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Research Article

The Role of Statins and Alzheimer's Disease: Systematic Review of Recent Human Studies

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Abstract

Objective: To analyze the published evidence on the impact of statins in the prevention and progression of Alzheimer's disease, focusing on mechanisms, clinical efficacy, and population subgroups through a systematic review following PRISMA methodology.

Design: Systematic review.

Data Sources: PubMed, Embase, Web of Science, and Scopus databases were searched for studies published from January 2020 to June 2025. Priority was given to systematic reviews, meta-analyses, cohort studies, clinical trials, and population-based studies in humans, published in English and Spanish.

Study Selection: Relevant human studies focused on statins and Alzheimer's disease or dementia were included. After applying selection and exclusion criteria, 14 studies were included and 70 were excluded after full-text review.

Data Extraction: A rigorous methodological quality assessment was conducted according to international guidelines. Variables collected included study type, population, type and dosage of statins, treatment duration, main outcomes, and genetic factors.

Results: Most studies show that statin use is associated with an 18% to 32% reduction in dementia risk, including Alzheimer's disease. The protective effect is more evident with lipophilic statins and in specific genetic subgroups. However, heterogeneity and methodological limitations exist.

Conclusions: Statins may play a relevant role, especially in personalized approaches, but further clinical trials and pharmacogenomic studies are necessary to define their specific utility and practical applications.

Keywords: Statins; Alzheimer's Disease; Dementia

Introduction

Alzheimer's disease (AD) is currently the leading cause of dementia worldwide, representing a major healthcare, social, and economic challenge in the context of progressive population aging. It is characterized by a progressive and irreversible neurodegenerative course associated with cognitive and functional decline that, in most cases, leads to total patient dependency [1].

The etiology of AD is complex and multifactorial, involving an interaction of genetic, environmental, and vascular risk factors. Several pathophysiological hypotheses have been proposed, including β-amyloid plaque accumulation, formation of tau neurofibrillary tangles, oxidative stress, neuroinflammation, and alterations in cholesterol homeostasis and cerebral lipid metabolism [2]. In recent years, research has advanced in identifying new diagnostic biomarkers and in approving specific therapies targeting amyloid and tau, although their long-term impact on disease progression and quality of life remains under evaluation [3].

There are non-modifiable risk factors such as advanced age, genetics (especially the presence of the ApoE-ε4 allele), and female sex, which increase the likelihood of developing the disease. However, certain risk factors are modifiable, including diabetes, hypertension, obesity, sedentary lifestyle, low educational level, traumatic brain injury, and unhealthy habits [4,5].

The human brain is the organ with the highest cholesterol concentration in the body, which is essential for synaptic and neuronal integrity. Brain cholesterol is synthesized locally and is tightly regulated. Experimental models and cellular studies have shown that alterations in cholesterol homeostasis may facilitate the production and aggregation of β-amyloid peptide (Aβ), contributing to senile plaque formation, one of the pathological hallmarks of AD. Furthermore, the ApoE protein, involved in lipid transport, is an important modifier of AD risk, particularly the ApoE-ε4 allele, which increases risk and lowers the age of dementia onset [6].

Consequently, the search for preventive or disease-modifying treatments, as well as the implementation of prevention and early diagnosis programs, constitutes a priority in current AD research. In this context, the study of lipid factors, cholesterol control, and the possible neuroprotective role of statins has gained particular relevance as potential tools for preventing or slowing AD [7].

Materials and Methods

A systematic literature review was conducted following PRISMA guidelines. Articles were searched for in PubMed/MEDLINE, Embase, Web of Science, and Scopus, covering the period from January 1, 2020, to June 30, 2025. MeSH descriptors and free-text terms related to statins, Alzheimer's disease, dementia, and cognitive impairment were used, combined via Boolean operators (AND/OR) (e.g., "statins" AND "Alzheimer's disease" OR "dementia"). The inclusion criteria were:

- Studies published between 2020 and 2025.
- Clinical trials, cohort studies, case-control studies, systematic reviews, and meta-analyses regarding statins and Alzheimer's disease/dementia.
- Articles published in English or Spanish.

The following were excluded:

- Studies with fewer than 100 subjects.
- Low-quality narrative reviews.
- Studies focused exclusively on non-Alzheimer dementias.

Two independent reviewers screened titles and abstracts, selected potentially eligible articles, and reviewed the full text, applying the defined criteria. Discrepancies were resolved by consensus. Data regarding study design, population characteristics, statin type and exposure, cognitive outcomes, and measures of association were extracted from the included studies; a narrative synthesis of the results was performed due to the heterogeneity of study designs and outcomes.

Results

Statins primarily act by inhibiting HMG-CoA reductase, a key enzyme in cholesterol biosynthesis. However, they also exert relevant pleiotropic effects in the central nervous system. These include reduction of neuronal cholesterol, which influences amyloid precursor protein (APP) biogenesis and decreases β-amyloid (Aβ) production. Additionally, statins have anti-inflammatory and antioxidant activity, contributing to attenuation of oxidative stress and neuroinflammation characteristic of Alzheimer's disease. They also improve endothelial function and promote cerebral perfusion, which could positively impact neurological health.

Not all statins cross the blood–brain barrier equally: lipophilic statins (simvastatin, atorvastatin) show greater penetration and have demonstrated better results in some preclinical and clinical studies [8].

Clinical Effects of Statins in Alzheimer's Disease: Meta-Analyses and Systematic Reviews (2020–2025)

Various recent meta-analyses, systematic reviews, cohort studies, and clinical trials have evaluated the relationship between statin use and AD risk. Table 1 summarizes the main findings reported between 2020 and 2025.

Reference	Type of study	Number of patients	Type of statins	Main conclusions
Westphal Filho FL., *et al*. 2025 [8]	Meta-analysis	7,000,000 (55 studies)	Various	Statin use was associated with a significant reduction in the risk of dementia (HR 0.86; 14% reduction, 95% CI: 0.82–0.91) and Alzheimer's disease (HR 0.82; 18% reduction, 95% CI: 0.74–0.90). Subgroup and secondary analyses confirmed that the neuroprotective effect was consistent and more pronounced with certain types of statins and in Asian populations.
Olmastroni E., *et al*. 2022 [9]	Meta-analysis	1,200,000 (21 studies)	Various (simvastatin, atorvastatin, pravastatin, etc.)	Statins were associated with a 20% reduction in the relative risk of dementia and a 32% reduction in Alzheimer's disease.
Du Y., *et al*. 2025 [10]	Systematic review	500,000 (multiple studies)	Various	Continuous statin use reduces the risk of Alzheimer's disease by 19%–25% in individuals older than 75 years, highlighting the importance of sustained exposure.
Funaki D., *et al*. 2023 [11]	Retrospective cohort	83,309 Japanese adults aged 65 years or older	Various (atorvastatin, rosuvastatin, simvastatin, pravastatin, among others)	Statin use for primary prevention reduced the risk of all-cause mortality (HR 0.40; 95% CI: 0.33–0.48) compared with the control group. Specifically, subgroups with vascular comorbidities such as diabetes or dementia showed a stronger protective benefit against mortality and cardiovascular events than those without these comorbidities.
Torrandell-Haro G., *et al*. 2020 [12]	Retrospective study	288,515 individuals	Various (except fluvastatin, which showed no significant benefit)	Statin use was associated with a lower incidence of Alzheimer's disease (1.10% vs 2.37%; RR ≈ 0.46) and overall dementia (3.03% vs 5.39%; RR ≈ 0.56). A significant reduction in other neurodegenerative disorders was also observed, except with fluvastatin, which showed no effect (RR ≈ 0.91; p = 0.71).
Kim MY., *et al*. 2020 [13]	Retrospective study	264,036 individuals	Various	Statin use was associated with a lower risk of dementia, with stronger protection in women with cardiovascular comorbidity. Rosuvastatin showed the greatest effect (HR ≈ 0.82), followed by pravastatin and atorvastatin. In women, the effect was more modest (HR ≈ 0.96), whereas in men it was somewhat greater (HR ≈ 0.92).

Table 1: Main Recent Studies on Statins and Alzheimer's Disease (2020–2025).

Discussion

Recent evidence converges on the hypothesis that statin therapy could play a relevant role in primary and possibly secondary prevention of AD, especially in patients with vascular risk and ApoE-ε4 carriers. Their mechanisms extend beyond cholesterol reduction, encompassing anti-inflammatory, antioxidant, and synaptic modulation processes that could delay the onset of AD-related neurodegeneration.

However, heterogeneity of results, scarcity of randomized controlled trials, and variability in response according to statin type, dose, and genetic profile limit the generalized recommendation of statins as a universal preventive drug for AD. Identifying patient subgroups most likely to benefit is essential, considering factors such as age, sex, comorbidities, genetics, and statin type.

Key priorities for future research include randomized primary prevention trials in individuals at high risk of developing Alzheimer's disease, as well as pharmacogenomic and personalized medicine studies to stratify populations according to genetic profile, with special attention to ApoE-ε4 status. There is also a need to develop specific biomarkers capable of evaluating the impact of statins on neurodegenerative processes beyond traditional plasma lipid parameters.

Conclusions

The relationship between cholesterol, lipid metabolism, and the pathophysiology of AD is firmly established at both the experimental and clinical levels.

The use of statins—particularly in primary prevention settings, in contexts of high cardiovascular risk, or in carriers of the ApoE-ε4 allele—has been associated in recent studies with a statistically significant reduction in the incidence of AD and dementia; this effect appears particularly pronounced with prolonged exposure and with specific lipophilic statins.

Nevertheless, the available evidence is heterogeneous regarding study designs, patient populations, and the types and dosages of statins used, as well as in the definition of cognitive outcomes. Consequently, the evidence remains insufficient to recommend statins as a universal preventive therapeutic standard against AD.

The approach must be individualized, integrated into both pharmaceutical and medical care, and based on a careful risk-benefit assessment—particularly in older patients with cardiovascular comorbidities, frailty, or polypharmacy—while always taking patient preferences into account.

New large-scale, randomized, longitudinal studies are required—incorporating neurodegenerative biomarkers, neuroimaging, and genotyping (including ApoE)—to clarify the patient subgroups for whom statin use offers maximum effectiveness and safety, to determine the optimal duration of treatment, and to explore potential differences between statin classes.

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