

Do statins cause dementia?

Statins or 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors are commonly used to treat dyslipidemia and have been shown to reduce the risk of atherosclerotic cardiovascular disease (ASCVD) and death.¹⁻⁵ Several case reports and studies have reported an association between use of statins and cognitive dysfunction.⁶⁻¹⁹ As a result, in 2012 the United States Food and Drug Administration (FDA) issued a drug safety communication update regarding labeling changes made to statin agents, which required manufacturers to add information regarding rare post-marketing reports of cognitive impairment, including memory loss, forgetfulness, amnesia, memory impairment, and confusion.²⁰ The FDA reviewed the Adverse Event Reporting System database and published literature including case reports, observational and randomized clinical trials, and noted that the data did not support an association between statins and significant cognitive dysfunction (e.g., dementia found in Alzheimer's disease).⁷⁻²⁰ The FDA noted that the post-marketing reports of cognitive adverse events were not serious and were reversible after statin discontinuation.²⁰ They also asserted that cognitive changes associated with use of statins were not common and that use of a specific statin, age of the patient, and dosage strength were not associated with development of cognitive impairment.

In contrast to statins being associated with cognitive impairment, it is important to note that multiple studies have been published showing that statins may be effective in *preventing* cognitive dysfunction or dementia.^{6,21-25} In addition to these conflicting studies, dyslipidemia and neurologic/psychiatric guideline/consensus statement recommendations are not consistent regarding statins' effects on cognitive function (see Table 1).

Table 1: Summary of guideline recommendations/consensus statements regarding statins and effects on cognitive function.

Guideline	Recommendations
Dyslipidemia guidelines	
AACE/ACE (2017) ⁵	Does not address use of statins and development of cognitive dysfunction/dementia
ACC/AHA (2013) ¹	No evidence statins cause dementia or cognitive changes; notes that patients who develop a confused state/memory impairment when receiving a statin should be evaluated for other causes including other drugs/medical conditions (e.g., neuropsychiatric disease)
NLA Statin Cognitive Safety Task Force (2014) ²⁶	Notes that concerns regarding statins and development of cognitive dysfunction arose from case reports
NLA Task Force on Statin Safety (2014) ²	Notes that the FDA required manufacturers to add information to the prescribing information regarding the potential for minor, reversible cognitive effects. Recommends that patients who present with cognitive changes be fully evaluated including a patient history and a physical examination
USPSTF (2016) ⁴	Notes evidence is limited regarding use of statins and cognitive effects; asserts there is no clear increased risk
Neurology/psychiatric guidelines	
AAN (2018) ²⁷	Does not address use of statins and development of cognitive dysfunction/dementia
APA (2014) ²⁸	Only addresses role of statins in delaying dementia (recommends against their use); does not address whether statins cause cognitive dysfunction/dementia
BAP (2017) ²⁹	Does not address use of statins and development of cognitive dysfunction/dementia; does not recommend statins for treatment or prevention of Alzheimer's disease
CCCDTD (2014) ³⁰	Does not address use of statins and development of cognitive dysfunction/dementia
EFNS (2010) ³¹	Does not address use of statins and development of cognitive dysfunction/dementia; cites insufficient evidence regarding use of statins for treatment or prevention of Alzheimer's disease
EFNS/ENS (2012) ³²	Does not address use of statins and development of cognitive dysfunction/dementia

AACE=American Association of Clinical Endocrinologist, AAN=American Academy of Neurology, ACC=American College of Cardiology, ACE=American College of Endocrinology, AHA=American Heart Association, APA=American Psychiatric Association, BAP=British Association for Psychopharmacology, CCCDTD=Canadian Consensus Conference on the Diagnosis and Treatment of Dementia, EFNS=European Federation of the Neurological Societies, EFNS/ENS=European Federation of the Neurological Societies/European Neurological Society, FDA=Food and Drug Administration, NLA=National Lipid Association, USPSTF=United States Preventative Services Task Force.

Several meta-analyses have been published which evaluated the potential association between statins and cognitive impairment or dementia; however, these have reported conflicting results.^{19,21,22,24,33-36} The most recently published meta-analysis by Chu et al evaluated whether statins are associated with an increased risk for development of mild cognitive impairment or dementia.³⁷ The authors used the following databases to identify relevant studies (searched from date of inception through December 27, 2017): ClinicalTrials.gov, Cochrane Library, Psychology and Behavior Sciences Collection, PubMed, and ScienceDirect. Studies were included if they were prospective cohorts with a minimum follow-up of 1 year in patients who were cognitively healthy at baseline (with no history of cognitive dysfunction). The studies also were required to have any of the following outcome measures: all-cause dementia, specific-cause dementia (Alzheimer’s disease, vascular dementia), or mild cognitive impairment. The authors excluded cross-sectional studies, retrospective case-control studies, and randomized controlled trials, and studies that did not evaluate any of the above listed endpoints. The studies’ methodological quality were rated using the Newcastle-Ottawa Scale.

The primary outcome of the meta-analysis was to determine the risk for cognitive impairment/dementia including all-cause dementia, Alzheimer’s disease, vascular dementia, and mild cognitive impairment after statin exposure.³⁷ The authors calculated fully adjusted relative risks (aRR) in order to provide pooled estimates; they also used a random effects model and the Cochran Q and I² tests to assess heterogeneity. Unlike previous meta-analyses, the authors also attempted to determine potential sources of heterogeneity. Finally, the authors performed subgroup analyses based on whether statins were hydrophilic or lipophilic.

A total of 25 studies were included in the analysis; 16 studies involved all-cause dementia (n=2,745,149), 14 involved Alzheimer’s disease (n=52,218), 3 studies involved vascular dementia (n=5,987), and 6 involved mild cognitive impairment (n=6,808).³⁷ The mean follow-up was 6.95 years (standard deviation 5.39). Table 2 summarizes the association of using a statin and the number of incident cases for each type of dementia or mild cognitive impairment. There was a significant reduction in risk of all-cause dementia, Alzheimer’s disease, and mild cognitive impairment that was associated with statin use. However, there was not a significant reduction in risk for vascular dementia.

Table 2: Use of statins and incident cases of dementia.³⁷

Type of dementia	Incident cases	aRR (95% CI)
All-cause dementia	35,688	0.849 (0.787-0.916)
Alzheimer’s disease	3120	0.719 (0.576-0.899)
Vascular dementia	422	1.012 (0.620-1.652)
Mild cognitive impairment*	359	0.737 (0.566-0.976)

aRR=adjusted relative risks, CI=confidence interval

*Based on results of 4 studies

All-cause dementia

In terms of current vs. former users of statins, current users had a lower risk of all-cause dementia (aRR=0.828; 95% confidence interval (CI) 0.692 – 0.990) unlike former users (aRR=1.125, 95% CI 0.818 – 1.547).³⁷ The authors noted heterogeneity for studies which assessed all-cause dementia (Q value=29.778, I²=49.627, p=0.013), but no publication bias. For the subgroup analyses, hydrophilic statins (pravastatin, rosuvastatin) were significantly associated with a reduced risk of all-cause dementia (aRR=0.877; 95% CI 0.818 – 0.940). Lipophilic statins (atorvastatin, simvastatin) were not associated with

a reduced risk for all-cause dementia (aRR=0.738; 95% CI 0.475 – 1.146). The authors noted that in the meta-aggression analysis, the covariates of white race and cholesterol >200 mg/dL were significant contributors to heterogeneity; other covariates (male gender, mean age, presence of cardiovascular disease, diabetes, etc.) did not contribute to heterogeneity.

Alzheimer's disease

Patients treated with statins were significantly less likely to develop Alzheimer's disease vs. patients who were not treated (aRR=0.719; 95% CI 0.576 – 0.899).³⁷ The authors noted large heterogeneity (Q value=28.779, $I^2=54.828$, $p=0.007$) and evidence of publication bias (t value=2.307, $p=0.039$). For the subgroup analyses, lipophilic statins were significantly associated with a reduced risk of Alzheimer's disease (aRR=0.639; 95% CI 0.449 – 0.908); use of hydrophilic statins did not significantly reduce risk for Alzheimer's disease (aRR=0.619; 95% CI 0.383 – 1.000). The authors were unable to perform an analysis of current vs. former users due a low number of studies that assessed this endpoint. In the meta-aggression analysis, only study duration, white race, and being an apoE4 carrier contributed to heterogeneity.

Vascular dementia

Based on 3 studies, patients who were treated with statins did not differ significantly from non-statin users in the incidence of vascular dementia (aRR=1.012; 95% CI 0.620 – 1.652).³⁷ There was no significant heterogeneity (Q value=3.256, $I^2=38.582$, $p=0.196$), but evidence of publication bias (t value=17.932, $p=0.035$).

Mild cognitive impairment

Finally, for mild cognitive impairment, based on 6 studies, patients who were treated with statins were less likely to develop mild cognitive impairment compared to non-statin users (aRR=0.737; 95% CI 0.556 – 0.976).³⁷ The author noted that there was significant heterogeneity (Q value=12.330, $I^2=59.449$, $p=0.031$) and evidence of publication bias (t value=4.051, $p=0.015$). After performing a meta-aggression analysis, the percentage of male patients and the number of covariates were found to be significant contributors to heterogeneity.

Chu et al also examined adverse events that occurred during the follow-up period.³⁷ They noted that only 1 study reported adverse events, which found that statins significantly increased the risk for liver dysfunction, myopathy, acute renal failure, and cataracts.³⁸

Chu et al concluded from their meta-analysis that statins may reduce the risk for all-cause dementia, Alzheimer's disease, mild cognitive impairment, but not vascular dementia.³⁷ The subgroup analyses showed that hydrophilic statins were of benefit in preventing all-cause dementia, while lipophilic statins may show a benefit in Alzheimer's disease. Some limitations of the study need to be noted. First, the included studies were observational in nature, and therefore, only an association between statins and their effects on cognition can be inferred. The authors also noted heterogeneity between the included studies for some of the analyses, so results should be interpreted with caution.

In summary, there are conflicting data regarding whether statins are associated with cognitive dysfunction and dementia.^{6-19,21,22,24,33-37} The most recently published meta-analysis by Chu et al found that statins may reduce the risk for all-cause dementia, Alzheimer's disease, mild cognitive impairment,

but not vascular dementia.³⁷ Further compounding the issue is that numerous studies have been published that show that statins may play a role in *preventing* cognitive dysfunction.^{6,21-25}

The FDA provided a safety update in 2012 highlighting labeling changes made to statin agents (added information regarding post-marketing reports of cognitive impairment associated with statin use).²⁰ However, the FDA noted that the available data did not support an association between statins and significant cognitive dysfunction (e.g. dementia found in Alzheimer's disease).

In addition to the above, guideline/consensus statement recommendations for dyslipidemia and neurology/psychiatry are not consistent; either they do not address the issue, state there is no evidence, note that the evidence is limited, or assert that there is no clear risk.^{1,2,4,5,26-32} The American College of Cardiology/American Heart Association and the National Lipid Association Task Force on Statin Safety recommend that patients with cognitive changes while taking statins be fully evaluated with a patient history and physical examination and consider other potential causes of cognitive dysfunction.^{1,2}

Therefore, in light of conflicting results from studies and inconsistent guideline/consensus statement recommendations, additional research is needed to more fully determine how statins affect cognitive function. In the meantime, patients should continue to take statins and be monitored for symptoms suggestive of cognitive dysfunction, including memory loss, forgetfulness, amnesia, memory impairment, and confusion.

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