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IMPACT OF STATIN USE ON COGNITIVE DECLINE IN AGEING WOMEN: A 24-YEAR LONGITUDINAL STUDY

Tze Jian Chin[1], Cassandra Szoeke[1,2]*, Alexandra Gorelik[1,3] and Ying Tan[4,5]

[1]Centre for Medical Research (Royal Melbourne Hospital), Faculty of Medicine Dentistry and Health Sciences, University of Melbourne, Parkville, VIC, Australia.
[2]Healthy Ageing Organisation, Parkville, VIC, Australia.
[3] Monash-Cabrini Department of Musculoskeletal Health and Clinical Epidemiology, Cabrini Health.
[4]Department of Mechanical Engineering, University of Melbourne, Parkville, VIC, Australia.
[5]School of Chemistry, Physics and Mechanical Engineering, Science and Engineering Faculty, Queensland University of Technology.

***Corresponding Author: Cassandra Szoeke**
Centre for Medical Research (Royal Melbourne Hospital), Faculty of Medicine Dentistry and Health Sciences, University of Melbourne, Parkville, VIC, Australia.

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ABSTRACT

Objective: Although statins are known as the first line of cholesterol treatment, how statins will affect cognition over time is not well understood and the literature is conflicting. In recent systematic reviews, it has been highlighted that only 11% of research examines more than a decade, yet data from composite reviews suggest timing is important. The existing studies have focused on short-term effect of statins on cognitive functions, mainly for men. Although women make up a large percentage of the older population, the benefits and risk of long-term statin treatment for primary prevention has not been investigated. Thus, the primary aim of this study was to evaluate the longitudinal prospective of statin use from 1992-2016 and cognitive function in healthy Australian women, and determine whether statin usage including type and duration of use modify this relationship in this 24-year follow-up period. **Methods:** 344 women (average age 58.49) from the WHAP study, were included in this analysis. Six cognitive domains (episodic memory, visuospatial, global cognitive function, speed of processing, attention and executive function) were assessed. Statin use was recorded across 24 years. **Results:** Controlling for age, education and cardiovascular risk score, statin use by women was associated with the greatest deteriorated episodic memory ($p = 0.002$) and visuospatial ability ($p = 0.02$) over time. Statin users were mostly in the low performing group compared to non-users across this 24-year period. Statin types also appear crucial as the lipophilic statins (atorvastatin and simvastatin) users demonstrated a poorer cognition than non-users ($p<0.05$) but opposite outcome were observed in the hydrophilic statin (rosuvastatin) group ($p = 0.04$). An important observation in our study was that the effect on cognition by statins may have to take ≥10 years to be apparent ($p<0.05$). **Conclusion:** We observed that independent of underlying vascular risk, statin use by women was associated with the greatest decline in episodic memory and visuospatial ability. Non statin users were also mostly seen to have a better cognition than statin users across this 24-year period. Types of statins do appear important and the effect of statins on cognitive decline could take up to many years before it is noticeable. It is important clinicians consider to mounting evidence of cognitive disturbance on initiating statins and selecting the types of statins.

KEYWORDS: Statins, women, ageing, cognition.

INTRODUCTION

Dementia is characterised by gradual cognitive decline, from memory loss to dysfunction in several cognitive domains.[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], two thirds of all dementia cases are women.[2] The 2022 Dementia Australia Prevalence Data discloses that there are currently around 487,50 people living with all forms of dementia and it is leading cause of death for women.[4] In addition, the few promising new agents have failed to show any cure for Alzheimer's disease (AD) in Phase III clinical trials.[5]

Abbreviations: AD = Alzheimer's Disease; BMI = Body Mass Index; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; CVD = Cardiovascular Disease; CVLT = California Verbal Learning Test; HDL = High-Density Lipoprotein; JUPITER = Justification for the Use of Statins in Primary Prevention; LDL = Low-Density Lipoprotein; MMSE = Mini Mental State Examination; REGARDS =

Reasons for Geographic and Racial Differences in Stroke; TG = Triglycerides; TMT = Trail Making Test; WHAP = Women's Healthy Ageing Project.

The proportion of the global population aged 60 years or older has raised from 8.6% in 1980 to 12% in 2014 and is projected to almost double by 2050 to 21%.[6] Women make up a larger percentage of the older population. In 2014, women accounted for 62% of people aged over 80. The impact of dementia/AD on women will be greater than for men. As there is very little research in any context involving women with dementia, there is a need for further studies in particular considering vascular risk given the known sex differences with vascular disease.[6]

Primary prevention studies have illustrated that statin therapy reduces the rate of cardiovascular events by ~20% but the study populations predominantly comprised of men[7], per se, restricting the ability to stratify results by sex.[7] 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.[7] 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 randomized controlled trials and observational data imply the conclusion that statins cause more side effects in women than in men.[8] In the Justification for the Use of Statins in Primary Prevention (JUPITER) study, a higher incidence of physician-reported diabetes mellitus was observed in women treated with statins compared with men.[8] Myalgia is the most well-known side effect of statin therapy which has reported in 20% of women.[7] 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.[9] Despite this, these factors have been ignored when statins prescribed.

There is also an ongoing debate on the relationship (benefits & risks) between statins and cognitive function in both short- and long-term use. Case reports raise the prospect that statins may be associated with cognitive impairment while some prospective studies demonstrate no cognitive benefits for any statin.[10] Moreover, past results are not truly convincing and many researchers have recommended a more thorough and detailed research methodology is required in order to resolve this ongoing debate.

Furthermore, researchers have shown that high total cholesterol levels in late life had a reduced risk of AD.[11] Hence, timing may be crucial. Given that women comprise up to two-thirds of all dementia sufferers, examination of female-specific cohorts and discussion of statin use by women in this field is crucial.[12] In this project, we have utilized the data from Women's Healthy Ageing Program (WHAP) with specific focus on statin use and cognition in Australian women. WHAP is the longest running study of women's health with over 24 years follow-up data and is uniquely positioned to examine the relationship between statins usage and cognitive function in Australian women from mid- to late-life.

METHODS

Cohort: Detailed methodology of WHAP cohort selection is explained elsewhere.[13] Briefly, a random cohort of Australian women from the Melbourne metropolitan area was selected by random telephone dialling in 1990, and were re-interviewed annually over eight years until 1999, then intermittently through to 2016. Participants were free of neurological conditions, such as dementia, at baseline. The WHAP exhibits a high retention rate of 52.3%, and utilises an extensive battery of validated measures covering: quality of life and ageing, cognition, cardiovascular health, musculoskeletal and bone health, and more.[13]

Demographics: Participants were included in this sub-study if they completed the 1992-2016 follow-up time point of the WHAP, and had completed health and statin intake sections of the questionnaires. Overall, 509 women completed assessments during the aforementioned period and 344 (67.58%) were included in this analysis. The remaining 165 participants were excluded due to incomplete information on neuropsychological testing.

Primary Outcome

Cognitive Assessment: A comprehensive neuropsychological battery was administered to participants between 1999 and 2016 by trained neuropsychologists. These included a simple verbal memory test from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery, Clock Drawing Test, California Verbal Learning Test (CVLT) II, Digit Span, Digit Symbol, Mini-Mental State Examination (MMSE), Trail Making Test A (TMT A) and Trail Making Test B (TMT B).

Factor

Statin Use: Participants self-reported statin use at follow-up time-points between 1992 and 2016, and recorded the name of the statin, dose taken, and frequency of use. Trained researchers cross-checked the reported statins against a medication list at each follow-up, which was then verified by a clinician.

Ever and Never Statin Use: Ever statin use was defined as a participant having reported statin use at any follow-up interviews of the WHAP between 1992 and 2016. Never statin use was defined as a participant not reporting use of statins at any follow-up.

Statin Use Duration: The duration of statin use was calculated by three different sources: from durations of use stated on a medication list completed by participants prior to clinical interviews at each follow-up between 1992 and 2016; reported use by each participant during follow-up interviews between 1992 and 2016; and cross-checking by a trained researcher.

Confounders

Clinical measures

1. **Body mass index:** The height and weight of participants were measured during clinical assessments. Height was measured with participants standing barefoot on a flat surface against a wall, and weight was measured using a digital scale on a flat surface. Body mass index (BMI) was then calculated using: weight(kg)/height(m)^2.
2. **Blood pressure:** Arterial pressure of the arm was measured with a sphygmomanometer via the auscultation method seated. The same arm was used to obtain two readings right after another for systolic and diastolic blood pressure (in mmHg) and averaged.
3. **Smoking Status:** Participants were asked the following question regarding their health behaviours: do you currently smoke cigarettes? Answers were recorded as "Yes" or "No".
4. **Education:** Years of education completed by participants was ascertained from self-report and further questioning during neuropsychological assessment. Participants were asked to state the years of primary, secondary and tertiary education they had completed.
5. **Medical and Family History:** Participants self-reported their medical history at follow-up and stated whether they currently suffer from diabetes or have suffered a heart attack. Participants were also asked to report family history of heart attacks.
6. **Lipid profile:** Blood samples were collected from participants the morning after an overnight fast. The lipid profile including total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides (TG) was measured by the Olympus AU2700 Chemistry-Immuno Analyser, which utilises colorimetric assays to determine lipid levels. Total cholesterol was determined by measurement of all lipoprotein subclasses using an enzymatic reaction between cholesterol and oxygen to form a coloured complex. HDL cholesterol levels were determined by conversion of cholesterol esters and oxygen to a quinone pigment via a direct clearance method. LDL cholesterol levels were ascertained from a basic calculation. TG levels were determined by an enzymatic reaction between triglycerides and water.

Data Analysis: Histograms and Shapiro-Wilk test were used to assess the normality of continuous outcomes. Differences between included and excluded participants as well as statin users and non-users were assessed using two-tailed independent-samples T-test for the collected data. ANCOVA was used to assess the impact of statin use on the change in cognition per year of follow-up, controlling for age, body mass index, education, LDL, HDL, triglyceride (TG), systolic blood pressure, smoking status for last 12 months, history of diabetes and family history of myocardial infarction. Least Significant Difference (LSD) was used to analyse multiple comparisons. IBM Statistical Package for Social Sciences (SPSS) software version 27.0 for Windows, SPSS Inc was used for all statistical analyses in this study.

Ethics: This study was approved by the University of Melbourne Human Research Ethics Committee (HREC:931149X, 1034765, 110525, 1339373, 010411, 1647448 & 1750632), and all participants provided written informed consent. Participants did not receive a stipend for participating in this study. The study was conducted in accordance with the National Health and Medical Council Ethical Conduct in Human Research a Declaration of Helsinki.

RESULTS

Cohort description

Five hundred and nine women were included in this analysis. Of them, 344 had complete information on statin characteristics and covariates as well as underwent ≥2 consecutive neuropsychological assessments time points from baseline in 1992 to 2016 assessments. A total of 165 participants was excluded from analysis for the following reasons: have only 1 neuropsychological assessment (n = 96), or having incomplete information on: neuropsychological assessment, statin usage or multiple variables (n = 69). Apart from age and systemic blood pressure, there was no statistically significant differences between these two groups (Table 1).

Table 1: Characteristics of the cohort comparing included and excluded participants starting from 1999 baseline (first neuropsychological assessment).

Characteristics	Total Sample (N = 509)	Included Participants (N =344)	Excluded Participants (N = 165)	p value
Age (Year)		58.49 (5.77)	61.07 (8.41)	**<0.001**
Education (Year)		11.00 (2.83)	12.63 (3.40)	0.07
Body mass index (kg/m^2)		27.00 (5.18)	27.79 (5.97)	0.20
LDL (mmol/L)		3.73 (0.94)	3.68 (1.06)	0.70
HDL (mmol/L)		1.46 (0.42)	1.41 (0.71)	0.43
TG (mmol/L)		1.31 (0.86)	1.39 (0.75)	0.46
Systemic blood pressure (mmHg)		127 (16)	133 (19)	**0.004**

Note: Data reported as average mean (SD). Independent-samples T test was used to analyse the data. Abbreviations: HDL = High-Density Lipoprotein; LDL = Low-Density Lipoprotein; TG = Triglycerides

General outcome of statin users against non-users

The changes in six different cognitive domains per year of follow-up were examined starting from the first neuropsychological assessment in 1999 to the endpoint of this study in 2016. There were two cognitive domains that caught our attention. First, we noticed that non statin users had an improved cognition per year of follow-up (0.08, 95% CI 0.04, 0.11) in visuospatial domain while statin users exhibited a decline visuospatial (-0.003, 95% CI -0.06, 0.05) (Table 2). Second, in episodic memory which was tested by using CVLT-II, both groups displayed an improved cognition but non-users performed significantly better than statin users (mean difference: 0.08, 95% CI 0.03, 0.13). There was no significant association observed between the comparisons of statin users and non-users in executive function, speed of processing, attention and global cognitive function.

Table 2: ANCOVA results showing the adjusted mean scores for changes in cognition per year of follow-up between non-users and statin users across the years starting from baseline in 1999 to 2016.

Cognitive Domains (Test)	Change in cognition per year of follow-up, Mean (95% CI)		Mean Difference (95% CI)	p value
	Non-Users (N=225)	Statin Users (N=96)		
Visuospatial (Clock Drawing)	0.08 (0.04, 0.11)	-0.003 (-0.06, 0.05)	0.08 (0.01, 0.15)	**0.02**
Episodic Memory (CERAD)	-0.15 (-0.17, -0.14)	-0.13 (-0.16, -0.11)	-0.02 (-0.05, 0.01)	0.21
Episodic Memory (CVLT-II)	0.16 (0.13, 0.18)	0.08 (0.04, 0.12)	0.08 (0.03, 0.13)	**0.002**
Speed of Processing (Digit Symbol)	0.72 (0.64, 0.82)	0.58 (0.45, 0.71)	0.15 (-0.02, 0.32)	0.07
Executive Function (TMT B)	1.10 (0.79, 1.42)	0.52 (0.05, 0.99)	0.58 (-0.02, 1.18)	0.06
Executive Function (TMT A)	0.21 (-0.11, 0.53)	0.61 (0.11, 1.11)	-0.40 (-1.04, 0.24)	0.22
Attention (Digit Span Backward)	0.001 (-0.02, 0.02)	0.01 (-0.01, 0.03)	-0.01 (-0.04, 0.02)	0.5
Global Cognitive Function (MMSE)	-0.03 (-0.09, 0.03)	-0.08 (-0.18, 0.01)	0.06 (-0.06, 0.17)	0.35

Note: Means are adjusted for age, body mass index, LDL, HDL, TG, systolic blood pressure, smoking status for last 12 months, history of diabetes and family history of myocardial infarction. Executive function was tested by the amount of time used to complete TMT A and TMT B. Abbreviations: CERAD = Consortium to Establish a Registry for Alzheimer's Disease; CVLT = California Verbal Learning Test; HDL = High-Density Lipoprotein; LDL = Low-Density Lipoprotein; MMSE = Mini Mental State Examination; TMT = Trail Making Test; TG = Triglycerides.

Types of Statins

We observed that the types of statins seemed to influence the cognition differently. In executive function which was tested by the amount of time used to complete TMT A, atorvastatin users required significantly greater time to complete the test compared to non-users (mean difference: -1.20, 95% CI -2.04, 0.37), however, non-users had more consistent executive function throughout the follow-up (p=0.005) (Table 3). Similar results were also observed in global cognitive function in which non-users recorded a better change of cognition per year of follow-up compare to simvastatin users (0.22, 95% CI 0.01, 0.44). On the other hand, in contrast to the two lipophilic statins above that displayed a worse cognition compared to non-users, rosuvastatin (hydrophilic statin) users seemed to have a slight improvement in their attention compared to non-users as they recorded a significantly better change in score throughout the follow-up (0.05, 95% CI 0.002, 0.11). There was however, no significant association found between the three main types of statin users (atorvastatin, simvastatin, rosuvastatin) and non-users in visuospatial, episodic memory and speed of processing.

Table 3: ANCOVA results showing the adjusted mean scores for changes in cognition per year of follow-up between non-users and types of statins across the years starting from baseline in 1999 to 2016.

Cognitive Domains (Test)	Change in cognition per year of follow-up, Mean (95% CI)				p value
	Non-Users (N=225)	Atorvastatin (N=35)	Simvastatin (N=20)	Rosuvastatin (N=27)	
Visuospatial (Clock Drawing)	0.07 (0.03, 0.10)	0.01 (-0.08, 0.09)	-0.05 (-0.17, 0.07)	0.06 (-0.05, 0.16)	0.25
Episodic Memory (CERAD)	-0.15 (-0.17, -0.14)	-0.16 (-0.20, -0.12)	-0.16 (-0.22, -0.10)	-0.11 (-0.16, -0.06)	0.46
Episodic Memory (CVLT-II)	0.15 (0.01, 0.12)	0.01 (0.03, 0.16)	0.09 (0.001, 0.18)	0.10 (0.02, 0.19)	0.38
Speed of Processing (Digit Symbol)	0.69 (0.61, 0.77)	0.71 (0.50, 0.91)	0.48 (0.19, 0.76)	0.92 (0.65, 1.19)	0.16
Executive Function (TMT B)	1.05 (0.75, 1.35)	0.56 (-0.18, 1.31)	1.80 (0.77, 2.84)	0.14 (-0.80, 1.07)	0.08
Executive Function (TMT A)	0.10 (-0.20, 0.40)**	1.30 (0.54, 2.06)**	0.81 (-0.31, 1.94)	0.27 (-0.80, 1.33)	**0.04**
Attention (Digit Span Backward)	0.00 (-0.02, 0.02)*	1.30 (-0.04, 0.03)	0.81 (-0.06, 0.05)	0.27 (0.01, 0.10)*	0.20
Global Cognitive Function (MMSE)	-0.05 (-0.10, 0.01)*	0.04 (-0.09, 0.18)	-0.27 (-0.47, -0.07)*	0.11 (-0.08, 0.29)	**0.03**

Note: Means are adjusted for age, body mass index, LDL, HDL, TG, systolic blood pressure, smoking status for last 12 months, history of diabetes and family history of myocardial infarction. Executive function was tested by the amount of time used to complete TMT A and TMT B. Abbreviations: CERAD = Consortium to Establish a Registry for Alzheimer's Disease; CVLT = California Verbal Learning Test; HDL = High-Density Lipoprotein; LDL = Low-Density Lipoprotein; MMSE = Mini Mental State Examination; TMT = Trail Making Test; TG = Triglycerides

** denotes values for p = 0.005 between comparisons of 2 groups

* denotes values for p = 0.04 between comparisons of 2 groups

Duration of Statin Usage

Non-users had an almost consistent visuospatial score throughout the follow-up (0.07, 95% CI 0.04, 0.10) but users with ≥10 years of statin usage illustrated a significant decline (-0.07, 95% CI -0.16, 0.03) instead. Furthermore, it was also observed that statin users of any duration appeared to have a poorer episodic memory (CVLT-II) and lower speed of processing scores compared to non-users (Table 4). Interestingly, TMT A and TMT B, the two tests that were used to assess executive function provided contradicting results. Although both tests showed a decrease in the cognition for both groups, TMT A showed that those who took statin for ≥10 years had a significantly greater decline in TMT A than non-users (mean difference: -1.77, 95% CI -2.70, -0.85) whereas TMT B showed that those who took statin for <10 years had a significantly slower drop than non-users (1.01, 95% CI 0.35, 1.67). No significant association was observed between non-users and statin users of any duration in attention and global cognitive function (Table 4).

Table 4: ANCOVA results showing the adjusted mean scores for changes in cognition per year of follow-up between non-users and users with <10 years & ≥10 years of statin consumption across the years starting from baseline in 1999 to 2016.

Cognitive Domains (Test)	Change in cognition per year of follow-up, Mean (95% CI)			p value
	Non-Users (N=225)	Users (<10 years) (N=52)	Users (≥10 years) (N=41)	
Visuospatial (Clock Drawing)	0.07 (0.04, 0.10)*	0.05 (-0.02, 0.11)	-0.07 (-0.16, 0.03)*	**0.03**
Episodic Memory (CERAD)	-0.15 (-0.17, -0.14)	-0.13 (-0.16, -0.10)	-0.15 (-0.20, -0.11)	0.48
Episodic Memory (CVLT-II)	0.15 (0.12, 0.18)*	0.09 (0.05, 0.14)	0.07 (-0.01, 0.14)*	0.05
Speed of Processing (Digit Symbol)	0.73 (0.64, 0.82)*	0.54 (0.39, 0.70)*	0.63 (0.40, 0.86)	0.14
Executive Function (TMT B)	1.10 (0.80, 1.41)*	0.09 (-0.46, 0.65)*	1.07 (0.24, 1.90)	**0.007**
Executive Function (TMT A)	0.17 (-0.15, 0.48)**	0.10 (-0.51, 0.70)	1.94 (1.11, 2.77)**	**<0.001**
Attention (Digit Span Backward)	0.003 (-0.01, 0.02)	0.02 (-0.01, 0.05)	-0.02 (-0.07, 0.02)	0.25
Global Cognitive Function (MMSE)	-0.04 (-0.10, 0.02)	-0.01 (-0.12, 0.11)	-0.17 (-0.32, -0.01)	0.21

Note: Means are adjusted for age, body mass index, LDL, HDL, TG, systolic blood pressure, smoking status for last 12 months, history of diabetes and family history of myocardial infarction. Executive function was tested by the amount of time used to complete TMT A and TMT B. Abbreviations: CERAD = Consortium to Establish a Registry for Alzheimer's Disease; CVLT = California Verbal Learning Test; HDL = High-Density Lipoprotein; LDL = Low-Density Lipoprotein; MMSE = Mini Mental State Examination; TMT = Trail Making Test; TG = Triglycerides

** denotes values for p<0.001 between comparisons of 2 groups

* denotes values for p<0.05 between comparisons of 2 groups

DISCUSSION

Our general findings of the poorer episodic memory by statin users are consistent with numerous previous studies that had reported similar effects of statins using similar neuropsychological test.[14] On the other hand, our visuospatial results which demonstrated that non

statin users were seen to have an improved cognition per year of follow-up while statin users exhibited a decline were in contrast with Hajjar and colleagues'.[15] study that also used 'Clock drawing' to access visuospatial domain. However, their study was short in follow-up (<12 months) compared to us (24 years) per se, unable to examine any long term effect of statin use.

In the analysis of type of statins and cognition, we observed that the types of statins seemed to influence the cognitive domains differently. Both lipophilic statins (simvastatin and atorvastatin) users recorded a worse cognition in global cognitive function and executive function respectively. On the contrary, rosuvastatin, a hydrophilic statin, seemed to slightly improve the users' attention throughout the follow-up compared to non-users. These results were also observed and reported by other studies.[16] Furthermore, in a population-based retrospective cohort in UK that recruited 465,085 participants, researchers noticed that fungus-derived statin (simvastatin) and lipophilic statins (atorvastatin and simvastatin) were associated with an increased risk of Alzheimer's disease (AD) compared to hydrophilic statin (rosuvastatin).[17] Van der Most.[18] also mentioned that several in vitro studies reported that statins, especially lipophilic statins are actually neurotoxic and induce cell death in glia and neurons. It has also been argued that the benefits of lipophilic statins may transcend into diverse adverse outcomes due to their easy penetration into extrahepatic tissues. Additionally, it has been thought that lipophilic statins could induce a higher risk owing to their increased ability to cross the blood-brain barrier, potentially reducing cholesterol level below the level needed for normal cognitive functioning.[19] Nonetheless, solid evidence is still lacking in this area.[20] Meanwhile, for rosuvastatin, it had also been reported to be able to significantly alleviate the cognitive impairment progression and the risks of dementia in patients in some studies.[21]

Besides that, our results also suggested that the negative impact on cognition by statin use could actually take years, in our case ≥10 years, to be evident, particularly on visuospatial, episodic memory and executive function. An important point raised in Pittsburgh Epidemiology of Diabetes Complications Study by showing that 7-12 years of statin use has enormous implication on people's functional status and quality of life since the odds of cognitive impairment almost quintupled in this group compared to non-statin users.[22] Power and colleagues explained that changes in the structure and function of the brain can occur many years before the diagnosis of dementia in their systematic review and methodological commentary.[23] In a patient survey-based analysis from 171 patients, Evans and Golomb also concurred with the idea that statin use for at least ten years is believed to be required for cognitive effects to become apparent.[24]

Pathophysiological mechanisms

Besides controlling the production of cholesterol, statins also stop the synthesis of downstream isoprenoids and mevalonate which seems to give rise to the effects of statins on neurological disorders.[25] When statins are administered in doses sufficient to compromise the synthesis of cholesterol, it is inevitable that the synthesis of CoQ10, dolichols and other vital biochemicals will be compromised as well.[26] Graveline.[27] further elaborated that the diminished bioavailability of intracellular CoQ10 and dolichols associated with the use of statins has the potential for seriously increasing oxidative damage and mitochondrial mutations. The anti-inflammatory benefits of statins are mediated by their special effect on the NF-kB cellular transcriptases and aggravated by inhibition of such antioxidants as CoQ10. The logical consequence of this is premature ageing and the progressive development of such chronic condition of aging such as incoordination and faulty memory which are seen in tens of thousands of statin users. It was reported that CoQ10 was present in very low concentrations in plasma and platelets from Parkinson's disease (PD) patients compared with non-PD controls.

Another notable effect of statin is the retardation on the prenylation of small G proteins.[25] such as Rho, Rac, Rab and Ras which may have deleterious consequences.[28] Multiple mechanisms have been linked to statins' neurotoxic effects via inhibiting proteasome activity and inducing degeneration, prompting apoptosis through the mitochondrial pathway via the activation of caspase-9 as initiator and caspase-3 as effector.[29] As a result, even though in many instances the beneficial effects of statins have been correlated with lessened levels of isoprenoids, there is also evidence that such reduction may lead to neurotoxicity.[30] Besides that, atorvastatin treatment at high concentrations has been demonstrated to inhibit neurite growth and proliferation as well as to reduce the viability of differentiated neuroblastoma NB2a cells.[31] In fact, HMG-CoA reductase inhibition by atorvastatin has also been shown to cause neurite loss by interfering with GGPP production in cultured neurons.[32] Apart from that, in neuronal membranes, statins have been observed to lower the number of synapses and impair synaptic vesicle release.[33] and decreases evoked post synaptic currents.[34] Nevertheless, the real mechanism by which statins might exacerbate cognitive functions is still unidentified.[35]

Age effects

Apart from the statins effects, it is generally known that aging results in change in drug pharmacodynamics and pharmacokinetics, so therapeutic effects may at times be augmented. Only bioavailability stays almost unchanged, because simultaneously slower absorption (among others owing to pH lowering, diminishing of mucous cells, debility of gastric contractility), a time of absorption intensifies (as a result of peristalsis).[36] Pharmacokinetics relies on body composition, albumin concentration, liver

metabolism and drug elimination, all of which may change with age. This may cause an elevation of drug concentration in elderly patients, increasing the side-effect risk.[36]

In addition, at least some degree of memory loss is inevitable in the age group of many people taking statins.[37] The authors in REGARDS study elaborated that there were a number of factors that could affect the association between statin use and cognitive impairment including raising age, geographic location, vascular disease and so on.[38] During aging, hippocampal cholesterol synthesis decreases but total cholesterol brain contents remain stable.[39] Additionally, a significant problem in elderly patients is the simultaneous use of many medications. It is estimated that two-drug therapy caused an interaction in 5.6% of patients, whereas five drugs interacted in 50% of patients and eight drugs interacted in all cases examined.[36]

We would like to emphasise that even though it is undeniable that natural aging is definitely one of the causes for the poorer cognitive scores recorded by the participants, however, the age factor was fully considered and adjusted in our results and it is still clear that statin is the factor that causes the worse cognitive outcomes as shown in our results.

Impact of neuropsychological tests used

We also noticed that the outcomes varied between different cognitive domains or different cognitive tests used. For example, our general results showed that there was significant difference between statin users and non-users in episodic memory and visuospatial but not in other cognitive domains. Muldoon and colleagues[40] explained that this is because standard neuropsychological tests try to split up cognitive function into its component processes but the separations are imperfect and individual tests actually assess more than one skill. Therefore, the observed treatment effects on cognitive function may not be selective for a particular domain.

Furthermore, the practice or learning effect as repeated testing in such a short time allows individuals to form lasting connections between items or blocking information together which can help with memory retention and schema recall are common.[41] Tao, Yang and Liu.[42] also noticed a similar trend in their studies where they observed that the cognitive test scores showed a significant learning effect in which the scores of various cognitive tests increased with the number of repetitions. Therefore, the practice or learning effects can obscure small or modest drug effects.[16]

Moreover, in episodic memory, our results demonstrated that non statin users generally recorded a significantly better cognitive scores than statin users in CVLT but not in CERAD. Even though both tests evaluate similar aspects of verbal episodic memory, most notably recall, encoding and recognition, crucial differences present regarding test construction and demands. The CVLT was constructed to test a wider range of verbal episodic memory-associated functions and is considered more demanding than CERAD.[43] It is also believed that CVLT may be more sensitive to subtle memory impairments than CERAD.[44] Hence, this emphasize the importance of selecting the appropriate neuropsychological tests in order to obtain a valid and reliable cognitive outcome.

Strengths and Limitations

To the best of our knowledge, this is the first epidemiological study to investigate the association between midlife statin use and late-life cognitive functioning in a female-specific cohort. Other strengths of current work include long period of follow-up that will enable analysis of within and between individual changes in CVD risks and cognition. However, a longer length of follow-up comes with attrition in participants, resulting in a reduced sample size and possible participation bias. Nevertheless, our dropout rate across 24 years is just 50% and it is actually a strength if compare to other studies since most of the studies have 50% attrition rate in just a 10-year-period. The detailed dataset did allow for adjustment for confounding variables and the employment of clinical standardized neuropsychological tests that have been demonstrated to be sensitive to CVD and age effects, and the availability of complete information on environmental, behavioural and clinical characteristics measured over a twenty-four-year period verified by trained researchers, providing us the ability to adjust for a wide array of covariates that may affect the relationship between statin use and cognitive functioning.

There are, however, some methodological limitations that need to be addressed. As in any cohort of long duration, those participants remaining in the follow-up were younger than those who were excluded. Younger participants are less likely to experience cognitive decline and dementia than older people due to a greater cognitive reserve.[1] suggesting a potential selection bias. As WHAP is a women-specific study, findings may not be generalizable to men. In addition, in comparison to the women in the Melbourne metropolitan population in the same age range, more women in the study cohort have completed secondary school (24% vs 42%).[45] Therefore, the study cohort represents more educated women and findings in the study may not be representative of the general population of women. Moreover, findings of this study are only directly applicable to Australian Caucasian women who immigrated to Melbourne prior to 1990.

Another point to highlight is that the MMSE, a standard neurocognitive test was selected as the cognitive assessment tool since MMSE is usually the only test that was used in numerous studies. It is normally used as the standard cognitive screening instrument in virtually all

studies involving the elderly population and cognition with excellent test-retest and inter-rater reliability.[21] The MMSE aims at screening cognitive functions in people suffering from or at risk for dementia.[46] that assesses orientation, attention, immediate and short-term recall, language, and ability to follow verbal and written commands. It has eleven main questions and is therefore practical to use serially and routinely.[47] However, the MMSE is also very insensitive to change. The observations that there were consistent significant differences in scoring between groups in our analysis, despite its lack of sensitivity suggests the observations were real.

Future goals

In summary, the experimental evidence indicates that independent of underlying vascular risk, statin use by women was associated with greatest deteriorated episodic memory and visuospatial domain. Non statin users were also mostly seen to have a better cognition than statin users across this 24-year period. Besides that, statin types also appear crucial as the lipophilic statins (atorvastatin and simvastatin) users demonstrated a poorer cognition than non-users but opposite outcome were observed in the hydrophilic statin (rosuvastatin) group. Our results are intriguing, as they indicate that the effect on cognition by statins may have to take years to be apparent. Thus, this study also managed to answer the calls of needing an extensive duration (≥10 years) of longitudinal studies. Clinical implications are relevant given types of statins have such impacts on cognition not just in our study but also others. In addition, even though some of the effects may be minor, they could affect performances on tasks like automobile driving which requires the integration of a broad array of cognitive abilities.[40]

Future studies should expand this work to examine the impact of statins in other groups. In addition, as observational studies often only assess more general associations which may prevent the detection of effects that are specific and considering 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, lifespan studies of statin usage on the cognition with a longer follow-up (≥20 or 30 years) are required to detect these age-associated differences in middle and older age adults. Future statin studies, especially longitudinal studies, should also consider the most appropriate neuropsychological tests that are sensitive enough to pick up minute cognitive changes. Last, a proper extension of this research would entail an evaluation of the effects of statins on the performance of tasks that impose complex cognitive demands that are analogous to situations faced in daily life.[40]

CONCLUSION

We observed that independent of underlying vascular risk, statin use by women was associated with the greatest decline in episodic memory and visuospatial domains over 24 years. This effect was statistically significant only after 10 years of statin use. Non statin users were also mostly seen to have a better cognition than statin users across this 24-year period. Types of statins do appear important and the effect of statins on cognitive decline could take up to many years before it is noticeable. To our knowledge, this is the first work examining 24 years of statin use on women with concurrent cognitive decline over decades. Further work should explore the cognitive impacts of treatment. It is important clinicians consider to mounting evidence of cognitive disturbance on initiating statins and selecting the types of statins.

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Author contributions

CS: study concept and design
TJC, CS, AG: data acquisition and analysis
TJC, CS, AG, YT: drafting the manuscript and figures
CS: PhD Supervisor first author

Potential Conflicts of Interest

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.

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