wjpmr, 2023,9(7), 16-26

SJIF Impact Factor: 5.922

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Research Article

ISSN 2455-3301

WJPMR

IMPACT OF STATIN USE ON COGNITIVE DECLINE IN AGEING WOMEN

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.

Article Received on 24/04/2023 **Article Revised on 14/05/2023** **Article Accepted on 04/06/2023**

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 scattered. At the same time, one in three women will develop dementia in their lifetime. The primary aim of this study is to evaluate the longitudinal prospective of statin use from 1992-2012 and cognitive function in healthy Australian women, and determine whether statin dose, type and duration of use modify this relationship on final time point in 2012. **Methods:** 240 women (average age 70.03) from the WHAP study, were included in this analysis. Cognitive function was assessed using the Mini Mental State Examination (MMSE). Statin use was recorded across two decades. **Results:** Adjusted MMSE score for current statins users were significantly lower when compare to non-users ($p = 0.009$). Those recently commencing a statin (treatment for 1-4 years) were more likely to be in the low performing group for global cognition. We also found users with inconsistent dosages (dose or type switching) had lower adjusted MMSE score compared to non-users ($p = 0.033$). Non-consistent or newly initiated use of statins resulted in reduced cognition while compared to persistent long-term use or no use at all ($p = 0.012$). **Interpretation:** We observed that independent of underlying vascular risk, current statin users, initiation of statin use by women (1-4 years of use) was associated with the greatest deterioration in MMSE. This effect is not simply reflective of the lipid levels in the women.

KEYWORDS: Statins, women, ageing, cognition.

Abbreviations: AD = Alzheimer's Disease; ADCLT = Alzheimer's Disease Cholesterol-Lowering Treatment; BMI = Body Mass Index; CVD = Cardiovascular Disease; HDL = High-Density Lipoprotein; LDL = Low-Density Lipoprotein; LEADe = The Atorvastatin/Donepezil in Alzheimer's Disease Study; MMSE = Mini Mental State Examination; PD = Parkinson disease; STOMP = The Effect of Statins on Skeletal Muscle function and Performance; TG = Triglycerides; WHAP = Women's Healthy Ageing Project

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] In Australia, dementia is the second leading cause of death.[3] and the leading cause of death for women.[3] Despite these high and increasing prevalence rates, there is no curative treatment for Alzheimer's disease (AD).[4] Current available medications for AD and dementia have comparatively small effect sizes and do not noticeably change disease progression.[5] In addition, the few promising new agents have failed in Phase III clinical trials.[6]

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%.[7] 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.[7]

Statins are among the most prescribed drugs globally with an estimated 25% of the world population older than 65 years presently under statin therapy and the numbers increasing.[8] In addition to secondary prevention, randomized controlled trials and meta-analyses have demonstrated a benefit of statins in lessening morbid and mortal cardiovascular events in seemingly healthy individuals as well as those with clinically evident cardiovascular disease.[9] According to the current ACC/AHA guideline, almost all patients with prior ACS events, and/or clinical atherosclerotic cardiovascular disease (ASCVD) or otherwise deemed to be a high risk like those with diabetes, require a statin for secondary prevention.[10]

It is not only cardiovascular disease that can be improved. Statins decrease stroke and coronary events by ~20% in high-risk women but half of the CV events happen in low-risk women.[11] 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.[11] 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.[11] per se, restricting the ability to stratify results by sex.[11] 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.[11] 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.[11] 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.

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.[16] Thus, the long-term effects of statins on cognitive function is yet to be fully understood. 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.

In addition, researchers have also shown that high mid-life and not late life total cholesterol is responsible for the increased risk of AD.[17] whereas high total cholesterol levels in late life had a reduced risk of AD.[18] 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.[19] In this project, we specifically focus on statins in women in the longest running study of women health in Australia. Women's Healthy Ageing Program (WHAP) has over 20 years follow-up data and is uniquely positioned to examine the relationship between statins usage, lipids and cognitive function in Australian women from mid- to late-life with consideration of type, dosage and duration of treatment.

METHODS

Cohort. Detailed methodology of WHAP cohort selection is explained elsewhere.[20] 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 2012. 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.[20]

Demographics. Participants included in this sub-study were those who completed the 2012 follow-up time point of the WHAP and had completed health and statin intake sections of the questionnaires. In 2012, 341 women (age 66-77) were contacted to participate in a late-life health study, of whom 262 (76.83%) consented with 252 completed assessments. Of these, 240 (95.24%) were included in this analysis, and 12 participants were excluded due to incomplete information on neuropsychological testing.

Clinical measures

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.

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.

Smoking Status. Participants were asked the following question regarding their health behaviours: do you currently smoke cigarettes? Answers were recorded as "Yes" or "No".

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.

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.

Lipid profile. Blood samples were collected from participants the morning after an overnight fast. The lipid profile including total cholesterol, LDL cholesterol, 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.

Statin Use. Participants self-reported statin use at follow-up time-points between 1992 and 2012, 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 2012. 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 2012; reported use by each participant during follow-up interviews between 1992 and 2012; and cross-checking by a trained researcher.

Statins Dosage. The dosage of statin use was categorized into users with consistent dosages and users with inconsistent dosages. Consistent dosage was defined as a participant not reporting any changes of type and dosage of statin use at any follow-up interviews between 1992 and 2012; inconsistent dosage was defined as a participant having reported changes of statin type or dosage at any follow-up interviews of the WHAP between 1992 and 2012; and cross-checking by a trained researcher.

Cognitive Assessment. A comprehensive neuropsychological battery was administered to participants by trained neuropsychologists. Mini Mental State Examination (MMSE) which was included in 2012, was used to test the global cognitive function. It is based on a 30 correct-answer points indicating cognitive deficit absence, and 0, maximum cognitive deficit.

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 Chi2 for categorical data and either two-tailed independent-samples T-test or U-test for continuous data. Generalised linear model with ANCOVA was used to assess the impact on statin use (type, duration, dosage) on cognitive decline, controlling for age, body mass index, education, systolic blood pressure, smoking status for last 12 months, history of diabetes and family history of myocardial infarction. In order to determine the role of lipid levels on cognition, we conducted a sub-analysis of lipids with global cognitive function. IBM Statistical Package for Social Sciences (SPSS) software version 26.0 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

252 women completed 2012 cognitive assessments and had complete data from 1992 (Figure 1). Of these 12 women were excluded due to incomplete information on statin characteristics, neuropsychological assessments and covariates. Final sample was available on 240 women aged 66 to 77 years were recorded (Table 1). There was no significant difference in demographic

characteristics between the included and excluded participants (Table 1). No significant differences in demographic characteristics were also observed between participants who had used statins since baseline (1992) and those who reported never taking statin at last follow-up (2012) (Table 1). Participants were followed for approximately twenty years and statins were used for between 1 and 21 years. Over the course of this study, there were 94 statin users (39.2%), with most participants using one statin (N=83, 88.3%), and 9 (9.6%) using at least two statins. Atorvastatin was the most frequently used statin (N=37, 39%), followed by simvastatin (N=26, 28%) and rosuvastatin (N=17, 18%). No significant difference in demographic characteristics between atorvastatin, simvastatin and rosuvastatin users were seen (Table 2).

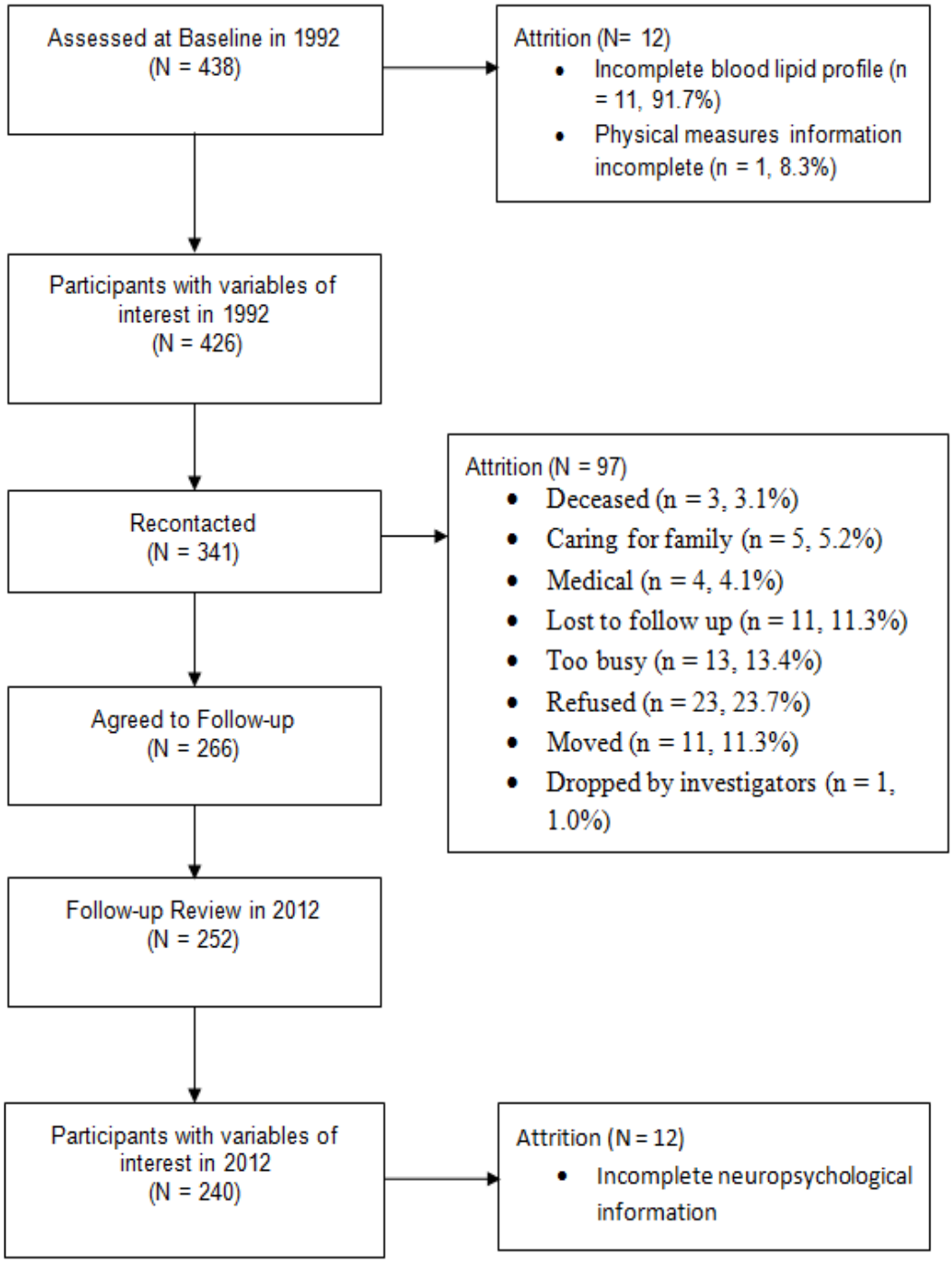

Figure 1: Flow diagram of the cohort attrition between baseline in 1992 and the follow-up review in 2012. Attrition characteristics are given for 1992, the period between 1992 and 2012 and for analyses of participants assessed in the 2012 follow-up review.

Table 1: Characteristics of the cohort (excluded & included participants, statins users and non-users) at 2012 follow-up review.

Characteristics	Total (N = 252)	Included Participants (N = 240)	Excluded Participants (N = 12)		Statins Users (N = 94)	Non-users (N = 146)	
Age (Year)		71.17 (2.66)	70.03 (2.72)	NS	70.35 (2.67)	69.82 (2.70)	NS
Education (Year)		9.00 (2.24)	12.44 (3.54)	NS	11.86 (3.67)	12.60 (3.44)	NS
Body mass index (kg/m^2)		30.98 (1.70)	28.06 (5.49)	NS	29.33 (5.51)	27.19 (5.28)	NS
Blood pressure (mm Hg)		141 (19.43)	139 (18.61)	NS	140 (19.48)	140 (18.80)	NS
Systolic Diastolic		86 (11.24)	83 (10.53)	NS	81(10.43)	84 (10.81)	NS
Cholesterol (mmol/L)		4.20 (1.56)	5.80 (1.14)	NS	5.17 (1.13)	6.19 (1.00)	NS
LDL (mmol/L)		2.20 (1.13)	3.42 (1.04)	NS	2.82 (1.01)	3.80 (0.89)	NS
HDL (mmol/L)		1.60 (0.71)	1.73 (0.43)	NS	1.66 (0.41)	1.77 (0.44)	NS
TG (mmol/L)		0.90 (0.42)	1.43 (0.68)	NS	1.52 (0.68)	1.38 (0.68)	NS

Note: Data reported as mean and standard deviation. Independent-samples T test was used to analyse the data. Abbreviations: HDL = High-Density Lipoprotein; LDL = Low-Density Lipoprotein; NS = Not Significant; TG = Triglycerides

Table 2: Characteristics of 3 main statins users in 2012 cohort.

Characteristics	Atorvastatin (N = 37)	Simvastatin (N = 26)	Rosuvastatin (N = 17)	
Age (Year)	69.76 (2.18)	71.08 (2.68)	69.94 (3.11)	NS
Education (Year)	12.92 (3.70)	10.92 (3.17)	12.00 (4.20)	NS
Body mass index (kg/m^2)	28.47 (5.03)	28.78 (4.35)	31.83 (6.54)	NS
Blood pressure (mm Hg)				
Systolic	138 (16.36)	144 (19.52)	134 (16.67)	NS
Diastolic	82 (10.83)	83 (9.48)	79 (6.78)	NS
Cholesterol (mmol/L)	5.05 (1.00)	5.20 (1.09)	5.26 (1.57)	NS
LDL (mmol/L)	2.73 (0.91)	2.86 (0.89)	2.92 (1.48)	NS
HDL (mmol/L)	1.71 (0.39)	1.64 (0.41)	1.66 (0.32)	NS
TG (mmol/L)	1.36 (0.59)	1.60 (0.82)	1.52 (0.55)	NS

Note: Data reported as mean (SD). One-Way ANOVA was used to analyse the data. Abbreviations: HDL = High-Density Lipoprotein; LDL = Low-Density Lipoprotein; NS = Not Significant; TG = Triglyceride

General outcome between statins and cognition

Non statin users were seen to perform significantly better than current statin users in MMSE [28.54 (0.14), 95% CI 28.28-28.81 vs 27.92 (0.19), 95% CI 27.56-28.29] at the endpoint of this study in 2012. There was no significant association observed between the comparisons of past statin users and non-users as well as past statin users with current users (Figure 2). Similar results were observed on other cognitive tests (results not shown).

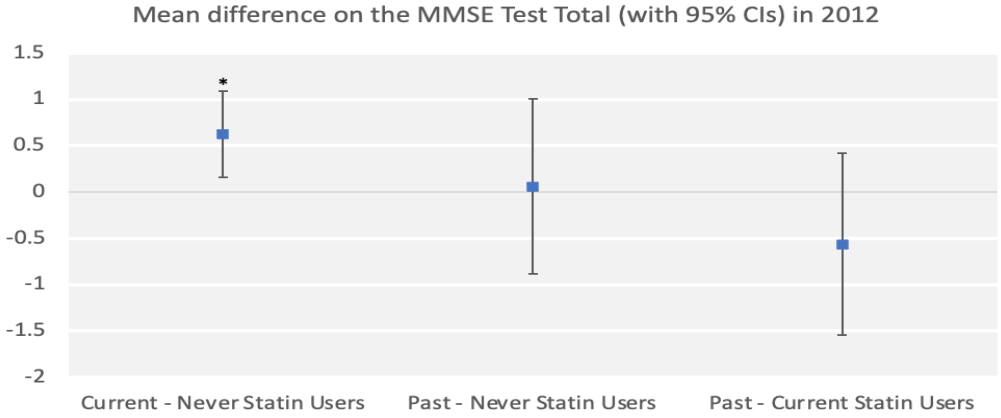

Figure 2: Mean difference of global cognitive scores with 95% CI at the endpoint of this study in 2012 for current, past and never statin users across the 20 years of follow up from 1992-2012. Note: Means are adjusted for age, body mass index, education, systolic blood pressure, smoking status for last 12 months, history of diabetes and family history of myocardial infarction. Analysis was conducted using general linear model (ANCOVA). Abbreviations: MMSE = Mini Mental State Examination * denotes values for p = 0.009.

Statins Variables (Types, Duration, Dosage)

No significant association was found between the three main types of statin user (atorvastatin, simvastatin, rosuvastatin) and non-users in the MMSE (Figure 3). Furthermore, non-users appeared to have a better global cognitive function than atorvastatin (p = 0.054) and rosuvastatin users (p = 0.057) respectively. In addition, we also compared the cognitive scores among the three statins but there was no significant relationship among them (results not shown).

Moreover, it was observed that statin users of short duration (1-4 years) seemed to have a poorer global cognitive function scores than non-users (p = 0.041). Non-users were also seen to record a better cognitive outcome than statin users in any duration. Interestingly, the MMSE scores appeared to slightly improve (not significantly) as the duration of statin usage increased between statin users for 5-9 years and users for ≥10 years with non-users (Figure 3).

Furthermore, we noted that statin users with inconsistent dosages also had a poorer global cognitive outcome than non-users (p = 0.033). For consistent dosage users, no significant relationship with non-users was reported. Similar to the previous 2 variables (type and duration), non-users demonstrated to have a better global cognitive outcome than statin users.

In addition, given that short duration statin users (1-4 years) and those with inconsistent dosages appeared to have a poorer MMSE score than non-users, we decided to carry out secondary analysis by combining these 2 cohorts. This group of statin users (statin users for 1-4 years or users with inconsistent dosages) was shown to have poorer global cognitive score than non-users (p = 0.012). No significant relationship was found between long term statin users (at least 5 years and consistent dosage users) and non-users. Nevertheless, albeit of no significant relationship achieved, non-users once again recorded a better cognitive outcome than statin users (Figure 3).

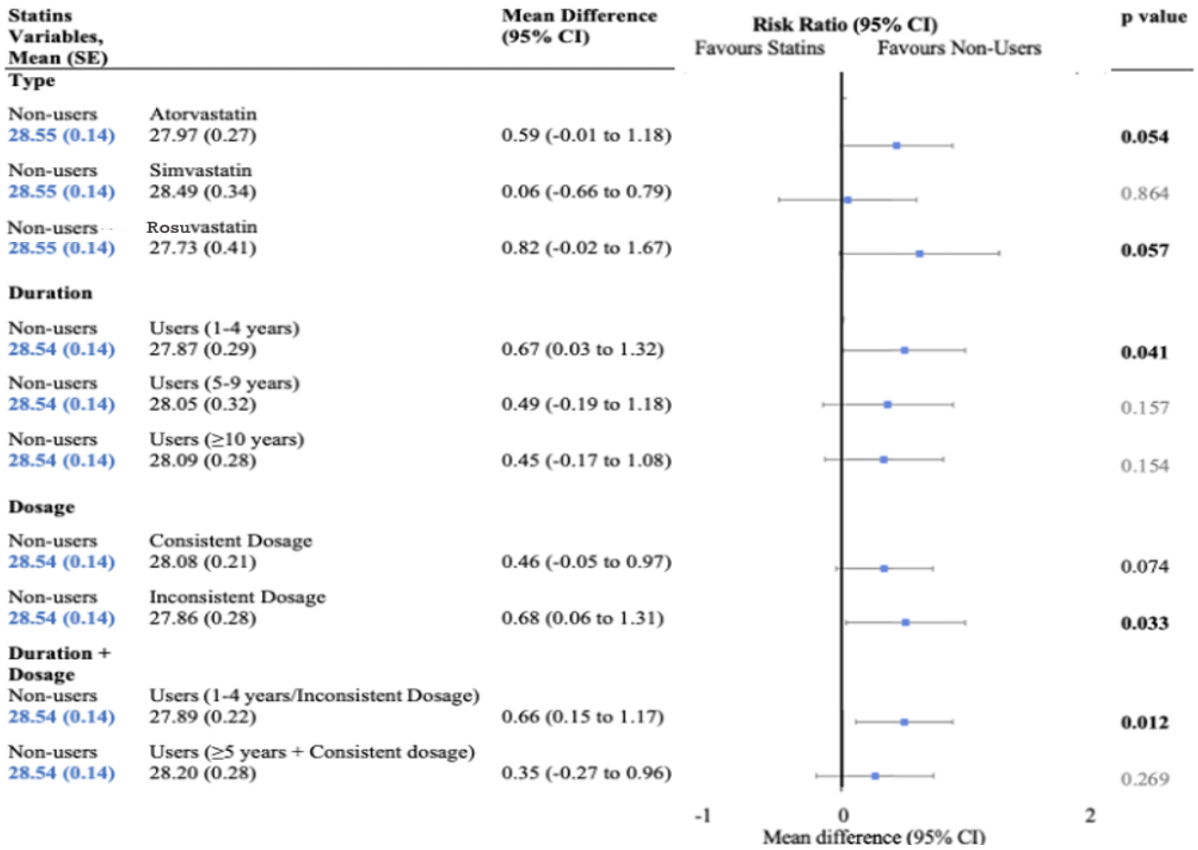

Figure 3: Forest plot showing the outcomes of MMSE and statins variables (types, duration of usage, consistent dosages & inconsistent dosages and the combination of duration & dosage) at the endpoint of this study in 2012 for non-users and statin users across the 20 years of follow up from 1992-2012. Note: The higher MMSE score is bolded. Means are adjusted for age, body mass index, education, systolic blood pressure, smoking status for last 12 months, history of diabetes and family history of myocardial infarction. Analysis was conducted using general linear model (ANCOVA). Abbreviations: MMSE = Mini Mental State Examination

Lipids & Cognition

Atorvastatin users had the lowest total cholesterol, LDL and TG but also the highest HDL compared to simvastatin and rosuvastatin users. However, the differences were not statistically significant among the statins (Table 2). In our sub-analysis of lipids with global

cognitive function, we realised that there is no significant differences between participants with borderline/undesirable lipids levels and those with desirable lipids levels (Table 3). Similar results were observed in our secondary analysis on other cognitive tests (results not shown).

Table 3: General linear model (ANCOVA) results demonstrating there was no significant difference of lipids and cognition. Results are portrayed as the adjusted means with standard errors and mean difference of cognitive scores with 95% CI of MMSE between LDL, HDL and TG at the endpoint of this study in 2012 across the 20 years of follow up from 1992-2012.

Lipids	Desirable, Mean (SE)	Borderline/Undesirable, Mean (SE)	Adjusted mean difference (95% CI)	p value
LDL	28.27 (0.16)	28.51 (0.16)	-0.24 (-0.71 to 0.23)	0.315
HDL	28.34 (0.14)	28.47 (0.18)	-0.14 (-0.60 to 0.33)	0.567
TG	28.48 (0.13)	28.19 (0.20)	0.29 (-0.19 to 0.76)	0.233

Note: Means are adjusted for age, body mass index, statin usage, education, systolic blood pressure, smoking status for last 12 months, history of diabetes and family history of myocardial infarction. Lipids grouping are based on NCEP cholesterol guidelines(51): Desirable (LDL: ≤3.34 mmol/L, HDL: >1.55 mmol/L, TG: <1.69 mmol/L), Borderline/Undesirable (LDL: ≥3.35 mmol/L, HDL: ≤1.55 mmol/L, TG: ≥1.69 mmol/L). Abbreviations: HDL = High-Density Lipoprotein; LDL = Low-Density Lipoprotein; MMSE = Mini Mental State Examination; NCEP = National Cholesterol Education Program; TG = Triglyceride

DISCUSSION

Our general findings of the poorer cognition by statin users are consistent with numerous previous studies that demonstrated that statins appeared to favour Alzheimer disease development.[21] Interestingly, an important point raised in a prospective withdrawal and rechallenge pilot study at the University of Nebraska Medical Center that such decline in MMSE score was able to be reversed through discontinuation of statins has enormous implication on people's functional status and quality of life.[22] Type of statins do not appear to be important on global cognitive function in our study, indicating that statins may affect cognition irrespective of their lipophilicity and dose.[21] thus, suggesting that they may favour Alzheimer's disease development.[23]

Short term use of statins

Moreover, we observed that initial statin users (1-4 years) but not long-term users with 5 or more years had a lower MMSE score than non-users, suggesting acute decline in memory happened for new statin users and this is consistent with the findings of others.[24] Besides that, we also noticed that only statin users with inconsistent dosages (change of dose or statins types) but not users with consistent dosages recorded a significantly poorer global cognition score than non-users. The cohort of statin users for 1-4 years or inconsistent dosage users showed a poorer cognitive outcome than non-users, further supporting the idea that inconsistent or initial statin use may cause non-specific or global cognitive deficits.

Pathophysiological mechanisms

Several in vitro studies reported that statins, especially lipophilic statins are actually neurotoxic and induce cell death in glia and neurons.[25] Two possible mechanism are proposed: 1). the reduced availability of cholesterol caused by statins might impair the integrity of the neuronal and glial cell membrane, resulting in slowed conduction of neuronal impulses.[26] and 2). the reduced re-myelination and reduction in coenzyme Q10 levels impairs mitochondrial function and may lead to an increase in oxidative stress.[27] Furthermore, lipophilic statins have been demonstrated to be proinflammatory in human monocytes *in vitro* and mice leukocytes *in* vivo, another pathway through which cognition could be aggravated in AD patients.[28]

Additionally, the brief impairment of cognitive functions by statins may be due to cholesterol's modulation of *N*-methyl-D-aspartate receptor function.[29] Nevertheless, the real mechanism by which statins might exacerbate cognitive functions is unidentified[30] and the current literature presents inconsistent outcomes on the relationship between lipophilic and hydrophilic statins with AD.[23] However, experts hypothesized on the role of cholesterol in the brain since some evidence showed that statins inhibit local synthesis of cholesterol in the central nervous system.[31]

Lipids and Cognition

There was no significant difference of lipid profiles (total cholesterol, LDL, HDL and TG) among the 3 most commonly used statins in our studies (atorvastatin, simvastatin and rosuvastatin). Moreover, no significant difference was also observed in our sub-analysis of LDL, HDL and TG on the global cognitive function of the participants. Given that brain cholesterol is almost fully synthesised *in situ* and not transferred from the plasma into the brain owing to the blood-brain barrier.[32] Hence, any changes in the cholesterol levels in plasma would not make much bigger changes in the brain.[34]

Furthermore, studies have demonstrated an age-dependent cholesterol-cognition relationship whereby beneficial effect of elevated cholesterol on cognitive functioning appears to be most evident before the age of

65 years or at very old ages (85 years and older).[34] Our results are also in tandem with Shepardson and colleagues'[35] review that exhibited studies showing a positive correlation with cholesterol levels were principally conducted early in the patient lives (50-60 years old) while studies demonstrating no correlation or negative correlation tended to be carried out later (age greater than 70 years).

Apart from 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.[36] 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.[37] Graveline[38] 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 chronic conditions 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 PD patients compared with non-PD controls.

There is also a claim that statin therapy instigates a significant deduction of isoprenoids in the brain with only a slender effect on cholesterol level.[39] Another notable effect of statin is the retardation on the prenylation of small G proteins[36] such as Rho, Rac, Rab and Ras which may have deleterious consequences.[40] 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.[41] 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.[42]

Apart from that, in neuronal membranes, statins have been observed to lower the number of synapses and impair synaptic vesicle release[43] and decrease evoked postsynaptic currents.[44] In addition, chronic cholesterol depletion by statin results in a significant reduction and functionality of the human serotonin H-1A receptors (5-HT1 A) expressed in CHO cells.[45] Such depletion could elucidate, at least in part, some of the psychiatric effects related to the chronic treatment with statins. Moreover, it has been suggested that lowering cholesterol beyond certain levels may impede the release of neurotransmitters at synapses and disrupt neuronal function.[42]

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 20 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 10 years 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-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.

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.[46] The MMSE aims at screening cognitive functions in people suffering from or at risk for dementia[47] 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.[48] 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.

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 and more highly educated than those who were excluded. Younger participants with a higher level of education are less likely to experience cognitive decline and dementia than older people with a lower level of education due to a greater cognitive reserve[49] 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%).[50] 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.

Future directions

In summary, the experimental evidence indicates that independent of underlying vascular risk, current statin use by women especially in the initial stage (1-4 years) was associated with greatest deteriorated cognitive scores. Dose rather than type appeared important with statin users with inconsistent dosages exhibiting worse global cognitive function than non-users and users with consistent dosages. Lipid profiles do not appear to play a critical role in our cognition, further highlighting that the outcome observed could be solely from the statin effects. Clinical implications are relevant given changes in dosing have such impacts on cognition not just in our study but also others.

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 consistent or inconsistent statins doses and duration of statin usage on the cognition with a longer follow-up (≥20 years) are required to detect these age-associated differences in middle and older age adults.

CONCLUSION

We observed that independent of underlying vascular risk (including lipid profile), recent statin use by women (within 1-4 years) and inconsistent dosages was associated with greatest deteriorated MMSE score compared to non-users global cognition. This effect was independent of lipids and sub-analysis showed it did not appear to play a pivotal role in cognition. It is important clinicians consider to mounting evidence of cognitive disturbance on initiating statins and with alterations to dosage.

ACKNOWLEDGEMENTS

We would like to acknowledge University of Melbourne, Melbourne Statistical Consulting Platform, the contribution of the participants and their supporters for their time and commitment for over 25 years to the University. We thank BioGrid for providing data linkage, Melbourne Health Pathology services for providing blood biomarker storage and analyses. We thank the research assistants who assisted in data collection. A full list of all researchers contributing to the project and the membership of our Scientific Advisory Board is available at http://www.medrmhwh.unimelb.edu.au /Research/WHAP.html. The Healthy Ageing Program has received support from National Health and Medical Research Council, Alzheimer's Association, Collier Trust, Scobie and Claire Mackinnon Foundation, JO and JR Wicking Trust, Shepherd Foundation, Brain Foundation, Mason Foundation, Ramaciotti Foundation, Alzheimer's Australia, and The Royal Australian College of Physicians.

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.

T.J. Chin, A. Gorelik and Y. Tan reports no disclosures relevant to the manuscript.

REFERENCES

1. Barnes DE, Whitmer RA, Yaffe K. Physical activity and dementia: The need for prevention trials. Exerc Sport Sci Rev., 2007; 35(1): 24-9.
2. International AsD. World Alzheimer Report 2016: Improving healthcare for people living with dementia. London, 2016.
3. Statistics ABo. Causes of Death, Australia, 2019; 2020. [Available from: https://www.dementia.org.au /statistics.
4. International AsD. World Alzheimer Report The Global Economic Impact of Dementia. London, 2010.
5. O'Brien JT, Burns A. Clinical practice with anti-dementia drugs: a revised (second) consensus statement from the British Association for Psychopharmacology. J Psychopharmacol, 2011; 25(8): 997-1019.
6. Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol, 2011; 10(9): 819-28.
7. International AsD. Women and Dementia: A global research review. London, 2015.
8. Alsehli AM, Olivo G, Clemensson LE, Williams MJ, Schioth HB. The Cognitive Effects of Statins are Modified by Age. Scientific Reports, 2020; 10(1): 6187.
9. Kostis WJ, Cheng JQ, Dobrzynski JM, Cabrera J, Kostis JB. Meta-analysis of statin effects in women versus men. Journal of the American College of Cardiology, 2012; 59(6): 572-82.

10. Opie LH, Dalby AJ. Cardiovascular prevention: lifestyle and statins-competitors or companions?: forum-review. South African Medical Journal, 2014; 104(3): 168-73.
11. Velam V, Kasala L, Chanda N. Statins in Females. Indian Journal of Cardiovascular Disease in Women-WINCARS, 2019; 4(02): 099-106.
12. Plakogiannis R, Arif SA. Women Versus Men: Is There Equal Benefit and Safety from Statins? Curr Atheroscler Rep., 2016; 18(2): 6.
13. Chen C-Y, Chuang S-Y, Fang C-C, Huang L-C, Hsieh IC, Pan W-H, et al. Gender Difference in Statin Intervention on Blood Lipid Control among Patients with Coronary Heart Disease. International Journal of Gerontology, 2013; 7(2): 116-21.
14. Roberts BH, Redberg RF. Gender disparity in statin response: are statins less effective in women? Clinical Lipidology, 2013; 8(2): 161-3.
15. Bhardwaj S, Selvarajah S, Schneider EB. Muscular effects of statins in the elderly female: a review. Clinical interventions in aging, 2013; 8: 47.
16. Banach M, Rizzo M, Nikolic D, Howard G, Howard V, Mikhailidis D. Intensive LDL-cholesterol lowering therapy and neurocognitive function. Pharmacology & Therapeutics, 170: 181-91.
17. Li G, Shofer J, Kukull W, Peskind E, Tsuang D, Breitner J, et al. Serum cholesterol and risk of Alzheimer disease: a community-based cohort study. Neurology, 2005; 65(7): 1045-50.
18. Reitz C, Tang M-X, Luchsinger J, Mayeux R. Relation of plasma lipids to Alzheimer disease and vascular dementia. Archives of neurology, 2004; 61(5): 705-14.
19. Direct H. Dementia statistics [Online], 2016. [cited 2021 13 May]. Available from: https://www.healthdirect.gov.au/dementia-statistics.
20. Szoeke CE, Robertson JS, Rowe CC, Yates P, Campbell K, Masters CL, et al. The Women's Healthy Ageing Project: fertile ground for investigation of healthy participants 'at risk' for dementia. Int Rev Psychiatry, 2013; 25(6): 726-37.
21. Mandas A, Mereu RM, Catte O, Saba A, Serchisu L, Costaggiu D, et al. Cognitive impairment and age-related vision disorders: Their possible relationship and the evaluation of the use of aspirin and statins in a 65 years-and-over Sardinian population, 2014b.
22. Padala KP, Padala PR, McNeilly DP, Geske JA, Sullivan DH, Potter JF. The effect of HMG-CoA reductase inhibitors on cognition in patients with Alzheimer's dementia: a prospective withdrawal and rechallenge pilot study. American Journal of Geriatric Pharmacotherapy, 10(5): 296-302.
23. Zissimopoulos JM, Barthold D, Brinton RD, Joyce G. Sex and Race Differences in the Association Between Statin Use and the Incidence of Alzheimer Disease. JAMA Neurology, 74(2): 225-32.
24. Taylor BA, Dager AD, Panza GA, Zaleski AL, Meda S, Book G, et al. The effect of high-dose atorvastatin on neural activity and cognitive function. American Heart Journal, 2018; 197: 166-74.
25. Van der Most PJ, Dolga AM, Nijholt IM, Luiten PG, Eisel UL. Statins: mechanisms of neuroprotection. Prog Neurobiol, 2009; 88(1): 64-75.
26. Miron VE, Zehntner SP, Kuhlmann T, Ludwin SK, Owens T, Kennedy TE, et al. Statin therapy inhibits remyelination in the central nervous system. Am J Pathol, 2009; 174(5): 1880-90.
27. Langsjoen PH, Langsjoen AM. The clinical use of HMG CoA-reductase inhibitors and the associated depletion of coenzyme Q10. A review of animal and human publications. Biofactors, 2003; 18(1-4): 101-11.
28. Kiener PA, Davis PM, Murray JL, Youssef S, Rankin BM, Kowala M. Stimulation of inflammatory responses in vitro and in vivo by lipophilic HMG-CoA reductase inhibitors. Int Immunopharmacol, 2001; 1(1): 105-18.
29. Korinek M, Vyklicky V, Borovska J, Lichnerova K, Kaniakova M, Krausova B, et al. Cholesterol modulates open probability and desensitization of NMDA receptors. J Physiol, 2015; 593(10): 2279-93.
30. Mandas A, Mereu RM, Catte O, Saba A, Serchisu L, Costaggiu D, et al. Cognitive impairment and age-related vision disorders: Their possible relationship and the evaluation of the use of aspirin and statins in a 65 years-and-over Sardinian population, 2014.
31. Lütjohann D, Stroick M, Bertsch T, Kühl S, Lindenthal B, Thelen K, et al. High doses of simvastatin, pravastatin, and cholesterol reduce brain cholesterol synthesis in guinea pigs. Steroids. 2004; 69(6): 431-8.
32. Dietschy JM, Turley SD. Cholesterol metabolism in the brain. Curr Opin Lipidol, 2001; 12(2): 105-12.
33. John S, Dharwadkar K, Motagi MV. Study on association between lipid profile values and psychiatric disorders. J Clin Diagn Res., 2014; 8(12): Wc04-6.
34. Reynolds CA, Gatz M, Prince JA, Berg S, Pedersen NL. Serum lipid levels and cognitive change in late life. J Am Geriatr Soc., 2010; 58(3): 501-9.
35. Shepardson NE, Shankar GM, Selkoe DJ. Cholesterol level and statin use in Alzheimer disease: I. Review of epidemiological and preclinical studies. Arch Neurol, 2011; 68(10): 1239-44.
36. Ling Q, Tejada-Simon MV. Statins and the brain: New perspective for old drugs. Prog Neuropsychopharmacol Biol Psychiatry, 2016; 66: 80-6.
37. Brown MS, Goldstein JL. Multivalent feedback regulation of HMG CoA reductase, a control mechanism coordinating isoprenoid synthesis and cell growth. J Lipid Res., 1980; 21(5): 505-17.
38. Graveline D. Adverse Effects of statin drugs: a physician patient's perspective. J Am Phys Surg, 2015; 20: 7-11.

39. Wood WG, Mőller WE, Eckert GP. Statins and neuroprotection: basic pharmacology needed. Mol Neurobiol. 2014; 50(1): 214-20.
40. Maeda A, Yano T, Itoh Y, Kakumori M, Kubota T, Egashira N, et al. Down-regulation of RhoA is involved in the cytotoxic action of lipophilic statins in HepG2 cells. Atherosclerosis, 2010; 208(1): 112-8.
41. Marcuzzi A, Tricarico PM, Piscianz E, Kleiner G, Brumatti LV, Crovella S. Lovastatin induces apoptosis through the mitochondrial pathway in an undifferentiated SH-SY5Y neuroblastoma cell line. Cell death & disease, 2013; 4(4): e585-e.
42. Mendoza-Oliva A, Zepeda A, Arias C. The complex actions of statins in brain and their relevance for Alzheimer's disease treatment: an analytical review. Current Alzheimer Research, 2014; 11(9): 817-33.
43. Mailman T, Hariharan M, Karten B. Inhibition of neuronal cholesterol biosynthesis with lovastatin leads to impaired synaptic vesicle release even in the presence of lipoproteins or geranylgeraniol. Journal of neurochemistry, 2011; 119(5): 1002-15.
44. Wasser CR, Ertunc M, Liu X, Kavalali ET. Cholesterol-dependent balance between evoked and spontaneous synaptic vesicle recycling. J Physiol, 2007; 579(2): 413-29.
45. Shrivastava S, Pucadyil TJ, Paila YD, Ganguly S, Chattopadhyay A. Chronic cholesterol depletion using statin impairs the function and dynamics of human serotonin1A receptors. Biochemistry, 2010; 49(26): 5426-35.
46. Hu W, Li Y, Zhao Y, Dong Y, Cui Y, Sun S, et al. Telmisartan and Rosuvastatin Synergistically Ameliorate Dementia and Cognitive Impairment in Older Hypertensive Patients With Apolipoprotein E Genotype, 2020.
47. Houx PJ, Shepherd J, Blauw GJ, Murphy MB, Ford I, Bollen EL, et al. Testing cognitive function in elderly populations: the PROSPER study. PROspective Study of Pravastatin in the Elderly at Risk. J Neurol Neurosurg Psychiatry, 2002; 73(4): 385-9.
48. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research, 1975; 12(3): 189-98.
49. Daffner KR. Promoting successful cognitive aging: a comprehensive review. J Alzheimers Dis., 2010; 19(4): 1101-22.
50. ABS. Census of population and housing: selected social and housing characteristics. Canberra: ABS, 2001.