lovastatin OR pravastatin OR fluvastatin OR atorvastatin OR rosuvastatin) AND (elderly OR cognition OR cognitive OR dementia OR alzheimer OR alzheimers) AND Interventional trials	Dec 2014: 14 Nov 2015: 2

(*Continued*)

10. ICTRP Search Portal (apps.who.int/trialsearch) [includes: Australian New Zealand Clinical Trials Registry; ClinicalTrilas.gov; ISRCTN; Chinese Clinical Trial Registry; Clinical Trials Registry - India; Clinical Research Information Service - Republic of Korea; German Clinical Trials Register; Iranian Registry of Clinical Trials; Japan Primary Registries Network; Pan African Clinical Trial Registry; Sri Lanka Clinical Trials Registry; The Netherlands National Trial Register]	(statins OR statin OR simvastatin OR lovastatin OR pravastatin OR fluvastatin OR atorvastatin OR rosuvastatin) AND (elderly OR cognition OR cognitive OR dementia OR alzheimer OR alzheimers) Recruitment status: ALL	Dec 2014: 24 Nov 2015: 1
TOTAL before de-duplication and first assessment		Dec 2014: 5982 Nov 2015: 879
TOTAL after de-dupe and first assessment		Dec 2014: 310 Nov 2015: 36

WHAT'S NEW

Last assessed as up-to-date: 11 November 2015.

Date	Event	Description
29 December 2015	New citation required but conclusions have not changed	Search updated, no new studies found. Conlcusions unchanged
11 November 2015	New search has been performed	The search was updated, no new studies found and conclusions not changed

HISTORY

Review first published: Issue 3, 2001

Date	Event	Description
7 November 2008	New citation required and conclusions have changed	The conclusions to this review have changed as studies are now included in this review, compared to the previous review in which there were no included studies. The conclusions are that there is no evidence from

(*Continued*)

		RCTs that statins prevent AD or dementia
7 November 2008	New search has been performed	The search of October 2007 retrieved new studies for consideration by the authors. Two studies have been included in this update (with a total of 26,340 participants), and several studies have been excluded
10 October 2007	New citation required but conclusions have not changed	A new author team has taken over the updating of this review
4 October 2006	New search has been performed	minor update of review
30 May 2001	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

BMcG: all work concerned with review.

DC: commenting on draft review.

RB: commenting on draft review.

PP: selection of studies, commenting on draft review.

Contact editors: J Grimley Evans and Lon Schneider (for 2008 update).

Consumer editor: Corinne Cavender.

This review was peer reviewed anonymously.

DECLARATIONS OF INTEREST

BMcG: none known.

DC: none known.

RB: none known.

PP: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- NIHR, UK.

This protocol/review was supported by the National Institute for Health Research, via a Cochrane Programme Grant to the Cochrane Dementia and Cognitive Improvement group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, National Health Service or the Department of Health

INDEX TERMS

Medical Subject Headings (MeSH)

Alzheimer Disease [prevention & control]; Anticholesteremic Agents [*therapeutic use]; Cognition [drug effects]; Dementia [*prevention & control]; Hydroxymethylglutaryl-CoA Reductase Inhibitors [therapeutic use]; Pravastatin [therapeutic use]; Randomized Controlled Trials as Topic; Simvastatin [therapeutic use]

MeSH check words

Adult; Aged; Aged, 80 and over; Humans; Middle Aged