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STATINS AND COGNITION: A SYSTEMATIC REVIEW & META-ANALYSIS

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ABSTRACT

Introduction: One in three women has the lifetime risk of developing dementia. Women are also at high risk of having dyslipidemia starting from childbearing until the menopause. Statins are known as the first line of cholesterol treatment and are well tolerated. However, recent research suggests that prolong use of statins might lead to an increased risk of developing neurocognitive disorders. The primary aim of this study was to review and consolidate the existing literature in order to better understand the impact of statins on cognition. **Methods:** MEDLINE (OVID) and EMBASE were searched from their inception to 9 March 2021. The search criteria comprised of abstracts written in English, with information related to both male and female. This review is registered on PROPSERO (ID: CRD42020132155). **Results:** Few studies have examined the relationship and cognitive function from mid-life whereby the follow-up time of most statin related studies (67.5%) did not exceed 5 years. Meta-analysis showed that while types of statins did not affect the cognition, there was a gender effect in that those that showed significant association were mainly male (≥70%). **Conclusion:** The findings from this systematic review and meta-analysis suggest that the mixed outcome reported could be due to the studies' design, the neuropsychological tests administered and the length of follow-up. The significant difference reported in the current statin studies was mainly driven by male statin users. These findings shed light on the importance of having long-term statin studies and the urgent need to focus on female statin users. **Abbreviations:** ACC/AHA = American College of Cardiology/American Heart Association; AD = Alzheimer's Disease, CVD = Cardiovascular Disease; JUPITER = Justification for the Use of Statins in Primary Prevention; LDL = Low-Density Lipoprotein; MMSE = Mini Mental State Examination; PRISMA = Preferred Reporting Items for Systematic Review and Meta-Analyses; REGARDS = REasosn for Geographic and Racial Differences in Stroke; SMD = standardised mean difference.

KEYWORDS: Statins, cognition, women, sex differences, duration.

INTRODUCTION

Dementia is a debilitating and common disease which presents with a decline in memory and at least one other cognitive domain that is of sufficient severity to impair daily activities.[1] Globally, 47 million people live with dementia now, and the number is predicted to almost triple reaching 131 million by 2050 as populations age.[2] Despite these high and increasing prevalence rates, there is no curative treatment for dementia.[3] Current available medications for AD and dementia have comparatively small effect sizes and do not noticeably change disease progression.[4] In addition, the few promising new agents have failed in Phase III clinical trials.[5]

There have been several papers which examine the potential of statins to improve risk of dementia.[6] Statins are among the most prescribed drugs globally with an estimated 25% of the world population age 65 and over presently under statin therapy and the numbers increasing.[7] According to the current ACC/AHA guideline, almost all patients with prior acute coronary syndrome events, and/or clinical atherosclerotic cardiovascular disease or otherwise deemed to be a high

risk, like those with diabetes, require a statin for secondary prevention.[8] Primary prevention with an aim of reducing LDL cholesterol levels to 100 mg/dL or less is recommended for these patients.

There is also an ongoing debate on the relationship (benefits & risks) between statins and cognitive function in both short- and long-term use. Most of the studies that examined statins and cognitive function are of no more than 5 years duration. Case reports raise the prospect that statins may be associated with cognitive impairment while some prospective studies demonstrate no cognitive benefits for any statin.[9] Thus, the long-term effects of statins on cognitive function are yet to be fully understood. Moreover, past results do not reveal a consistent picture and many researchers have recommended a more thorough and detailed research methodology is required in order to resolve this ongoing debate.

Furthermore, the absence of sex-specific information is important in the context that women make up a larger percentage of the older population accounting for 62% of people aged over 80 in 2014. As such, the impact on women will be greater than for men. On top of that, cardiovascular disease (CVD) remains the second leading cause (19.9%) of death in Asia-Pacific women after cancers.[10] Even though it is true that males are more likely to acquire cardiovascular disease than females by age group as women develop cardiovascular disease at an older age (usually 10 years later) but both genders are exposed to the same classic risk factors.[11] There are also differences in the risk for CHD between men and women.[12] The lifetime risk of CHD after 40 years of age has been estimated at 32% for women and 49% for men. The incidence of coronary events increases with age, with women trailing behind men by 10 years but the ratio for incidence narrows increasingly with progressing age.[12]

In addition to its benefits in CVD prevention, statins are associated with 20% risk reduction of stroke and coronary events in high-risk women but half of the cardiovascular events happen in low-risk women.[10] Unlike men, where the primary and secondary prevention benefit with statins have been well established, the benefits and risks of statin treatment for primary prevention remain less well defined in women.[10] Previous meta-analyses have suggested that some of the benefits of statin therapy do not apply to women for primary prevention and that all-cause mortality is not reduced in women.[12] It has also been suggested that women had a significantly lower overall LDL-C success rate than men.[13] Primary prevention studies have illustrated that statin therapy reduces the rate of cardiovascular events by ~20% but the study populations predominantly comprised of men[10], per se, restricting the ability to stratify results by sex.[10] Meanwhile in secondary prevention settings, statins lower risk of recurrent CVD events and mortality, with benefits of equivalent magnitude in women and men but women are under-represented with <20% of total participants.[10] Thus, questions remain about the efficacy and safety of statins to prevent CVD in women.

The safety concerns regarding statins are crucial in women. In addition to evidence that statins are less effective in women than men, both RCTs and observational data imply the conclusion that statins cause more side effects in women than in men.[14] In the JUPITER study, a higher incidence of physician-reported diabetes mellitus was observed in women treated with statins compared with men.[14] Myalgia is the most well-known side effect of statin therapy which has reported in 20% of women[10] and is a main cause of intolerance and discontinuation. Furthermore, evidence supporting sex-based differences in statin metabolism implicates, in part, distinguished differences in body-fat content between women and men. Females tend to have a higher percentage of body fat, which influences volume of distribution of some drugs and can significantly raise the half-life of a variety of medications like the more lipophilic statins.[15] Despite this, these are not taken into consideration into prescription.

Therefore, the primary objective of this study is to summarize and consolidate the existing literature in order to better understand the impact of statins on cognition and cognitive decline, with specific attention to knowledge gaps examining duration of therapy and sex differences in statin studies.

METHODS

Data Sources and Searches

A search of the EMBASE and MEDLINE (OVID) electronic databases was conducted systematically to identify research articles that have investigated the association between statins and cognition from their inception to 9 March 2021. The terms used were: "statin*", "cognit*", "dementia*" and "Alzheimer's disease" (where * indicates a truncation). The search criteria comprised of abstracts written in English, with information related to both male and female. The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement guideline is followed in this review[16] (Supplementary 1). The review is registered on PROPSERO with the ID: CRD42020132155.

Study Selection

The titles and abstracts of full-text articles were examined by two authors (TJC/SF) for eligibility, with original research, post-hoc and secondary analyses included in this review. For meta-analysis purpose, only studies with continuous outcomes were considered.

Data Extraction and Quality Assessment

We extracted the following information from all eligible studies: participant characteristics, study characteristics including year of publication, objectives, sample size,

setting, duration of follow-up and cognitive outcomes. For continuous outcomes, we extracted summary statistics to calculate the standardised mean differences at end of follow-up. One reviewer independently extracted the data and it was checked by another. The National Institutes of Health (NIH) quality assessment tool was used to assess the quality of the included studies.

Data Synthesis and Analysis

The results of the systematic review are described narratively. Meta-analyses were performed when information existed from two or more studies.

Continuous outcomes were summarized as standardized mean differences (SMDs), using the Hedges *g* metric.[17] SMDs express a difference as a fraction of the pooled standard deviation of the measurements and allow comparisons across measurements with different instruments, provided that studies come from populations that would have comparable variability in the various measurement scales.

All meta-analyses were conducted with a random effects model as substantial between-study diversity was expected a priori. Review Manager (Revman) software version 5.4 for Macintosh Operating System was used for all statistical analyses in this study.

RESULTS

A total of 634 papers were found in the first search. After removing duplications and applying inclusion and exclusion criteria, a total of 97 articles were eventually included for qualitative analysis, including 54 longitudinal studies, 27 randomised controlled trials (RCT), 9 cross-sectional studies and 7 case-control studies. 21 studies met inclusion criteria for meta-analysis (13 RCTs, 7 longitudinal, 1 cross-sectional) (Figure 1).

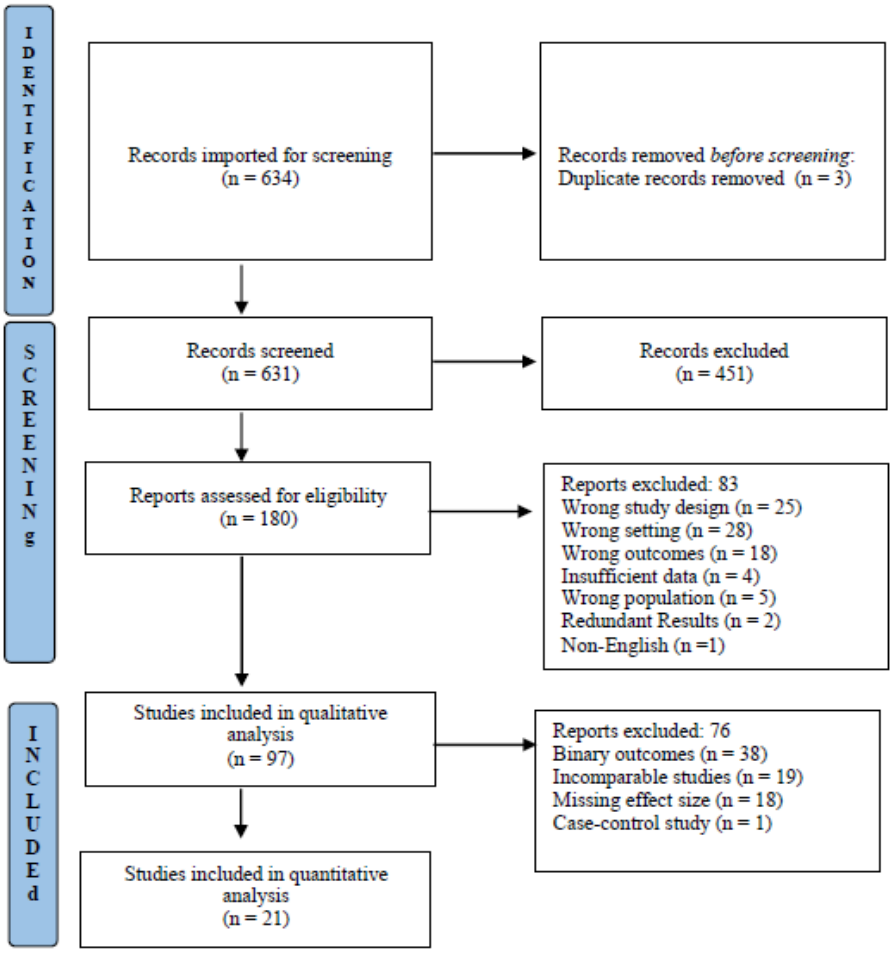

Figure 1: PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram depicting literature search process.

QUALITATIVE ANALYSIS

Cross-sectional Research

The 9 cross-sectional studies included in this review reported conflicting findings in relation to association between statin use and cognition. Three studies[18-20] showed improvements in cognitive function and reduced AD incidence in statin users. However, three other studies[21-23] reported that statins were related to greater amyloid deposition, early marker of cerebrovascular

diseases and increased risk of cognitive impairment, while another three studies[24-26] demonstrated no statistically significant associations between statin use and cognition. Moreover, six cross-sectional studies[18,21,25-28] relied upon standard neuropsychological batteries to measure changes in cognition, with the remaining studies utilized probable AD diagnosis[20,29] and neuroimaging biomarkers[23] as outcome measures.

In a large cohort study among statin users age 60 or over (n=10,086), Wolozin and colleagues reported that the prevalence of probable AD in the cohort taking lovastatin and pravastatin was 60% to 73% lower than the patients using other medications normally took in the treatment of cardiovascular disease or hypertension ($p<0.001$), whereas no significant difference for simvastatin takers was observed.[30] In a study conducted at University Health Network-Toronto Rehabilitation Institute which compared the differences in global cognition and cognitive domains between high and low-dose statin users, high-dose statin use was associated with higher visuospatial memory (odds ratio, OR [95% confidence interval, CI] =0.12 [0.02–0.66], P=0.01) and executive functioning (OR=0.25 [0.06–0.99], P=0.05). However, the researchers had no access to data regarding whether patients switched between high- and low-dose statin use prior to inclusion into the study[18], so the attribution of causality in this cross-sectional study is difficult.

The Neurological Disorders in Central Spain Study observed no differences between statin users and non-users on neuropsychological assessments after adjusting for gender, age, depressive symptoms, education, blood cholesterol levels, premorbid intelligence, and medications that potentially influence cognitive function. Statistical differences were, however, detected on univariate analysis. A restrictive neuropsychological test battery, examining a limited number of cognitive domains, may have contributed to the lack of association observed.[27] In the REGARDS Study which assessed a larger sample of 24,595 subjects with a prior validated instrument of global cognitive status (Six-Item Screener), little effect on cognition was seen with statin use (OR: 0.98, CI: 0.87 – 1.10) or statin type (lipophilic vs hydrophilic) (OR: 1.03, CI: 0.86–1.24).[31]

On the other hand, Glodzik and colleagues reported that statins were related to greater amyloid deposition ($p = .004$) in a group of 156 subjects (age 60.4 ±10.4, 67% female][21] A similar outcome was also observed in another study examining long term statin use on neuroimaging biomarkers of aging and dementia.[32] In that study, the individuals with long-term statin exposure had poorer white matter integrity in the genu of the corpus callosum compared to the statin-untreated group, consistent with the coexistence of higher cerebrovascular risk factor burden in this long-term statin usage group. However, both these studies were not able to systematically consider variations in statin dose or indications for therapy since specific classes of medication could have affected amyloid deposition differently. In addition, no information about treatment duration was available.

The reported mixed outcome of the cross-sectional studies discussed here could be due to several limitations including reporting biases, inadequate information on duration and specific dosages of statin exposure. Moreover, cross-sectional research by its very nature, cannot assess longitudinal effects or infer causation. Given that the cognitive effects of statins can take up to ten years to become apparent, longitudinal examination of this association would be more appropriate.[33]

Longitudinal Research

The majority (59.3%) of longitudinal studies included in this systematic review reported positive associations between statin use and reduced cognitive decline/dementia, including AD, with 28 (51.85%) of the included studies having longitudinal data for at least 5 years. The follow-up period of these studies was between 0.25 and 69 years, the baseline mean age was mostly aged 65 or over, and the sample size ranged from 18 to 835,049.

The Israel Diabetes and Cognitive Decline study identified improvements in overall cognition, memory and executive function in statin users compared to non-users, independent of cholesterol levels after eight years of follow-up. However, despite the prolong follow-up, cognition was assessed only once at last follow-up. Furthermore, the study detected effects despite the small cohort (n=106).[34] Over a longer follow-up of ten years and with a larger sample (n=3,334) that comprised of an elderly cohort (mean age 74), the Cardiovascular Health Study showed that the use of statins was associated with a very faint reduction in the rate of cognitive decline.[35] However, the confidence interval for this result was wide, and bias by indication may have contributed to these findings.

The Indianapolis-Ibadan Dementia Project observed a reduced risk of incident AD (OR=.40, P=.029) in African American persons over a follow-up of 8 years, notably in consistent statin users only compared with inconsistent statin users. However, the included participants were of advanced age (mean age: 76.6).[36] Also with an aged cohort (mean age: 78.4), the Ginkgo Evaluation of Memory Study associated participants without mild cognitive impairment (MCI) at baseline statin use with a reduced risk of both AD and dementia after a mean follow-up of 6 years compared with individuals with MCI.[37]

Over a shorter period (up to 3 years), Wolozin and colleagues[38] found a reduced incidence of dementia in simvastatin users compared with atorvastatin and lovastatin users. Furthermore, gender imbalance was also present with 94.4% of the participants being male. Over

a similar follow-up period (mean 3.4 years), Steenland and colleagues[39] observed reduced cognitive decline in statin users compared with non-users. Slower decline in the Clinical Dementia Rating Sum of Boxes (p=0.006) and a higher level of global function (MMSE) were seen in statin users with normal cognition at baseline compared with non-users. No differences in cognitive decline were seen in those with mild cognitive impairment. This indicated a potential false positive finding, with outcome measures based on several neuropsychological indices.

Conversely, the Adult Changes in Thought Study[40] conducted in 2004 was unable to detect an association between statin use and incident and probable dementia in a cohort of 2,356 subjects age 65 and over. However, when the additional analysis was undertaken by the study team in 2010, they were able to link statin use with a lower risk of AD over a longer duration of follow-up (mean of 6.1 years) and with a larger cohort of men and women ≥ 65 years of age (n=3,099). Li and colleagues also noticed that statin therapy in early old age, but not in late age (≥80), may be associated with a lower risk of AD.[41]

Similarly, the Cache County Study of 4,895 participants aged 65 or older inversely associated statin use with the prevalence of dementia at baseline (adjusted OR, 0.44, 95% CI). However, a subsequent analysis performed three years later did not reveal a reduced onset of AD associated with statin use (adjusted OR for dementia, 1.04, 95% CI; adjusted OR for AD, 0.85, 95% CI). Nonetheless, given that the statin users constituted just 6.3% of the total cohort, reporting bias may have occurred.[42]

In addition, despite a longer follow-up (12 years), the Religious Orders Study of Catholic clergy also could not link statin use with cognitive changes, AD incidence or pathology. Given that the participants were of advanced age (mean of 74.9 at baseline) and the cohort included few baseline statin users (12.8%), demonstrating an association would have been difficult.[43] Additionally, long term study (10 years) by Joosten and colleagues conducted in a cohort of 4,095 subjects (mean age 53.99, 0.523 M:F ratio), demonstrated no relation of statin use to incident of AD or change in cognition after adjustment for confounders (B, -0.82; 95%CI, -2.77 to 1.14; p=0.41). Since statin use increased with cardiovascular risk, the study may have been subject to indication bias.[44]

Interestingly, a large retrospective cohort study conducted by Strom and colleagues associated both statin use and non-statin lipid lowering agent use with acute memory loss within 30 days of exposure. Nonetheless, the study indicated potential detection bias of memory loss from frequent consultations with physicians and potential misclassification of outcome.[45] In another observational study, Mandas and colleagues also reported a significant negative association between statin use, with or without aspirin, and with raised development of AD ($p<0.05$) among a group of patients, predominantly female (71.23%), aged 65 or older from geriatric units (n=1,1168). Cognitive function, however was not the main outcome of interest.[46]

Treatments and Intervention trials

Several (51.9%) included clinical trials have reported reduced cognitive decline with statin use, with notable improvements in some cognitive domains such as memory and verbal fluency. Other trials (44.4%) claimed no significant associations between cognitive function with statin use and only one trial identified minor decrements in cognitive functioning with statins.[47] However, many (92.6%) of these trials were of short duration (≤3.2 years) with the majority of trials having relatively low participant numbers.

In a study of asymptomatic middle-aged adults at increased risk for AD, subjects that were treated for four months of simvastatin 40 mg daily demonstrated greater improvement in some cognitive measures including: working memory, verbal fluency, construction tasks and verbal delayed free recall without significant changes in amyloid β-42 levels, compared with placebo.[48] Similarly, simvastatin use was also linked with a slower progression of AD symptoms over a 26-week trial (n=44). Nonetheless, authors of both studies indicated the need for larger trials with longer follow-up.[48,49]

A pilot proof-of-concept trial noted positive effects on the progression of cognitive and behavioural decline in participants with mild to moderate AD after a minimum follow-up of 3 months with atorvastatin use.[50] However, the positive effects are only evident in patients with elevated cholesterol levels. Furthermore, another RCT also showed that there were beneficial effects in various neurocognitive tests of atorvastatin in a dose of 10 mg daily for a 6-month duration, compared with placebo group.[51] Both studies, regrettably were short in duration, with trials of longer duration more likely to produce benefits on cognitive function.

The Alzheimer's Disease Cooperative Study found no link between simvastatin use and AD symptom progression after 18 months despite significant lowering of cholesterol and a dosage up-titration after 6 weeks.[52] In addition, no association between 80 mg atorvastatin and global functioning or cognition in mild to moderate AD patients (n=640) could be determined by The Lipitor's Effect in Alzheimer's Dementia (LEADe) study over the same duration.[53] A post-hoc analysis of Galantamine Clinical Trials was also unable to determine any differences in cognitive function between statin users and non-users(n=669). Participants, however had AD at baseline and were of advance age (mean age: 75.1).[54]

Moreover, the Prospective Study of Pravastatin in Elderly at Risk (PROSPER) trial, a large RCT examining

5,806 participants aged from 70 to 82 with pre-existing vascular disease or an increased risk could not associate 40 mg per day of pravastatin use with cognitive decline.[55] Nevertheless, it notably did not measure cognitive function as a primary outcome and followed participants for a relatively short period of time (3.2 years).

Interestingly, in a trial consisting of 283 hypercholesterolemic participants, a slight decline in neuropsychological performance was observed in the group taking 10 or 40 mg simvastatin, compared with placebo.[56] Still, this trial was short in duration (6 months) with the neuropsychological battery being chosen to be sensitive to the changes expected in response to statin use. Given that only few trials have reported such findings and the study was small in size (only 189 participants were taking simvastatin), further investigation is essential.

CASE-CONTROL RESEARCH

Almost 86% of the included case control studies (6 out of 7) reported positive associations in relation to statin use, with statin use associated with reduced prevalence of AD and dementia. Two of the case-control studies relied upon neuropsychological battery to measure changes in cognition, with the remainder (n=5) utilizing probable AD and dementia diagnosis as outcome measures. Improvements in episodic memory function, and reduced AD and dementia were observed in statin users compared with non-users in 6 studies. Only one study noted no significant changes or improvement of cognition for statin use.[57]

In the case-control study that has the largest number of participants (9,257) from Taiwan, the dementia risk decreased by 9% per year of treatment with statins (adjusted odds ratio = 0.91; 95% confidence interval, 0.85-0.97). It was also observed that the use of high average dose statins for more than 1 year was associated with a lower risk of dementia than use of low average dose. However, there was no substantial difference in risk of dementia between lipophilic and hydrophilic statin users. Nevertheless, the accuracy of the dementia diagnosis in the National Health Insurance Research Database (NHIRD) was not yet validated at the time of the study. As the claims database reflected more common daily practice involving primary physicians, it was likely that dementia would only be diagnosed when it caused significant functional impairments. Thus, less severe cases might not be identified, resulting in the underrepresentation of those with milder cognitive dysfunction, who were likely to be misclassified as normal. Misclassifying mild cases as controls would have the consequence that the association between statin use and reduced dementia risk could be underestimated.[58]

Similarly, analysis of the Canadian Study of Health and Aging revealed a reduced risk of cognitive impairment and dementia in statin and lipid-lowering agent users compared with controls. Nevertheless, this result should be treated with caution as the number of statin users was small (0.74%).[59] In another study that has a small sample size (n=37), statin use duration was associated with improved episodic memory based upon Word List Learning and Word list Delated Recall tests, with a more pronounced effect was seen with use longer than the median duration of 15.3 years (adjusted OR 2.59, 95% CI) after adjustment for confounders. Participants were recruited for the Familial Hypercholesterolemia (FH) North Karelia mutation and subsequently were not randomised.[60] Hajjar and colleagues also found similar results in participants with hypercholesterolemia where statin use was associated with reduced dementia and AD prevalence over a short follow-up of 10.6 months. Statin users also experienced improvements in global function (MMSE) (p=0.025) compared with controls.[61]

Case-controls studies appear to indicate that statin use contributes to a better cognitive outcome. However, most of the included studies had small sample sizes (only 3 studies had more than 1,000 subjects) with cognitive changes based upon self-report rather than clinical assessments. Moreover, the indication bias and lack of consideration of comorbidities were the common limitations in the case-control studies. Future research should examine adverse cognitive effects associated, with comprehensive neuropsychological assessments and large sample sizes necessary to support these findings.

Meta-Analysis

Twenty-one studies were included in the meta-analysis and they were all either longitudinal (n=7), RCTs (n=13) or cross-sectional studies (n=1). All the studies provided standardised mean differences for the effect of statins on cognition or cognitive decline via standard neuropsychological measures.

Statins on Cognition

For this meta-analysis, the impact of the duration of statins studies follow-up on cognition were examined. They were stratified into two groups: duration of follow-up with <5 years and ≥5years. In the first group (duration of <5 years) with 15 studies, the meta-analysis of statin studies provided a meta-estimate of the standardised mean difference between statin users and non-user SMD = 0.05 (95% CI -0.02 to 0.12, p=0.19) point. For the second group (duration of ≥5 years) with 5 studies, similar to the initial result, the meta-analysis revealed a SMD = -0.30 (95% CI -0.81 to 0.20, p=0.24). In addition, there was no association between type of statin used and cognition. Results of the meta-analysis have been summarized in a forest plot (Figure 2 and Figure 3).

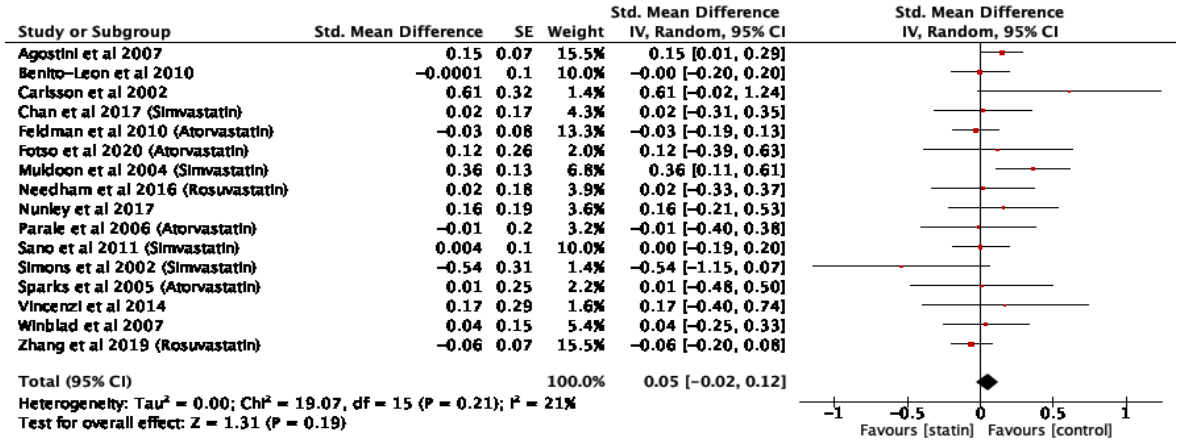

Figure 2: Forest plot for the standardised mean differences (SE) with 95% CI of statin studies duration of <5 years on cognition. Only studies with a specific type of statins used are labelled.

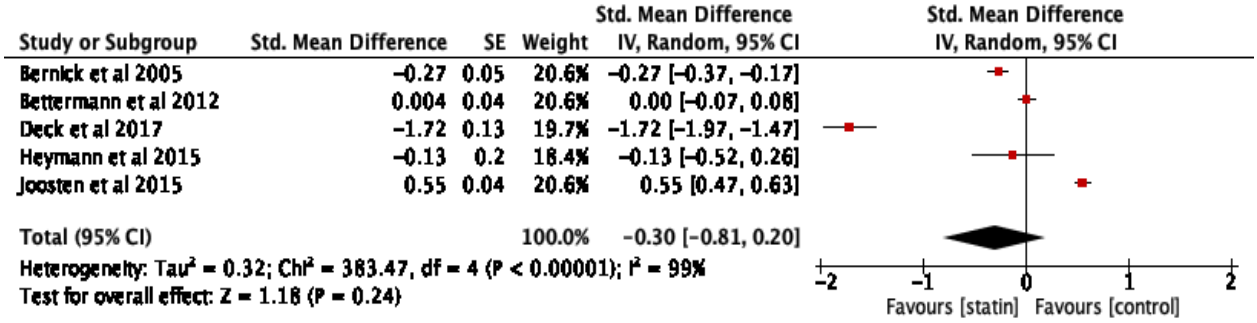

Figure 3. Forest plot for the standardised mean differences (SE) with 95% CI of statin studies duration of ≥5years on cognition.

Sex differences

We were also curious about the disparity of cognition in different genders, for this meta-analysis, there was insufficient information to stratify the cognitive outcome based on sex, therefore, we grouped studies based on the percentage of included males and females. Interestingly, we realised that statins studies that showed stronger association between effects of statins on cognition were comprised of predominantly male (≥70%) cohorts, in our case, the meta-analysis revealed a 0.13 (95% CI 0.00 to 0.25, p=0.04) point favouring a better cognitive outcome for non-statin users. Results of the meta-analysis have been summarized in a forest plot (Figure 4). In fact, there was no difference observed in mixed cohorts with roughly similar male: female ratio (Supplementary 3-4). This suggests that the reported significant association between statins and cognition in the statin studies were actually mainly caused by male statin users.

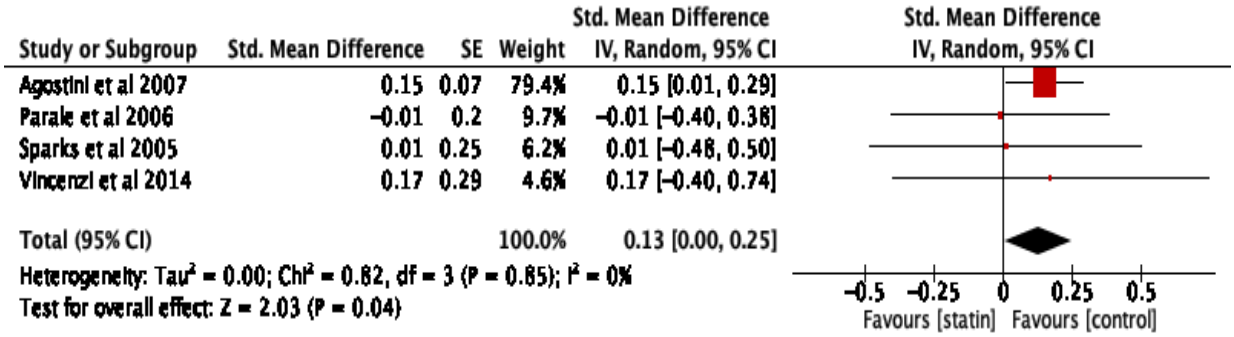

Figure 4: Forest plot for the standardised mean differences (SE) with 95% CI of statin studies with ≥70% of male population on cognition.

DISCUSSION

Status of current research

The majority of case-control studies have associated statin use with reduced cognitive decline, and prevalence of AD and dementia in late-life participants. Of 97 reviewed studies, 55 reported positive associations between statin use and reduced cognitive decline. However, few studies have examined the association

between statin use and cognitive decline in participants under the age of 65 (during midlife).

Positive findings were also apparent in more than half (51.9%) of the included randomized controlled trials and 44.4% of the trials demonstrated no significant relationship between statin use and cognitive function. Despite higher levels of function being observed in some cognitive domains, for example, verbal fluency and memory recall, many of the trials reporting such findings had small participant numbers and were short in duration (≤3.2 years). Nevertheless, conducting larger trials may be impractical, given potential costs and contingencies involved.

Moreover, mixed outcomes were reported in the included cross-sectional studies. Houx and colleagues explained that many follow up studies involving cognition in medical settings have been less successful than they might have been. One important reason for this can be found in, possibly related to the choice of the neuropsychological tests used. In many cases, MMSE is the only test that is used. It is normally used as the standard cognitive screening instrument in virtually all studies involving the elderly population and cognition, but for reasons specified below, it is not very suitable in follow up studies. It aims at screening various areas of cognition, including crystallised functions, which are unlikely to change. Moreover, the MMSE aims at screening cognitive functions in people suffering from or at risk for dementia.[62]

Additionally, in Swiger and colleagues' systematic review and meta-analysis, short term data show an absence of adverse events of statins on cognition while long term data encourage a beneficial role of statins in the prevention of dementia.[6] Our own meta-analysis results, in fact, showed no impact in both short and long term data. The reason behind this discordance between reports and trial results might be that cognitive adverse events are more prone to happen at high statin doses, which comprises only less than 20% in clinical practice.[63] Other considerations such as constitutional differences in drug metabolism, drug interactions[64] and ingestion of grapefruit can cause higher statin blood levels and subsequent adverse outcomes.[9] In addition, solubility of different statins in water versus lipid, genetic variance, differential response and sex differences could contribute to various mixed results.[65]

Furthermore, the drawback of most (67.5%) of these studies in our review had follow-up times of <5 years, thus, any long term effect on cognition might not have been detectable.[66] In fact, out of 21 studies in our meta-analysis, there was only one study that has a 10-year follow-up period. Researchers have also called on the need for long-term carefully designed longitudinal studies to be performed to resolve this controversial association. Besides, elders over 65 years of age are the largest proportion that consume statins and this is the group that are at highest risk for amyloidosis, cardiovascular and neurocognitive deficits[67]; so to establish any causal relationship between statin use and neurocognitive effects is challenging. Narrow descriptions of cognitive outcomes were used and were not intended to pick up signals of adverse cognitive events of statins.

Apart from that, our meta-analysis showed that types of statins do not appear important but we noticed that there was a gender bias in that those that showed significant association were mainly male (≥70%), thus it is difficult to generalize the findings to women. The findings of this review support the notion that statin studies should provide greater attention to female cohorts given that women differ from men with regard to brain morphology and cognition, hormonal changes in midlife, as well as the prevalence and incidence of CVD and dementia in late-life. Moreover, half of the cardiovascular events happen in low-risk women.[10] Unlike men, where the primary and secondary prevention benefits with statins have been well established, the benefits and risks of statin treatment for primary prevention remain less well defined in women.[10] Thus, questions remain about the efficacy and safety of statins to prevent CVD in women.

Gaps in current research

Many of the existing research in this field highlighted the need for long-term studies conducted from mid-life to clarify the relationship between statin use and cognitive decline.[68] Since changes in the structure and function of the brain can occur many years before the diagnosis of dementia, it has been suggested that taking statins from midlife has potential in delaying cognitive decline.[68]

Thus, the appropriate timing to commence statin therapy, dose and the duration of treatment necessary to obtain cognitive benefits should be the main focus of future research.[69] Statin use for at least ten years is believed to be required for cognitive effects to become apparent.[33] It is still unclear whether cognitive decline associated with AD and dementia may differ with exposure to long-term statin use. Besides that, studies should provide greater attention to sex differences. Statin trials are predominantly males and there are insufficient female only cohort studies. Together, these mean that questions regarding the benefits of statin in women as well as possible differential effects of statins between men and women.[70] Researchers further recommended that owing to the mentioned difficulties of conducting large trials, the performance of long-term, carefully designed observational studies rather than RCT are believed to be the most logical option to clarify the association of statin use with AD and dementia.[71]

Strengths and Limitations

Our systematic review is unique in that it provides the most comprehensive analysis of the literature to date, it provides a transparent analysis of published data organized by duration of studies and type of statins used.

It also highlights the paucity of statin studies with long duration (≥10 years) and as a result, the lack of understanding and clarity of the effects of long term statin usage on our cognition. Besides that, another strength to note is that this review managed to demonstrate that male cohorts were mainly the reason behind studies that reported significant associations between statins and cognition and it stresses the importance of focusing on female statin users or trials with female-only cohorts.

Our review of the published literature has limitations. First, our meta-analysis only includes studies that provide sufficient continuous outcomes. Second, data are sparse regarding the cognitive effect of statins at high doses, which is crucial given the increasing use of high-dose statins for secondary prevention. Third, publication bias and selective outcome reporting threaten the validity of all meta-analyses. When these biases operate, statistically significant findings are more likely to be reported in full, compared to findings of no difference and statistically nonsignificant results.

Few large clinical trials did not meet eligibility criteria for this study but warrant mentioning. Among these is the Prospective Study of Pravastatin in Elderly at Risk (PROSPER) trial, a large RCT examining 5,806 participants aged from 70 to 82 with pre-existing vascular disease or an increased risk could not associate 40 mg of pravastatin use with cognitive decline.[55] Nevertheless, it notably did not measure cognitive function as a primary outcome and followed participants for a relatively short period of time (3.2 years). Similarly, the Cache County Study of participants aged 65 or older inversely associated statin use with the prevalence of dementia at baseline (adjusted OR, 0.44, 95% CI) (n=4,895). However, a subsequent analysis after three years did not reveal a reduced onset of AD associated with statin use (adjusted OR for dementia, 1.04, 95% CI; adjusted OR for AD, 0.85, 95% CI). Nonetheless, given that the statin users constituted just 6.3% of the total cohort, reporting bias may have occurred.[42]

CONCLUSION

The findings from this systematic review and meta-analysis suggest that the mixed outcome reported could be due to the heterogeneity of the studies' design, the sensitivity of identifying minute cognitive changes by the neuropsychological tests administered, and the length of follow-up sufficiently required to detect changes in cognition. Sex differences remain important in this field with the significant difference shown in the current statin studies was mainly driven by male statin users. We did not observe significant differences between the duration of follow-up but this area is limited by only 11% of studies with duration over a decade, and few studies have shown that statin effects on cognition could take more than a decade. These findings shed light on the importance of having long-term statin studies and the urgent need to focus on female statin users.

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Declaration of Conflicting Interests

C. Szoeke: The Principal Investigator of WHAP (CSz) is supported by the National Health and Medical Research Council. Dr. Szoeke has provided clinical consultancy and been on scientific advisory committees for the Australian Commonwealth Scientific and Industrial Research Organisation, Alzheimer's Australia, University of Melbourne and other relationships which are subject to confidentiality clauses. She has been a named Chief Investigator on investigator driven collaborative research projects in partnership with Pfizer, Merck, Bayer and GE. She has been an investigator on clinical trials with Lundbeck. She may accrue revenues from patent in pharmacogenomics prediction of seizure recurrence.

T.J. Chin, S. Finch, A. Gorelik and Y. Tan declare that there is no conflict of interest.

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