ISSN Print: 2664-7591
ISSN Online: 2664-7605
Impact Factor: RJIF 5.2
IJAN 2022; 4(2): 20-25
www.pharmaceuticaljournal.in
Received: 10-08-2022
Accepted: 13-09-2022

Dr. S Anandkumar
Assistant professor, department of Pharmacy Practice, The Erode College of Pharmacy and Research Institute, Erode, Tamil Nadu, India

B Ajith Kumar
Doctor of Pharmacy, The Erode College of Pharmacy and Research Institute, Erode, Tamil Nadu, India

Christina Ponnachen
Doctor of Pharmacy, The Erode College of Pharmacy and Research Institute, Erode, Tamil Nadu, India

Sarfaraas Ahamath S
Doctor of Pharmacy, The Erode College of Pharmacy and Research Institute, Erode, Tamil Nadu, India

D Syed Ali Fathima
Doctor of Pharmacy, The Erode College of Pharmacy and Research Institute, Erode, Tamil Nadu, India

Corresponding Author:
Dr. S Anandkumar
Assistant professor, department of Pharmacy Practice, The Erode College of Pharmacy and Research Institute, Erode, Tamil Nadu, India

Effect of statin therapy on cognition level: A systematic review

Dr. S Anandkumar, B Ajith Kumar, Christina Ponnachen, Sarfaraas Ahamath S and D Syed Ali Fathima

DOI: https://doi.org/10.33545/26647591.2022.v4.i2a.39

Abstract
Statins are a widely prescribed class of drugs to lower cholesterol. On 28 February 2012, the United States Food and Drug Administration (FDA) issued a new warning for the labelling of statin drugs regarding potential adverse effects on cognition. This article aims analyse to review the effect of statin therapy on cognition level. We performed a systematic, computer-aided search of MEDLINE, EMBASE, and the Cochrane Central Register from January 2008 to October 2021. The age wise cognition impairment and pointed out the age group from 61-70 years showed the highest impairment. whereas long-term data suggest a beneficial role in the prevention of dementia.

Keywords: Prevention of dementia, highest impairment, perception, memory, judgement, perceptual speed

Introduction
Perception, memory, judgement, perceptual speed, spatial manipulation, and reasoning are all cognitive abilities. Different cognitive abilities have different developmental trajectories across the lifespan, according to both cross-sectional and longitudinal studies, and can be categorised into two broad types: The first type is described as 'crystallised' and involves accumulated knowledge and expertise and relies on long term memory [1].
Cognition impairment is a state of cognitive dysfunction that falls somewhere between normal cognition and dementia, which is defined as cognitive dysfunction involving two domains that interferes with daily activities and leads to a progressive loss of independence. Individuals with cognition impairment have difficulty performing objective cognitive tasks, but not to the point of impairing instrumental daily activities. The distinction between MCI and dementia is often blurred because the demands of daily activities vary greatly depending on age, occupation, family situation, and other factors. When considering potential deleterious effects of statins, we should remember that cognition impairment and dementia are very common in individuals older than age 65 years and can have a variety of causes including primary degenerative conditions such as Alzheimer's disease, front temporal dementia, Parkinson's disease, and dementia with Lewy bodies.

Statins
Statins are a widely prescribed class of drugs to lower cholesterol. Their mode of action is primarily via inhibition of HMG-CoA (hydroxymethylglutaryl-coenzyme A) reductase, the rate-limiting enzyme in the cholesterol biosynthesis pathway. Despite the widespread use of statins to lower cholesterol and reduce cardiovascular morbidity and mortality, statin therapy discontinuation and non-adherence is still a problem [11, 12]. The most common reason for statin therapy discontinuation is statin-associated muscle symptoms (SAMSs), which are the most well-documented statin side effect, despite the lack of a unifying mechanism. In addition, statins may cause other, more serious side effects, the most well-known of which is new-onset type 2 diabetes mellitus, the mechanisms of which are less well understood. Other potential side effects include neurological and cognitive effects, hepatotoxicity, renal toxicity, and others (gastrointestinal, urogenital, reproductive), all of which have yet to be proven.

Statins and Cognition

On 28 February 2012, the United States Food and Drug Administration (FDA) issued a new warning for the labelling of statin drugs regarding potential adverse effects on cognition, 1 based on post-marketing surveillance reports, case reports, observational studies, and randomized controlled trials (RCTs). Post-marketing reports (case series of 60 to 171 individuals) have described ill-defined memory impairment, reversible upon statin discontinuation, and some observational studies have described adverse cognitive effects that recurred with re-challenge. Other reviewers examining RCT and observational study data reported that there is no conclusive evidence that statins cause or contribute to clinically meaningful cognitive impairment, and may actually provide a slight benefit in dementia prevention.

Cognitive Function

The effects of statins on cognitive function have received increasing, and arguably disproportionate, attention in recent years. Data from clinical trials thus far has been inconsistent, not only in terms of results, but also analytical methods, population characteristics, existence of baseline cognitive impairments, statin(s) studied, and cognitive endpoints employed. Despite these differences, the majority of studies support a role for protection against cognitive impairment and dementia in patients without baseline cognitive dysfunction following long-term statin use.

A number of mechanisms have been implicated in statin-induced protection against cognitive impairment, including both cholesterol-dependent and -independent mechanisms. Increased LDL levels and total cholesterol have both been independently associated with cognitive impairment, thus the lowering of these lipoprotein levels, through statin treatment or other pharmacological/dietary means, has been suggested as a strategy for preventing cognitive impairment. Despite this apparent disease link, statins have not only been implicated in cholesterol-associated reductions in cognitive impairment, but have also been found to reduce the odds of cognitive impairment independent of lipid levels

Methods

Data source: We performed a systematic, computer-aided search of MEDLINE, EMBASE, and the Cochrane Central Register from January 2008 to October 2021 and we augmented this search by scrutinizing reference lists of relevant articles and making inquiries among colleagues, collaborators, and experts in the field. An optimal search strategy was devised on the basis of previous literature 28 with the aid of information a list. We did not assign language filters. To assess for publication bias, we sought to identify conference abstracts without an associated manuscript publication and other unpublished research by searching Current Controlled Trials. We reviewed the full text of all studies included in a recent large network meta-analysis of statins (and their adverse effects) and perused the reference lists of RCTs identified through our other approaches.

We included only articles published in English during full text review. All articles selected in the abstract screening phase were retrieved and examined in full text for eligibility. We abstracted the following information from all eligible studies: participant characteristics, study characteristics including objectives, year of publication, sample size, setting, country, funding mechanism, duration of follow-up, randomization method, reporting of dropouts, intervention and comparator details, and cognitive outcomes and harms. Cross-references of the full text retrieved articles were also searched. Data were collected independently from each publication and captured using a standardized word document form. Data were extracted from text, tables and figures.

Inclusion criteria

Randomised control trial, case reports and series, cross sectional studies, descriptive, prospective or retrospective studies in which evaluated the statin therapy effect on cognition level were included. The articles abstracts were reviewed from the period of January 2008 to October 2021.

Exclusion criteria

Articles with uncertain lead-in time of treatment relative to cognitive testing, incomplete reporting of methods and patients with previous or present history of impaired cognition were excluded.

Results

Figure 1 shows the literature search and article selection flow chart. Overall, we found that studies were at low to moderate risk of bias. Procedures for randomized sequence generation and allocation concealment were deemed adequate in only 13(52%) and nine (36%) studies, respectively, of the 41 studies included in the review. In contrast, blinding of participants, personnel, and outcome assessors was adequate in the majority of studies.

The initial search identified 118 records; after screening, 41were considered potentially eligible. These 41full-text articles were assessed for eligibility;16 met eligibility for qualitative synthesis (8short-term and 8 long-term cognition studies) and 11 for quantitative synthesis.

Table 1: shows the age wise classification of cognition impairment.

1-21 years group showed an average of 1%. 21-30 years group showed an average of 13%. 31-40 years group showed an average of 26%. 41–50 years group showed an average of 63%.51-60 years group showed an average of 165%. 61-70 years group showed an average of 185%. 71-80 years group showed an average of 161%. 81-90 years group showed an average of 81%. 91-100 years group showed an average of 25%.

Table 1: Age wise classification

Demographics (Age)	Average %
1-21 years	1
21-30 years	13
31-40 years	26
41-50 years	63
51-60 years	165
61-70 years	185
71-80 years	161
81-90 years	81
91-100 years	25

Table 2: Gender wise classification

Demographics (Gender)	Average %
Male	56.2
Female	43.8

The following Table.2 contains demographics classification based on the information from the 41 articles. The average percentage of demographics distributions according to the studies and the data are calculated by means of average from all the studies we included in inclusion criteria. Table 4 showed the total population from revised article shows that males were 56.2% and female were 43.8% had effects on cognition level due to statin therapy.

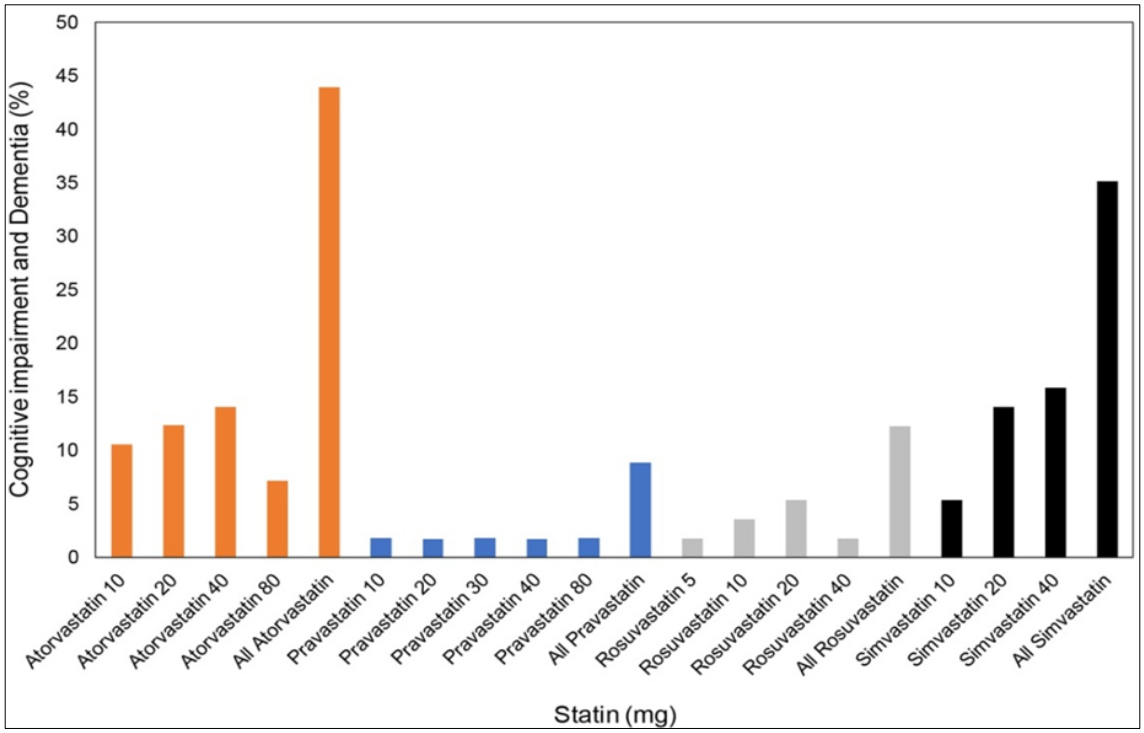

Fig 1: Cognition Impairment (%)

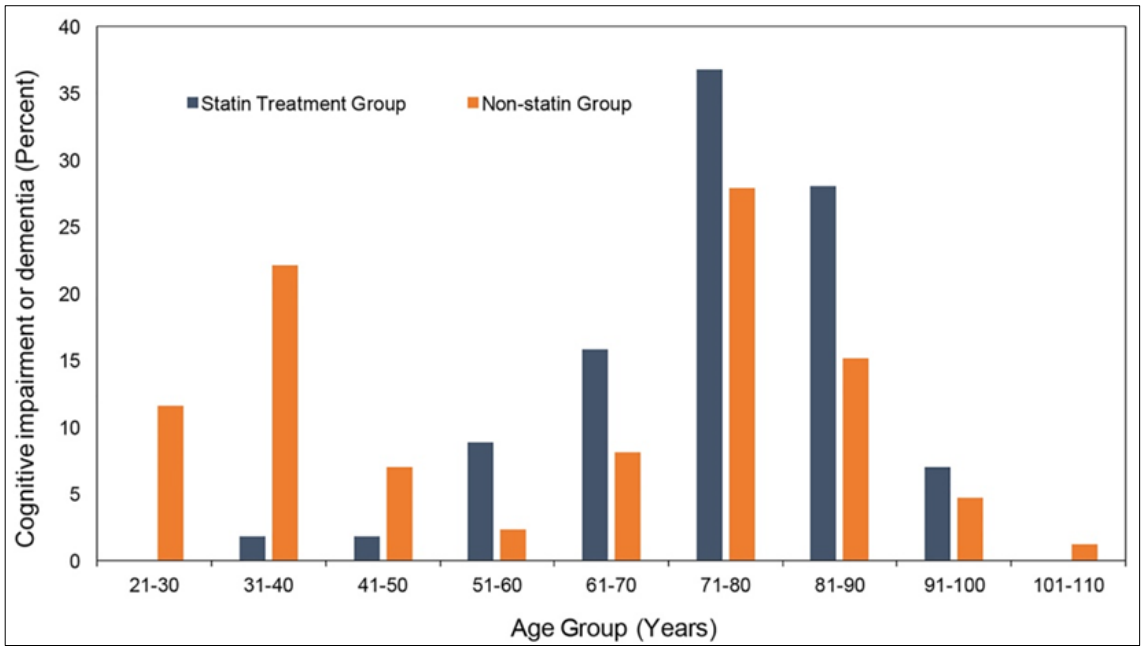

Fig 2: Cognition Impairment among Age groups

Figure 1 and 2 shows us the data collected from the following articles about the cognitive impairment caused due to different statins based on their doses and compares the impairment between the age groups using statin and non-statin group.

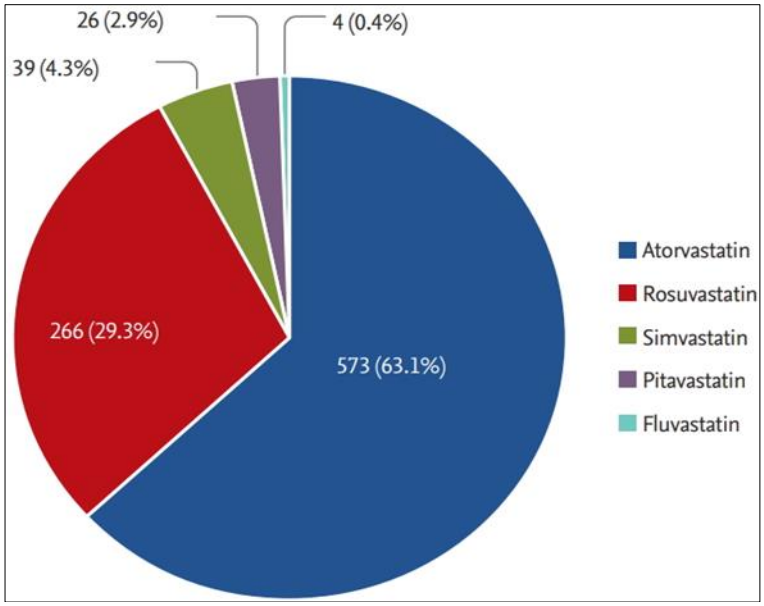

Fig 3: Early efficacy and safety of statin therapy

Table 3: Clinical development of various statins on neurodegenerative disorders.

Drug	Approved Indication	Outcome
Simvastatin	Alzheimer's Disease	Change in Cerebrospinal Fluid (CSF), Regional Cerebral Blood Flow on MRI and Beta-amyloid.
Simvastatin	Parkinson's Disease	Change in MDS-UPDRS (data related to person's mood and mental state).
Simvastatin	Multiple Sclerosis	Effect on cerebral blood flow and glutamate level using MRI technique.
Lovastatin	Parkinson's Disease	Change in MDS-UPDRS (data related to patient's mood and mental state).
Lovastatin	Alzheimer's Disease	Changes in CSF-beta levels and other biomarkers.
Lovastatin	Multiple Sclerosis	Changes in the gadolinium positive lesions numbers.
Atorvastatin	Alzheimer's Disease	Changes in regional cerebral flow and endothelial function. Changes in the metabolite concentration in brain area and rate of perfusion in brain area.
Atorvastatin	Multiple Sclerosis	The occurrence of >T2 lesions with or without gadolinium lesion (Gdþ) enhancement.

Table 3 provides a brief overview on the clinical development of various statins on neurodegenerative disorders. Use of simvastatin has caused change in Cerebrospinal Fluid (CSF), regional cerebral blood flow on MRI and Beta-amyloid and MDS-UPDRS (data related to person's mood and mental state). Lovastatin also caused Change in MDS-UPDRS, CSF-beta levels and other biomarkers and gadolinium positive lesions numbers. Atorvastatin caused changes cerebral flow and endothelial function, changes in the cerebral flow and endothelial function.

From our review we have taken 41 articles and analysed and concluded that following statins with different doses used and their average relative reduction.

Pravastatin 5mg caused 15% reduction, 10mg caused 20%, 20mg caused 24%, 40 mg caused 29%, 80 mg caused 33%.

Simvastatin 5 mg caused 23%, 10 mg caused 27%, 20mg caused 32%, 40 mg caused 37%, 80 mg caused 42%.

Atorvastatin 5 mg caused 31%, 10 mg caused 37%, 20mg caused 43%, 40 mg caused 49%, 80 mg caused 55%.

Rosuvastatin 5 mg caused 38%, 10 mg caused 43%, 20mg caused 48%, 40 mg caused 53%, 80 mg caused 58%.

Table 4: Average relative reduction in LDL cholesterol concentrations

	5 mg	10 mg	20 mg	40 mg	80 mg
Pravastatin	15%	20%	24%	29%	33%
Simvastatin	23%	27%	32%	37%	42%
Atorvastatin	31%	37%	43%	49%	55%
Rosuvastatin	38%	43%	48%	53%	58%

Discussion

In this systematic review and meta-analysis of adults without a history of cognitive dysfunction were reviewed and overall, we found that studies were at low to moderate risk of bias. The strengths of the present study include clear taxonomy effects of statin therapy, use of a priori eligibility criteria, focus on objective outcome measures, formal assessment of bias, and quantitative synthesis.

We have outlined the demographics classification based on the information from the 41 articles. The average percentage of demographics distributions according to the studies and the data are calculated by means of average from all the studies we included in inclusion criteria. Table 4 showed the total population from revised article shows that males were 56.2% and female were 43.8% had effects on cognition level due to statin therapy. Table 3 summarized the age wise cognition impairment and pointed out the age group from 61-70 years showed the highest impairment of 185% followed by 51-60 years showed 165% followed by 71-80 years showed 161%.

We considered all statins together as a class effect; although another review found no difference in the prevention of dementia by lipophilicity, there is a paucity of head-to-head comparisons between lipophilic and hydrophilic statins. We cannot exclude differential effects of a particular statin on cognition in this review. Moreover, we focused on adults without a history of cognitive dysfunction; it is uncertain how the results might apply to those with baseline cognitive dysfunction or other patient subgroups. This pooled result

must be interpreted cautiously given the heterogeneity in study design, exposure, outcome, and comparability.

Conclusion

The results of the available studies are most consistent with no significant short-term cognitive detriments associated with statin therapy in patients without baseline cognitive dysfunction, whereas long-term data suggest a beneficial role in the prevention of dementia. Given these findings, it's debatable whether the FDA's class warning about statins' potential cognitive side effects is still necessary.

Future post-marketing surveillance efforts should concentrate on a critical analysis of re-challenge effects, as well as factors not addressed in statin clinical trials, such as excessively high dosage and adherence to guidelines. At this time, patients and doctors can rest easy about concerns about statin therapy's neurocognitive effects, and the evidence does not support a change in practice guidelines. Future studies looking into statins and cognition should use a clear taxonomy, establish protocols, and focus on objective outcome measures, as proposed in this study.

Reference

1. Timimi F, Ray S, Jones E, Aase L, Hoffman K. Patient-reported outcomes in online communications on statins, memory, and cognition: qualitative analysis using online communities. Journal of Medical Internet Research. 2019 Nov 28;21(11):e14809.
2. Wagstaff LR, Mitton MW, Arvik BM, Doraiswamy PM. Statin-associated memory loss: Analysis of 60 case reports and review of the literature. Pharmacotherapy. 2003;23(7):871-880.
3. Sparks DL, Khachaturian AS, *et al*. Do statins reduce risk of incident dementia and Alzheimer disease? 2:217-224.2020 [cited 1 December 2020].
4. Christina Max, Renin LL. Statins and cognition effects A comparative study [Internet]. 2019 [cited 1 December 2019]. Available from:
5. Roy S, Weinstock J, Ishino A, Benites J, Pop S, Perez C *et al*. Association of Cognitive Impairment in Patients on 3-Hydroxy-3-Methyl-Glutaryl-CoA Reductase Inhibitors; c2013, 2017 Jul;9(7):638.
6. Redirecting [Internet]. Doi.org. 2021 [cited 1 December 2021]. Available from:
7. Archive of "British Journal of Clinical Pharmacology". [Internet]. Ncbi.nlm.nih.gov.
8. Pharmacotherapy of mild cognitive impairment. Dialogues in Clinical Neuroscience. 2004;6(4):391-395.
9. Swiger K, Manalac R, Blumenthal R, Blaha M, Martin S. Statins and Cognition: A Systematic Review and Meta-analysis of Short- and Long-term Cognitive Effects.
10. [PDF] Mild Cognitive Impairment: An Overview by · 10.1017/S1092852900016151 [Internet]. Citationsy.
11. Thompson P, Panza G, Zaleski A, Taylor B. Statin-Associated Side Effects; c2018
12. Sultan W, Sapkota A, Khurshid H, Qureshi I, Jahan N, Went T, *et al*. Statins' Effect on Cognitive Outcome After Traumatic Brain Injury; c2018
13. Alsehli A, Olivo G, Clemensson L, Williams M, Schiöth H. The Cognitive Effects of Statins are Modified by Age; c2016
14. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials; c2019.
15. Statins and Cognitive Impairment: Not a Culprit, Protective in Some? ∗[Internet]. Journal of the American College of Cardiology; c2012
16. Strom BL, Schinnar R, Karlawish J, Hennessy S, Teal V, Bilker WB. Statin therapy and risk of acute memory impairment [Internet]. JAMA internal medicine. U.S. National Library of Medicine.
17. McFarland AJ, Anoopkumar Dukie S, Arora DS, Grant GD, McDermott CM, Perkins AV, *et al*. Molecular mechanisms underlying the effects of statins in the Central Nervous System [Internet]. International journal of molecular sciences. U.S. National Library of Medicine.
18. Swiger KJ, Manalac RJ, Blumenthal RS, Blaha MJ, Martin SS. Statins and cognition: A systematic review and meta-analysis of short- and long-term cognitive effects [Internet]. Mayo Clinic Proceedings. Elsevier; c2013
19. Ott BR, Daiello LA, Dahabreh IJ, Springate BA, Bixby K, Murali M, *et al*. Do statins impair cognition? A systematic review and meta-analysis of randomized controlled trials [Internet]. Journal of General Internal Medicine. Springer US; c2015
20. Rojas-Fernandez CH, Goldstein LB, Levey AI, Taylor BA, Bittner V. The National Lipid Association's Safety Task Force None; An assessment by the Statin Cognitive Safety Task Force: 2014 update [Internet]. Journal of clinical lipidology. U.S. National Library of Medicine; c2012.
21. Poly TN, Islam MM, Walther BA, Yang HC. Association between use of Statin and risk of dementia: A meta-analysis of observational studies [Internet]. Neuroepidemiology. U.S. National Library of Medicine; [cited 2021Dec2]. Available from.
22. RH E. Approach to the patient who is intolerant of statin therapy [Internet]. The Journal of clinical endocrinology and metabolism. U.S. National Library of Medicine; c2015.
23. Qureshi S, Resham M. Strain-guided management of potentially cardiotoxic cancer; c2017.
24. Suraweera C, de Silva V, Hanwella R. Simvastatin-induced cognitive dysfunction: Two case reports Journal of Medical Case Reports. BioMed Central; c2016.
25. FDA Drug Safety Communication: important safety label changes to cholesterol-lowering statin drugs. US FDA website. http://www. fda.gov/Drugs/DrugSafety/ucm293101.htm. Accessed August 15, 2013.
26. Zamrini E, McGwin G, Roseman JM. Association between statin use and Alzheimer's disease. Neuroepidemiology. 2004;23(1-2):94-98.
27. Zandi PP, Sparks DL, Khachaturian AS, *et al*. Do statins reduce risk of incident dementia and Alzheimer disease? Arch Gen Psychiatry. 2005;62(2):217-224.
28. Bettermann K, Arnold AM, Williamson J, *et al*. Statins, risk of dementia, and cognitive function: secondary analysis of the Ginkgo Evaluation of Memory study. J Stroke Cerebrovasc Dis. 2012;21(6):436-444.
29. Beydoun M, Beason-Held LL, Kitner-Triolo MH, *et al*. Statins and serum cholesterol's associations with

incident dementia and mild cognitive impairment. J Epidemiol Community Health. 2011;65(11):949-957.
30. Evans M, Golomb B. Statin-associated adverse cognitive effects: survey results from 171 patients. Pharmacotherapy. 2009;29(7):800-811.
31. Karl Richardson, Marisa Schoen, Benjamin French, Craig Umscheid A, Matthew Mitchell D, Steven Arnold E, *et al*. Statins and cognitive funcntion: a systemic review; c2013.
32. Bob Schultz G, Denise Pattern K, Daniel Berlau J. The role of statins in both cognitive Impairment and protection against dementia: a tale of two mechanisms; c2018.
33. Castantinoladecola MD, Neal Parikh S. Statins and Cognitive Impairment; c2019.
34. Ahamed Alsehli M, Gaia Olivo, Helgi Schioth B. The Cognitive Effects of Statins are Modified by Age; c2020.
35. Carlos Rojas-Fernandez H, Jean-Christy Cameron F. Is Statin-associated Cognitive Impairment Clinically Relevent?; c2012.
36. Kelly Bilodeau. Do Statins increase the risk of dementia?; c2021.
37. Suraweera C, de Silva V, Hanwella R. Simvastatin-induced cognitive dysfunction: Two case reports. Journal of Medical Case Reports. BioMed Central; c2016.
38. Zhou Z, Ryan J, Ernst ME, *et al*. Effect of Statins on Cognitive Decline and Dementia in Older Adults; c2021.
39. Brain Storm L, Rita Schinnar, Jason Karlawish, *et al*. Satins Therapy and Risk of Acute Memory Impairment; c2015.
40. Anish Adhikari, Swetapadma Tripathy, Jonna Peterson. Association between statins use and cognitive function: A systematic review of randomized clinical trials and observational studies; c2021.