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A Comprehensive Review of Statins' Dual Role in Alzheimer's Disease

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Abstract

Introduction: Alzheimer's disease (AD), the primary cause of dementia, affects millions. Statins, used for cholesterol lowering, may have a dual role in AD development and treatment, potentially offering neuroprotection but with unclear clinical outcomes and heterogeneous data. This review assesses statins' role, cognitive effects, therapeutic uses, and limitations in AD.

Methods: A systematic search of PubMed, Scopus, and Google Scholar (1995–2024) using MeSH keywords) Alzheimer's disease, Cognitive disorders, Dementia, Memory impairment, Neurodegenerative diseases, Statins(identified 268 articles, refined to 98 based on relevance and quality. Studies included primary and secondary research on statins' cognitive effects.

Results: Evidence on statins' cognitive impact in AD is mixed. Some studies suggest benefits through reduced beta-amyloid (Aβ) production and anti-inflammatory effects, particularly in ApoE4 carriers or early-stage AD, while others report reversible cognitive impairment, especially with lipophilic statins. Observational studies show conflicting results compared to randomized controlled trials (RCTs), with limitations in study design and dosage variability. Statins therapy is recommended for AD patients with metabolic disorders.

Conclusion: Statins' cholesterol-lowering, anti-inflammatory, and antioxidant properties offer potential neuroprotection, but their impact on AD pathology remains unclear due to heterogeneous data and unexamined dose-response relationships. Long-term RCTs with stratified patient groups (e.g., by statin type, disease stage, or ethnicity) are needed to clarify efficacy and risks.

Keywords: Alzheimer's disease, Cognitive disorders, Dementia, Memory impairment, Neurodegenerative diseases, Statins.

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Introduction

Dementia is a clinical syndrome with acquired impairments in cognitive domains [1]. Alzheimer's disease (AD), the most common form of dementia, was first described by Alois Alzheimer in 1907 in a female patient with memory deficits and neuropsychiatric disorders [2]. It has gradually become recognized as the main criterion for describing presenile dementia, distinct from age-related cognitive decline [3]. The prevalence of AD increases dramatically after the age of 65 years [4].

AD accounts for approximately 70% of dementia cases, and its incidence increases exponentially with age [6]. The prevalence of the disease has been reported to range from approximately 3% in individuals aged 65–74 years to nearly 50% in individuals over 85 years [6]. In the United States, the number of affected individuals was estimated to be approximately 5 million in 2007 and is projected to increase to 13 million by 2050 [7]. Female gender, low educational level, cardiometabolic disorders, and vascular disease are important risk factors for the development of AD [8]. Accurate differential diagnosis of AD from other dementias (such as vascular dementia and frontotemporal dementia) is crucial, but the lack of definitive biomarkers and the sometimes inconclusive results of methods such as positron emission tomography (PET) imaging have created persistent diagnostic challenges [5].

The increasing global burden of AD highlights the urgent need to develop effective therapeutic strategies [3]. In the meantime, growing evidence suggests a potential role for statins in the prevention and management of AD

[9]. These compounds, which are primarily known for their cholesterol-lowering properties and cardiovascular benefits, have recently gained attention for their neuroprotective properties. Emerging studies have explored the complex relationship between statins and AD, highlighting their dual potential in this neurodegenerative disorder [9].

The objective of this review is to synthesize existing findings and relevant research to enhance the understanding of the potential mechanisms through which statins may exert beneficial or detrimental effects in the context of AD. Furthermore, this work aims to identify areas requiring further investigation to elucidate the dualistic properties of statins in this neurodegenerative condition. Ultimately, this review seeks to provide evidence-based insights to inform clinical practice and contribute to the development of effective therapeutic strategies for AD.

Methods

A systematic review was conducted of English-language articles, case reports, reviews, and meta-analyses published between January 1995 and August 2024 in PubMed, Scopus, and Google Scholar. Medical Subject Headings (MeSH)-based keywords included "Alzheimer's disease", "Cognitive disorders", "Dementia", "Memory impairment", "Neurodegenerative diseases", and "Statins". The initial search yielded 268 articles. Inclusion criteria required studies to focus on statins' cognitive effects in AD, include human or preclinical data, and use robust methodologies (e.g., RCTs, cohort studies, or meta-analyses). Exclusion criteria eliminated non-English studies, those lacking cognitive outcomes, or with unclear methodologies. After screening for relevance, novelty, and methodological rigor, 98 articles were selected. Quality assessment followed the Newcastle-Ottawa Scale (NOS) for observational studies and the Cochrane Risk of Bias Tool for RCTs, evaluating study design, sample size, blinding, and outcome reporting. Data extraction included study design, population, statin type, dosage, duration, and cognitive outcomes.

Pathophysiology of Alzheimer's Disease

The main neurological features of AD include amyloid-beta (Aβ) plaques and tau protein tangles in the brain, along with shrunken nerve connections and dysfunctional mitochondria [10]. While Aβ buildup plays a major role, it doesn't fully explain AD progression: Aβ plaques contribute to nerve cell damage and tau-related degeneration, but tau tangles can also form independently of Aβ [10, 11]. Additional early mechanisms involve breakdown of the blood-brain barrier (especially in people with APOE gene variants), which may even precede Aβ accumulation [13]. Other significant contributors include blood vessel dysfunction and imbalances in growth factors/nitric oxide that disrupt brain blood flow [14]. Though Lewy bodies (abnormal protein deposits) are more typical of other dementias, they occasionally co-occur with AD pathology.

MicroRNAs (miRNAs) are small molecules that regulate brain cell activities like memory formation and nerve cell survival [15]. They operate throughout neurons, including cell bodies, branches, and connections, to control receptors essential for brain signaling. When miRNAs malfunction, they contribute to AD by disrupting nerve connections early in the disease process [16,17]. Specifically, they drive AD progression by increasing harmful amyloid-β plaques, altering the processing of Alzheimer-related proteins (amyloid precursor protein (APP) and β-site amyloid precursor protein cleaving enzyme 1 (BACE1)), promoting tau protein tangles, and changing cellular skeleton proteins like cofilin [18]. Notably, miRNAs such as miR-331-3p and miR-9-5p can serve as early warning signs for AD [18]. Cholesterol-lowering statin drugs also influence AD by modifying miRNA activity—either directly through cholesterol pathways or indirectly via proteins like proprotein convertase subtilisin/kexin type 9 (PCSK9), which may reduce inflammation and slow disease progression [18,19].

The clinical presentation of AD is characterized by progressive memory loss, cognitive decline, language impairment, sensorimotor dysfunction, and personality alterations. However, the trajectory of these symptoms can vary significantly among individuals, with some patients exhibiting a period of relative stability or even perceived improvement over several years [20]. Notably, early-onset AD (EOAD), which manifests at a younger age (typically before 65 years), often presents with a more rapid progression and may be characterized by less prominent initial memory loss but more pronounced executive dysfunction, visuospatial deficits, and behavioral disturbances [21].

Other forms of dementia, such as VaD, can frequently coexist with and exacerbate the cognitive decline associated with AD. Consequently, AD can be viewed as a genetically influenced disorder with significant cerebrovascular contributions [22]. Vascular dementia is the second most common cause of dementia, characterized by cerebrovascular events like stroke, white matter lesions, demyelination, and often cerebral amyloid angiopathy. Therefore, vascular injury represents a critical factor in neuronal loss and synaptic dysfunction. Neuroinflammation, impaired autophagy, oxidative stress,

and apoptosis have been identified as key mechanisms underlying endothelial and neuronal cell damage in various neurological and psychiatric disorders, including AD [23, 24].

The current pharmacological management of AD primarily focuses on symptomatic relief using cholinesterase inhibitors, such as donepezil, rivastigmine, tacrine (less commonly used due to hepatotoxicity), and galantamine. Additionally, N-methyl-D-aspartate (NMDA) receptor antagonists, such as memantine, are prescribed for the treatment of more advanced cognitive impairment in AD patients [25]. Regrettably, these agents have generally demonstrated limited efficacy in modifying the underlying pathological progression of AD[26].

A significant proportion of individuals with AD also present with concurrent metabolic and cardiovascular disorders, for which statins are frequently prescribed as a first-line treatment. Consequently, statins probably exert an influence on the cognitive function of AD patients. Indeed, reports have indicated that statins can have both beneficial and detrimental effects on cognitive performance [27, 28]. Some studies have suggested that statin use may mitigate the progression of bradykinesia in older adults and improve working memory function in some adults [28, 29].

Overview of Statin Mechanisms of Action and Therapeutic Applications

Statins, formally known as 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR) inhibitors, competitively inhibit the rate-limiting enzyme in the mevalonate pathway, thereby suppressing cholesterol biosynthesis [30]. These agents are extensively employed in managing hypercholesterolemia and dyslipidemia to attenuate primary cardiovascular disease (CVD) incidence and mitigate secondary risks in affected patients, while also demonstrating efficacy in preventing non-alcoholic fatty liver disease (NAFLD) progression [31, 32]. Since the initial approval of lovastatin, seven additional statins—atorvastatin, fluvastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin—have received U.S. Food and Drug Administration (FDA) authorization[32]. Pharmacokinetically, short half-life statins (e.g., simvastatin) require evening administration to align with nocturnal hepatic cholesterol synthesis, whereas long-acting agents (e.g., atorvastatin, rosuvastatin) permit flexible dosing [33]. Mechanistically, statins reduce circulating LDL and VLDL cholesterol while modestly elevating HDL cholesterol by upregulating hepatic LDL receptor expression, thereby enhancing cholesterol clearance [34]. Concurrently, they diminish the synthesis of isoprenoid intermediates, leading to Rho-associated protein kinase (ROCK) suppression [35]. This inhibition of protein prenylation underlies their pleiotropic effects—including immunomodulation, endothelial protection, and cardioprotection [36, 37] yet also contributes to adverse events such as myalgia, neuropathy, and hyperglycemia[38,39]. Clinically, statins ameliorate endothelial dysfunction, atherosclerosis, thrombosis, and vasculitis [40–42], conferring benefits independent of lipid profiles. Consequently, they are recommended for both primary CVD prevention in high-risk populations and secondary prevention in established CVD patients [43, 44].

Statins are categorized based on their lipophilicity into two main groups: hydrophilic (water-soluble), such as rosuvastatin, and lipophilic (fat-soluble), such as atorvastatin [45]. A major adverse effect, particularly when statins are combined with other lipid-lowering agents (fibrates), is rhabdomyolysis. Statins may also potentially increase the risk of type 2 diabetes mellitus and peripheral neuropathy through interactions with pancreatic β-cells and neuronal metabolism [46,47]. The use of statins significantly elevates intracellular free fatty acid levels in skeletal muscle, which may inhibit the insulin signaling cascade, leading to reduced glucose clearance and impaired glucose tolerance [48]. Furthermore, long-term statin therapy can induce alterations in the gut microbial flora, potentially contributing to insulin resistance, hyperglycemia, and the development of type 2 diabetes [49]. In this context, the development of insulin resistance may also play a detrimental role in the neuropathology of AD [50]. Molecular signaling pathways that utilize insulin in the periphery also mediate synaptic transmission, neuronal and glial metabolism, and neuroinflammatory responses in the brain [51]. Insulin resistance in the brain can be defined as the impaired ability of neural cells to respond to insulin, resulting in disruptions in synaptic, metabolic, and immune functions [52]. Type 2 diabetes is associated with insulin resistance in the brain, and research suggests that impaired brain insulin signaling is a feature of AD. However, the etiological relationship between these two conditions, or whether they are both consequences of aging, remains to be fully elucidated [52,53].

Statins and Alzheimer's disease

As previously mentioned, the increasing utilization of statins, particularly in elderly populations for the primary and secondary prevention of cardiovascular diseases, has established them as a widely prescribed class of drugs globally [54]. It has been reported that approximately 30% of individuals over the age of 40 in the United States use statins [55]. This widespread and often long-term use raises

concerns about the potential impact of statins on cognitive function in both healthy individuals and those with pre-existing cognitive impairment [27]. Indeed, a subset of patients with underlying cardiovascular disease treated with statins has reported experiencing some degree of cognitive decline [56]. However, the overall evidence regarding the effect of statins on cognition in both healthy elderly individuals and those with or at risk of dementia remains a subject of ongoing investigation and debate.

Evidence derived from observational and prospective studies has not yielded definitive conclusions regarding the beneficial or detrimental effects of statins on cognitive functions in patients with AD [57,58]. Randomized controlled trials (RCTs) and observational studies with longitudinal follow-up examining statin use and subsequent cognitive outcomes generally do not support a preventative effect of statin consumption on cognitive decline or the development of dementia [57]. Similarly, the administration of statins to individuals at increased risk of cardiovascular diseases has not demonstrated a protective effect against the onset of AD [58].

Conflicting reports exist regarding the long-term effects of statin therapy on cognitive function, with some suggesting both positive and negative impacts [59]. A key question remains whether patients with hypercholesterolemia or normal cholesterol levels and coexisting cardiovascular conditions, who are treated with statins, face an increased risk of developing AD or if the underlying dyslipidemia itself contributes to a higher likelihood of future neurodegeneration. For instance, one longitudinal study indicated that middle-aged individuals with hypercholesterolemia exhibit an elevated risk of AD [60]. Consequently, the modification of cardiovascular risk factors using statins might be beneficial in AD prevention. However, the use of statins in patients with pre-existing cardiovascular disease but normal cholesterol levels may be associated with cognitive impairment in some individuals [61].

Figure 1 illustrates statins' dual effects in AD, depicting pathways for neuroprotection (e.g., reduced Aβ production, anti-inflammatory effects, enhanced cerebral blood flow) and potential harm (e.g., cholesterol depletion, oxidative stress via CoQ10 reduction). The schematic highlights lipophilic vs. hydrophilic statins' BBB penetration and miRNA modulation, with annotations clarifying correlational vs. causal evidence.

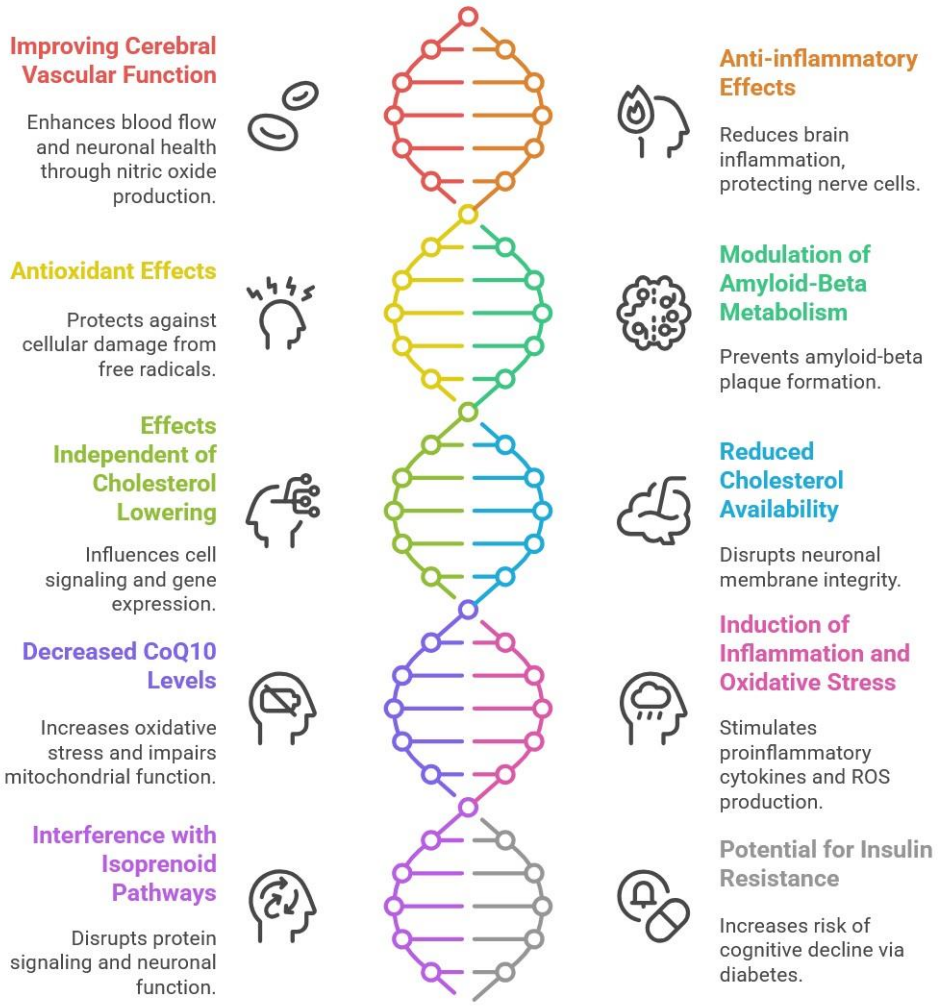

Fig. 1. Proposed Mechanisms of Statins in Modulating Cognitive and Neurodegenerative Diseases: A Dual-Edged Sword

Potential Detrimental Effects of Statins on Alzheimer's Disease

Several earlier studies have reported an association between statin therapy and cognitive disturbances. For instance, atorvastatin was linked to cognitive impairment in the initial phase of its clinical trials, although this was not consistently reported as a significant adverse event in later, larger phase III trials [62]. However, post-marketing surveillance, based on numerous case reports, has raised the possibility of a reversible cognitive impairment associated with statin use [63]. A clinical trial involving lovastatin administered to 308 healthy individuals demonstrated a significant impairment in psychomotor function and memory compared to placebo [64]. A study by Evans et al. in 171 patients suggested that the discontinuation of statin therapy could lead to the improvement of statin-induced cognitive impairment [65]. Based on such findings, the FDA issued a statement in 2012 advising healthcare professionals to inform patients about the potential risk of cognitive side effects before initiating statin treatment, while ultimately concluding that the cardiovascular benefits of statins generally outweigh the potential risks [66].

Some research has suggested a potential association between lipophilic statins, such as atorvastatin and simvastatin, and a higher incidence of reversible cognitive disturbances [67,68]. Lipophilic statins exhibit greater permeability across the BBB compared to their hydrophilic counterparts, potentially leading to more pronounced central nervous system effects. One retrospective cohort study indicated that the use of lipophilic statins was associated with an increased risk of developing AD compared to hydrophilic statins. Furthermore, the potency of the statin did not appear to significantly influence the risk of AD in this study [69].

The underlying mechanisms of statin-induced cognitive dysfunction are hypothesized to involve a reduction in cholesterol availability, which is crucial for the structural integrity of neuronal and glial cell membranes [70]. Furthermore, statin-induced depletion of coenzyme Q10 (CoQ10) may impair neuronal mitochondrial function by increasing oxidative stress [71]. Dumont et al. demonstrated that CoQ10 possesses the capacity to reduce Aβ production and improve cognitive function in a transgenic mouse model of AD [72].

It can be inferred that cholesterol depletion in neurons may elevate the risk of statin-associated cognitive impairment, potentially increasing susceptibility to AD [73]. In vitro and in vivo studies have demonstrated that lipophilic statins can induce the release of pro-inflammatory cytokines from human monocytes [74]. Furthermore, lipophilic statins have been shown to promote the production of reactive oxygen species (ROS) in monocytes [75]. Conversely, rosuvastatin, a hydrophilic statin, has exhibited anti-inflammatory effects by suppressing the secretion of pro-inflammatory cytokines from cultured microglial cells [76]. Thus, the induction of pro-inflammatory cytokines and ROS by lipophilic statins, but not typically by hydrophilic statins, could contribute to the adverse effects of this drug class on memory and potentially increase the risk of AD progression. In animal models, statin-induced reductions in isoprenoid and cholesterol levels have been associated with increased Aβ plaque deposition [77]. However, these experimental findings have not been consistently correlated with clinical outcomes in AD patients. Bagheri et al. found that activated microglia can release pro-inflammatory neurotransmitters, leading to neuroinflammation. Statins may exert neuroprotective effects by inhibiting microglial activation and the subsequent release of pro-inflammatory cytokines, thereby mitigating neuroinflammation and associated degenerative consequences [78]. This suggests a complex interplay where certain statin properties might have both detrimental and beneficial effects in the context of AD pathology.

Case reports documenting cognitive disturbances associated with individual variability in response to statins warrant consideration. For instance, an analysis of 60 case reports involving patients treated with atorvastatin and simvastatin revealed that nearly half of the cases experienced some degree of cognitive impairment within two months of initiating therapy, with these cognitive deficits generally resolving upon discontinuation of the statin [79].

Potential Beneficial Effects of Statins on Alzheimer's Disease

Statin therapy, particularly in dyslipidemic patients homozygous for the ApoE4 allele, has shown promise in potentially delaying the progression of AD [80]. Other studies have indicated a lower incidence and prevalence of AD among patients receiving statin treatment [81]. The protective effects of statins against AD development are often linked to the ApoE4 allele, which is associated with elevated circulating cholesterol levels. The expression of the ApoE4 allele and hypercholesterolemia are established risk factors for AD. Notably, approximately 95% of AD patients carry the ApoE4 allele, which is implicated in the disease's pathogenesis and disrupted

cholesterol metabolism in the brain [82]. Interestingly, early initiation of statin therapy may represent an effective preventative strategy for AD, although its efficacy might diminish in the more advanced stages of the disease [83]. It is crucial to acknowledge that pathological changes in the brain can commence 15 to 20 years prior to the emergence of clinical AD symptoms. Therefore, primary prevention strategies implemented during the preclinical phase of AD are paramount for mitigating disease progression [84].

Several studies have indicated that statin users exhibit better cognitive outcomes compared to non-users, with some suggesting this effect is more pronounced with lipophilic statins [85]. A preclinical study corroborates that the effects of statins may be independent of brain HMG-CoA reductase inhibition, potentially mediated through anti-inflammatory and antioxidant mechanisms [86]. A Taiwanese study involving 719 AD patients treated with statins demonstrated that early statin use significantly slowed AD progression [83]. Conversely, a prospective study following 6992 patients treated with various statins from 1993 to 2005 found no association between statin use (or lipophilicity) and the future development of AD [87]. A recent systematic review and meta-analysis concluded that statin therapy has no significant impact on neurocognitive function in patients with established AD, while suggesting that high-potency statins might be beneficial in preventing AD symptoms [88]. These conflicting findings underscore the complexity of the relationship between statin use and AD, necessitating further well-designed studies to clarify the potential benefits and risks in different patient populations and disease stages.

Evidence suggests that statins, either alone or in combination with angiotensin-converting enzyme inhibitors (ACEIs), have shown potential in preventing the development of AD and post-traumatic brain injury dementia [89]. An observational analysis indicated that one year of statin use was associated with a 20% reduction in AD incidence [90]. A systematic review and meta-analysis by Chou et al. demonstrated that statin therapy reduces the risk of mild cognitive impairment and AD, but appears to have no significant effect on VaD [91]. Furthermore, the administration of statins following a stroke has been associated with a decreased likelihood of developing post-stroke dementia [92].

Statins have been shown to enhance cerebral blood flow (CBF) by improving endothelial function and promoting the release of NO [93]. Furthermore, these agents may impede the formation and deposition of Aβ through their anti-inflammatory and antioxidant properties, as well as by inducing alpha-secretase activity [94]. Alpha-secretase plays a crucial role in the non-amyloidogenic processing of the amyloid precursor protein (APP), leading to the degradation of Aβ and potentially preventing its formation and subsequent hippocampal damage in AD [95].

Emerging evidence suggests that the impact of statin use on cognitive function may be influenced by an individual's ethnicity. For instance, research indicates that the effects of these drugs on cognitive deficits appear to be less pronounced in Mexican populations but more significant in African populations [96].

Neutral effects of statins on Alzheimer's disease

A substantial body of research also indicates that statins likely have no significant effect in preventing or alleviating the symptoms of established dementia. For instance, a double-blind study involving 406 patients with mild to moderate AD treated with simvastatin over 18 months demonstrated that the drug did not provide significant protection against disease progression [97]. Similarly, a randomized, placebo-controlled clinical trial by Feldman et al. showed that 72 weeks of atorvastatin treatment in 640 patients with mild to moderate AD did not result in any beneficial effects on their cognitive function [98]. Furthermore, a systematic review and meta-analysis encompassing 25 RCTs with 46,836 statin users concluded that treatment with this drug class was not associated with either improvement or worsening of cognitive performance [61].

It is important to note that many of the aforementioned studies primarily focused on cardiovascular outcomes rather than the long-term cognitive consequences of statin use. Furthermore, the design of some of these investigations may have inherent limitations in their ability to accurately detect subtle cognitive changes, particularly in patients with pre-existing cardiovascular disease [58]. The diverse effects of statins on cognitive function and the pathogenesis of AD, encompassing potential benefits, risks, and neutral findings, are summarized in Table 1.

Table 1. Effects of statins on cognitive function and Alzheimer's disease pathology.

Type of study	Results	References
Observational study	Long-term use of statins may affect cognitive function in healthy individuals and patients with dementia.	Bitzur [27]
Randomized controlled trials and observational studies	Statin use does not have a preventive effect on cognitive decline or dementia.	Power et al. [57]
Cochrane Review	The use of statins in older people at risk of vascular disease has no effect on preventing dementia.	McGuinness et al. [58]
Clinical trial	Atorvastatin caused reversible cognitive impairment in a phase 1 clinical trial.	Posvar et al. [62]
Double-blind randomized clinical trial	Lovastatin leads to significant impairment in psychomotor performance and working memory compared to placebo.	Muldoon et al. [64]
Patient survey-based analysis	Discontinuing statins improves cognitive impairment.	Evans et al. [65]
Observational and review study	Lipophilic statins are associated with a higher rate of reversible cognitive dysfunction.	Sahebzamani et al. [67]
Population-based, retrospective cohort study	Lipophilic statins are associated with a higher risk of developing AD compared to hydrophilic statins.	Zhang et al. [69]
Case report	About 50% of patients treated with atorvastatin and simvastatin develop cognitive dysfunction within two months.	Wagstaff et al. [79]
Comparative study and prospective clinical trial	Statin users, especially lipophilic statins, had superior cognitive scores compared to non-users.	Sierra et al. [85]
Population-based study	Early use of statins is associated with a significant reduction in the progression of AD.	Lin et al. [83]
Prospective study	The protective effects of statins against the progression of AD are independent of their degree of lipophilicity.	Haag et al. [81]
Systematic review and meta-analysis	Statin use has no detrimental effect on cognitive function in patients with AD.	Olmastroni et al. [88]
Observational study and meta-analysis	The use of statins is associated with a dose-dependent reduction in the risk of AD by about 20%.	Wood et al. [90]
Systematic review and meta-analysis	Statin therapy reduces the risk of mild cognitive impairment and AD, but has no effect on vascular dementia.	Chu et al. [91]
Meta-analysis and observational study	Statins have protective effects against dementia after stroke.	Yang et al. [92]
Randomized, double-blind, placebo-controlled trial	Simvastatin failed to provide any protective effect in patients with mild to moderate AD over 18 months.	Sano et al. [97]
Randomized placebo-controlled clinical trial	Treatment with atorvastatin for 72 weeks in patients with mild to moderate AD did not have a positive effect on cognitive function.	Feldman et al. [98]
Systematic review and meta-analysis	Statin treatment was not associated with cognitive dysfunction.	Ott et al. [61]

Evidence Gaps and Limitations

The evidence is mixed due to differences in study design (observational vs. RCT), statin type (lipophilic vs. hydrophilic), dosage, treatment duration, and patient populations (e.g., ethnicity, disease stage). Observational studies suggest correlations but cannot establish causality, while RCTs often lack long-term cognitive endpoints. Discrepancies may arise from varying BBB penetration, dose-response effects, or unaccounted comorbidities. For example, lipophilic statins may confer greater neuroprotection but also higher risks of cognitive side effects.

Conclusion

Statins' role in AD remains inconclusive due to heterogeneous evidence. Their cholesterol-lowering, anti-inflammatory, and antioxidant properties suggest neuroprotective potential, particularly in early AD or ApoE4 carriers, but risks of cognitive impairment, especially with lipophilic statins, persist. Observational studies show conflicting correlations, while RCTs lack consistent causal evidence. Limitations include inadequate focus on treatment duration, dosage, and patient stratification. Future research should prioritize long-term RCTs with cognitive outcomes as primary

endpoints, stratifying by statin type, disease stage, ethnicity, and ApoE genotype. Preclinical studies exploring dose-response relationships and miRNA pathways are also needed to clarify statins' therapeutic potential in AD. Current evidence supports continuing statin therapy in AD patients with metabolic disorders, balancing cardiovascular benefits against potential cognitive risks.

Highlights

What Is Already Known?

Alzheimer's disease is the leading cause of dementia, and statins, primarily used for cholesterol lowering and cardiovascular risk reduction, have been suggested to possess a dual role in its pathogenesis and treatment. While statins have established cardiovascular benefits in AD patients with comorbidities and exhibit potential neuroprotective properties through cholesterol modulation, anti-inflammatory, and antioxidant mechanisms, the existing evidence regarding their impact on cognitive function in AD remains heterogeneous and inconclusive. Prior research, often focused on cardiovascular outcomes, has yielded conflicting results, necessitating further investigation into the precise effects of statins on AD neuropathology, considering factors such as treatment duration and dose-response relationships.

What Does This Study Add?

This review clarifies that how statins affect thinking and memory in individuals with AD is still not fully understood. The research findings are mixed, with some suggesting potential advantages like reducing a harmful protein in the brain and protecting nerve cells. However, other studies raise concerns about statins possibly worsening thinking abilities. Importantly, the current research has limitations, especially in consistently looking at how long people take statins and at what dose. Therefore, more carefully planned future studies that primarily focus on cognitive outcomes are needed to clearly determine if and how statins can be helpful or harmful in Alzheimer's disease.

Authors' Contributions

SMA and MMAB conceived and designed the study, conducted research, and collected and organized data. GP, MMAB, and SMA wrote the initial and final draft of the article and provided logistical support. All authors have critically reviewed and approved the final draft.

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Conflict of Interest

Conducting this research did not result in any conflict of interest for the authors, and its results have been reported completely transparently and without bias.

Consent For Publication

Not applicable.

Ethics approval

This research project, with the code IR.BMSU.REC.1403.020, has been approved by the Ethics Committee of Baqiyatallah University of Medical Sciences.

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The extent of AI use

The authors used ChatGPT (OpenAI) to assist with language editing and clarity improvements during manuscript preparation. All content was reviewed and verified by the authors.

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