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FULL RESEARCH PAPER
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Statin use and risk of dementia or Alzheimer's disease: a systematic review and meta-analysis of observational studies

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Aims As the potential impact of statins on cognitive decline and dementia is still debated, we conducted a meta-analysis of observational studies to examine the effect of statin use on the risk of Alzheimer's disease (AD) and dementia.

Methods and results PubMed, Cochrane, and EMBASE were searched since inception to January 2021. Inclusion criteria were: (i) cohort or case–control studies; (ii) statin users compared to non-users; and (iii) AD and/or dementia risk as outcome. Estimates from original studies were pooled using restricted maximum-likelihood random-effect model. Measure of effects were reported as odds ratio (OR) and 95% confidence intervals (CIs). In the pooled analyses, statins were associated with a decreased risk of dementia [36 studies, OR 0.80 (CI 0.75–0.86)] and of AD [21 studies, OR 0.68 (CI 0.56–0.81)]. In the stratified analysis by sex, no difference was observed in the risk reduction of dementia between men [OR 0.86 (CI 0.81–0.92)] and women [OR 0.86 (CI 0.81–0.92)]. Similar risks were observed for lipophilic and hydrophilic statins for both dementia and AD, while high-potency statins showed a 20% reduction of dementia risk compared with a 16% risk reduction associated with low-potency statins, suggesting a greater efficacy of the former, although a borderline statistical significance ($P = 0.05$) for the heterogeneity between estimates.

Conclusion These results confirm the absence of a neurocognitive risk associated with statin treatment and suggest a potential favourable role of statins. Randomized clinical trials with an *ad hoc* design are needed to explore this potential neuroprotective effect.

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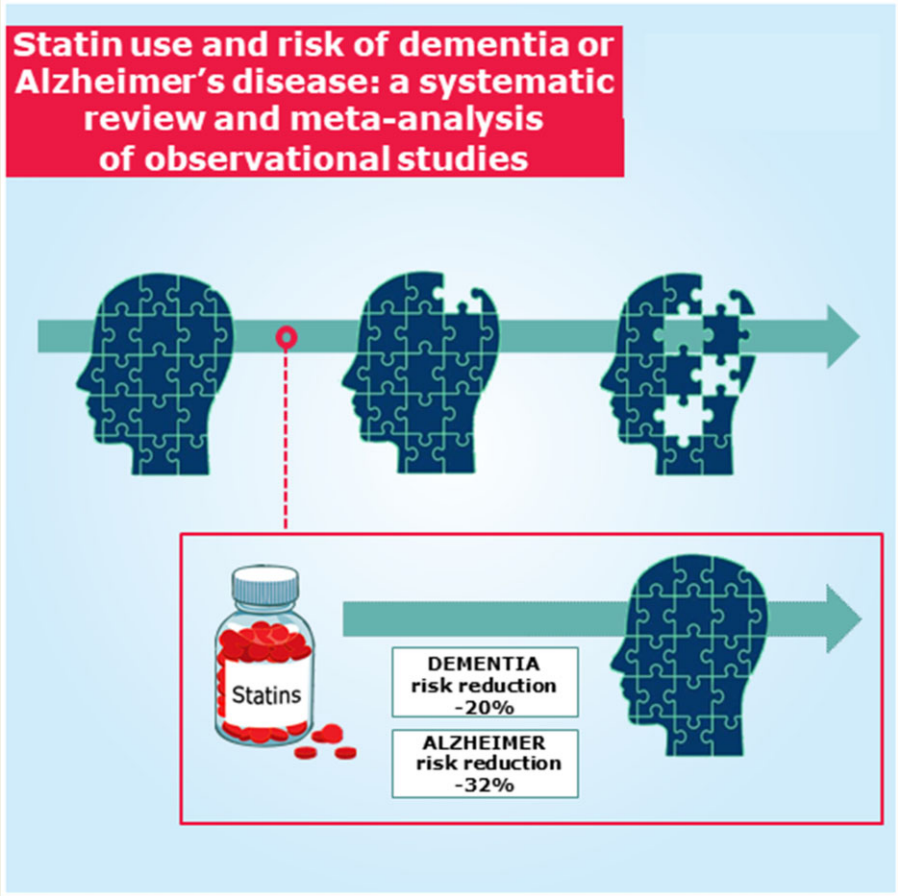
Graphical Abstract



Keywords Statins • Alzheimer's disease • Dementia • Meta-analysis • Observational studies

Introduction

Statins are a class of cholesterol-lowering drugs with proven cardiovascular benefits, validated in different groups of patients.[1] Statins are the cornerstone of pharmacotherapy for atherosclerotic cardiovascular disease, and with the increasing epidemiological burden of hypercholesterolaemia[2,3] and as newer more stringent lipid goals recommended by latest guidelines,[1,4] their use is increasingly growing, making statins one of the most commonly prescribed medications worldwide. The role of statins in primary and secondary prevention of cardiovascular disease has been highlighted by the efficacy and safety results reported in a large number of randomized controlled trials and meta-analyses investigating the effects of statins in primary and secondary prevention populations and in subgroups.[5,6] For each 1 mmol/L reduction in LDL cholesterol, statin reduced the relative risk of major cardiovascular events by 22%, major coronary events by 23%, and coronary artery disease death by 20%. Although cholesterol reduction is the major effect of statins, a number of other, potentially important, effects have been suggested (pleiotropic effects). Among such effects that may be potentially relevant for the onset and clinical progression of dementia and cognitive decline are the anti-inflammatory and antioxidant effects of statins as well as the effect on blood flow and suppression of reactive oxygen species.[7] Statins are generally well-tolerated and have an excellent safety profile but, as with all drugs, adverse reactions may occur in some patients.[8,9]

Case reports have brought to the attention the reported adverse effect of statin use on cognition,[10–12] including memory loss, which led in 2012 the US Food and Drug Administration to issue a black box warning for possible adverse effects of statins on cognitive performance. Consumer concerns regarding potential adverse effects of statins are prevalent, so that memory and/or cognitive changes are the second most frequently reported adverse effect during statin therapy.[13] These concerns can compromise acceptance or adherence to statin medications essential to reduce atherosclerotic

cardiovascular risk. With increasing body of evidence, short-term data suggest a lack of adverse effect of statins on cognition, while long-term data seem to support a beneficial role for statins in the prevention of dementia.[14,15] Large-scale trials did not find that statin treatment was associated with dementia or cognitive test scores,[16,17] while in small-scale trials the results have been mixed.[18–20] Also, evidence from observational studies have provided inconsistent results so far,[21–23] with meta-analyses showing variable effects, depending on type of included studies, type of outcome, and characteristics of statins.[22,24,25]

Considered this background, the aim of this study is to provide an updated systematic review and meta-analysis of all observational studies reporting data on the risk of Alzheimer's disease (AD) and/or dementia, in individuals treated with statins compared with subjects not receiving a lipid-lowering therapy.

Methods

This systematic review and meta-analysis has been performed and reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and MOOSE (Meta-analyses Of Observational Studies in Epidemiology) guidelines and recommendations.[26,27] Because all the analyses were performed on the basis of previous published studies, no ethical approval or informed consent was required.

Search strategy

A systematic and comprehensive literature search was performed on Pubmed, EMBASE databases, and Cochrane Library to retrieve eligible articles from inception to January 2021. Search strategy comprised a combination of terms relevant to the research question, including 'dementia', 'Alzheimer', and 'statin' with Boolean operators as appropriate (see Supplementary material online). The search was restricted to English language and articles available as full text (studies published as abstract were excluded, as well as letters, comments, editorials, case reports).

Studies selection

According to PRISMA guidelines, all records retrieved from the search were systematically and sequentially screened, according to titles and abstracts. Each article included after the abstracts screening phase was independently evaluated for full-text eligibility. Any disagreement during each phase was resolved by discussion with a third author.

We included studies which met the following criteria: (i) observational studies (cohort or case–control studies); (ii) adult subjects; (iii) statin users compared to non-users; and (iv) reporting an adjusted estimate [such as odds ratio (OR)/risk ratio (RR)/hazard ratio] and 95% confidence intervals (CIs) for AD and/or dementia risk as outcome. References of included studies were additionally reviewed for other relevant articles, which were not retrieved from the literature search. In case of two or more studies based on the same cohort of subjects and exploring the same outcome(s), only the most recently published was selected and included in the meta-analysis.

Outcomes definition

Primary outcomes were AD and dementia defined according to clinical criteria, as the United States National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA),[28] the International Classification of Diseases-10/9th edition (ICD-9-CM/ICD-10),[29] the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders-IV-TR (DSM),[30] or the mini-mental state examination (MMSE) or its modified version (3MSE).[31]

Data extraction and quality assessment

Data from the included studies were extracted independently by two authors. Data on sample size, method used for the outcomes definition, estimates of the association of interest, were extracted using a standardized electronic form. Additionally, we collected data about study design and cohort baseline characteristics (i.e. age and sex).

All included studies were also independently evaluated by two co-authors to assess the risk of several bias. Screening was performed for five main bias categories (selection bias, performance bias, attrition bias, detection bias, and reporting bias). An overall, synthetic grade was produced for each study. The methodological quality of the included studies was evaluated based on the items of modified Newcastle-Ottawa Scale, comprising patient selection, study group comparability and outcome assessment.[32] The observational studies scored 0 to 9. Divergent opinions were discussed among authors and a consensus was reached.

Statistical analysis

Outcomes from original studies were pooled and compared using DerSimonian–Laird random-effects method. Measure of effects were reported as OR and 95% CIs. The *I*-square (I^2) test was adopted to evaluate the influence of heterogeneity on the output of the meta-analysis. I^2 values of 0%, 25%, 50%, and 75% represented no, low, medium, and high heterogeneity, respectively. Heterogeneity was tested using Cochran Q statistic and the I^2 metric.[33] A *P*-value of <0.05 was accepted as statistically significant. Publication bias was evaluated visually by examining the funnel plot measuring the standard error as a function of effect size, as well as statistically by using the Egger test.[34] We then performed a subanalysis based on patients aged ≥75 years, as well as several stratified analyses according to study design (cohort or case–control studies), sex (men or women), type of statin [predominantly 'hydrophilic' statins (rosuvastatin and pravastatin) or predominantly 'lipophilic' statins (atorvastatin, simvastatin, lovastatin, and fluvastatin)],[35] and statin potency ['high potency' statins (atorvastatin, rosuvastatin, and simvastatin) or 'low potency' statins (any other statins)] as defined by included studies. A test of between-group differences based on the Q_b statistic is also reported. This test investigates the difference between the group-specific overall effect sizes.

The analyses and the corresponding graphical visualization of forest and funnel plots were conducting using both STATA Version 16 and R Software Program Version 4.0.2.

The data underlying this article are available in the article and in its online supplementary material.

Results

Descriptive study characteristics

The flow diagram of the literature searches and study selection is shown in *Figure 1*. Finally, 46 observational studies (38 cohort studies and 8 case–control studies) were included in the meta-analysis. The main characteristics of the studies are summarized in *Table 1*. All these studies were published between 2000 and January 2021. Samples sizes ranged from 123 to 2 004 692 patients, and 14 out of 46 studies reported a mean participant age ≥75 years old. All studies were of high methodological quality, with only one study reporting a Newcastle-Ottawa scale score of 5 points (Supplementary material

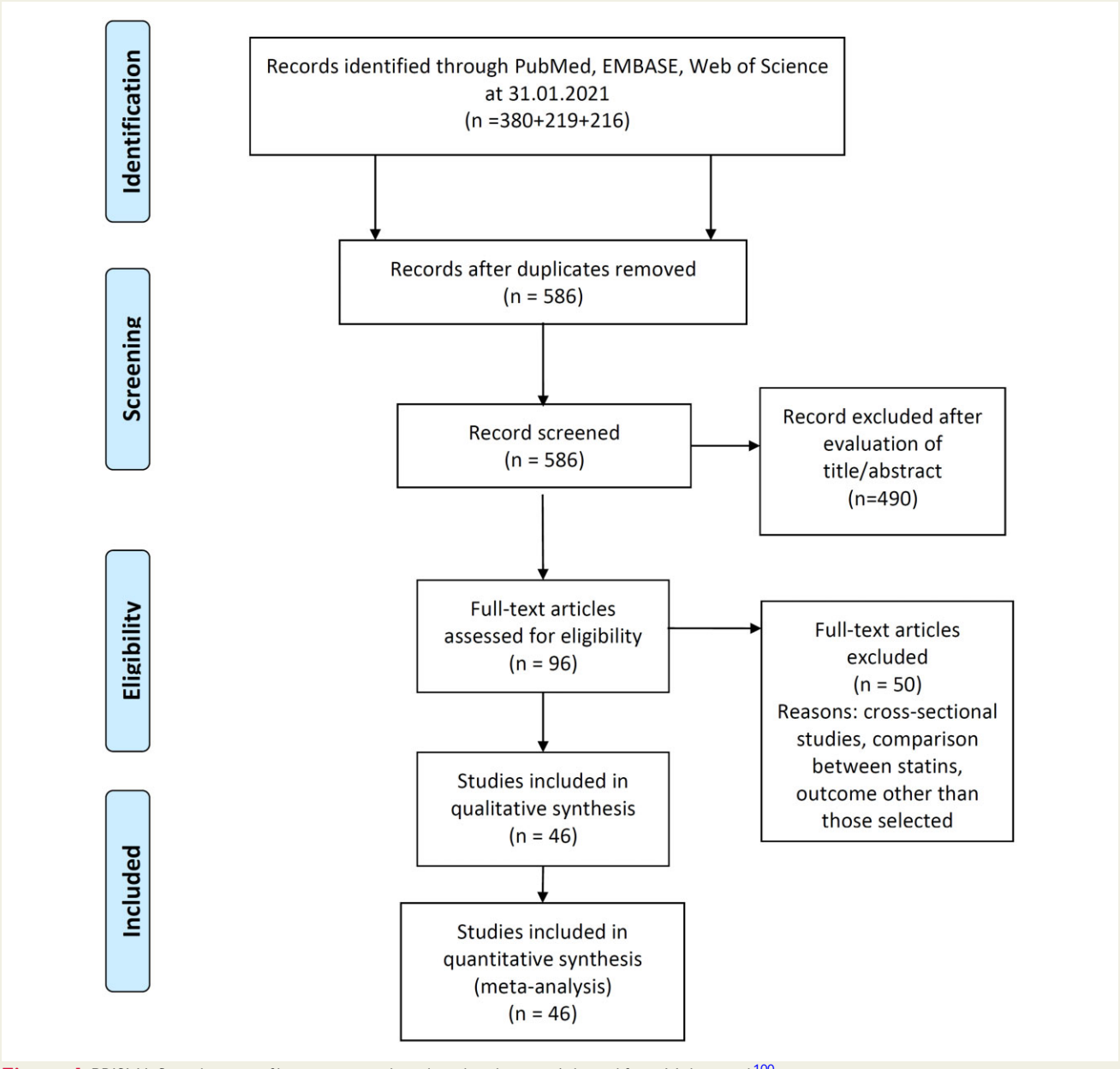


Figure 1 PRISMA flow diagram of literature search and study selection. Adapted from Moher *et al.*[100]

online, *Figure S1*). In total, 25 studies reporting adjusted estimates only for dementia risk, 10 only for AD risk, and 11 studies reporting estimates for both the outcomes.

Meta-analyses results

Overall, 36 observational studies (*N* 5 738 737) were included in the analysis of dementia risk (*Figure 2*). We found that statin use was associated with a decreased risk of dementia [OR 0.80 (CI 0.75–0.86)]. Similarly, the analysis of 21 studies (*N* 1 188 377) showed a significant 32% reduction in the risk of AD among statin users [OR 0.68 (CI 0.56–0.81)] (*Figure 3*). Visual examination of funnel plots and statistical testing of data from the observational studies for each outcome revealed an apparent publication bias only for dementia risk (Supplementary material online, *Figure S2A and B*).

The subgroup analysis of patients aged ≥75 years confirmed a statin-associated risk reduction, yielding a 18% reduction in the risk of dementia [OR 0.82 (CI 0.72–0.93)] and 27% reduction in the risk of AD [OR 0.73 (CI 0.54–0.98)] (Supplementary material online, *Figure S3A and B*).

In subgroup analyses by type of study design (cohort or case–control), no apparent effect modification was found for both the outcomes. Pooled estimates confirmed the risk reduction for dementia, both in cohort studies and in case–control studies [OR 0.81 (CI

Table 1 Characteristics of observational studies included

Study	Design	N° total	Age (minimum as for inclusion criteria; mean)	Sex (% M)	Outcomes	Diagnostic test	Newcastle-Ottawa scale score
Jick *et al.* 2000[36]	CC	1364	≥50; NA	39.5	D	NINCDS-ADRDA	7
Rockwood *et al.* 2002[37]	CC	1315	≥65; 78.05	38.0	D, AD	3MSE	8
Yaffe *et al.* 2002[38]	Co	1037	None; 71.1	0.0	D	3MSE	6
Zamrini *et al.* 2004[39]	CC	3397	None; 73	100.0	AD	ICD-9-CM	7
Li *et al.* 2004[40]	Co	2356	≥65; 75.1	40.2	D	DSM-IV, NINCDS-ADRDA	8
Reitz *et al.* 2004[41]	Co	1168	≥65; 78.4	33.3	AD	NINCDS-ADRDA	7
Rea *et al.* 2005[42]	Co	2798	≥65; 75.0	40.1	D, AD	NINCDS-ADRDA	6
Zandi *et al.* 2005[43]	Co	5092	≥65; 74.4	45.0	D, AD	DSM-III-R, NINCDS-ADRDA, 3MSE	8
Green *et al.* 2006[44]	CC	2378	None; 67.0	38.6	AD	NINCDS-ADRDA	7
Szwast *et al.* 2007[45]	Co	1146	≥70; 77.3	30.7	D	DSM-III-R, ICD-10	8
Wolozin *et al.* 2007[46]	Co	1 290 071	≥65; 74.6	94.4	D	ICD-9	6
Zigman *et al.* 2007[47]	Co	123	None; 51.2	22.8	AD	consensus conference (clinical agreement)	5
Sparks *et al.* 2008[48]	Co	2068	≥70; 74.7	45.7	AD	DSM-IV, NINCDS/ADRDA	7
Arvanitakis *et al.* 2008[49]	Co	929	>40; 74.9	31.3	AD	MMSE	8
Cramer *et al.* 2008[50]	Co	1674	≥60; 70.2	41.7	D	DSM-IV, NINCDS-ADRDA, 3MSE	7
Smeeth *et al.* 2009[51]	Co	729 529	None; NA	50.3	D, AD	clinical chart record	8
Haag *et al.* 2009[52]	Co	6992	None; 69.4	40.0	AD	DSM-III-R, NINCDS-ADRDA	7
Hippisley-Cox *et al.* 2010[53]	Co	2 004 692	≥30; 45.8	49,4	D	clinical chart record	6
Li *et al.* 2010[54]	Co	3099	≥65; 75.4	40.5	AD	DSM-IV, NINCDS-ADRDA	7
Beydoun *et al.* 2011[55]	Co	1604	≥50; 57.6	61.5	D	DSM-III-R, NINCDS-ADRDA	7
Parikh *et al.* 2011[56]	Co	377 838	≥65; 75.5	97.9	D	ICD-9-CM	6
Bettermann *et al.* 2012[57]	Co	3069	≥75; 78.6	53.8	D, AD	3MSE, ADAS-Cog	7
Ancelin *et al.* 2012[58]	Co	6830	≥65; 73.7	39.7	D, AD	DSM-IV, NINCDS-ADRDA	8
Douiri *et al.* 2013[59]	Co	1682	None; NA	53.9	D	MMSE, AMT	7
Chen *et al.* 2014[60]	CC	27 716	≥50; 77.5	48.8	D	ICD-9-CM	7
Chen *et al.* 2014[61]	Co	18 170	≥50; 66.8	52.3	D, AD	ICD-9-CM	7
Chou *et al.* 2014[62]	Co	103 637	≥60; NA	46.1	D, AD	ICD-9-CM	8
Ma *et al.* 2014[63]	Co	634	≥65; 75.3	0.0	AD	NINCDS-ADRDA	8
Lin *et al.* 2015[64]	Co	1438	≥50; NA	30.8	AD	ICD-9-CM	8
Chao *et al.* 2015[65]	Co	256 265	≥60; 73.2	49.7	D	ICD-9-CM	8
Chuang *et al.* 2015[66]	Co	123 300	≥20; 54.6	49.1	D	ICD-9-CM	8
Yang *et al.* 2015[67]	Co	3688	≥65; NA	33.9	D	ICD-9-CM	8
Hendrie *et al.* 2015[68]	Co	974	None; 76.6	30.3	D, AD	DSM-IV, ICD-10	6
Chitnis *et al.* 2015[69]	Co	8062	None; 74.5	47.0	D	ICD-9-CM	8
Wu *et al.* 2015[70]	CC	4006	≥65; 72.9	49.9	D	ICD-9-CM	8
Booker *et al.* 2016[71]	CC	23 912	≥70; 80.4	39.0	D	ICD-10	7
Pan *et al.* 2018[72]	Co	9448	≥20; 62.5	55.0	D	ICD9-CM	8
Wändell *et al.* 2018[73]	Co	12 096	≥45; 72.3	54.4	D	ICD-10	7
Liu *et al.* 2018[74]	Co	2012	None; 74.3	NA	D	ICD-9-CM	8
Redelmeier *et al.* 2019[75]	Co	28 815	≥65; 76	38.7	D	ICD-9-CM	8
Chang *et al.* 2019[76]	Co	100 610	None; 71.7	46.0	D	ICD-9-CM	8
Kim *et al.* 2020[77]	Co	143 174	≥65; 72.2	40.3	D	ICD-10	8
Lee *et al.* 2020[78]	Co	112 036	≥50; NA	48.4	D	ICD-9-CM	7
Lee *et al.* 2020[79]	Co	6182	≥40; 66.6	38.6	D, AD	ICD-10	7
Torrandell-Haro *et al.* 2020[80]	Co	288 515	≥45; 66.6	45.1	D, AD	ICD-9-CM	9
Zingel *et al.* 2020[81]	CC	24 472	≥65; 80.2	42.3	D	ICD-10	8

3MSE, Modified Mini-Mental State Examination; AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; CC, case–control study; Co, cohort study; D, dementia; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; M-ACE, The Mini-Addenbrooke's Cognitive Examination; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NA, not available; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.

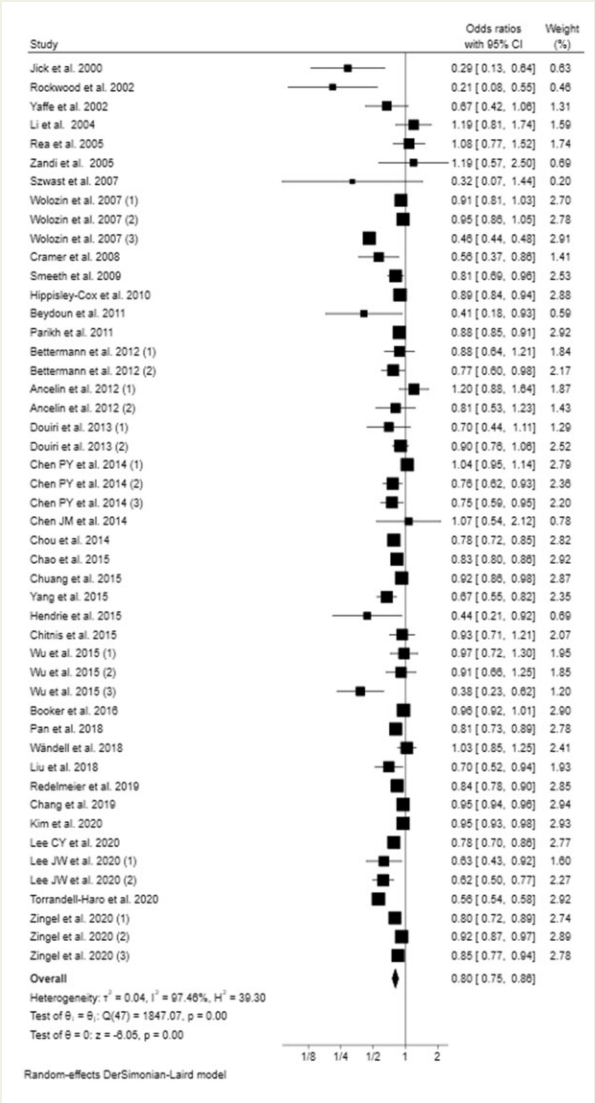


Figure 2 Meta-analysis of statin use and dementia risk.

0.74–0.88) and OR 0.85 (CI 0.77–0.93), respectively, Supplementary material online, *Figure S4A*], and for AD [OR 0.70 (CI 0.58–0.84) and OR 0.56 (CI 0.41–0.78), respectively, Supplementary material online, *Figure S4B*]. The Q_b statistic suggested no differences between estimates for both dementia and AD risks ($P = 0.43$ and $P = 0.27$, respectively).

In the stratified analyses by sex, men and women showed the same reduction in the risk of dementia [both OR 0.86 (CI 0.81–0.92), Supplementary material online, *Figure S5A*]. We observed a non-significant reduction in the risk of AD both for men [OR 0.71 (CI 0.47–1.06)] and women [OR 0.85 (CI 0.48–1.49)], but this evaluation has been limited by the low number of studies reporting this information (Supplementary material online, *Figure S5B*).

Furthermore, lipophilic and hydrophilic statins induced similar reductions in the risk of dementia [OR 0.83 (CI 0.76–0.90) and OR 0.80 (CI 0.71–0.89), respectively, Supplementary material online, *Figure S6*] and AD [OR 0.61 (CI 0.46–0.81) and OR 0.59 (CI 0.43–0.82), respectively, Supplementary material online, *Figure S6*]. Also in this case, the Q_b statistic suggested no differences between estimates for both dementia and AD risk ($P = 0.61$ and $P = 0.88$, respectively).

Finally, in the stratified analysis by statin potency, high-potency and low-potency statins showed a similar reduction in the risk of dementia [OR 0.80 (CI 0.72–0.88) and OR 0.84 (CI 0.79–0.90), respectively, Supplementary material online, *Figure S7*]. However, the Q_b statistic showed a borderline statistical significance ($P = 0.05$), suggesting a possible heterogeneity between estimates and leaving open the possibility of a greater efficacy of high-potency statins in reducing the risk of developing dementia.

Discussion

Our up to date meta-analysis of 46 observational studies evaluating the association between statin therapy and the incidence of neurocognitive diseases showed that the use of statins not only did not increase the risk of neurocognitive disorders, but rather was associated with a significant risk reduction of 20% of dementia and 32% reduction of AD. This effect was confirmed in the analysis by study design, emphasizing the robustness of this evidence. The benefit was confirmed in both men and women, without any difference in the risk reduction of dementia (-24% in both groups) and with a non-significant risk reduction for AD, probably due to low number of studies reporting the stratified estimates and to heterogeneity among studies.

Our results are in line with a recent meta-analysis including only prospective studies in patients with mean age ≥60 years without cognitive impairment at baseline[82] as well as other previous pooled evaluations with different sets of inclusion criteria.[22,83,84]

The majority of the studies included middle-aged adults, a key age-range for an effective cardiovascular disease prevention strategy bur also to highlight the potential modulation by statin treatment of cognitive function in the decades ahead. However, our stratified analysis suggests that the beneficial effect of statins is also present in subjects at higher risk of developing dementia due to older age. In the study by Chou *et al.*,[62] the 20% risk reduction observed in the general population ≥60 years was shown to be similar in the subgroup analysis performed according to age (60–69, 70–79, and ≥80 years). Other studies provide evidence of the protective effects of statins also in subjects at higher risk of developing dementia due to predisposing conditions. Chen *et al.*[61] analysed the incidence of AD among 28 321 patients diagnosed with type 2 diabetes and ≥50 years, showing that a regular statin use was associated with a 13% risk reduction. Zigman *et al.*[47] reported similar evidence in an analysis of patients with Down syndrome, a condition that increases dramatically the risk of dementia also at relatively younger ages. Moreover, an early statin use was significantly associated with risk reduction in studies evaluating the progression of dementia in subjects with mild cognitive impairment.[57,64]

We also stratified our meta-analysis based on the type of statins: hydrophilic and lipophilic statins appear to produce similar and significant reductions in the risk of dementia and AD. This is in contrast with previous studies reporting a protective effect limited to lipophilic statins.[85] Interestingly, in the study by Wu *et al.*,[70] the analysis of the effect of different statins showed that higher doses of high-potency statins (atorvastatin and rosuvastatin) had the strongest

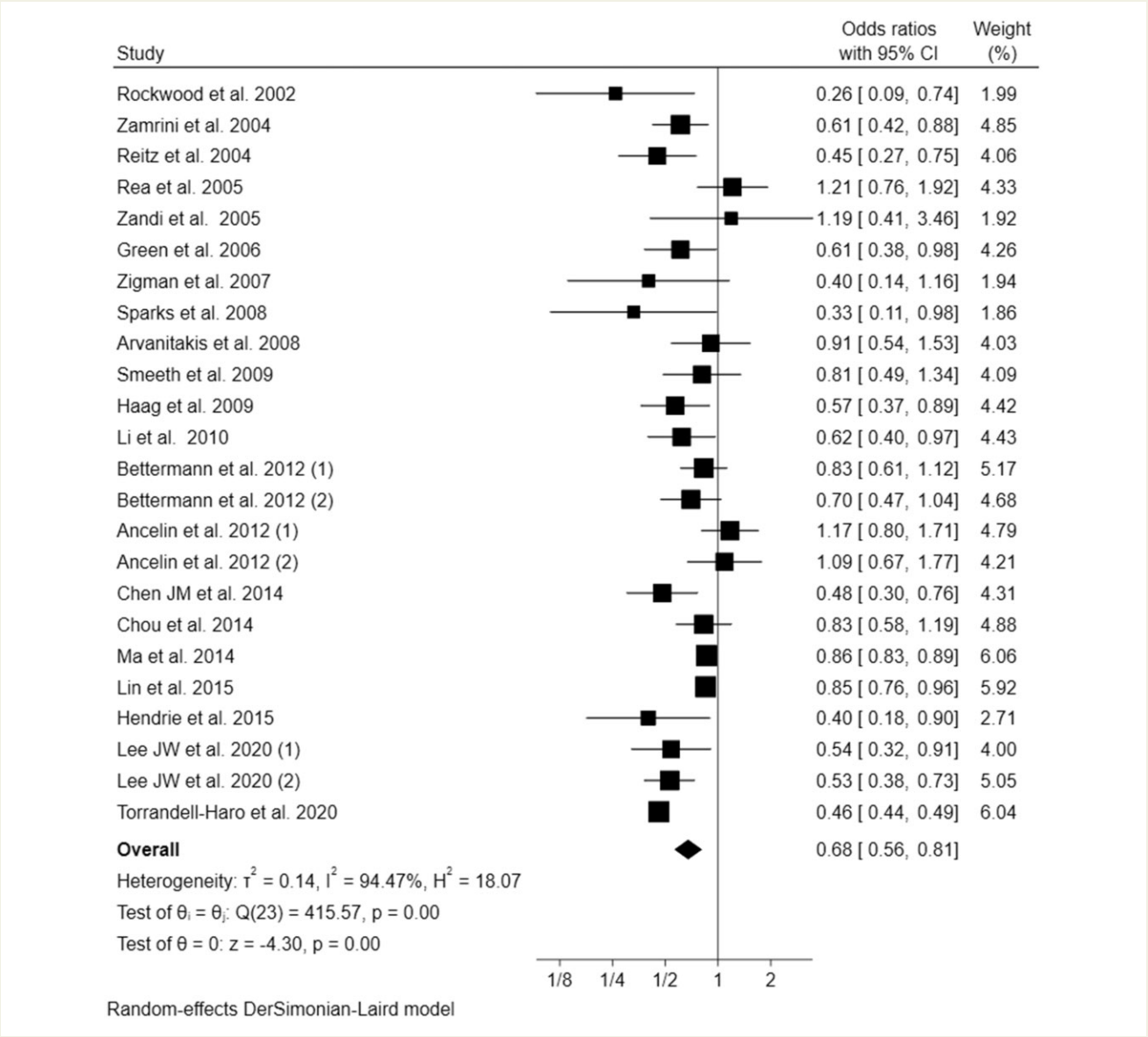


Figure 3 Meta-analysis of statin use and risk of Alzheimer's disease.

protective effect, suggesting that the potency of statin, rather than drug lipofilicity, was the major factor in reducing dementia. This seems to be confirmed also in our stratified analysis by statin potency, where high-potency statin use was associated with a 20% risk reduction compared with a reduction of 16% of dementia associated with low-potency statins. Our updated meta-analysis included also recent studies, in which the use of rosuvastatin was superior than in the past. Assuming a greater effect for high-potency statins, we might expect the increased use of hydrophilic rosuvastatin in more recent studies to narrow the gap that was observed in previous studies between hydrophilic and lipophilic statins. Indeed, in the analysis by Redelmeier *et al.*,[75] the relative risk of dementia with rosuvastatin (accounting for 20% of total statin prescriptions and 70% of hydrophilic statin prescriptions) was 0.78 (95% CI 0.67–0.91), driving the risk reduction with hydrophilic statins [RR 0.76 (95% CI 0.67–0.86), compared to 0.91 (95% CI 0.84–0.98) for lipophilic statins]. However, we have also to note that a potential confounding factor in these studies might be represented by the different baseline clinical phenotypes and cardiovascular risk of patients taking high-potency vs. low/medium-potency statins.[81]

There may be several mechanisms by which statins exert effects on cognition. It has been suggested that some statins may cross the blood–brain barrier and modulate brain cholesterol metabolism, directly altering neurotransmission and synaptic plasticity,[86] but this hypothesis is still debated. Statins have also been shown to reduce oxidative stress and inflammation, increase endothelial nitric oxide synthase, and improve endothelial function and blood flow.[87] Furthermore, the statin-mediated effect on cognition could be simply

related to their ability in reducing blood cholesterol. However, data from the Hebbinghaus study,[88] where a PCSK9 monoclonal antibody was used, and extremely low LDL cholesterol levels achieved, in the range of 0.8 mmol/L or less, showed no cognitive function deterioration and there were no associations between LDL cholesterol levels and cognitive changes. Further evaluations are need to clarify this aspect.

A growing body of evidence suggests a close association between lipids and vascular changes in dementia. Hyperlipidaemia, particularly in mid-life, seems to be associated with an increased risk of dementia, potentially by promoting damage to the brain vasculature. Consequently, treating hyperlipidaemia would be expected to reduce the risk of dementia.[21] The hypothesis that statins reduce the risk of dementia by reducing LDL cholesterol levels is supported by the results of studies in which statin use was unrelated to dementia risk for participants with desirable cholesterol levels, but it was associated with a reduced risk in participants with high-cholesterol levels.[38,47] Moreover, this is in line with evidence from Mendelian randomization studies showing that low LDL-C levels due to 3-hydroxy-3-methylglutaryl-CoA reductase genetic variants did not appear to increase the risk of AD or dementia,[89,90] as included subjects have lower cholesterol levels since birth, and supports the observation of a greater benefit with high-potency statins.[70] However, this hypothesis is reasonable for dementia with multifactorial aetiology and for AD with a relevant ischaemic component, whereas it may not be relevant in 'pure' AD forms linked to ApoE genotype and at early onset, which however are rare, particularly among participants in observational studies on statin use.

In the elderly cohort of the Cardiovascular Health Study, Bernick *et al.*[91] showed that the use of statins was associated with a slight reduction in the rate of cognitive decline during a 7-year period, compared with individuals not taking statins, independently of baseline serum lipid levels. In a subset of participants who underwent two magnetic resonance imaging scans, no differences were observed in white matter or atrophy measures between statin-users and untreated subjects. However, untreated but drug-eligible patients had a greater accumulation of silent subcortically infarcts than the statin-treated group, suggesting the possibility that the accelerated cognitive decline in the statin eligible but untreated participants was due to subclinical vascular disease.

Discordant observations in AD patients might indeed be influenced by the variable degree of concurrent ischaemic cerebrovascular lesions, which may impact the effect of statins on the atherothrombotic contribution to the cognitive decline seen in AD patients. The relative abundance of ischaemic lesions and the predictable impact of aggressive LDL-C-lowering therapy vs. the potential direct effect of statins on amyloid-β or other pathophysiological mechanism(s) of AD might account for the observed different clinical outcomes associated to statin therapy.

The evidence of a neuroprotective effect of statins emerges from observational studies, but not clinical trials.[92] The only long-term randomized trial in the elderly population is the PROSPER (Prospective Study of Pravastatin in Elderly at Risk), which reported comparable cognitive function declines in patients treated with pravastatin or placebo.[17,93] The Simvastatin Heart Protection Study found no effect on cognitive impairment or dementia after 5 years of follow-up, but the study did not control for dementia risk factors, and dementia ascertainment did not follow the rigorous standards required currently.[16] Moreover, the relatively short follow-up time and a low incidence of dementia may limit drawing conclusions. In the recent Heart Outcomes Prevention Evaluation-3 (HOPE-3) study,[94] which evaluated whether cardiovascular medications can delay cognitive decline, participants were randomized to candesartan plus hydrochlorothiazide or placebo and to rosuvastatin (10 mg) or placebo, using a 2×2 factorial design. The primary cognitive outcome measure was change in DSST (Digit Symbol Substitution Test) score. Results showed that candesartan/hydrochlorothiazide, rosuvastatin, and their combination did not reduce or increase the rate of cognitive or functional decline over median follow-up of 5.7 years; the authors suggested that the failure to observe any benefit could be attributed to the relatively short follow-up, the difficulty in retrieving all data and making a correct diagnosis by telephone interviews, and the healthy volunteer bias. A recently published randomized controlled trial on hypertensive patients aged ≥60 years found that rosuvastatin alleviated the progression of cognitive impairment and reduced the risk of dementia over an average of 7-year follow-up.[95] The ongoing STAREE trial, involving healthy individuals aged ≥70 years treated with 40 mg atorvastatin or placebo, with development of dementia among primary outcome measures, has an estimated completion date of 2023.

Our study has several limitations. First, the heterogeneity of diagnostic criteria for dementia, and the use of clinical diagnosis not necessary supported by standardized cognitive test (for example based on ICD codes), as well as different methods to assess the use of statins across included studies may limit the generalizability of the results. This criticism was addressed by Li *et al.*,[96] who evaluated the associations between statin use and the typical AD-related neuropathological outcomes, neurofibrillary tangles, and neuritic plaques using brain autopsy. After controlling for age at death, gender, cognitive score at entry, brain weight, and the presence of microvascular lesions, statin users had a significantly reduced risk for all the outcomes. More in general, this study is a pooled synthesis of observational studies which are susceptible to the effects of bias and confounding by known and unknown factors that are not adequately controlled for, and thus results should be interpreted cautiously, though observational studies can provide data on long-term effects and rarer adverse effects. As an example, the protective effect could be partially explained by the so-called 'healthy user bias', which is the propensity for patients who receive one preventive therapy (as statins) to also seek other preventive services or adopt healthy behaviours.[97] The effect of an unmeasured confounder, which might overinflate the observed protective effect was addressed by Corrao *et al.*[98] In their analysis, a confounder that is three times less frequent among statin users would increase the risk of dementia of five times, or even more, in order to fully explain the observed exposure–outcome association.

Conclusions

The results of this complete and up to date meta-analysis of observational studies:

- suggest that statins are unlikely to cause dementia or cognitive decline, supporting the good safety profile and indications of statin treatment in adult and elderly patients to prevent cardiovascular events;
- support the indication by the recent cardiovascular prevention guidelines[1] strongly recommending the use of statins in secondary prevention in all older subjects and in primary prevention in subjects up to 75 years at high/very high cardiovascular risk to prevent cardiovascular events[99];
- highlight that, regarding the possible role of statin therapy for the prevention of dementia, the weakness of pooled data from clinical trials[24] and the risk of bias inherent in the observational design, do not allow such a recommendation;
- suggest that indications that aggressive lipoprotein management and statin use as strategy for preventing cognitive decline in elderly persons, requires specifically designed randomized clinical trials, with larger populations, longer follow-up, and standardized and recognized methods for the diagnosis of dementia.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

Data availability statement

The data underlying this article are available in the article and in its online supplementary material.' has been added at the end of Method section.

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