

Effects of Plasma Lipids and Statins on Cognitive Function

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Abstract

Objective: Dementia is the fourth most common cause of death in developed countries. The relationship between plasma lipids and cognitive function is complex and controversial. Due to the increasing life expectancy of the population, there is an urgent need to control vascular risk factors and to identify therapies to prevent and treat both cognitive impairment and dementia. Here, we reviewed the effects of plasma lipids and statins on cognitive function.

Data Sources: We searched the PubMed database for research articles published through November 2017 with key words including “plasma lipids,” “hyperlipidemia,” “hypercholesterolemia,” “statins,” and “cognition function.”

Study Selection: Articles were retrieved and reviewed to analyze the effects of plasma lipids and statins on cognitive function and the mechanisms underlying these effects.

Results: Many studies have examined the relationship between plasma lipids and cognitive function, but no definitive conclusions can be drawn. The mechanisms involved may include blood-brain barrier injury, the influence on small blood vessels in the brain, the influence on amyloid deposition, and a neuroprotective effect. To date, most studies of statins and cognition have been observational, with few randomized controlled trials. Therefore, firm conclusions regarding whether mid- or long-term statin use affects cognition function and dementia remain elusive. However, increasing concern exists that statins may be a causative factor for cognitive problems. These adverse effects appear to be rare and likely represent a yet-to-be-defined vulnerability in susceptible individuals.

Conclusions: The association between plasma lipids and cognition, the mechanism of the influence of plasma lipids on cognitive function, and the association between statins and cognitive function are complex issues and currently not fully understood. Future research aimed at identifying the mechanisms that underlie the effects of plasma lipids and statins on cognition will not only provide important insight into the causes and interdependencies of cognitive impairment and dementia, but also inspire novel strategies for treating and preventing these cognitive disorders.

Key words: Cognitive Function; Dementia; Plasma Lipids; Statins

INTRODUCTION

Aging populations face an increase in disease burden due to chronic neurodegenerative conditions, among which dementia is a major contributor. The World Health Organization reported that 47.5 million people were affected by dementia worldwide in 2015. The social and economic implications are enormous, resulting in an estimated annual global societal cost of 604 billion dollars, corresponding to 1.0% of the worldwide gross domestic product.^[1] The three most common dementia subtypes are Alzheimer’s disease (AD), vascular dementia (VaD), and mixed dementia (combined AD and VaD pathology), among which AD is the most common type, accounting for 60–70% of all cases, with a prevalence of approximately 1% in those aged 60–64 years, which increases to 40% in

those aged 85 years or older.^[2] VaD accounts for a further 17–25% of cases,^[2] with an estimated prevalence rates of 1.6% and 1.7% in Europe^[3] and China,^[4] respectively. However, many people have mixed AD/VaD. Vascular risk factors such as diabetes, hypercholesterolemia, hypertension, and smoking can contribute to both VaD and AD, and

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approximately one-third of AD cases are due to modifiable vascular risk factors^[5] because of their potential impact on the neurovascular unit.^[6] Due to the increasing life expectancy of the population, there is an urgent need to control vascular risk factors and to identify therapies to prevent and treat both cognitive impairment and dementia. Here, we reviewed the association between plasma lipids and cognition function and the underlying mechanisms.

PLASMA LIPIDS AND COGNITIVE FUNCTION

In the Finnish study titled Cardiovascular Risk Factors Aging and Dementia, midlife measures of total cholesterol were significant predictors of cognitive impairment. Moreover, it was shown that a high midlife cholesterol level increased the risk for VaD.^[7] Some studies have reported that higher levels of late-life cholesterol were associated with a higher risk of VaD. In contrast, a longitudinal study of 1159 elderly Chinese individuals found associations between the elevated levels of total cholesterol and low-density lipoprotein (LDL) and the accelerated cognitive decline.^[8] The literatures generally suggest that the risk of mild cognitive impairment (MCI) and dementia is associated with hypertriglyceridemia, high LDL levels, and low high-density lipoprotein (HDL) levels.^[9,10] A large cohort study ($n = 7087$) showed that a high triglyceride level was the only component of metabolic syndrome that was significantly associated with the incidence of VaD (hazard ratio [HR]: 2.27); no such association was found for AD (HR: 0.90).^[11] Hypertriglyceridemia-induced/associated atherosclerosis might contribute to cognitive decline in patients with type 2 diabetes.^[12] Panza *et al.*^[13] noted that hypertriglyceridemia was associated with increased risk of dementia syndromes, particularly VaD. An elevated LDL level is particularly atherogenic and may be closely related to VaD.^[14] A Swedish study ($n = 60$) found that higher apolipoprotein B (ApoB) levels at baseline predicted dementia at least 3 years later, although all forms of dementia were included in this small study.^[15] One study also indicated that the ApoB/LDL ratio might be a potential clinical index for vascular cognitive impairment.^[16]

Most cross-sectional studies that included participants aged over 75 years showed an association between increased HDL cholesterol (HDL-C) levels and better performance on cognitive tests.^[17] In addition, a prospective study has confirmed the association of lower ApoA-I levels with increased dementia risk.^[18] A higher ApoB/ApoA-I ratio increased the risk of cognitive decline over 2 years in cognitively normal individuals.^[19] Therefore, an elevated ApoA-I level and a decreased ApoB/ApoA-I ratio might be associated with decreased dementia risk.

In contrast, one study found that higher levels of late-life cholesterol were associated with a lower risk for VaD.^[20] Other large studies of older adults have found an association of high triglyceride^[21] and LDL levels with better cognitive performance.^[22] Furthermore, in a recent longitudinal study of 192 adults with AD, rising LDL levels were associated with a trend toward improvement in functional performance.^[23]

Recently, one study reported that high total serum cholesterol in late life was not associated with MCI, AD, VaD, any form of dementia, or cognitive decline.^[24] Vicario *et al.*^[25] reported that only dyslipidemia was unrelated to cognitive impairment in the Cardiovascular Prevention Program ($n = 1365$). The latest research showed that late-life measurements of HDL-C and triglycerides were not associated with increased risk of VaD, and HDL-C was not associated with the risk of MCI, AD, or any form of dementia.^[24] A pooled analysis of two Finnish prospective population-based cohort studies ($n = 13,275$) found that the baseline ApoB level was not associated with incident AD or dementia 10 years later.^[26]

The relationship between plasma lipids and cognition is very complex and controversial. As with blood pressure, inconsistencies might reflect the timing of cholesterol measurements according to age, with older people possibly being less likely to receive lipid-lowering therapy (an example of the so-called “generational effect”) and differences in the clinical onset of dementia.

MECHANISM OF THE INFLUENCE OF PLASMA LIPIDS ON COGNITIVE FUNCTION

Blood-brain barrier injury

Brain cholesterol is involved in synapse development, synapse formation, dendrite differentiation, axonal elongation, and long-term potentiation.^[27] In the adult brain, the synthesis of primary cholesterol occurs in astrocytes and to a lesser extent in neurons.^[28] Cholesterol is transported within the brain by local lipoproteins. Brain cholesterol metabolism is unrelated to metabolism in peripheral tissues and the central nervous system (CNS), and plasma cholesterol/lipoprotein compartments are strictly segregated by the blood-brain barrier (BBB).

The BBB is created by the tight junctions between the endothelial cells of brain microvascular tissue and the astrocyte foot processes surrounding capillary endothelial cells.^[29] BBB injury has been recognized as a contributory factor to the development and progression of cognitive impairment. Recently, multiple studies have reported that rats fed with high energy diets, specifically diet rich in saturated fats and cholesterol, exhibited increased BBB permeability along with cognitive dysfunction.^[30-32] Although normal aging increases BBB permeability,^[33] oxidized LDL (oxLDL) promotes endothelial cell activation including increased the adhesion of monocyte to the vascular wall and the induction of the nuclear factor- κ B pathway. A recent study showed that the activation of microvascular endothelial cells by LDL increased the secretion of the inflammatory mediators such as tumor necrosis factor alpha and interleukin-6 and decreased the membrane localization of the tight junction protein ZO-1.^[28] LDL isolated from patients with hypercholesterolemia was more oxidized and inflammatory in endothelial cells than that isolated from healthy age-matched participants.^[28] In conjunction with these studies, another investigation demonstrated

that anti-inflammatory and lipid-lowering agents could reverse the high fat-induced BBB damage in rats.^[30] The reversal of BBB damage would, therefore, be expected to be accompanied by improvement in cognitive function. Inflammation and lipid oxidation might play an important role in the development of VaD.

HDL-C might be involved in the removal of excess cholesterol from the brain mediated by ApoE and heparin sulfate proteoglycans in the subendothelial space of cerebral microvessels. In addition, HDL particles reverse the inhibitory effect of oxLDL particles on endothelium-dependent arterial relaxation and inhibit cytokine-induced expression of endothelial cell adhesion molecules.^[34] Paraonase 1 is an A-esterase with peroxidase-like activity present on the surface of HDL that decreases the peroxidation of LDL.^[35] These might be related to the protective effect of HDL against cognitive decline.

Influence on small blood vessels in the brain

Although several studies have reported no association between LDL cholesterol (LDL-C) and magnetic resonance imaging markers of cerebral small vessel disease,^[36,37] one cohort study ($n = 1919$) revealed a significant relationship among increased HDL-C, decreased LDL-C, and white matter hyperintensity (WMH) progression.^[38] Furthermore, in 1135 acute ischemic stroke patients, hypercholesterolemia, hypertriglyceridemia, or the use of lipid-lowering medication was associated with a decreased severity of WMH.^[39] Unfortunately, the authors were unable to assess the contribution of statin therapy to the observed association, which might have confounded their findings. Although a smaller cohort study ($n = 112$) showed no association between midlife total cholesterol and WMH two decades later, lipid-lowering therapy reduced the risk of WMH in later life.^[40] And low HDL levels increased the severity of white matter changes.^[41]

Influence on the deposition of amyloid

Some evidences indicate that changes in brain cholesterol homeostasis are associated with the main pathological features of AD, especially amyloid beta ($A\beta$). Evidences also suggest that amyloidogenic amyloid precursor protein (APP) processing might preferentially occur in the cholesterol-rich regions of membranes known as lipid rafts and that alterations in cholesterol levels could exert their effects by altering the distribution of APP-cleaving enzymes within the membrane. Functional cell biology studies further support the critical involvement of lipid raft cholesterol in the modulation of $A\beta$ precursor protein processing by β -secretase and γ -secretase, resulting in altered $A\beta$ production. Decreased cholesterol levels have been shown to inhibit β -secretase activity while increasing the activity of α -secretase, the major proteolytic enzyme involved in APP metabolism.^[42]

Experimental studies suggested that high cholesterol accelerated the production of $A\beta$, the putative pathologic species in AD, by shifting APP metabolism from α to β cleavage products.^[43] Animal studies showed that intervention

with a high cholesterol diet led to memory deficits, increased oxidative stress, and doubled the concentration of amyloid in the hippocampus.^[44] One study demonstrated that LDL from AD and AD with VaD patients was more damaging to endothelial barrier properties and increased release of inflammatory cytokines.^[28] However, HDL-C could prevent aggregation and polymerization of $A\beta$, thus slowing or even preventing the development of AD.^[39,40] HDL-C was also reported to have anti-inflammatory properties.^[42]

ApoE is an important protein involved in cerebral cholesterol transport and influences aggregation and clearance of $A\beta$ peptide. The ApoE $\epsilon 4$ allele in both homozygosis and heterozygosis increases the risk of developing AD.^[45] The $\epsilon 4$ allele is associated with a higher risk of atherosclerosis and higher plasma levels of total cholesterol and LDL-C.^[34] In addition, several other genes involved in cholesterol metabolism have been reported to be associated with AD including adenosine triphosphate-binding cassette subfamily A member 7,^[46] clusterin, and sortilin-related receptor (SORL1).^[34]

Neuroprotective effect

In addition, *in vitro* studies have shown that cholesterol acts as an antioxidant and therefore plays a protective role in dementia pathogenesis, possibly through intercepting prooxidants to create oxysterols, which are less toxic than free radicals.^[20] High cholesterol might have a protective effect by increasing gamma-glutamyltransferase. This enzyme plays an important role in amino acid uptake and transport and could reduce the neurotoxic effects of amino acids.^[47]

STATINS AND COGNITIVE FUNCTION

Statins are a class of drugs that inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase, which is the rate-limiting enzyme in the cascade of cellular cholesterol biosynthesis. Statins thereby reduce the formation and entry of LDL-C into the circulation and upregulate LDL receptor activity, lowering LDL-C and triglycerides and increasing HDL-C. At present, firm conclusions regarding whether mid- or long-term statin use might influence cognitive decline and dementia remain elusive.^[48] Statins have neuroprotective effects through a variety of mechanisms. At the same time, the cognitive problems caused by statins should not be overlooked.

To date, most studies on statins and cognition are observational, and few randomized controlled trials (RCTs) have been conducted. Two large, double-blind, placebo-controlled RCTs of statins, the Heart Protection Study (HPS),^[49] and the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial, have been conducted.^[50,51] In the HPS, simvastatin had no effect on cognitive decline, compared to the control.^[49] In the PROSPER trial, pravastatin treatment was not associated with a change in cognitive test results.^[50,51] Several observational studies (conducted almost exclusively in adults aged >65 years) have considered the

association between statin use at the baseline study visit and subsequent cognitive decline or incident dementia. Likewise, no association was observed between baseline statin (irrespective of their lipophilicity) use and incident dementia in the Three-City study, in which the follow-up period was 7 years.^[52] However, the Gingko Evaluation of Memory Study showed that time-updated statin use was associated with a reduced risk of dementia in participants without MCI at baseline.^[53] New statin use during follow-up was reported to be associated with a reduced risk of incident dementia.^[54] Trials of statins assessing outcomes relevant to cognition and dementia are rare. Several observational studies have observed an association between statin use and dementia. These have been systematically reviewed by several groups of authors. All reviews found significant heterogeneity between studies and reported the biases and confounding factors commonly associated with observational research, making conclusive results and implications for practice difficult to establish and disseminate.^[55-57]

Many previous studies have demonstrated the beneficial effects of statins on endothelial dysfunction and chronic inflammation.^[58] However, statins might also confer neuroprotection by other mechanisms. For example, statins, particularly lipophilic statins, might cross the BBB and exert antioxidant and anti-inflammatory effects within the CNS or modulate cholesterol metabolism in the brain.^[59,60] Experiments in animal and cell models of AD have also suggested that statins modulate A β ; however, few evidences currently support a similar effect in humans.^[61] In addition, statins might modulate brain tau metabolism.^[61,62]

However, increasing concern exists that statins may be a causative factor of cognitive problems. Randomized trials, case reports, observational studies, and postmarketing surveillance have all reported data regarding cognitive impairment in people using statins.^[53,63,64] Symptoms of confusion, forgetfulness, and memory loss have been reported within a few days after therapy, while other reports described symptom onset years after commencing statin use. Overall, the symptoms were not serious and reversed within a few weeks of ceasing statin therapy. Subsequently, at least three groups have systematically evaluated the situation and found no significant evidence showing that statins cause cognitive impairment.^[65-67] The consistency of the independent findings of all recent reviews further shows that, to date, the evidence does not indicate an adverse effect of statins on cognitive function. Furthermore, these adverse effects seem to be rare and likely represent some yet-to-be-defined vulnerability in susceptible individuals.^[68]

CONCLUSIONS

The associations between plasma lipids and cognition and the underlying mechanism, and the relationship between statins and cognitive function are complex and currently not fully understood. Given the aging population, there is an urgent need to identify treatments to prevent and treat cognitive impairment and dementia. Statins have important

benefits in patients with or at high risk of cardiovascular and/or cerebrovascular events that far outweigh the putative risks of cognitive dysfunction as an adverse effect. The true incidence of these adverse effects cannot be determined with currently available data. Nevertheless, because of the potentially serious nature of cognitive dysfunction, the widespread use of statins, and the high prevalence of cognitive impairment resulting from any causes (particularly aging and concomitant cardiovascular and cerebrovascular diseases), patient reports regarding cognition should be taken seriously and be appropriately evaluated. Future research aimed at identifying the mechanisms that underlie plasma lipid and statin effects on cognition will not only provide important insights into the causes and interdependencies of cognitive impairment and dementia but also inspire novel strategies for treating and preventing these cognitive disorders.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Corriveau RA, Bosetti F, Emr M, Gladman JT, Koenig JI, Moy CS, *et al.* The science of vascular contributions to cognitive impairment and dementia (VCID): A framework for advancing research priorities in the cerebrovascular biology of cognitive decline. *Cell Mol Neurobiol* 2016;36:281-8. doi: 10.1007/s10571-016-0334-7.
2. McGuinness B, Craig D, Bullock R, Passmore P. Statins for the prevention of dementia. *Cochrane Database Syst Rev* 2016;CD003160. doi: 10.1002/14651858.CD003160.pub3.
3. Rizzi L, Rosset I, Roriz-Cruz M. Global epidemiology of dementia: Alzheimer's and vascular types. *Biomed Res Int* 2014;2014:908915. doi: 10.1155/2014/908915.
4. Ji Y, Shi Z, Zhang Y, Liu S, Liu S, Yue W, *et al.* Prevalence of dementia and main subtypes in rural northern China. *Dement Geriatr Cogn Disord* 2015;39:294-302. doi: 10.1159/000375366.
5. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: An analysis of population-based data. *Lancet Neurol* 2014;13:788-94. doi: 10.1016/S1474-4422(14)70136-X.
6. Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, *et al.* Vascular contributions to cognitive impairment and dementia: A statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011;42:2672-713. doi: 10.1161/STR.0b013e3182299496.
7. Solomon A, Kåreholt I, Ngandu T, Wolozin B, Macdonald SW, Winblad B, *et al.* Serum total cholesterol, statins and cognition in non-demented elderly. *Neurobiol Aging* 2009;30:1006-9. doi: 10.1016/j.neurobiolaging.2007.09.012.
8. Ma C, Yin Z, Zhu P, Luo J, Shi X, Gao X, *et al.* Blood cholesterol in late-life and cognitive decline: A longitudinal study of the Chinese elderly. *Mol Neurodegener* 2017;12:24. doi: 10.1186/s13024-017-0167-y.
9. Panza F, Frisardi V, Seripa D, Imbimbo BP, Sancarlo D, D'Onofrio G, *et al.* Metabolic syndrome, mild cognitive impairment, and dementia. *Curr Alzheimer Res* 2011;8:492-509. doi: 10.2174/156720511796391818.
10. Carlsson CM. Type 2 diabetes mellitus, dyslipidemia, and Alzheimer's disease. *J Alzheimers Dis* 2010;20:711-22. doi: 10.3233/JAD-2010-100012.

11. Raffaitin C, Gin H, Empana JP, Helmer C, Berr C, Tzourio C, *et al.* Metabolic syndrome and risk for incident Alzheimer's disease or vascular dementia: The three-city study. *Diabetes Care* 2009;32:169-74. doi: 10.2337/dc08-0272.
12. Hasnain M, Vieweg WV. Possible role of vascular risk factors in Alzheimer's disease and vascular dementia. *Curr Pharm Des* 2014;20:6007-13. doi: 10.2174/1381612820666140314153440.
13. Panza F, Solfrizzi V, Logroscino G, Maggi S, Santamato A, Seripa D, *et al.* Current epidemiological approaches to the metabolic-cognitive syndrome. *J Alzheimers Dis* 2012;30 Suppl 2:S31-75. doi: 10.3233/JAD-2012-111496.
14. Shoji T, Hatsuda S, Tsuchikura S, Shinohara K, Kimoto E, Koyama H, *et al.* Small dense low-density lipoprotein cholesterol concentration and carotid atherosclerosis. *Atherosclerosis* 2009;202:582-8. doi: 10.1016/j.atherosclerosis.2008.04.042.
15. Gatz M, Reynolds CA, Finkel D, Pedersen NL, Walters E. Dementia in Swedish twins: Predicting incident cases. *Behav Genet* 2010;40:768-75. doi: 10.1007/s10519-010-9407-4.
16. Qian C, Tan F. Ratio of apoB/LDL: A potential clinical index for vascular cognitive impairment. *BMC Neurol* 2016;16:243. doi: 10.1186/s12883-016-0766-1.
17. van Vliet P, van de Water W, de Craen AJ, Westendorp RG. The influence of age on the association between cholesterol and cognitive function. *Exp Gerontol* 2009;44:112-22. doi: 10.1016/j.exger.2008.05.004.
18. Ma C, Li J, Bao Z, Ruan Q, Yu Z. Serum levels of apoA1 and apoA2 are associated with cognitive status in older men. *Biomed Res Int* 2015;2015:481621. doi: 10.1155/2015/481621.
19. Song F, Poljak A, Crawford J, Kochan NA, Wen W, Cameron B, *et al.* Plasma apolipoprotein levels are associated with cognitive status and decline in a community cohort of older individuals. *PLoS One* 2012;7:e34078. doi: 10.1371/journal.pone.0034078.
20. Mielke MM, Zandi PP, Sjögren M, Gustafson D, Ostling S, Steen B, *et al.* High total cholesterol levels in late life associated with a reduced risk of dementia. *Neurology* 2005;64:1689-95. doi: 10.1212/01.WNL.0000161870.78572.A5.
21. Yin ZX, Shi XM, Kraus VB, Fitzgerald SM, Qian HZ, Xu JW, *et al.* High normal plasma triglycerides are associated with preserved cognitive function in Chinese oldest-old. *Age Ageing* 2012;41:600-6. doi: 10.1093/ageing/afs033.
22. Lv YB, Yin ZX, Chei CL, Brasher MS, Zhang J, Kraus VB, *et al.* Serum cholesterol levels within the high normal range are associated with better cognitive performance among Chinese elderly. *J Nutr Health Aging* 2016;20:280-7. doi: 10.1007/s12603-016-0701-6.
23. de Oliveira FF, Chen ES, Smith MC, Bertolucci PH. Longitudinal lipid profile variations and clinical change in Alzheimer's disease dementia. *Neurosci Lett* 2017;646:36-42. doi: 10.1016/j.neulet.2017.03.003.
24. Anstey KJ, Ashby-Mitchell K, Peters R. Updating the evidence on the association between serum cholesterol and risk of Late-life dementia: Review and meta-analysis. *J Alzheimers Dis* 2017;56:215-28. doi: 10.3233/JAD-160826.
25. Vicario A, Del Sueldo M, Fernández RA, Enders J, Zilberman J, Cerezo GH, *et al.* Cognition and vascular risk factors: An epidemiological study. *Int J Hypertens* 2012;2012:783696. doi: 10.1155/2012/783696.
26. Tynkkyinen J, Hernesniemi JA, Laatikainen T, Havulinna AS, Sundvall J, Leiviskä J, *et al.* Apolipoproteins and HDL cholesterol do not associate with the risk of future dementia and Alzheimer's disease: The national Finnish population study (FINRISK). *Age (Dordr)* 2016;38:465-73. doi: 10.1007/s11357-016-9950-x.
27. Iuliano L, Crick PJ, Zerbinati C, Tritapepe L, Abdel-Khalik J, Poirot M, *et al.* Cholesterol metabolites exported from human brain. *Steroids* 2015;99:189-93. doi: 10.1016/j.steroids.2015.01.026.
28. Dias HK, Brown CL, Polidori MC, Lip GY, Griffiths HR. LDL-lipids from patients with hypercholesterolaemia and Alzheimer's disease are inflammatory to microvascular endothelial cells: Mitigation by statin intervention. *Clin Sci (Lond)* 2015;129:1195-206. doi: 10.1042/CS20150351.
29. Abbott NJ, Friedman A. Overview and introduction: The blood-brain barrier in health and disease. *Epilepsia* 2012;53 Suppl 6:1-6. doi: 10.1111/j.1528-1167.2012.03696.x.
30. Pallebage-Gamarallage M, Lam V, Takechi R, Galloway S, Clark K, Mamo J, *et al.* Restoration of dietary-fat induced blood-brain barrier dysfunction by anti-inflammatory lipid-modulating agents. *Lipids Health Dis* 2012;11:117. doi: 10.1186/1476-511X-11-117.
31. Freeman LR, Granholm AC. Vascular changes in rat hippocampus following a high saturated fat and cholesterol diet. *J Cereb Blood Flow Metab* 2012;32:643-53. doi: 10.1038/jcbfm.2011.168.
32. Davidson TL, Monnot A, Neal AU, Martin AA, Horton JJ, Zheng W, *et al.* The effects of a high-energy diet on hippocampal-dependent discrimination performance and blood-brain barrier integrity differ for diet-induced obese and diet-resistant rats. *Physiol Behav* 2012;107:26-33. doi: 10.1016/j.physbeh.2012.05.015.
33. Chui HC, Ramirez-Gomez L. Clinical and imaging features of mixed Alzheimer and vascular pathologies. *Alzheimers Res Ther* 2015;7:21. doi: 10.1186/s13195-015-0104-7.
34. Appleton JP, Scutt P, Sprigg N, Bath PM. Hypercholesterolaemia and vascular dementia. *Clin Sci (Lond)* 2017;131:1561-78. doi: 10.1042/CS20160382.
35. Cheraghi M, Shahsavari G, Maleki A, Ahmadvand H. Paraoxonase I activity, lipid profile, and atherogenic indexes status in coronary heart disease. *Rep Biochem Mol Biol* 2017;6:1-7.
36. Gouw AA, van der Flier WM, Fazekas F, van Straaten EC, Pantoni L, Poggesi A, *et al.* Progression of white matter hyperintensities and incidence of new lacunes over a 3-year period: The Leukoaraiosis and Disability study. *Stroke* 2008;39:1414-20. doi: 10.1161/STROKEAHA.107.498535.
37. van Dijk EJ, Prins ND, Vrooman HA, Hofman A, Koudstaal PJ, Breteler MM, *et al.* Progression of cerebral small vessel disease in relation to risk factors and cognitive consequences: Rotterdam scan study. *Stroke* 2008;39:2712-9. doi: 10.1161/STROKEAHA.107.513176.
38. Longstreth WT Jr, Arnold AM, Beauchamp NJ Jr, Manolio TA, Lefkowitz D, Jungreis C, *et al.* Incidence, manifestations, and predictors of worsening white matter on serial cranial magnetic resonance imaging in the elderly: The cardiovascular health study. *Stroke* 2005;36:56-61. doi: 10.1161/01.STR.0000149625.99732.69.
39. Jimenez-Conde J, Biffi A, Rahman R, Kanakis A, Butler C, Sonni S, *et al.* Hyperlipidemia and reduced white matter hyperintensity volume in patients with ischemic stroke. *Stroke* 2010;41:437-42. doi: 10.1161/STROKEAHA.109.563502.
40. Vuorinen M, Solomon A, Rovio S, Nieminen L, Kåreholt I, Tuomilehto J, *et al.* Changes in vascular risk factors from midlife to late life and white matter lesions: A 20-year follow-up study. *Dement Geriatr Cogn Disord* 2011;31:119-25. doi: 10.1159/000323810.
41. Crisby M, Bronge L, Wahlund LO. Low levels of high density lipoprotein increase the severity of cerebral white matter changes: Implications for prevention and treatment of cerebrovascular diseases. *Curr Alzheimer Res* 2010;7:534-9.
42. He Q, Li Q, Zhao J, Wu T, Ji L, Huang G, *et al.* Relationship between plasma lipids and mild cognitive impairment in the elderly Chinese: A case-control study. *Lipids Health Dis* 2016;15:146. doi: 10.1186/s12944-016-0320-6.
43. Lepara O, Valjevac A, Alajbegović A, Začiragić A, Nakas-Ićindić E. Decreased serum lipids in patients with probable Alzheimer's disease. *Bosn J Basic Med Sci* 2009;9:215-20.
44. Gamba P, Testa G, Gargiulo S, Staurengi E, Poli G, Leonarduzzi G, *et al.* Oxidized cholesterol as the driving force behind the development of Alzheimer's disease. *Front Aging Neurosci* 2015;7:119. doi: 10.3389/fnagi.2015.00119.
45. Viticchi G, Falsetti L, Vernieri F, Altamura C, Altavilla R, Luzzi S, *et al.* Apolipoprotein E genotype and cerebrovascular alterations can influence conversion to dementia in patients with mild cognitive impairment. *J Alzheimers Dis* 2014;41:401-10. doi: 10.3233/JAD-132480.
46. Beecham GW, Hamilton K, Naj AC, Martin ER, Huentelman M, Myers AJ, *et al.* Genome-wide association meta-analysis of neuropathologic features of Alzheimer's disease and related dementias. *PLoS Genet* 2014;10:e1004606. doi: 10.1371/journal.pgen.1004606.
47. Dziedzic T, Slowik A, Gryn EA, Szczudlik A. Lower serum triglyceride level is associated with increased stroke severity. *Stroke*

- 2004;35:e151-2. doi: 10.1161/01.STR.0000128705.63891.67.
48. Power MC, Weuve J, Sharrett AR, Blacker D, Gottesman RF. Statins, cognition, and dementia-systematic review and methodological commentary. *Nat Rev Neurol* 2015;11:220-9. doi: 10.1038/nrneurol.2015.35.
 49. Collins R, Armitage J, Parish S, Sleight P, Peto R. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: A randomised placebo-controlled trial. *Lancet* 2002;360:7-22. doi: 10.1016/S0140-6736(02)09327-3.
 50. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, *et al.* Pravastatin in elderly individuals at risk of vascular disease (PROSPER): A Randomised controlled trial. *Lancet* 2002;360:1623-30. doi: 10.1016/S0140-6736(02)11600-X.
 51. Trompet S, van Vliet P, de Craen AJ, Jolles J, Buckley BM, Murphy MB, *et al.* Pravastatin and cognitive function in the elderly. Results of the PROSPER study. *J Neurol* 2010;257:85-90. doi: 10.1007/s00415-009-5271-7.
 52. Ancelin ML, Carrière I, Barberger-Gateau P, Auriacombe S, Rouaud O, Fourlanos S, *et al.* Lipid lowering agents, cognitive decline, and dementia: The three-city study. *J Alzheimers Dis* 2012;30:629-37. doi: 10.3233/JAD-2012-120064.
 53. Bettermann K, Arnold AM, Williamson J, Rapp S, Sink K, Toole JF, *et al.* Statins, risk of dementia, and cognitive function: Secondary analysis of the ginkgo evaluation of memory study. *J Stroke Cerebrovasc Dis* 2012;21:436-44. doi: 10.1016/j.jstrokecerebrovasdis.2010.11.002.
 54. Chou CY, Chou YC, Chou YJ, Yang YF, Huang N. Statin use and incident dementia: A nationwide cohort study of Taiwan. *Int J Cardiol* 2014;173:305-10. doi: 10.1016/j.ijcard.2014.03.018.
 55. Wong WB, Lin VW, Boudreau D, Devin EB. Statins in the prevention of dementia and Alzheimer's disease: A meta-analysis of observational studies and an assessment of confounding. *Arch Gen Psychiatry* 2013;62:217-24. doi: 10.1001/archpsyc.62.2.217.
 56. Song Y, Nie H, Xu Y, Zhang L, Wu Y. Association of statin use with risk of dementia: A meta-analysis of prospective cohort studies. *Geriatr Gerontol Int* 2013;13:817-24. doi: 10.1111/ggi.12044.
 57. 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. *Mayo Clin Proc* 2013;88:1213-21. doi: 10.1016/j.mayocp.2013.07.013.
 58. Satoh M, Takahashi Y, Tabuchi T, Minami Y, Tamada M, Takahashi K, *et al.* Cellular and molecular mechanisms of statins: An update on pleiotropic effects. *Clin Sci (Lond)* 2015;129:93-105. doi: 10.1042/CS20150027.
 59. Sierra S, Ramos MC, Molina P, Esteo C, Vázquez JA, Burgos JS, *et al.* Statins as neuroprotectants: A comparative *in vitro* study of lipophilicity, blood-brain-barrier penetration, lowering of brain cholesterol, and decrease of neuron cell death. *J Alzheimers Dis* 2011;23:307-18. doi: 10.3233/JAD-2010-101179.
 60. Carlsson CM, Xu G, Wen Z, Barnet JH, Blazel HM, Chappell RJ, *et al.* Effects of atorvastatin on cerebral blood flow in middle-aged adults at risk for Alzheimer's disease: A pilot study. *Curr Alzheimer Res* 2012;9:990-7. doi: 10.2174/156720512803251075.
 61. Serrano-Pozo A, Vega GL, Lütjohann D, Locascio JJ, Tennis MK, Deng A, *et al.* Effects of simvastatin on cholesterol metabolism and Alzheimer disease biomarkers. *Alzheimer Dis Assoc Disord* 2010;24:220-6. doi: 10.1097/WAD.0b013e3181d61fea.
 62. Pollen DA, Baker S, Hinerfeld D, Swearer J, Evans BA, Evans JE, *et al.* Prevention of Alzheimer's disease in high risk groups: Statin therapy in subjects with PSEN1 mutations or heterozygosity for apolipoprotein E epsilon 4. *Alzheimers Res Ther* 2010;2:31. doi: 10.1186/alzrt55.
 63. Evans MA, Golomb BA. Statin-associated adverse cognitive effects: Survey results from 171 patients. *Pharmacotherapy* 2009;29:800-11. doi: 10.1592/phco.29.7.800.
 64. Zandi PP, Sparks DL, Khachaturian AS, Tschanz J, Norton M, Steinberg M, *et al.* Do statins reduce risk of incident dementia and Alzheimer disease? The cache county study. *Arch Gen Psychiatry* 2005;62:217-24. doi: 10.1001/archpsyc.62.2.217.
 65. Richardson K, Schoen M, French B, Umscheid CA, Mitchell MD, Arnold SE, *et al.* Statins and cognitive function: A systematic review. *Ann Intern Med* 2013;159:688-97. doi: 10.7326/0003-4819-159-10-201311190-00007.
 66. Kelley BJ, Glasser S. Cognitive effects of statin medications. *CNS Drugs* 2014;28:411-9. doi: 10.1007/s40263-014-0147-5.
 67. 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. *J Gen Intern Med* 2015;30:348-58. doi: 10.1007/s11606-014-3115-3.
 68. Rojas-Fernandez C, Hudani Z, Bittner V. Statins and cognitive side effects: What cardiologists need to know. *Endocrinol Metab Clin North Am* 2016;45:101-16. doi: 10.1016/j.ecl.2015.09.007.

血脂和他汀类药物对认知功能的影响

摘要

目的：在发达国家，痴呆被列为第四大常见死因。血脂与认知功能之间的关系非常复杂和矛盾。由于预期寿命的增加，迫切需要控制血管性危险因素，寻找预防和治疗认知障碍和痴呆的治疗方法。在这篇文章中，我们回顾了血脂和他汀类药物对认知功能的影响。

方法：通过计算机检索 PubMed 数据库，搜索 2017 年以前发表的文章，文章关键词为“血脂，”“高脂血症，”“高胆固醇血症，”“他汀类药物，”“认知功能。”

结果：目前，关于血脂和认知功能的研究很多，但尚无定论，其机制可能是血脑屏障被破坏、影响脑小血管、影响淀粉样蛋白的沉积以及神经保护作用。迄今为止，大多数关于他汀类药物和认知功能的研究都是观察性研究，很少有随机对照试验。因此，关于中期或长期使用他汀类药物是否会改善认知功能和痴呆仍然难以确定，同时他汀类药物可能导致认知障碍的不良反应也不容忽视。这些不良反应非常罕见，且与个体易感性有关。

结论：血脂和认知功能、血脂影响认知功能可能的机制以及他汀类药物和认知功能的关系非常复杂，而且尚未有定论。未来的研究旨在确定血脂和他汀类药物对认知功能影响的机制，不仅将为认知障碍和痴呆的病因和相互关系提供重要见解，而且还将启发治疗和预防认知障碍的新策略。