Association of blood lipids, atherosclerosis and statin use with dementia and cognitive impairment after stroke: a systematic review and meta-analysis

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Highlights

What is already known on this topic

- Stroke patients are at known higher risk of cognitive decline.
- It is uncertain whether blood lipids, atherosclerosis and statin use are associated with dementia and cognitive impairment after stroke.

What this study adds

- This systematic review suggests that atherosclerosis may be an important risk factor for post-stroke dementia and cognitive impairment.
- Statins have a potential role in reducing the risk of post-stroke cognitive decline.
- Future studies are needed to confirm these findings.

Abstract

Background: Trial and observational evidence is conflicting in terms of the association of blood lipids, atherosclerosis and statin use with dementia and cognitive impairment in the general population. It is uncertain whether the associations occur in stroke patients, who are at known higher risk of cognitive decline. This systematic review was to synthesize the evidence for these associations among stroke patients.

Methods: MEDLINE, EMBASE, the Cochrane Library and trial registries were searched. We included randomized controlled trials or observational cohort studies conducted among patients with stroke and reported on the association of blood lipids, atherosclerosis or statin use with dementia or cognitive impairment. Meta-analysis was conducted separately for crude and maximally adjusted odds ratios (ORs) and hazard ratios (HRs).

Results: Of 18,026 records retrieved, 56 studies (one RCT and 55 cohort studies) comprising 38,423 stroke patients were included. For coronary heart disease, the pooled OR of dementia and cognitive impairment was 1.32 (95%CI 1.10-1.58, n=15 studies, I^2=0%) and 1.23 (95%CI 0.99-1.54, n=14, I^2=26.9%), respectively. Peripheral artery disease was associated with dementia (OR 3.59, 95%CI 1.47-8.76, n=2, I^2=0%) and cognitive impairment (OR 2.70, 95%CI 1.09-6.69, n=1). For carotid stenosis, the pooled OR of dementia and cognitive impairment was 2.67 (95%CI 0.83-8.62, n=3, I^2=77.9%) and 3.34 (95%CI 0.79-14.1, n=4, I^2=96.6%), respectively. For post-stroke statin use, the pooled OR of dementia and cognitive impairment was 0.89 (95%CI 0.65-1.21, n=1) and 0.56 (95%CI 0.46-0.69, n=3, I^2=0%), respectively. No association was observed for hypercholesterolemia. These results were mostly consistent with adjusted ORs or HRs, which were reported from limited evidence.

Conclusion: Atherosclerosis may be associated with an increased risk of post-stroke dementia. Post-stroke statin use was associated with decreased risk of cognitive impairment. To confirm whether or not statins confer advantages in the post-stroke population in terms of preventing cognitive decline over and above their known effectiveness in reducing risk of further vascular events, further stroke trials including cognitive assessment and observational analyses adjusted for key confounders, focusing on key subgroups or statin use patterns are required.

Keywords: Stroke; Dementia; Cognitive impairment; Blood lipids; Atherosclerosis; Statins

1. Introduction

Stroke patients have a significantly higher risk of dementia and cognitive impairment than the general population (Kuzma et al. 2018; Savva et al. 2010), with 10% to 30% developing dementia five years after stroke (Pendlebury and Rothwell 2009). There is some evidence that cognitive impairment may be linked to modifiable cardiovascular risk factors and atherosclerosis in the general population. These factors are more common in people with stroke, making them a potential target for dementia prevention (Savva et al. 2010).

While hypercholesterolemia has been recognized as a major risk factor for atherosclerosis, its role in dementia or cognitive impairment remains unclear. High total cholesterol in mid-life is associated with increased risk of cognitive impairment in later life, but the association of cholesterol measured in later life with cognitive impairment is less clear cut (Anstey et al. 2017; Anstey et al. 2008). Similarly, the evidence as to whether atherosclerosis is associated with dementia is mixed. Some observational evidence suggests coronary heart disease and peripheral artery disease are risk factors for cognitive impairment, with substantial heterogeneity across studies (Wolters et al. 2018; Rafnsson et al. 2009). Two large-scale trials, the Heart Protection Study (HPS) and the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), did not find that statin treatment, the first-line pharmacological therapy for hyperlipidemia and primary prevention of coronary heart disease, was associated with dementia or cognitive test scores (Heart Protection Study Collaborative 2002; Trompet et al. 2010). In small-scale trials, however, the results have been mixed (Carlsson et al. 2008; Summers et al. 2007; Muldoon et al. 2004; Gibellato et al. 2001; Muldoon et al. 2000; Santanello et al. 1997; Gengo et al. 1995; Cutler et al. 1995; Kostis et al. 1994; Harrison and Ashton 1994).

The associations of atherosclerosis and lipid levels with dementia may be different in groups with high risk of dementia, such as stroke patients. The Prevention of Decline in Cognition after Stroke Trial (PODCAST) found that intensive lipid-lowering treatment was associated with better cognitive function six months after stroke (Bath et al. 2017). Current systematic reviews have explored the links between blood lipids, atherosclerosis or statin use with dementia and cognitive impairment, but they neither included patients with stroke nor conducted analysis specifically for the stroke subgroup (Anstey et al. 2017; Anstey et al. 2008; Wolters et al. 2018; Meng et al. 2014; McGuinness et al. 2016; Chu et al. 2018; Larsson and Markus 2018; Zhang et al. 2018; Xu et al. 2015; Swiger et al. 2013; Macedo et al. 2014; Wong et al. 2013; Richardson et al. 2013; Muangpaisan et al. 2010; Power et al. 2015; Zhou et al. 2007).

We conducted a systematic review and meta-analysis to summarize relevant findings from randomised controlled trial (RCT) and observational cohort study on the association of blood lipids, atherosclerosis and statin use with dementia and cognitive impairment among patients with stroke.

2. Methods

2.1 Protocol Registration

This systematic review was prospectively registered with the PROSPERO (Registration number: CRD42017054858) (Yang Z et al. 2017).

2.2 Literature Searches

Our latest search was conducted in the electronic literature databases: MEDLINE (Ovid), EMBASE (Ovid), and the Cochrane Library from the inception to March 2019. A combination of the three following groups of text or MeSH terms constituted the search strategies: (1) stroke, cerebrovascular disease; (2) cholesterol, triglycerides, lipids, hypercholesterolemia, dyslipidemia, atherosclerosis, coronary heart disease, carotid artery stenosis, peripheral artery disease, statins, risk factors, predictors; and (3) dementia, cognitive impairment, Alzheimer's disease, cognitive function (Table S1 in supplement). We searched completed studies registered on ClinicalTrial.gov, WHO International Clinical Trials Registry Platform, and the Cochrane Dementia and Cognitive Improvement Group's

specialized register (ALOIS) in March 2019 (Table S1 in the Supplement). We also scanned the reference lists of relevant systematic reviews and eligible primary studies.

2.3 Inclusion Criteria

We included observational cohort studies or RCTs conducted among patients with stroke, regardless of study time, location, settings, data sources, sample size, stroke subtype, study quality, confounders adjusted, publication type and language. We excluded studies in which only patients with TIA or subarachnoid haemorrhage were enrolled and studies where there was less than three month follow up after stroke. Primary outcomes of interest in this review consist of (1) any dementia, (2) any cognitive impairment and (3) any mild cognitive impairment/cognitive impairment no dementia (MCI/CIND). The secondary outcomes were the change in scores or follow-up scores of cognitive tests (e.g. Mini–Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) score). Exposures of interest were blood lipid level (including hypercholesterolemia and lipid fractions), coronary heart disease, peripheral artery disease, carotid stenosis or post-stroke statin treatment (including statin use, initiation, continuation, withdrawal, dose, type, and adherence).

2.4 Study Selection

Four reviewers independently selected records through scanning the title and abstract based on the inclusion criteria. We then assessed the full-text articles for eligibility. Any disagreement was resolved by consensus. A flowchart of study inclusion was developed in the format recommended by the PRISMA statement (Moher et al. 2009).

2.5 Data Extraction and Risk of Bias Assessment

We extracted data using an electronic pre-designed form. Data items were pre-specified on the PROSPERO registered protocol.

We assessed risk of bias for each cohort study using the QUIPS tool (Hayden et al. 2013). We evaluated six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting (Table S2 in the Supplement). For RCTs, we used the Cochrane tool to assess risk of bias, consisting of seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessor, incomplete outcome data, selective outcome reporting, and other bias (baseline imbalance indicative of problems in randomization and major changes to the protocol) (Higgins et al. 2011).

Information was extracted by one reviewer and checked by the other reviewer. Any disagreement was resolved by consensus.

2.6 Data Analysis

Since heterogeneity is common in prognostic factor studies, meta-analyses were conducted using a random-effects model with generic inverse variance. Data from cohort studies and RCTs were analyzed separately. When data were available, maximum-adjusted associations were synthesized separately from unadjusted associations. For binary outcomes (e.g. dementia and cognitive impairment), we pooled odds ratios or hazard ratios for binary exposure (e.g. hypercholesterolemia and coronary heart disease) and pooled mean difference for continuous exposure (e.g. lipid fractions). For cognitive test scores, we did not conduct meta-analysis because of differences in tests used and how scores were summarized. Studies which provided insufficient or problematic data for the calculation of the effect size were not included in the meta-analysis, but their results were summarized.

To assess statistical heterogeneity across studies, we tested the hypothesis of no heterogeneity using chi-squared test and quantified heterogeneity using the I^2 statistic. We conducted subgroup analyses for potential sources of clinical heterogeneity: stroke type (ischemic, hemorrhagic, mixed and unclear) and length of follow-up (up to 6 months versus more than 6 months). We conducted meta-regression on mean age and length of follow-up as numerical variables for the association of hypercholesterolemia and coronary heart disease with dementia and

cognitive impairment, respectively. We then stratified mean age (>=65 versus <65 years) in the meta-regression to explore whether the associations of interest differed between older-aged and middle-aged patients. Possible publication bias was assessed using funnel plot and Egger's test for the meta-analysis where at least nine studies were included. All the analyses were conducted using Stata 15.0.

2.7 Sensitivity Analysis

We conducted sensitivity analysis with restriction to similar exposure definition (definitions of lipid disorder, specific coronary heart disease and degree of carotid stenosis). We restricted the analysis to the studies involving more general diagnostic criteria of dementia, including Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Diseases (ICD) (Pendlebury and Rothwell 2009). We only included studies using MMSE for the outcome of any cognitive impairment and further restricted analysis to MMSE<24, which was a cut-off commonly used in epidemiological studies on cognitive impairment (Pendlebury and Rothwell 2009). Sensitivity analysis excluding relatively low-quality studies (more than two assessment domains of QUIPS rated as high risk of bias) was also conducted.

3. RESULTS

3.1 Study inclusion characteristics

From a total of 18,026 records (17,476 potentially relevant publications and 550 registration records), we included 56 studies (59 publications) with 38,423 patients in this review (Fig. 1). 53 studies were published in full text and 3 were in conference abstract (Table 1). One study was an RCT and the rest were observational cohort studies. 52 studies were published in English, three in Chinese and one in Spanish. Among the included studies, 42 studies provided sufficient information for quantitative analysis in our review. Only 7 studies were primarily focused on the factors of interest in this review and the other 49 extensively explored multiple factors in addition to the ones of our interest. 43 studies were based in hospital, 12 were community-based and one unclear. It was explicitly reported in 39 studies that pre-stroke dementia was excluded. Sample size varied from 41 to 14,807. The mean age of patients ranged from 41.0 to 80.2 years (median 68.0 years) and the length of follow-up ranged from 3 months to 25 years (median 1 year). Details about exposure and outcomes in each included study are shown in Table S3 in the Supplement.

3.2 Risk of bias assessment

The number of assessment domains rated as high risk of bias ranged from 0 to 5 (Table 1). The main issues of quality of included cohort studies lay in completeness of follow-up, confounding, and statistical analysis and reporting (Fig. S1-A in the Supplement). Most studies failed to include over 80% of stroke patients in the final analysis due to loss of follow-up before the cognitive assessment. This loss of follow-up was not accounted for in most of the studies, which led to a high risk of bias in the domain of statistical analysis. A majority of studies did not adjust for any potential confounders. In the PODCAST trial, participants and personnel were not blinded, memory problem and some cardiovascular factors at baseline were not comparable between the two groups, and some major changes (e.g. sample size, LDL-cholesterol target, treatment duration) were made to the original protocol (Fig. S1-B in the Supplement).

3.3 Blood lipids

Of the 42 studies investigating the association between lipid level and post-stroke cognitive outcomes, 31 studies were included in the meta-analysis for the exposure of hypercholesterolemia or lipid fractions. The pooled crude or adjusted estimates did not suggest a significant association of hypercholesterolemia with post-stroke dementia, cognitive impairment or MCI/CIND (Fig. 2, Table 2). Publication bias may exist in the evidence for dementia (P-value of Egger's test = 0.020) but is less likely for cognitive impairment (P-value = 0.518) (Fig. S2 in the Supplement). Subgroup analyses by length of follow-up and stroke subtype did not find any significant association (Table S4 and

S5 in the Supplement). Studies involving statin treatment to define hypercholesterolemia tended to find reverse association of hypercholesterolemia with post-stroke dementia or cognitive impairment (Table S6 in the Supplement). In the sensitivity analysis restricted to DSM criteria or excluding low-quality studies, hypercholesterolemia was associated with a decreased risk of dementia and cognitive impairment, respectively, with marginal statistical significance (Table S7 and S8 in the Supplement). Meta-regression did not find the association of hypercholesterolemia with dementia or cognitive impairment differed by mean age or length of follow-up (Table S9 in the Supplement). When different lipid fractions were analyzed separately, we did not observe any associations with post-stroke dementia or post-stroke cognitive impairment (Table S10 in the Supplement). Studies which did not report sufficient data for meta-analysis found no association between blood lipids and dementia, except three studies suggesting higher low-density lipoprotein (LDL) level was associated with increased risk of dementia and cognitive impairment after stroke and one study showing the opposite association (Table S11 in the Supplement). Of four observational studies investigating cognitive test scores, two studies suggested hypercholesterolemia was associated with improved cognitive function (Mattis dementia rating scale-initiation/perseveration subscale (MDRS I/P) score change and animal naming) (Table S11 in the Supplement). This, along with the reverse association shown in Table S6 in the Supplement, may be an artefact of how hypercholesterolemia was defined, since statin use was in some cases taken as a marker of hypercholesterolemia.

In the PODCAST trial with a total of 77 participants, intensive lipid-lowering treatment (target LDL <1.3 mmol/l) using statins after stroke, when compared with guideline target treatment (target LDL <3.0 mmol/l), was not associated with significantly lower risk of dementia within two years after stroke (OR 0.18, 95%CI: 0.01-3.98). Cognitive test scores did not differ significantly between the two groups at the end of 2-year follow-up, though there were some differences for specific items (interference accuracy, animal naming and some components of the trail and stroop tests) in favor of the intensive treatment (Table S12 in the Supplement).

3.4 Coronary heart disease

With 36 studies included, 30 provided relevant data for the meta-analysis. Prior coronary heart disease was positively associated with post-stroke dementia (Fig.3A, Table 2). This association was not observed for post-stroke cognitive impairment or MCI/CIND. There was no evidence of publication bias for dementia (P-value of Egger's test = 0.835) or cognitive impairment (P-value = 0.977) (Fig. S2 in the Supplement). Four studies provided adjusted estimates, and these did not find any association of coronary heart disease with dementia or cognitive impairment (Table 2). We did not find any significant difference between the subgroups of stroke type and length of follow-up (Table S4 and S5 in the Supplement). Sensitivity analyses by exposure definition, diagnostic criteria or study quality gave similar results to the main analysis (Table S6-8 in the Supplement). Meta-regression did not find any effects of changes in age or length of follow-up on the association of coronary heart disease with post-stroke dementia or cognitive impairment (Table S9 in the Supplement). Three studies which did not provide sufficient data for meta-analysis suggested no association between coronary heart disease and post-stroke dementia or cognitive impairment (Table S11 in the Supplement). In one study, coronary heart disease was not associated with the change in MMSE or MDRS I/P scores (Table S12 in the Supplement).

3.5 Peripheral artery disease

Only four studies involving peripheral artery disease were included, of which three contributed to the quantitative analysis. PAD was associated with increased risk of post-stroke dementia and cognitive impairment (Fig. 3B, Table 2), but not with MCI/CIND. The association with dementia was attenuated when adjusted (Table 2). The study which was not included in the analysis suggested no association with cognitive impairment (Table S11 in the Supplement).

3.6 Carotid stenosis

Of 11 studies on carotid stenosis included in the review, 8 contributed to the meta-analysis. With substantial heterogeneity across the studies, no significant association with post-stroke dementia or cognitive impairment was

found based on the crude estimates (Fig. 3C, Table 2). One study reporting an adjusted estimate showed a positive association between carotid stenosis and post-stroke dementia (Table 2). Three studies which were not included in the meta-analysis due to insufficient data suggested no association between carotid stenosis and post-stroke dementia (Table S11 in the Supplement).

3.7 Post-stroke statin treatment

Of the 9 studies on lipid lowering treatment, five contributed to the quantitative analysis. In one study, post-stroke statin use was not significantly associated with dementia (Fig.4) but the reverse association was significant in another study with adjustment for confounders (Table 2). This study found that the reverse association between statin use and dementia risk was not modified by age, gender, and stroke subtypes but prior hyperlipidemia, which showed a more prominent association. This study also suggested that high-dose statins, lipophilic statins and longer duration of statin use tended to confer more benefits on preventing dementia after stroke. For cognitive impairment, three studies consistently observed post-statin use was associated with a decreased risk (Fig.4, Table 2) and this association was also found in a study with an adjusted estimate reported (Table 2). This potential protective effect of statins still existed in the sensitivity analysis excluding low-quality studies (Table S8 in the Supplement).

Three studies which did not provide sufficient data for meta-analysis found no significant difference in the risk of post-stroke cognitive decline between post-stroke statin users and non-users (Table S11 in the Supplement). For cognitive test scores, one study suggested post-stroke statin use was not associated with better MMSE scores but another study observed better cognitive function (change in MDRS I/P scores) among post-stroke statin users (Table S12 in the Supplement).

4. Discussion

There was some evidence that existing atherosclerotic disease manifest by coronary heart disease, peripheral artery disease and carotid stenosis may be associated with increased risk of post-stroke dementia. Some studies found post-stroke statin use was associated with decreased risk of post-stroke cognitive impairment. These associations were also found in limited evidence with confounder adjustment where available. We did not find any consistent evidence of an association of hypercholesterolemia with post-stroke dementia or cognitive impairment. We did not find these associations significantly differed by stroke subtype, length of follow-up, exposure definition, diagnostic criteria and mean age of participants.

Our review found some evidence of a link between atherosclerosis and dementia or cognitive impairment in people with stroke. Dementia and cognitive impairment are considered as potential consequences of atherosclerosis of extracranial or intracranial vessels, or as the independent but convergent disease processes of dementia and atherosclerosis sharing some major pathophysiological elements, such as cholesterol, inflammation and Apolipoprotein E e4 (APOEe4) polymorphism (Casserly and Topol 2004). Alternatively, coronary heart disease and carotid stenosis may have direct causal links to cognitive impairment. Stroke patients with coronary heart disease are more likely to experience cardiac dysfunction, which has potentially detrimental effects on brain health (Wolters et al. 2018). Embolisation and hypoperfusion are considered as the main potential mechanisms of cognitive impairment in carotid stenosis (Dutra 2012).

In line with the association between atherosclerosis and cognitive impairment, we observed that post-stroke statin use was associated with a lower risk of cognitive impairment, with a larger potential effect of higher dose and longer duration of statin use on post-stroke dementia prevention. Some pleiotropic pathways of statins which reduce atherosclerosis risk may also contribute to the potential protective effects on cognition. Animal models have shown that statins can decrease anti-inflammatory action, attenuate formation of beta-amyloid (β-amyloid) and neurofibrillary, derive antiproliferative and antithrombotic benefits and improve endothelial dysfunction, which may help protect cognitive function (Pedrini et al. 2005; Vaughan 2003; Amin-Hanjani et al. 2001; Delanty et al. 2001;

Fassbender et al. 2001; Vaughan and Delanty 1999). We found limited available evidence on the difference in the effects of statins between some key subgroups and statin use patterns (e.g. statin initiation, continuation, withdrawal, dose, type, or adherence), which require further analyses to explore using individual-level data.

In the general population, a recent meta-analysis found coronary heart disease was associated with an increased risk of dementia (Wolters et al. 2018), which was consistent with our pooled results post stroke and one systematic review combining cross-sectional and cohort studies of stroke patients (Surawan et al. 2017). A Cochrane review including HPS and PROSPER trials did not find any effect of statins on dementia risk or cognitive impairment among people at risk of vascular disease (McGuinness et al. 2016). On the other hand, several meta-analyses of observational studies have found statin use to be significantly associated with a reduced risk of all-cause dementia, with potentially more benefits from higher dose and longer duration of treatment (Chu et al. 2018; Larsson and Markus 2018; Zhang et al. 2018; Xu et al. 2015; Swiger et al. 2013; Macedo et al. 2014; Wong et al. 2013). However, strong evidence is still lacking (Wong et al. 2013; Richardson et al. 2013; Muangpaisan et al. 2010; Power et al. 2015; Zhou et al. 2007).

On the other hand, we found a lack of association of blood lipids with post-stroke dementia or cognitive impairment. This finding is consistent with studies in the general population, where the association depends on age and length of follow-up: mid-life total cholesterol is associated with dementia and cognitive decline in later life, but there is no association between later life cholesterol and these outcomes (Anstey et al. 2017; Anstey et al. 2008; Meng et al. 2014). This difference between mid-life and later life might also exist among patients with stroke, although the difference was not significant in our meta-regression with relatively limited evidence on mid-life patients. In our review, the relatively short periods of follow-up may have precluded any significant association of blood lipids with post-stroke dementia or cognitive impairment. It should also be noted that the neutral association may partly result from the unreliable or unclear definitions of lipid disorders. As per our analysis, the association even tended to be reverse where statin treatment was not accounted for or was taken as a marker of hypercholesterolemia, which also implied the possible benefits of statins. Even in the relatively high-quality cohort studies, this reverse association possibly due to involving statin treatment in the definition of hypercholesterolemia is common. However, when lipid level was clearly defined, such as the PODCAST trial, patient group with lower LDL level achieved better improvement in some cognitive scores (Bath et al. 2017). It is thus important for the future studies to disentangle the potential effects of hyperlipidemia from those of statin use on post-stroke cognitive impairment. In this review, we provided a comprehensive summary of current clinical evidence on the association of blood lipids, atherosclerosis and statin use with post-stroke dementia and cognitive impairment.

Our review has some limitations. First, we only included studies with published results. However, funnel plots and Egger's test suggested that publication bias for most associations was limited. Second, we identified substantial heterogeneity across the studies in some meta-analysis, with a resulting imprecise estimate of the association. Due to the limited number of included studies, we cannot explore the source of heterogeneity for some relationships of interest. Where applicable, however, our subgroup analysis, meta-regression or sensitivity analysis did not find evidence suggesting the associations of hypercholesterolemia and coronary heart disease with post-stroke dementia or cognitive impairment differed by potential heterogeneity sources, including stroke subtype, participant mean age, length of follow-up, exposure definition and diagnostic criteria. Third, there was limited evidence from randomised controlled trials in this regard and the included studies were mostly observational cohort studies. These studies had a high risk of bias regarding completeness of follow up, with most completing follow-up in less than 80%. A majority of included studies did not adjust for any potential confounders or account for loss of follow-up. Fourth, hypercholesterolemia, coronary heart disease, peripheral artery disease and statin use were not clearly defined in most of the included studies. Fifth, our review cannot confirm the long-term cognitive outcomes because the follow-up period in most included studies providing quantitative results was less than 3 years. Finally, while

some studies investigated the association of interest, due to insufficient information provided in the articles we were only able to describe their results in our review without quantitative synthesis.

5. Conclusions

Coronary heart disease, peripheral artery disease and carotid stenosis may be associated with an increased risk of post-stroke dementia. Post-stroke statin use was associated with decreased risk of post-stroke cognitive impairment. Further statin trials (e.g. among patients with intracerebral hemorrhage) incorporating cognitive outcomes, and further observational analyses, with proper adjustment for key confounders, a clear exposure definition, a longer follow-up period, or a focus on key subgroups, could provide important information to confirm whether or not statins confer advantages in the post-stroke population in terms of preventing cognitive decline over and above their known effectiveness in reducing risk of further vascular events.

Conflict of Interest: None reported.

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Table 1. Characteristics of included studies

Study ID	Design [a]	Region	Setting	Sample size	Stroke type	Mean age (year)	Female (%)	Exclusion of Pre-stroke dementia	Length of follow-up	Exposure subgroups	Exposure measured at baseline	Outcome (diagnostic criteria)	Outcome Incidence (%)	Number of domains rated high risk of bias
Alexandrova and Danovska 2016	prospective	Bulgaria	hospital	47	ischemic	63	44.7	yes	1y	lipids	yes	CI (MMSE<24)	42.6	2
Allan et al. 2011	prospective	UK	hospital	355	unclear	80	48.2	yes	8y	HC, CHD	yes	dementia (DSM IV)	23.9	3
Altieri et al. 2004	prospective	Rome	hospital	191	either	71.3	30.9	yes	4y	HC, CS, CHD	yes	dementia (ICD-10)	21.5	4
Ankolekar et al. 2014	prospective (RCT data)	multiple*	hospital	1572	either	69.2	40.1	No	3m	HC	yes	CI (MMSE-M<14, TICS-M<20,or Category fluency<10), MMSE-M, TICS-M, Category fluency	40	4
Barba et al. 2000	prospective	Spain	hospital	251	either	69	47.0	No	3m	HC, lipids, CHD	yes	dementia (DSM-IV)	30	5
Bath et al. 2017 [b]	RCT	UK	GP and hospital	77	ischemic	74	22.9	yes	2y	Intensive LLT	yes	dementia (DSM IV) cognitive tests	2.3	2
Benedictus et al. 2015	prospective	France	hospital	167	hemorrhagic	64	41.3	yes	6m	HC	yes	CI (MMSE) MMSE	37	4
Biffi et al. 2016	prospective	US	hospital	738	hemorrhagic	74.3	48.0	yes	47.4m	CHD, statins	yes	dementia (ICD-10) TICS-M	41.1	4
Caratozzolo et al. 2016	prospective	Italy	hospital	105	either	67.7	37.1	yes	1y	HC,HT, CS, CHD	yes	dementia (DSM IV)	35.2	3
Censori et al. 1996	prospective	Italy	hospital	104	ischemic	64.9	36.5	yes	3m	CHD	unclear	dementia (NINDS-AIREN)	14.4	3
Chaudhari et al. 2014	prospective	India	hospital	102	either	59.4	26.5	No	6m	HC, lipids, CHD, PAD	yes	VaD,VCI-ND (NINDS-AIREN)	18.6(VaD) 26.5(VCI-ND)	3
Chen et al. 2016	retrospective	China	hospital	56	ischemic	63.8	37.5	yes	12m	HC, CHD	yes	VCI (NINDS-CSN)	55.4	4

Study ID	Design [a]	Region	Setting	Sample size	Stroke type	Mean age (year)	Female (%)	Exclusion of Pre-stroke dementia	Length of follow-up	Exposure subgroups	Exposure measured at baseline	Outcome (diagnostic criteria)	Outcome Incidence (%)	Number of domains rated high risk of bias
Desmond et al. 2000; Desmond et al. 2002	prospective	US	hospital	453	ischemic	72	52.5	yes	3m	HC, CHD	yes	dementia (DSM-III-R)	26.3	3
Douiri et al. 2013	prospective	UK	community	1682	either	unclear	46.1	unclear	10y	HC, CHD, statins	yes	CI (MMSE<24 or AMT<8)	31.5(3m)	2
Fan et al. 2011	prospective	China	hospital	98	either	unclear	29.6	unclear	3m	lipids, CHD	unclear	CI (MMSE<19,22 or 26, or MoCA<26)	unclear	4
Gomez-Viera et al. 2002	prospective	Cuba	hospital	301	ischemic	68.9	44.2	yes	6m	HC, CHD	yes	CI (MMSE)	29.1	4
Huang et al. 2015	prospective	China	hospital	350	ischemic	41.0	30.3	unclear	5.8y	HC, CHD, PAD, statins	yes	CI (TICS-M≤31)	39.4	3
Inzitari et al. 1998	prospective	Italy	hospital	338	either	70.8	47.9	yes	1y	CHD	yes	dementia (ICD-10)	16.8	3
Jacquin et al. 2014	prospective	France	hospital	220	either	66.1	44.1	yes	3m	HC, CHD	yes	CI(MMSE≤26 and MoCA<26)	47.2	4
Khedr et al. 2009	prospective	Egypt	hospital	81	either	57.7	33.3	yes	3m	lipids, CS, CHD	yes	dementia (DSM-IV)	21	2
Klimkowicz-Mrowiec et al. 2006	prospective	Poland	hospital	195	either	67.5	42.6	yes	3m	lipids, CHD	yes	dementia (DSM-IV)	22.6	4
Kokmen et al. 1996	retrospective	US	community	971	ischemic	unclear	49.9	yes	25y	CS, CHD	unclear	dementia (medical records)	48	3
Li et al. 2017 [b]	prospective	China	hospital	365	ischemic	65.2	49.0	yes	1y	lipids, CS, CHD	yes	CI (MMSE<24)	37.2	2
Liman et al. 2011	prospective	Germany	community	630	either	70.2	51.4	yes	3y	CHD	unclear	CI (MMSE<24)	14.8	2
Lin et al. 2003	prospective	Taiwan	hospital	283	ischemic	64.4	33.6	yes	3m	HC	yes	dementia (ICD-10NA)	9.2	4
Lin et al. 2005 [b]	prospective	China	hospital	512	ischemic	66.8	47.9	yes	3m	HC	unclear	VD (DSM-IV)	12.6	4

Study ID	Design [a]	Region	Setting	Sample size	Stroke type	Mean age (year)	Female (%)	Exclusion of Pre-stroke dementia	Length of follow-up	Exposure subgroups	Exposure measured at baseline	Outcome (diagnostic criteria)	Outcome Incidence (%)	Number of domains rated high risk of bias
Loeb et al. 1992	prospective	Italy	hospital	108	ischemic	65.1	17.6	unclear	8y	HC, CS	unclear	dementia (DSM-III)	23.1	3
Mahon et al. 2017	prospective	New Zealand	GP and hospital	257	either	67.9	47.1	unclear	4y	HC, CHD	yes	CI (MoCA<26)	84.4	5
Mellon et al. 2015	prospective	Ireland	hospital	226	ischemic	68.1	41.2	unclear	6m	HC, CS, statins	yes	CI (MoCA<=25)	23.1	3
Mok et al. 2012	prospective (RCT data)	Hongkong	hospital	100	ischemic	75.2	48.0	yes	2y	HC, lipids, CHD, statins	yes	CI(CDR>=1) CDR,MMSE,MDRS I/P	33	1
Moroney et al. 1999 [b]	prospective	US	community	122	unclear	75.4	69.7	yes	2.1y	lipids	yes	dementia (Roman et al)	50	1
Moulin et al. 2016	prospective	France	community	218	hemorrhagic	67.5	45.9	yes	4y	HC, CHD	yes	dementia (National Institute on Aging-Alzheimers Association criteria)	28.9	1
Naco et al. 2013	retrospective	Albania	hospital	78	either	70.3	47.4	unclear	unclear	HC, CS	unclear	CI (MMSE<24)	47.4	5
Newman et al. 2007	prospective (RCT data)	US, Canada, UK	GP and hospital	3680	ischemic	66.3	37.5	unclear	2y	lipids, statins	yes	CI (MMSE<28) MMSE	unclear	1
Pan et al. 2018	retrospective	Taiwan	hospital	14807	either	64.7	42.8	yes	7.5y	statins	No	dementia (ICD-9)	16.2	1
Patel et al. 2002	prospective	UK	community	645	unclear	69.3	46.8	unclear	3m	CHD	yes	CI (MMSE<24)	38.4	2
Pendlebury and Rothwell 2019	prospective	UK	community	2080	either	unclear	unclear	yes	5y	HC, lipids, CHD, PAD	yes	dementia (DSM-IV)	16.2	0
Portegies et al. 2016	prospective	Netherlands	community	993	unclear	79.9	60.4	yes	unclear	HC	yes	dementia (McKhann & Roman)	14.7	1
Racic et al. 2011	prospective	Bosnia and Herzegovina	hospital	251	either	unclear	unclear	yes	3m	HC, CHD	yes	dementia (NINDS-AIREN)	19.5	3
Sachdev et al. 2009	prospective	UK	hospital	104	ischemic	70.2	44.2	yes	3-6m	HC, CHD	yes	VMCI (consensus)	43.3	3

Study ID	Design [a]	Region	Setting	Sample size	Stroke type	Mean age (year)	Female (%)	Exclusion of Pre-stroke dementia	Length of follow-up	Exposure subgroups	Exposure measured at baseline	Outcome (diagnostic criteria)	Outcome Incidence (%)	Number of domains rated high risk of bias
Saxena et al. 2008	prospective	Singapore	hospital	141	either	71.5	45.5	No	6m	CHD	yes	CI (AMT<=7)	40.4	4
Schmidt et al. 1993	prospective	US	hospital	41	ischemic	67.4	39.0	yes	6m	HC	yes	CI (Mattis Dementia Rating Scale<=136)	36.6	3
Srikanth et al. 2004	prospective	Australia	community	88	either	69.3	41.0	No	1y	HC	yes	dementia (DSM-IV) CIND	12.5(dementia) 37.5(CIND)	3
Stephan et al. 2015	prospective	UK	community	283	unclear	77.3	58.3	yes	2y	CHD, PAD	yes	dementia (AGECAT)	29.7	3
Surawan et al. 2018	prospective	Thailand	hospital	401	ischemic	64.2	46.1	yes	6m	HC, lipids	yes	CI (MMSE<=23)	56.6	2
Talelli et al. 2004 [b]	prospective	Greece	hospital	171	ischemic	66.2	40.9	yes	1y	HC, CS, CHD	yes	CI (MMSE<24)	39.2	2
Tveiten et al. 2014	prospective	Norway	hospital	50	hemorrhagic	70.8	52.0	unclear	3.8y	CHD	yes	CI (MoCA<=23)	54	3
Winovich et al. 2017	prospective	US	community	346	ischemic	80.2	56.8	yes	1.6y	lipids	yes	CI (decrease by>=5 on MMSE)	unclear	2
Yang et al. 2007 [b]	prospective	China	hospital	403	ischemic	66.9	46.0	yes	3m	CS, CHD	unclear	dementia (DSM-IV)	21.6	1
Yang et al. 2015; Mok et al. 2016	prospective	Hongkong	hospital	1013	either	69.2	44.3	yes	3-6m	HC, CHD	unclear	dementia (DSM-IV)	8.7	1
You et al. 2017	prospective (RCT data)	Australia, China, South Korea	hospital	231	hemorrhagic	62.2	35.5	unclear	3m	CHD	yes	CI (MMSE<=24)	32.5	4
Zhou et al. 2004	prospective	China	hospital	434	ischemic	67.6	47.2	No	3m	CHD	yes	dementia (DSM-IV) CI (MMSE)	27.2 (dementia) 37.1 (CI)	5

Study ID	Design [a]	Region	Setting	Sample size	Stroke type	Mean age (year)	Female (%)	Exclusion of Pre-stroke dementia	Length of follow-up	Exposure subgroups	Exposure measured at baseline	Outcome (diagnostic criteria)	Outcome Incidence (%)	Number of domains rated high risk of bias
Zhou et al. 2015	prospective	China	hospital	195	ischemic	60.5	47.2	yes	3m	lipids, statins	yes	CI (△MMSE<-2)	18.7	3
Kramer et al. 2015 [c]	retrospective	UK	community	408	ischemic	76.6	unclear	yes	6.5y	CHD	unclear	dementia (Clinical)	29.2	NA
Naco et al. 2015 [c]	prospective	unclear	hospital	249	unclear	68.5	28.5	yes	unclear	HC, CS	unclear	dementia (DSM-IV)	27.7	NA
Verma et al. 2013 [c]	prospective	unclear	unclear	56	unclear	unclear	unclear	yes	6m	HC	unclear	VCI (NINDS-AIREN)	39.3	NA

[a] Studies are all cohort study unless otherwise specified.

[b] Studies are primarily aiming to investigate at least one of the factors of interest in our review.

[c] Studies with only conference abstract available, for which risk of bias was not assessed.

*Regions involved in the study Ankolekar et al. 2014 included Australia, Canada, Mainland China, Denmark, Egypt, Georgia, Greece, Hong Kong, India, Ireland, Italy, Malaysia, New Zealand, Norway, Philippines, Poland, Romania, Singapore, Spain, Sri Lanka, Sweden, Turkey, and United Kingdom.

Abbreviation: AGECAT, Automated Geriatric Examination for Computer-Assisted Taxonomy; AMT, Abbreviated Mental Test; CDR, clinical dementia rating scale; CHD, coronary heart disease, including angina and myocardial infarction; CI, cognitive impairment; CIND, cognitive impairment no dementia; CS, carotid stenosis; DSM, Diagnostic and Statistical Manual of Mental Disorders; HC: hypercholeterolemia; HT: hypertriglyceridemia; ICD, International Classification of Diseases; m, month; MDRS I/P, Mattis dementia rating scale—initiation/perseveration subscale; MMSE, Mini–Mental State Examination; MoCA, Montreal Cognitive Assessment; NINDS-AIREN, National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences; NINDS-CSN, National Institute of Neurological Disorders and Stroke and Canadian Stroke Network; PAD, peripheral artery disease; TICS-M, Telephone Interview for Cognition Scale-Modified; UK, United Kingdom; US, United States; VaD, vascular dementia; VCI-ND, vascular cognitive impairment no dementia; VMCI, vascular mild cognitive impairment; y, year.

Table 2. Association of hypercholesterolemia, atherosclerosis and statin use with dementia and cognitive impairment

Exposure	Outcome	Unadjusted estimate				Adjusted estimate			
		Number of studies	Effect size (95%CI)	P-value for effect size	I^2 (%)	Number of studies	Effect size (95%CI)	P-value for effect size	I^2 (%)
Odds ratio									
Hypercholesterolemia	Dementia	9	0.88 (0.69, 1.12)	0.301	8.3	0	NA	NA	NA
	MCI/CIND	3	1.29 (0.77, 2.16)	0.333	0	0	NA	NA	NA
	CI	12	1.05 (0.78, 1.41)	0.751	70.6	2[a]	0.49 (0.17, 1.45)	0.199	54.6
Hypertriglyceridemia	Dementia	1	0.91 (0.21, 3.88)	0.900	NA	0	NA	NA	NA
Coronary heart disease	Dementia	15	1.32 (1.11, 1.58)	0.002	0	0	NA	NA	NA
	MCI/CIND	2	0.83 (0.27, 2.59)	0.746	44.4	0	NA	NA	NA
	CI	14	1.23 (0.99, 1.54)	0.066	26.9	2[b]	0.71 (0.32, 1.54)	0.382	0
Peripheral artery disease	Dementia	2	3.59 (1.47, 8.76)	0.005	0	0	NA	NA	NA
	MCI/CIND	1	1.61 (0.54, 4.83)	0.396	NA	0	NA	NA	NA
	CI	1	2.70 (1.09, 6.69)	0.032	NA	0	NA	NA	NA
Carotid stenosis*	Dementia	3	2.67 (0.83, 8.63)	0.099	77.9	1[c]	2.00(1.10, 3.64)	0.035	NA
	CI	4	3.34 (0.79, 14.1)	0.101	96.6	1[d]	0.99 (0.76, 1.29)	0.95	
Post-stroke statin use	Dementia	1	0.89 (0.65, 1.21)	0.440	NA	0	NA	NA	NA
	CI	3	0.56 (0.46, 0.69)	<0.001	0	1[e]	0.33 (0.12, 0.90)	0.031	NA
Hazard ratio									
Hypercholesterolemia	Dementia	1	0.67 (0.31, 1.47)	0.320	NA	3[f]	1.02 (0.86, 1.25)	0.851	0
Coronary heart disease	Dementia	1	1.56 (1.00, 2.43)	0.050	NA	2[g]	1.11 (0.85, 1.44)	0.447	0
Peripheral artery disease	Dementia	0	NA	NA	NA	1[h]	1.27 (0.90, 1.79)	0.180	NA
Post-stroke statin use	Dementia	1	0.82 (0.75, 0.90)	<0.001	NA	1[i]	0.81 (0.73, 0.89)	<0.001	NA
Type of statins**	Dementia	1				1[i]			
Atorvastatin			0.77 (0.68, 0.88)	<0.001	NA		0.78 (0.68, 0.89)	<0.001	NA
Fluvastatin			0.80 (0.63, 1.00)	0.060	NA		0.76 (0.61, 0.95)	0.014	NA
Lovastatin			1.16 (0.96, 1.40)	0.124	NA		1.00 (0.83, 1.21)	1.000	NA
Pravastatin			0.99 (0.78, 1.25)	0.934	NA		0.86 (0.68, 1.09)	0.208	NA
Rosuvastatin			0.49 (0.38, 0.63)	<0.001	NA		0.53 (0.41, 0.68)	<0.001	NA
Simvastatin			0.83 (0.70, 0.99)	0.032	NA		0.82 (0.69, 0.98)	0.024	NA

Exposure	Outcome	Unadjusted estimate				Adjusted estimate			
		Number of studies	Effect size (95%CI)	P-value for effect size	I^2 (%)	Number of studies	Effect size (95%CI)	P-value for effect size	I^2 (%)
Dose of statins**	Dementia	1				1[i]			
High			0.72 (0.65, 0.80)	<0.001	NA		0.72 (0.65, 0.80)	<0.001	NA
Low			1.43 (1.22, 1.67)	<0.001	NA		1.21 (1.03, 1.42)	0.020	NA
Solubility of statins**	Dementia	1				1[i]			
Lipophilic			0.79 (0.72, 0.87)	<0.001	NA		0.78 (0.71, 0.86)	<0.001	NA
Hydrophilic			1.26 (0.99, 1.61)	0.060	NA		1.21 (0.95, 1.55)	0.123	NA
Duration of statin use**	Dementia	1				1[i]			
<1 year			1.40 (1.25, 1.56)	<0.001	NA		1.25 (1.12, 1.39)	<0.001	NA
1-3 years			0.81 (0.70, 0.95)	0.007	NA		0.78 (0.67, 0.91)	0.001	NA
>3 years			0.26 (0.21, 0.32)	<0.001	NA		0.28 (0.23, 0.35)	<0.001	NA

*If the percentage of carotid stenosis was presented in the report, we defined carotid stenosis disease as any greater severity above the category of the least severity.

**The reference group was no statin use.

Adjustment:

a. Mok 2012: age, diastolic blood pressure, cortical gray matter volume ratio quartiles (selected based on statistical significance in univariable analysis); Talelli 2004: age, sex, education level, living area, atrial fibrillation, hypertension, diabetes, coronary heart disease, smoking, alcohol drinking, stroke lesion site, hemispheric site, carotid plaques, degree of carotid stenosis, depression, carotid artery intima media thickness.

b. Liman 2011: age, sex, Barthel index, pre-stroke institutionalization, stroke subtype, hypertension, diabetes, atrial fibrillation; Talelli 2004: age, sex, education level, living area, atrial fibrillation, hypertension, diabetes, hypercholesterolemia, smoking, alcohol drinking, stroke lesion site, hemispheric site, carotid plaques, degree of carotid stenosis, depression, carotid artery intima media thickness.

c. Yang 2007: age, education level, alcohol drinking, stroke history, atrial fibrillation, dysphonia.

d. Mellon 2015: age, sex, stroke severity.

e. Mok 2012: age, diastolic blood pressure, cortical gray matter volume ratio quartiles (selected based on statistical significance in univariable analysis)

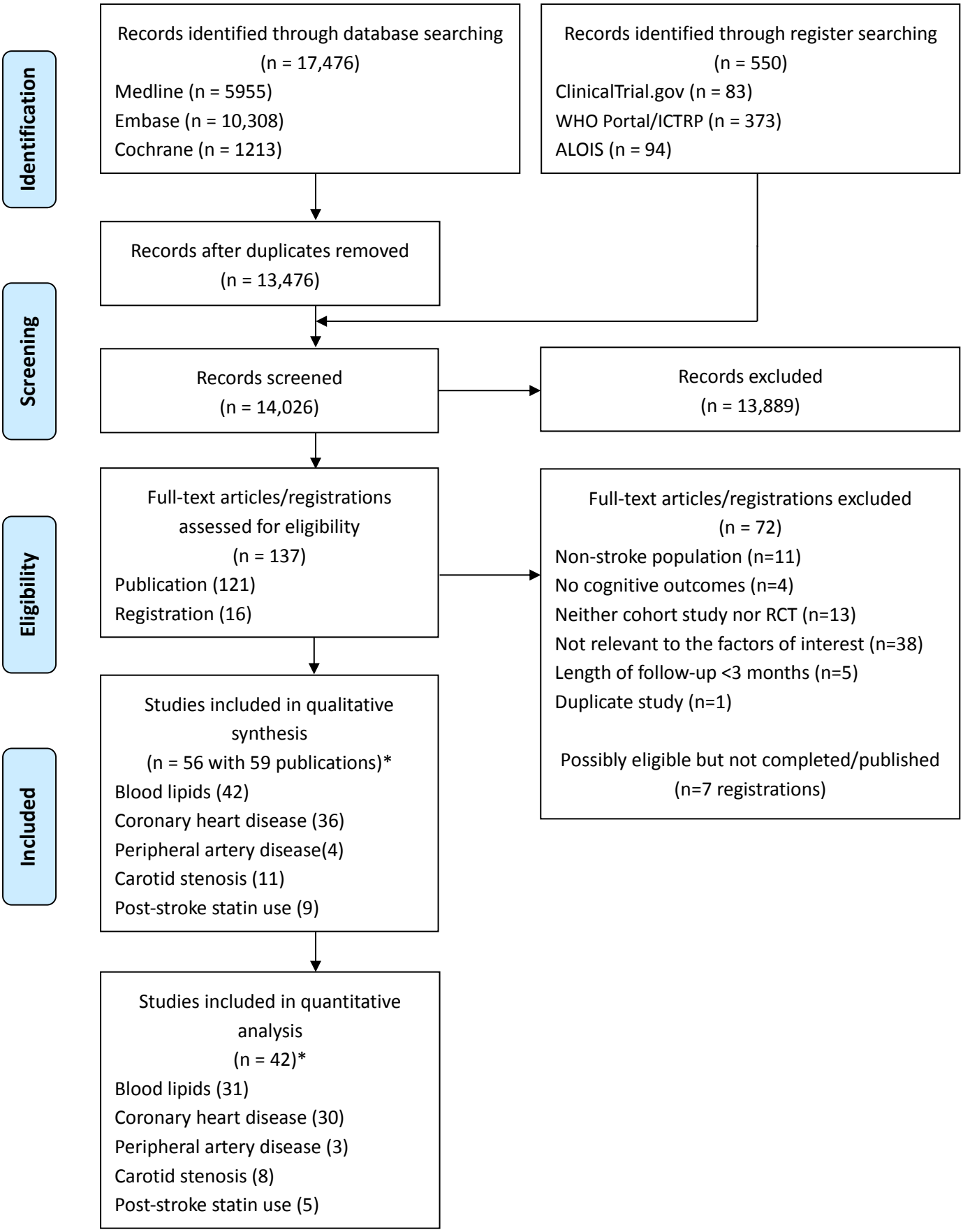
f. Moulin 2016: age; Pendlebury 2019: age, sex, education, stroke severity; Portegies 2016: age, sex, time between center visit and index date, hypertension, low HDL cholesterol, BMI, diabetes, smoking, transient ischemic attack, atrial fibrillation.

g. Moulin 2016: age; Pendlebury 2019: age, sex, education, stroke severity.

h. Pendlebury 2019: age, sex, education, stroke severity.

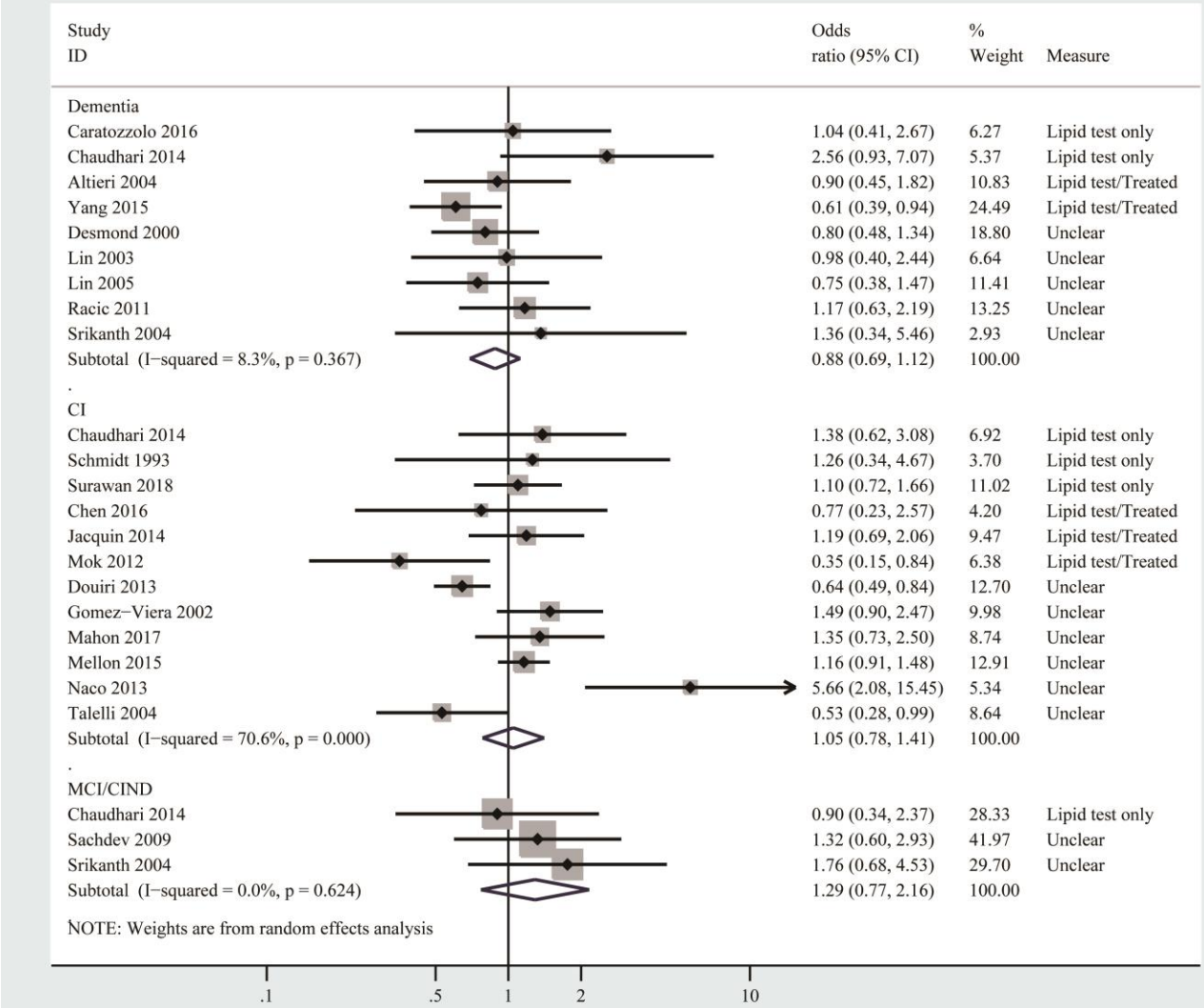
i. Pan 2018: age, sex, socioeconomic status, comorbidity, medication.

Abbreviation: CI, cognitive impairment; MCI/CIND, mild cognitive impairment/cognitive impairment no dementia; NA, not applicable.



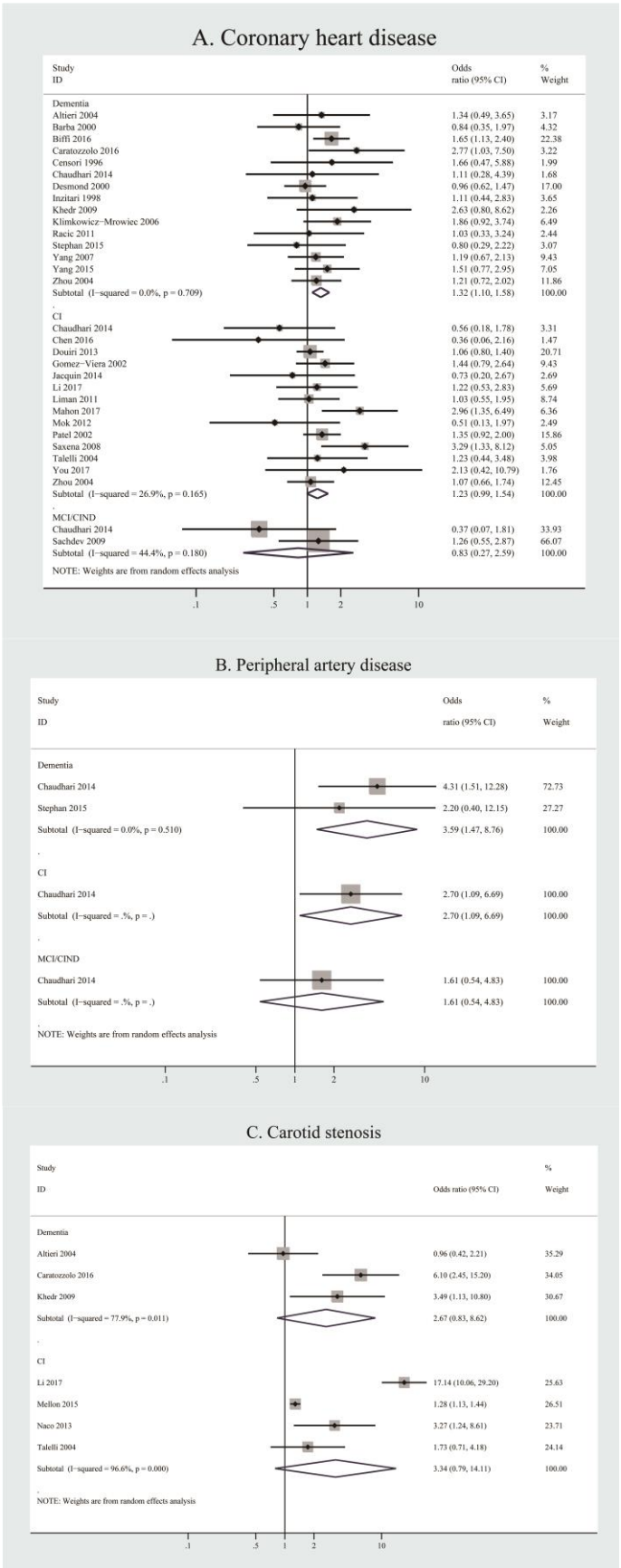
* Studies investigating these factors were not mutually exclusive.

Fig. 1. Flowchart of study inclusion



CI, cognitive impairment; MCI/CIND, mild cognitive impairment/cognitive impairment no dementia

Fig. 2. Association of hypercholesterolemia with post-stroke dementia and cognitive impairment



CI, cognitive impairment; MCI/CIND, mild cognitive impairment/cognitive impairment no dementia

Fig. 3. Association of atherosclerosis with post-stroke dementia and cognitive impairment

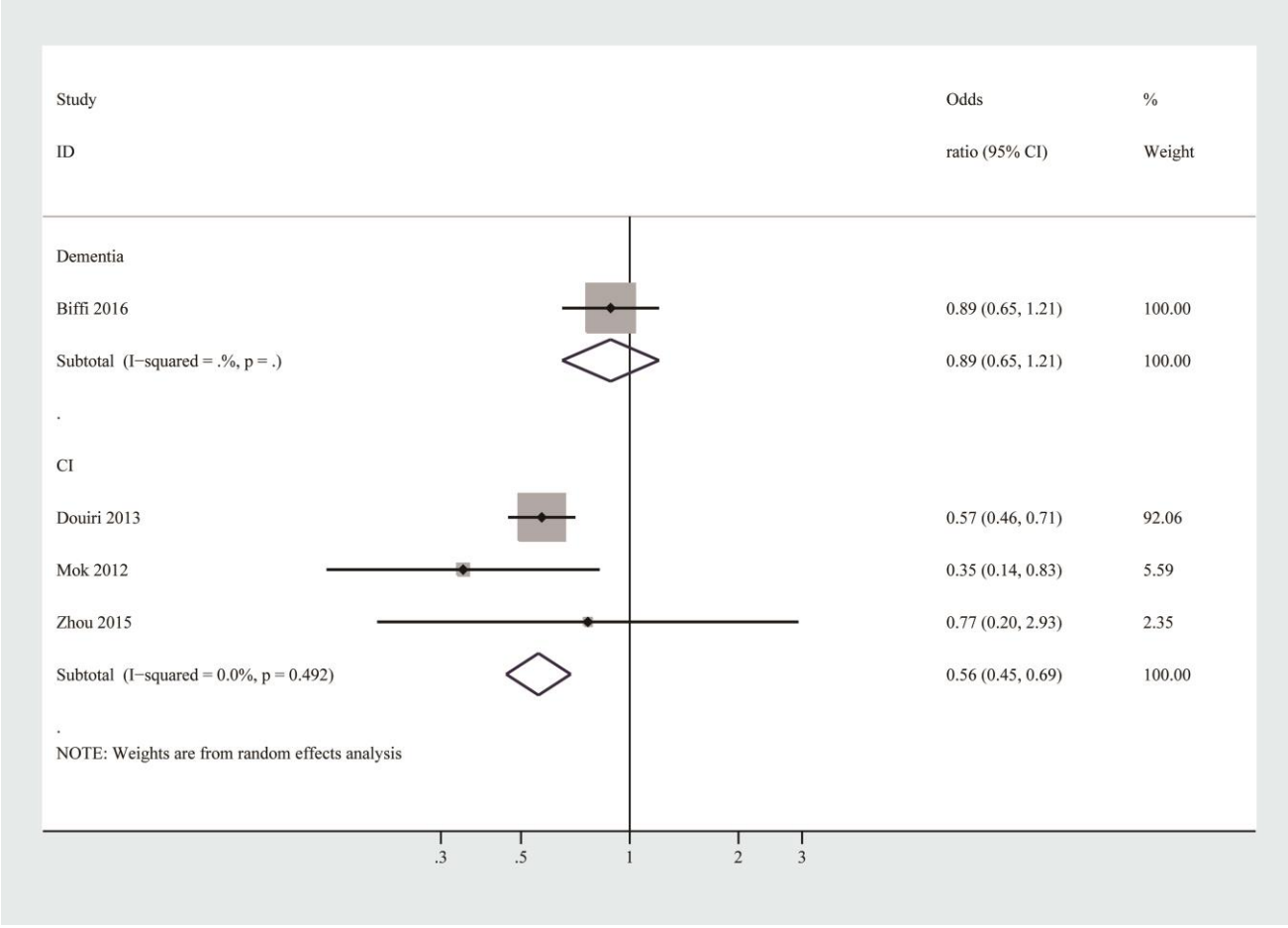


Fig. 4. Association of statin use after stroke with post-stroke dementia and cognitive impairment