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REVIEW ARTICLE

Statin use and dementia risk: A systematic review and updated meta-analysis

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Abstract

Dementia affects 55 million people globally, with the number projected to triple by 2050. Statins, widely prescribed for cardiovascular benefits, may also have neuroprotective effects, although studies on their impact on dementia risk have shown contradictory results. In this systematic review and meta-analysis, we searched PubMed, Embase, and Cochrane following Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. We assessed the risk of dementia, Alzheimer's disease (AD), and vascular dementia (VaD), with subgroup analyses by gender, statin type, and diabetes status. Fifty-five observational studies including over 7 million patients were analyzed. Statin use significantly reduced the risk of dementia compared to nonusers (hazard ratio [HR] 0.86; 95% confidence interval [CI]: 0.82 to 0.91; $p < 0.001$). It was also associated with reduced risks of AD (HR 0.82; 95% CI: 0.74 to 0.90; $p < 0.001$) and VaD (HR 0.89; 95% CI: 0.77 to 1.02; $p = 0.093$). Subgroup analyses revealed significant dementia risk reductions among patients with type 2 diabetes mellitus (HR 0.87; 95% CI: 0.85 to 0.89; $p < 0.001$), those with exposure to statins for more than 3 years (HR 0.37; 95% CI: 0.30 to 0.46; $p < 0.001$), and populations from Asia, where the greatest protective effect was observed (HR 0.84; 95% CI: 0.80 to 0.88). Additionally, rosuvastatin demonstrated the most pronounced protective effect for all-cause dementia among specific statins (HR 0.72; 95% CI: 0.60 to 0.88). Our findings underscore the neuroprotective potential of statins in dementia prevention. Despite the inherent limitations of observational studies, the large dataset and detailed subgroup analyses enhance the reliability of our results. Future randomized clinical trials are necessary to confirm these findings and enlighten clinical guidelines.

KEYWORDS
Alzheimer's disease, dementia, meta-analysis, neuroprotection, statins, systematic review, vascular dementia

Highlights

- Largest meta-analysis to date on statins and dementia risk, including 55 studies and more than 7 million patients.
- Statin use linked to lower risks of all-dementia, AD, and VaD.
- Numerous significant subgroup results highlight statins' diverse neuroprotective effects.
- Findings support statins as a public health tool, especially in low-income countries.
- Future research should explore the impact of statins across diverse patient populations.

1 | INTRODUCTION

Dementia is a complex neurodegenerative syndrome characterized by progressive cognitive decline, significantly impairing daily functioning.[1,2] Currently affecting an estimated 55 million people worldwide, the prevalence is projected to triple by 2050, primarily due to the aging global population.[3–5] Recent advancements in disease-modifying therapies (DMTs) for Alzheimer's disease (AD), including anti-amyloid monoclonal antibodies, offer new avenues for treatment by targeting amyloid-β plaques.[6–9] While these therapies have shown promise in slowing cognitive decline, their clinical benefits remain modest, and concerns about side effects, such as amyloid-related imaging abnormalities, limit their broad applicability.[6] Consequently, treatment remains largely aimed at symptomatic patients, underscoring the urgent need for effective preventive strategies.[2] With AD and vascular dementia (VaD) as the leading causes of dementia,[10,11] the development of preventive interventions is critical to address this growing global health crisis.[12]

Statins, widely prescribed for their lipid-lowering and cardiovascular benefits,[13,14] have gained significant attention in the past two decades for their potential neuroprotective effects.[15] These drugs act by inhibiting β-hydroxy β-methylglutaryl coenzyme A (HMG-CoA) reductase, which not only reduces cholesterol levels but also exerts pleiotropic effects on brain health.[16,17] Proposed mechanisms for these neuroprotective effects include anti-inflammatory properties, modulation of proteins linked to neurodegeneration, enhancement of cerebral blood flow through low density lipoprotein (LDL) reduction, and influence on neurotransmitter activity, all contributing to improved cerebral perfusion and reduced neuronal damage.[17–19] However, previous studies assessing the impact of statins on dementia risk have yielded contradictory results, with observational studies often suggesting a protective effect,[20–22] while clinical trials[23–26] have not demonstrated this benefit. This discrepancy underscores the complexity of understanding the role of statins in neurodegenerative diseases and highlights the need for further research to clarify their potential benefits in dementia prevention.

Addressing this gap is crucial, particularly given the important methodological issues of previous studies. Prior meta-analyses[27,28] have identified the protective effects of statins in reducing the development of dementia, though they often relied on limited outcomes and effect measures, without fully exploring alternative relationships. Our study goes further by incorporating a larger dataset, encompassing over 7 million patients from 55 observational studies, and performing analyses not previously undertaken, including detailed subgroup analyses by gender, statin exposure duration, type, the presence of diabetes mellitus, geographic region, and other factors. This comprehensive approach allows for a broader examination of outcomes, providing a more robust and nuanced understanding of the relationship between statin use and dementia risk. Our findings aim to fill the existing gap in the body of evidence, offering solid insights to guide preventive strategies for dementia and to mitigate the imminent public health crisis posed by the rising prevalence and costs of this condition.[29–31]

2 | METHODS

2.1 | Protocol and registration

This systematic review and meta-analyses were conducted following the Cochrane Handbook guidelines for Systematic Review and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Tables S1 and S2). This study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42024563349 on 10/07, 2024.

2.2 | Eligibility criteria

Studies were included if they met the following eligibility criteria: (1) Observational studies (cohort or case–control), (2) analyzing the risk of one or more of the following clinical outcomes: dementia (all-cause dementia), AD, or VaD, (3) involving patients aged 18 years or older who were statin users (4) and reporting data relevant to the association between statin use and any of the clinical outcomes of interest. Excluded were studies that (1) contained overlapping populations with other included studies, (2) lacked a control or placebo group for comparison, and (3) had designs such as case reports, reviews, opinion pieces, technical reports, guidelines, animal studies, in vitro experiments, or randomized clinical trials (Table S3).

Accordingly, we aimed to address the following question: Is there any association between statin use and the incidence of dementia?

2.3 | Search strategy

We conducted a systematic search of published studies in PubMed, Cochrane Central, and Embase. Additionally, our search extended to abstracts, articles, and scientific presentations. For each selected database, both Medical Subject Headings (MeSH) terms and input terms were adapted according to the specific syntax rules, utilizing Boolean connectors (OR, AND) for term combination, as detailed in Table S4. The search strategy was executed by authors (F.L.W.F. and A.M.A.). To ensure the inclusion of additional studies, we evaluated the references of the included articles and systematic reviews of the literature. Furthermore, an alert was set up in each database for notifications regarding the publication of studies relevant to our search criteria.

Studies identified in the databases and references from articles were integrated into the reference management software (Rayyan). Duplicates were removed through both automatic and manual screening. Titles and abstracts of the identified articles were independently reviewed by two authors (F.L.W.F. and F.M.T.) who also independently extracted data according to predefined search criteria and quality assessment protocols. In cases of discrepancy between reviewers, a third reviewer (A.M.A.) made the final decision on inclusion.

2.4 | Data extraction and risk of bias assessment

To summarize the main findings, three authors (F.L.W.F, P.R.M.L., and V.K.T.S.) independently collated data extracted from the included articles, including authors and year, study design, characteristics of the patient sample (size, age, time of follow-up, clinical data, and study group), assessment method, and conclusions regarding to evaluate the association of statins and the development of dementia.

We employed the Newcastle-Ottawa Scale (NOS) for the quality assessment of the observational studies. For each study, a 1 to 9 score was assigned, indicating whether it was low, moderate, or good quality. The domains assessed for case–control studies were: selection, comparability, and exposure, while for cohort studies were selection, comparability, and outcome. The quality assessment was independently analyzed by two researchers (F.L.W.F. and P.R.M.L.). The discrepancy between reviewers was resolved in agreement by the two reviewers for the final decision. We present in Figure S1 a summary of the quality assessment for the studies included in this systematic review. The form used to apply the NOS, along with the keywords utilized during the assessment, is also provided in Supplementary Material 1.

2.5 | Endpoints and definitions

The primary outcomes of interest were: (1) dementia risk (hazard ratios [HR], odds ratio [OR], relative risks [RR]), (2) AD risk (HR, OR), and (3) VaD risk (HR, OR). Although we refer to the outcome as AD risk, the correct term according to recent literature[11] is Alzheimer's dementia. This nomenclature was chosen because most included studies adopted it to define their outcomes. The secondary outcomes of interest were the relationships observed in subgroup analyses: (1) population with type 2 diabetes mellitus, (2) specific statins, (3) statins lipophilicity, (4) statins potency, (5) gender and its relationship with the primary outcomes, (6) exposure duration, and (7) study origin segregated by continent. Subgroup analyses were conducted only when (a) sufficient studies reported relevant subgroup data and (b) the effect sizes were presented in comparable metrics (e.g., HR, OR, or RR) across studies.

2.6 | R Statistical analysis

Treatment effects on reducing dementia risk were assessed using pooled HR, OR, and RR, each accompanied by 95% CIs. Heterogeneity among studies was evaluated using the I^2 and Tau^2 statistics. A random-effects model was applied across all analyses since we expected high heterogeneity due to the observational studies. Funnel plots and Egger test random-effect models will be utilized to assess publishing bias for pooled outcomes with high heterogeneity and more than 10 included studies. Statistical analyses were performed using R statistical software, version 4.2.3 (R Foundation for Statistical Computing). Sensitivity analysis was performed with the leave-one-out method and Baujat plots.

For subgroup analyses, only studies providing specific data for the subgroup of interest and presenting comparable effect measures were included. For example, the subgroup analysis for sex included only studies that explicitly reported data disaggregated by gender and reported in the same effect measure. Similarly, the diabetes subgroup analysis required explicit data on patients with type 2 diabetes mellitus. These criteria were established to ensure consistency and reliability in the analyses.

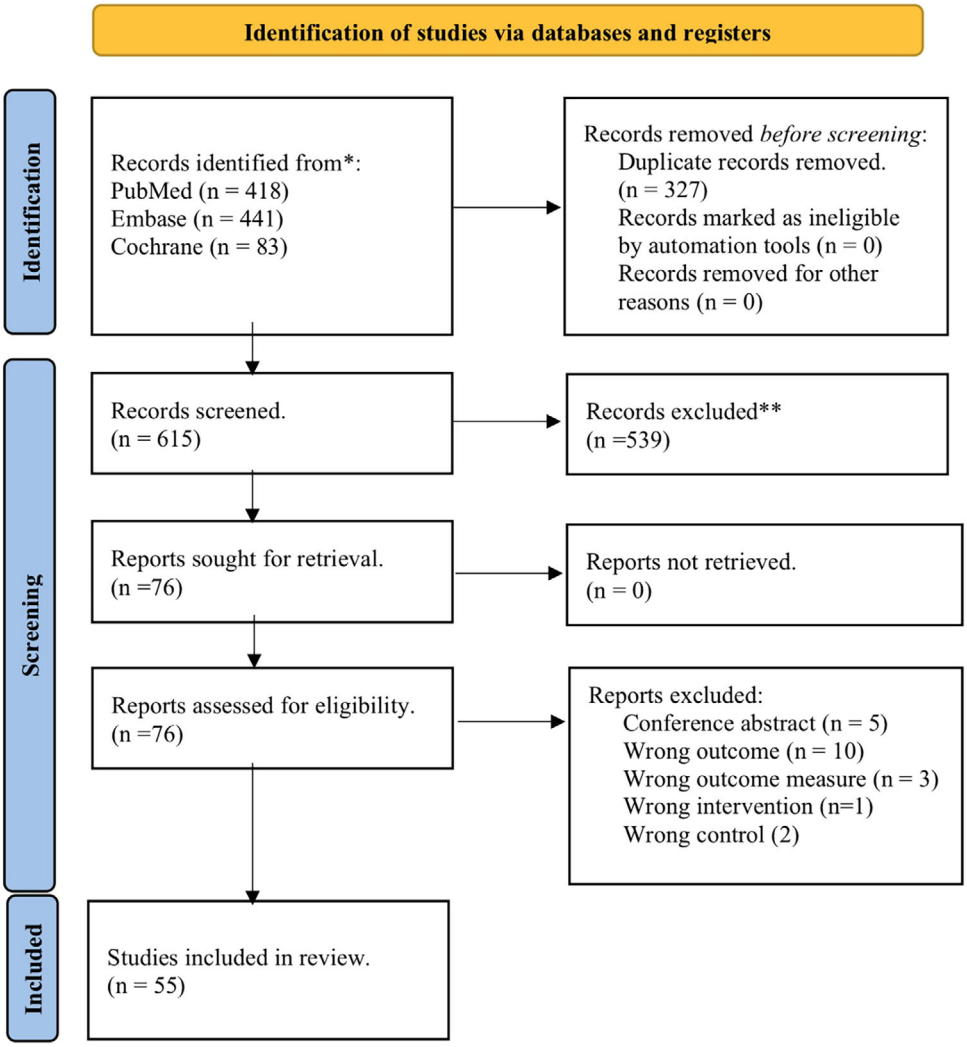

FIGURE 1 PRISMA 2020 flow diagram depicting the systematic review process, including database and register searches. **Records excluded during title and abstract screening for not meeting the eligibility criteria. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

3 | RESULTS

3.1 | Study selection and population characteristics

As detailed in Figure 1, the initial search yielded 942 studies. Seventy-six studies were thoroughly assessed for inclusion and exclusion criteria after duplicate articles and unrelated studies were eliminated. Ultimately, we included 55 studies in our systematic review (Supplementary Material 2), which collectively encompassed 7,786,651 participants. The mean age of participants was calculated based on studies that provided this information. Two separate calculations were performed to account for missing standard deviation (SD) values: one estimated the mean age with SD as 72.32 years (SD: 7.30), while the general mean age without SD was 72.50 years. The average proportion of male participants was 47.81%, and the mean follow-up duration was 7.13 years. Additional details on baseline population characteristics and statin therapy, including dosage, duration, and method of exposure assessment, are provided in the Supplementary Material (Tables S3 and S5).

Geographically, most studies were conducted in America (23 studies), followed by Asia (19), Europe (12), and Oceania (1). The assessed outcomes varied, with the majority of studies focusing exclusively on dementia (D) (29 studies). Other studies evaluated AD (10), D and AD (9), D, AD, and VaD (6), or D and VD (1).

In terms of study design, most were cohort studies (45 studies; 81.82%), followed by case–control studies (nine studies; 16.36%), and one study (1.82%) with characteristics of both designs. The effect measures reported were predominantly HR, reported in 42 studies (76.36%), followed by OR in eight studies (14.55%) and RR in five studies (9.09%). The subsequent meta-analyses adhered strictly to the effect measures reported in the original studies, ensuring consistency in the synthesis of results.

3.2 | All-dementia outcomes

The all-dementia outcome underwent extensive investigation due to the substantial number of studies reporting relevant data. The initial meta-analyses, aimed at providing a comprehensive overview of the effect of statins as a drug class on dementia risk, included 32 studies for HR analysis, 6 for OR analysis, and 5 for RR analysis. These analyses revealed a statistically significant protective effect of statins, with HR 0.8578 (95% CI: 0.8168–0.9009), OR 0.8677 (95% CI: 0.8187–0.9196), and RR 0.6745 (95% CI: 0.5203–0.8744) (Figure 2, S2A and S2B, respectively). However, these results exhibited high heterogeneity according to the I^2 statistic.

A subgroup analysis involving four studies also identified a statistically significant protective effect in patients with type 2 diabetes mellitus, with HR 0.8677 (95% CI: 0.8466–0.8892) and moderate heterogeneity (I^2 = 38%) (Figure 2). The influence of study origin was further explored by stratifying studies by continent. Asia emerged as the region with the highest number of included studies (17) and demonstrated the greatest protective effect, with HR 0.8366 (95% CI: 0.7960–0.8793). The Americas, represented by eight studies, demonstrated a statistically significant protective effect (HR 0.8751; (95% CI: 0.8464–0.9048). Conversely, Europe (six studies) and Oceania (one study) displayed confidence intervals crossing the line of neutrality. Regarding heterogeneity, I^2 statistics revealed moderate heterogeneity in the Americas (I^2 = 42.6%) and high heterogeneity in Asia and Europe (Figure S2C).

3.2.1 | Analyses of statin therapy properties

Several subgroup analyses were conducted to assess the effects of varying durations of statin exposure and the distinct properties of the drugs within this class.

The primary finding was a progressive increase in the protective effect of statins with longer exposure durations. In a subgroup analysis of five studies evaluating patients exposed to less than 1 year of statin therapy, the HR was 1.0723 (95% CI: 1.0017–1.1479). Another subgroup comprising four studies with exposure durations of 1 to 3 years showed HR 0.7996 (95% CI: 0.6396–0.9997). Finally, a subgroup analysis of patients exposed to more than 3 years of statin therapy, including six studies, revealed a statistically significant 63% reduction in dementia risk (HR 0.3685; 95% CI: 0.2979–0.4558; $p < 0.001$). Heterogeneity was moderate in the subgroup with less than 1 year of exposure but high in the remaining groups (Figure 3). Two additional analyses involving smaller datasets and different exposure durations are presented alongside the aforementioned results in Figure S2D.

An analysis focusing on statin lipophilicity included five studies reporting this characteristic. Statistically significant results were observed only for lipophilic statins (HR 0.8501; 95% CI: 0.7726–0.9354), with high heterogeneity (I^2 = 81.5%) (Figure S2E). Regarding statin potency, only two studies provided relevant data. Subgroup analysis revealed statistically significant results exclusively for high-potency statins (HR 0.7232; 95% CI: 0.6706–0.7799) (Figure S2F). Finally, subgroup analyses of specific statins (simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, and pitavastatin) were conducted (Figure S2G). Of these, only fluvastatin, atorvastatin, and rosuvastatin showed statistically significant results. Rosuvastatin, analyzed in a subgroup of 7 studies, demonstrated the greatest risk reduction for dementia, approximately 28% (HR 0.7242; 95% CI: 0.5992–0.8753), albeit with high heterogeneity (I^2 = 93%). Atorvastatin reduced dementia risk by approximately 11% in a subgroup with eight studies, and fluvastatin by 7%, in an analysis with seven studies.

3.2.2 | Analyses regarding gender

Only six studies reported results stratified by gender, which were included in this analysis. Men experienced a slightly greater reduction in dementia risk compared to women (HR 0.8555; 95% CI: 0.7792–0.9392; and HR 0.8618; 95% CI: 0.7489–0.9919, respectively) (Figure S2H). A more detailed investigation into gender-specific effects of individual statins was conducted using three studies providing these data. Among male patients, atorvastatin was the only statin showing statistical significance (HR 0.8797; 95% CI: 0.7997–0.9676). Conversely, in women, pravastatin, lovastatin, and rosuvastatin demonstrated statistically significant effects. Rosuvastatin exhibited the most pronounced risk reduction among women, with HR 0.6646 (95% CI: 0.4773–0.9254), albeit with high heterogeneity (I^2 = 75%) (Figure S2I).

3.3 | AD

The analyses of AD risk included 18 studies for H analysis and eight studies for OR analysis. Statins were associated with a statistically significant protective effect. The pooled HR was 0.8165 (95% CI: 0.7393–0.9018), with moderate heterogeneity (I^2 = 52.9%) (Figure 4A). Similarly, the OR analysis indicated a protective effect, with an OR of 0.5778 (95% CI: 0.4250–0.7856), though the heterogeneity was high (I^2 = 76%) (Figure S3A). Similarly to the previous All-dementia outcome, the influence of study origin was assessed through subgroup analysis by continent. Asia demonstrated the greatest reduction in AD risk, although this analysis included only three studies, yielding an HR of 0.7109 (95% CI: 0.6308–0.8012). Europe also contributed three studies; however, the results were not statistically significant. The Americas, which included the largest number of studies (11), showed a statistically significant protective effect with an HR of 0.8544 (95% CI: 0.8278–0.8819) and low heterogeneity (I^2 = 14.9%) (Figure S3B).

3.3.1 | Analyses of statin therapy properties

Subgroup analyses were conducted to explore the effects of statin therapy duration and lipophilicity. Exposure duration analyses revealed

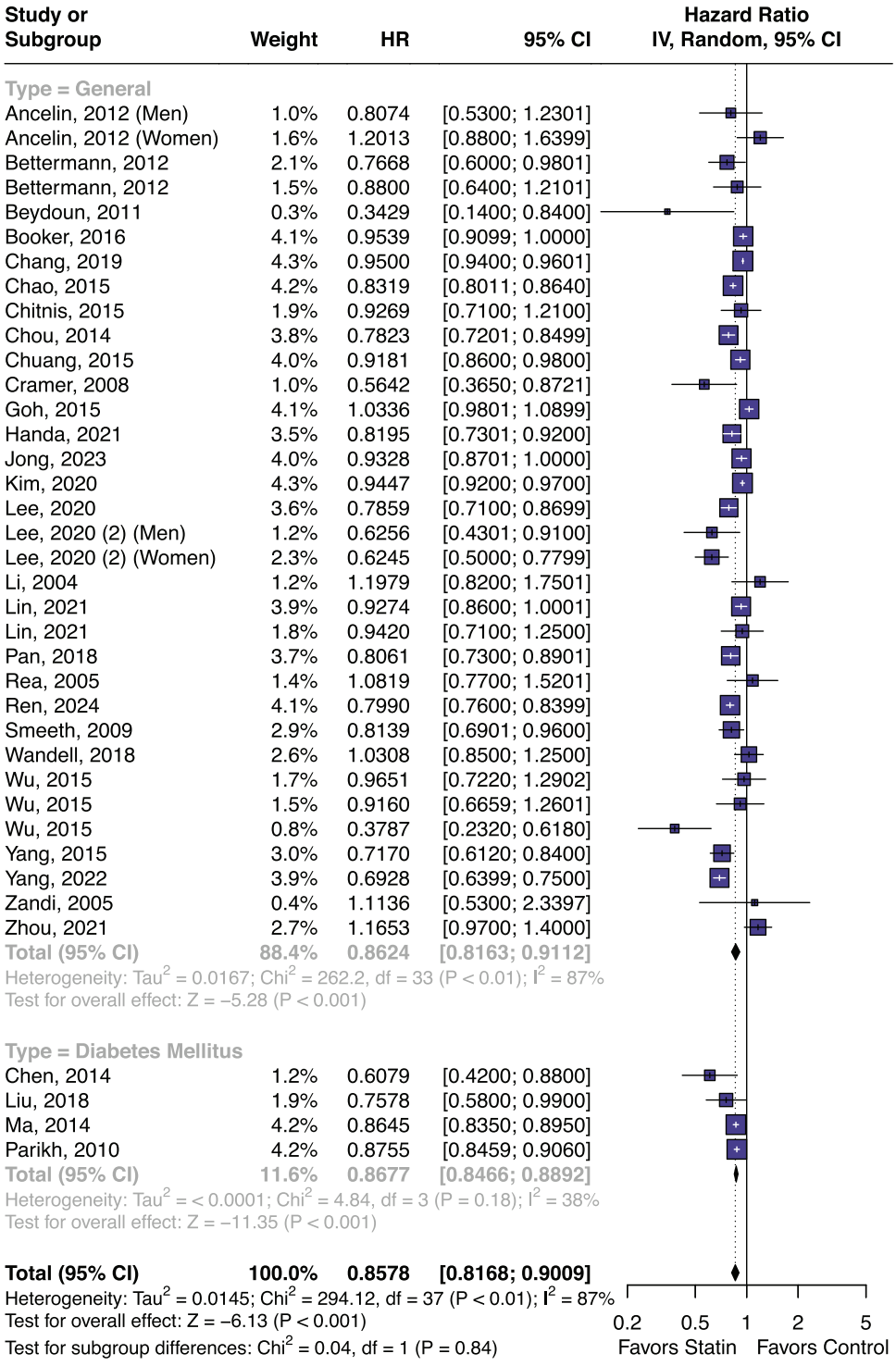

FIGURE 2 Forest plot of statin use and risk of all-cause dementia in the general population and in a subgroup of patients with type 2 diabetes mellitus. The HR pooled analysis demonstrated a significant protective effect of statins on both groups. HR, hazard ratios.

no statistically significant results across all subgroups, including durations of less than 1 year, 1–3 years, and greater than 3 years. These subgroups consisted of two, two, and three studies, respectively (Figure S3C). Analyses based on statin lipophilicity included five studies per subgroup and showed statistically significant results for both hydrophilic and lipophilic statins, with low heterogeneity in both cases. Hydrophilic statins demonstrated a slightly stronger protective effect, with an HR of 0.8339 (95% CI: 0.7645–0.9096), compared to lipophilic statins, which had an HR of 0.8497 (95% CI: 0.8220–0.8784) (Figure S3D).

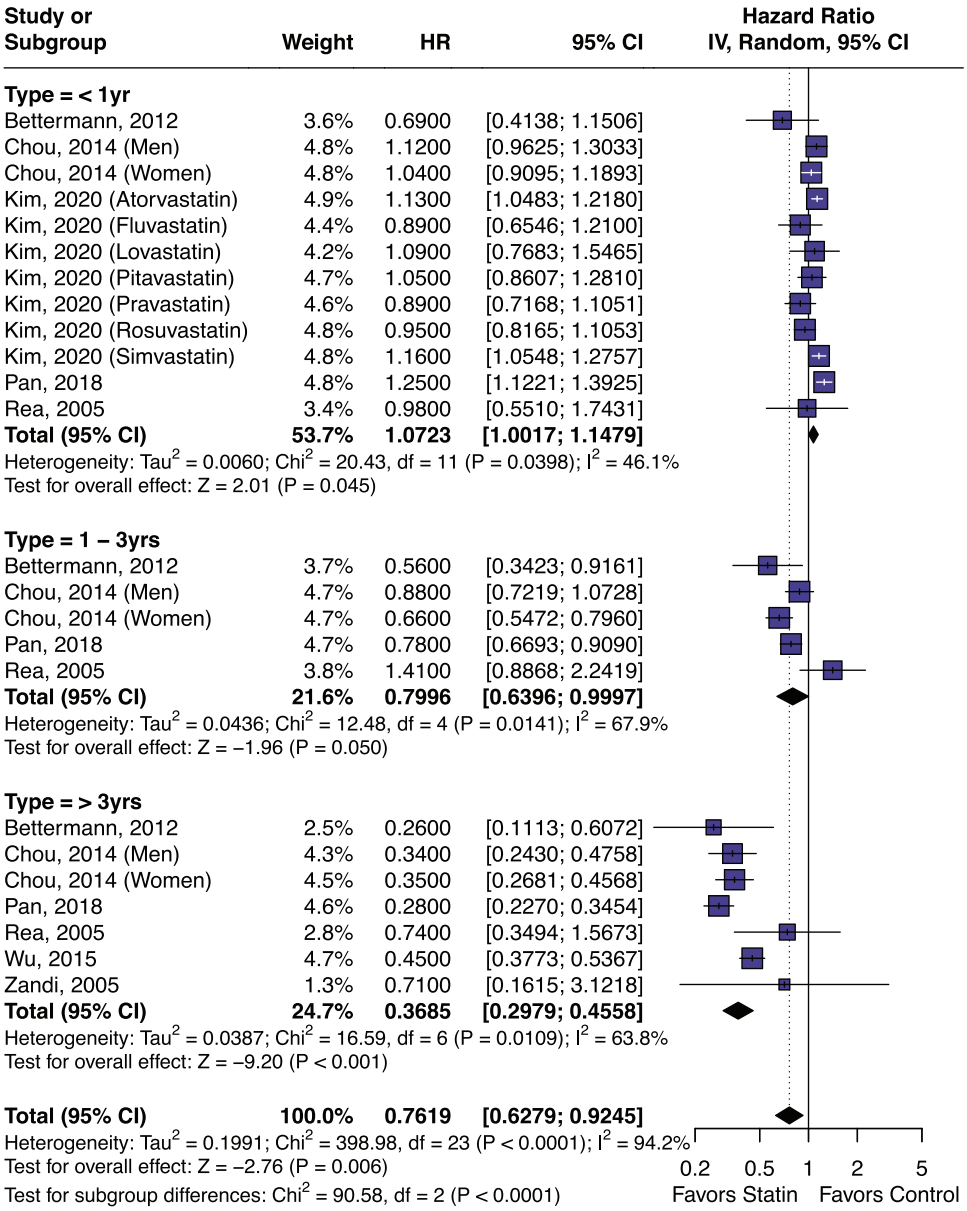

FIGURE 3 Forest plot of statin use and risk of all-cause dementia stratified by exposure duration (patients exposed to less than 1 year of statin therapy, 1–3 years, and greater than 3 years). The HR pooled analysis highlights the time-dependent protective effect of statin use on all-cause dementia risk. HR, hazard ratios.

3.4 | VaD

The analysis of VaD outcomes revealed mixed findings. Hazard ratio analysis, based on five included studies, did not show statistical significance, with HR 0.8857 (95% CI: 0.7690–1.0202) (Figure 4B). However, OR analysis, including only two studies, demonstrated a statistically significant protective effect, with OR 0.7131 (95% CI: 0.6230–0.8163) (Figure S4A). Subgroup analysis by continent was restricted to the Americas and Asia, as these were the only regions with studies reporting VaD outcomes. In the Americas, the results were not statistically significant. Conversely, Asia, with three included studies, exhibited a statistically significant protective effect, with HR 0.8590 (95% CI: 0.7534–0.9793) (Figure S4B).

3.5 | Quality assessment

The quality assessment using the NOS revealed a range of scores across the included studies, reflecting overall good methodological quality. The scores ranged from 6 to 9, with an average of 7.62 (SD: 0.83), indicating a moderate to low risk of bias. Notably, 58.2% of studies (32 out of 55) scored ≥8, highlighting their strong methodological rigor. Cohort studies generally exhibited higher methodological quality compared to case–control studies. Cohort studies had scores ranging from 6 to 9, with an average of 7.71 (SD: 0.84). Several cohort studies achieved the maximum score of 9, including Chang et al., 2019, Li et al., 2020, Rajan et al., 2024, Ren et al., 2024, Torrandell-Haro et al., 2020, Wolozin et al., 2007, and Zissimopoulos et al., 2016. However, some

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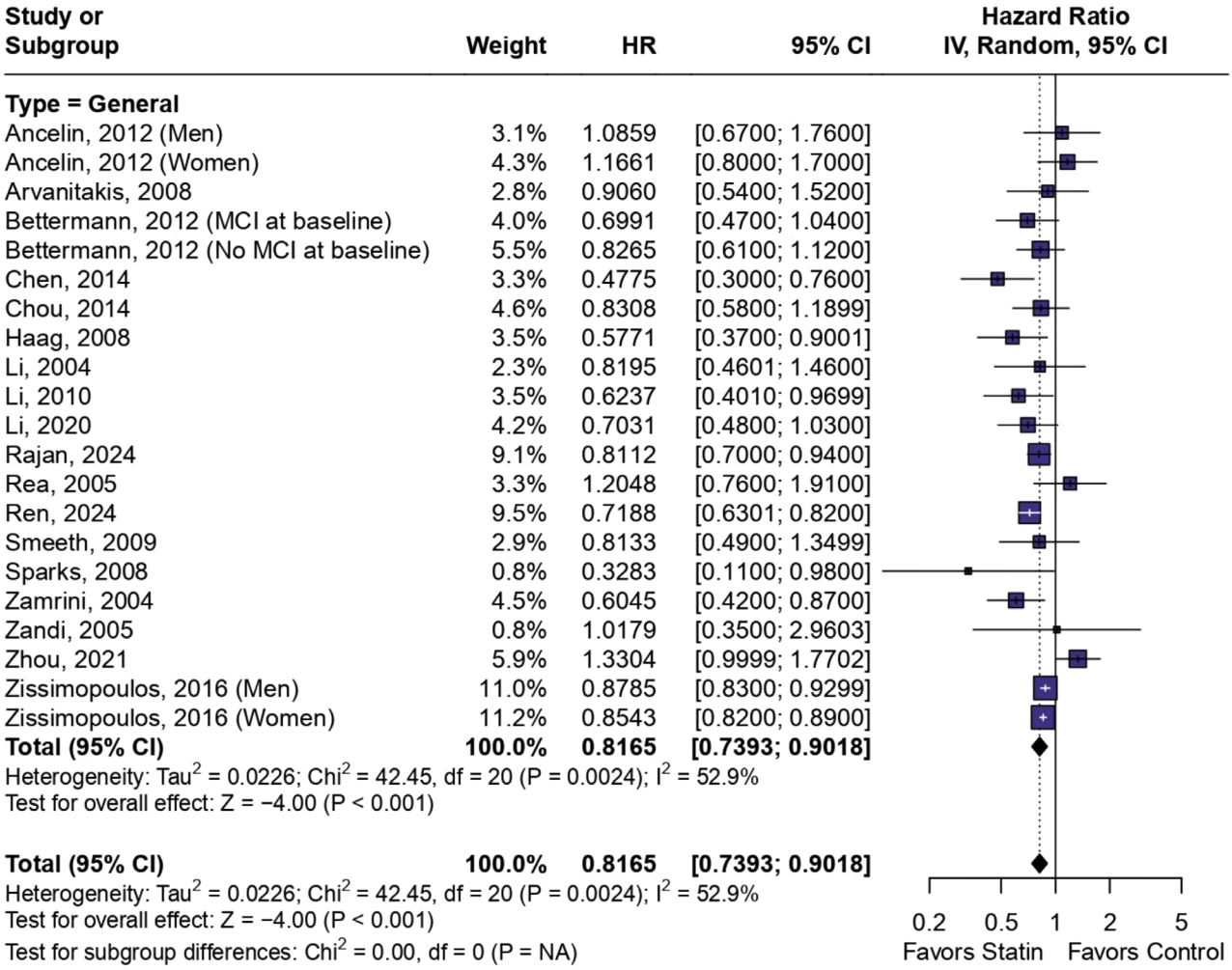

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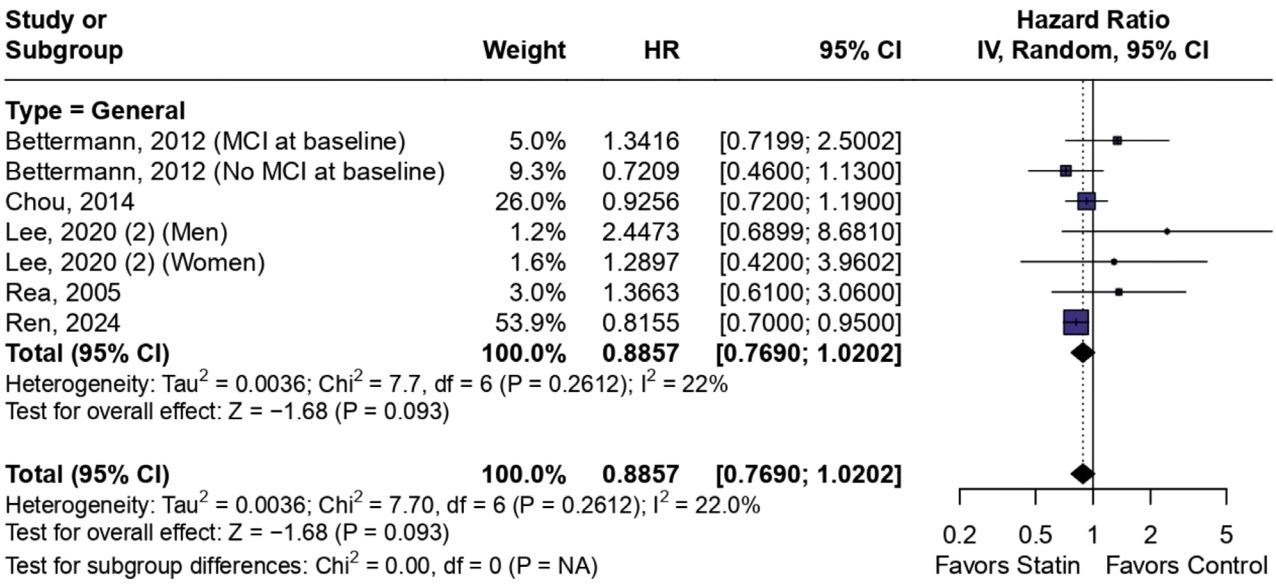

FIGURE 4 Forest plot depicting the association between statin use and the risk of AD and VaD in the general population. (A) The pooled HR analysis revealed a significant protective effect of statins against AD. (B) The pooled HR analysis did not indicate a statistically significant protective effect of statins against VaD. AD, Alzheimer's disease; HR, hazard ratios; VaD, vascular dementia.

cohort studies, such as Dufouil et al., 2005, Handa et al., 2021, Khokhar et al., 2018, and Rea et al., 2005, scored 6, reflecting potential concerns regarding comparability and outcome domains. Case–control studies exhibited a narrower range of scores, from 7 to 8, with an average score of 7.33 (SD: 0.50). Among these, the highest score of 8 was achieved by Zingel et al., 2021, Rockwood et al., 2002, and Wu et al., 2015. In contrast, Hajjar et al., 2002, a hybrid case–control/cohort study, scored 6, reflecting methodological limitations in comparability.

4 | SENSITIVITY ANALYSIS

Both All-dementia HR and AD HR outcomes had high heterogeneity. Funnel Plots and Egger tests were performed to further comprehend the impact of this heterogeneity on the robustness of our results and assess the publication bias. Figure 5A represents the all-dementia HR outcome, showing substantial asymmetry ($p < 0.05$). As a result, there is the possibility of publishing bias. The Egger test results for this outcome reveal the presence of publication bias, as evidenced by the significant *p*-value (0.0105) and negative bias estimate (−1.4541). Conversely, the AD HR outcome has no significant indication of asymmetry (Figure 5B), as confirmed by the Egger test with $p > 0.05$ ($p = 0.3090$) and nonsignificant bias estimate (−0.4240). Thus, there is no apparent sign of publishing bias, with a minor and insignificant estimate.

Some of the other assessed outcomes had high heterogeneity. However, leave-one-out analysis and Baujat plots were chosen since less than 10 studies were included in each outcome (Figure S5). The subgroup analysis for DM patients all-dementia HR resulted in statistically significant with mild heterogeneity. Thus, leave-one-out analysis was performed, indicating that Chen et al., 2014 was the study with major contribution to overall heterogeneity. Excluding this study from analysis, the heterogeneity lowered to 0% (I^2), with a HR of 0.87 (95% CI: 0.85–0.89) (Figure S5N).

The lipohilic statin subgroup from all-dementia HR outcome also had high heterogeneity and leave-one-out analysis was conducted. In this subgroup, Chang et al., 2019 accounted for the greater heterogeneity. When excluded from analysis, the resulting HR is 0.80 (95% CI: 0.76–0.86) and 0% I^2 (Figure S5B).

Rosuvastatin in men HR leave-one-out sensitivity analysis was also performed (Figure S5J). The only significative heterogeneity reduction happens when Chou et al., 2014 is omitted from analysis (HR 0.87; 95% CI: 0.80-0.95; $I^2 = 0\%$). Rosuvastatin in women HR leave-one-out sensitivity analysis was similarly conducted (Figure S5K) and revealed that both Chou et al., 2014 and Kim et al., 2020 contribute to the outcome heterogeneity. Excluding Chou et al., 2014 (HR 0.81; 95% CI: 0.76–0.88; $I^2 = 0\%$) and Kim et al., 2020 (HR 0.54; 95% CI: 0.40–0.72; $I^2 = 0\%$). Lastly, atorvastatin in men HR was performed (Figure S5L), identifying two sources for the heterogeneity: Chou et al., 2014 and Kim et al., 2020. When the first is excluded, the heterogeneity becomes 0% (I^2) with an HR 0.92 and 95% CI: 0.88 to 0.96. Excluding the second, the resultant HR is 0.83, with 95% CI of 0.73 to 0.93 and $I^2 = 0$.

VaD HR resulted in statistically nonsignificant with low heterogeneity. However, when performed the leave-one-out and excluding Lee J et al., 2020 (men), the heterogeneity became 2% (I^2) and resulted in an HR of 0.87 (95% CI: 0.82–0.98) (Figure S5O).

The Baujat plot for all-dementia OR (Figure S5Q) enables us to identify Rockwood et al., 2002 as the most contributor for the outcome heterogeneity, whereas Zingel et al., 2021 (Medium Dosage) has the most influence on overall results. Even after identifying the study that most contributed to heterogeneity, the leave-one-out analysis did not yield significant results, with high I^2 remaining unchanged (Figure S5P). Additionally, the most substantial reduction in I^2 (59%) was observed when Rockwood et al., 2002, was excluded from the analysis.

Given the substantial heterogeneity of AD OR outcome, a leave-one-out sensitivity analysis was performed (Figure S5R). The study that influenced the most in the heterogeneity of this outcome was Kim et al., 2021. The leave-one-out analysis revealed that when it is excluded, the OR becomes 0.53 (95% CI: 0.42 to 0.66) with an I^2 of 0%, representing the absence of heterogeneity.

The sensitive analysis for RR of all dementia was carried out by methodically excluding each individual study included in the meta-analysis (Figure S5T). When both Redelmeier et al., 2019 and Torrandell-Haro et al., 2020 were excluded the heterogeneity reached 0%. This indicates that they are both contributing to overall heterogeneity. Excluding Redelmeier et al., 2019, the RR was 0.56 (95% CI: 0.54–0.58) with an I^2 of 0.0%. Leaving out Torrandell-Haro et al., 2020 resulted in an RR of 0.87 (95% CI: 0.81–0.93) and an I^2 of 0%.

5 | DISCUSSION

Our systematic review and meta-analysis resulted in a comprehensive study, encompassing 55 observational studies and an unprecedented number of 7,786,651 patients in the literature on this topic. The main findings from the pooled analyses were as follows: (1) statin use significantly reduced the risk of all dementia, AD, and VaD; (2) longer exposure durations were associated with greater protective effects; (3) geographic variation highlighted stronger effects in Asia and America; (4) rosuvastatin showed the greatest reduction in dementia risk; (5) male patients experienced slightly greater risk reductions; and (6) the results were consistent across the meta-analyses with different effect measures used in the study.

Dementia is one of the most common neurodegenerative diseases, currently affecting approximately 55 million people worldwide, with 60% of these individuals living in low- and middle-income countries.[3] Epidemiological data show that this condition correlates with age, affecting 1.83% of individuals aged 60–69 years and rising steeply to 35.72% in those aged 90–99 years.[4] As the global population continues to age, these trends present significant challenges for public health systems worldwide.[31] The current economic burden generated by dementia costs to public health was estimated to reach 1.314,4 billion US dollars in 2019. Individually, each patient demands 23.796 US dollars.[30] Given this, strategies for dementia prevention are increasingly being studied in view of understanding the risk and protective factors associated with this condition.[32–37]

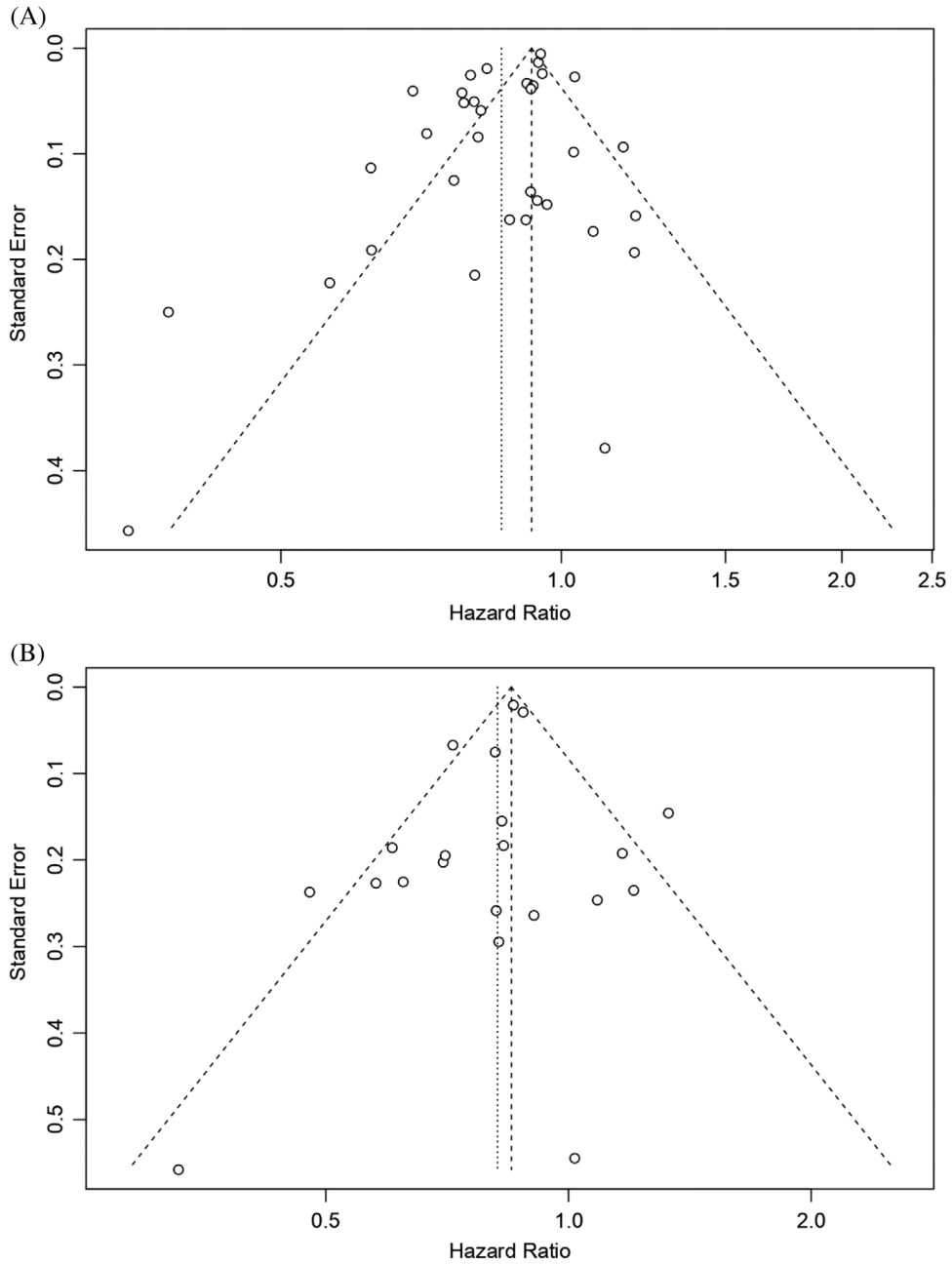

FIGURE 5 Funnel plots for sensitivity analysis. (A) Funnel plot of 34 studies included in all-dementia hazard ratio meta-analysis. (B) Funnel plot of 21 studies included in Alzheimer´s disease hazard ratio meta-analysis.

Conversely, statins emerge as an extremely relevant class of medications due to their low cost, wide global availability, and proven benefits in primary and secondary prevention of cardiovascular events through the reduction of serum cholesterol levels. This is achieved by inhibiting the mitochondrial enzyme HMG-CoA, also known as 3-hydroxy-3-methylglutaryl coenzyme A.[13,14,38,39] In addition to this primary mechanism of action, other mechanisms have been investigated due to the pleiotropic effects (independent of cholesterol) observed with statins.[17,19,40] Among these cholesterol-independent benefits, their anti-inflammatory effects, modulation of the transcriptional activity of proteins with neurodegenerative properties, and influence on neurotransmitter activity stand out, particularly due to their significant implications for the central nervous system (CNS).[17,18,41–51] Such mechanisms may exert an important role in cognitive function, with evidence both supporting and refuting these hypotheses.[16] Our results, consistent with previous studies by Poly et al., 2020 and Olmastroni et al., 2022, indicate significant dementia risk reduction, supporting the potential neuroprotective role of this class of medications[27,28] Despite the statistically significant results, there is considerable heterogeneity in the pooled analysis for all dementia HR, OR, and RR, which could impact the robustness of the findings. Such heterogeneity was anticipated due to the inclusion of a

substantial number of observational studies employing different diagnostic methods for dementia and distinct approaches to assessing medication use. Additionally, our subgroup analysis revealed a progressive increase in the protective effect of statins with longer exposure durations, culminating in a 63% reduction in dementia risk among patients exposed for more than 3 years. These findings further support the hypothesis that statins' neuroprotective effects may depend on sustained exposure, reinforcing their potential role as preventive agents.

The pharmacological properties of statins, particularly their ability to cross the blood–brain barrier (BBB), and their potential effects on the CNS are critical factors influencing their differential impact on neurodegeneration. Lipophilic statins, such as atorvastatin and simvastatin, exhibit greater passive diffusion across cellular membranes, facilitating significant BBB penetration.[16,17] This property enables them to exert direct effects on brain cholesterol metabolism, amyloid-beta processing, and neuroinflammation.[18] However, their broad tissue distribution also raises concerns about potential off-target effects, including neurotoxicity in specific contexts.[52] In contrast, hydrophilic statins, including pravastatin and rosuvastatin, require active transport mechanisms for cellular entry, resulting in a more hepatoselective profile and minimal CNS exposure.[53] While this limits their direct neuroprotective effects, it also minimizes the risk of neurotoxicity, presenting a safer profile for patients with CNS vulnerabilities.[19] Our study revealed distinct patterns in the effects of these statins. Subgroup analyses demonstrated a statistically significant risk reduction for all-cause dementia among lipophilic statins, whereas the results for hydrophilic statins were not significant. Notably, in the analysis for specific statins, rosuvastatin exhibited the greatest protective effect. This finding aligns with its reduced propensity for neurotoxicity and suggests that systemic mechanisms, such as anti-inflammatory and cholesterol-lowering effects, may play a critical role. Conversely, in an analysis focused on AD, a different scenario was identified. Both hydrophilic and lipophilic statins demonstrated significant protective effects, highlighting a nuanced relationship that will be further explored in the AD section of this discussion.

The geographical variation observed in our subgroup analyses provides valuable insights into the potential interplay between regional cardiovascular risk factors and the observed effectiveness of statin use in reducing dementia risk. Our study identified Asia as the continent with the most pronounced protective effect against all-cause dementia and AD. These findings may be partly explained by the high prevalence of modifiable cardiovascular risk factors in Asian populations, including hypertension, diabetes, and dyslipidemia. This heightened burden of cardiovascular risk factors could make Asian populations particularly responsive to the pleiotropic effects of statins. In America, the protective effect of statins was also statistically significant, though slightly less pronounced than in Asia. The lower heterogeneity observed in these studies may reflect more consistent management of cardiovascular risk factors in these regions. However, it is important to note that all studies included from the Americas were conducted exclusively in populations from the United States and Canada, leaving Latin American populations unrepresented. The subgroup analysis for European studies did not demonstrate significant reductions in dementia risk or AD. This may reflect differences in healthcare systems and prescribing practices and further analysis identifies a critical gap in representation from Eastern Europe. Oceania had also only one study, exclusively from Australia, further limiting insights into population diversity. These findings align with the previous study from The Global Cardiovascular Risk Consortium, which similarly identified significant gaps in representation for Africa, Latin America, and certain regions of Asia and Europe.[54] The under-representation of these populations highlights an important limitation in the global applicability of our findings and underscores the importance of prioritizing diverse, globally inclusive research efforts to better understand regional variations and current scenarios worldwide.

Gender differences appear to be a significant determinant in neuroscience studies through playing a key role in differences observed between men and women in clinical practice.[16,55] A previous meta-analysis assessing the prevalence of dementia between male and female sexes identified a higher prevalence of dementia and AD among females.[4] Following this trend of understanding sex differences, our study identified, contrary to the previous meta-analysis by Olmastroni et al.,[28] a statistically significant difference for dementia risk stratified by gender, indicating a higher risk reduction in male patients. An additional analysis performed in our study, stratified by specific statin agent in each gender, identified atorvastatin as the only statin with statistical significance among men. In the female population, the use of lovastatin, pravastatin, and rosuvastatin demonstrated statistical significance in reducing the risk of dementia, with rosuvastatin showing the greatest reduction. This difference in the number of statistically significant results for each gender highlights the greater homogeneity observed among the female population in the three studies included in this analysis: Chou et al,. 2014, Hippisley-Cox et al., 2010, and Lee et al., 2022. Finally, the leave-one-out analyses for the effects of Rosuvastatin and Atorvastatin, the two agents with the highest potential for dementia risk reduction according to our results, indicated that both Chou et al., 2014, and Kim et al., 2020, were the primary contributors for the observed heterogeneity in the male population. Their exclusion resulted in an I^2 heterogeneity of 0% and a statistically significant reduction in dementia risk.

AD is the most prevalent etiology of dementia, accounting for 60% to 80% of cases of this clinical syndrome,[11,35] being characterized by elevated levels of amyloid-beta in the composition of extracellular senile plaques and hyperphosphorylated tau in intracellular neurofibrillary tangles.[10] Our subgroup analysis for AD identified a statistically significant risk reduction among statin users, which is aligned with previous meta-analyses.[28] A subgroup analysis revealed a significantly higher risk reduction, with low heterogeneity, for developing this condition among hydrophilic statin users when compared to lipophilic statin users. This result contradicts previously proposed concepts by Carlsson et al. in 2009 that only lipophilic statins would be effective in reducing the risk for AD.[56] Our results robustly reinforce the role of statins as a preventive strategy for AD. Other lipid-lowering agents were analyzed in observational studies included in our systematic review, such as Ancelin et al., 2012, Dufouil et al., 2005, and

Rockwood et al., 2002, without demonstrating statistical significance in reducing the risk of dementia or AD.

VaD results from a continuum of vascular cognitive impairment (VCI), a recently recognized entity predominantly caused by cerebrovascular diseases,[57,58] that affects 5% to 10% of individuals with dementia.[11] However, when considered in association with other mechanisms causing dementia, in a concept known as mixed dementia,[59] it can account for 20% to 40% of cases, representing the second most prevalent etiology of dementia.[60] Our analysis of statin use associated with VaD revealed a significant risk reduction of up to 30% among statin users with moderate heterogeneity in the OR analysis and 11% with no statistical value and low heterogeneity in the HR analysis. This discrepancy between both effect measures prompted us to conduct detailed sensitivity analyses for these outcomes. A leave-one-out analysis of the VaD OR did not yield significant results. However, when performing this analysis on the VaD HR, we identified that the male population in the study by Lee J et al., 2020 was the primary contributor to the heterogeneity in this analysis. Excluding this study reduced the heterogeneity to 2% (I^2) and resulted in a statistically significant 13% reduction in VaD risk. Current strategies for the primary prevention of VCI involve modifying vascular risk factors such as hypertension, hypercholesterolemia, and diabetes, which are implicated in the pathophysiology of this condition.[60] Among these, treating hypercholesterolemia is currently recommended as a reasonable preventive modality for individuals at risk for VCI, with class IIb/level B evidence.[61] Secondary prevention, in cases of ischemic stroke or transient ischemic attack (TIA), follows the guidelines of the American Heart Association and American Stroke Association.[62] Ultimately, patients who already have VaD but have not had a previous episode of ischemic stroke or TIA should initiate statin therapy according to the patient's cardiovascular risk, as recommended by the most recent evidence.[13,14] Our results provide greater robustness to the scientific evidence supporting statins as a protective factor for VaD and risk of VCI.

The neuroprotective potential of statins, as demonstrated in our systematic review and meta-analyses of observational studies, has not been consistently validated in randomized controlled trials (RCTs). The PROSPER trial,[23] the only long-term RCT focused on an elderly population, did not find significant differences in cognitive decline between pravastatin and placebo groups. Similarly, the Simvastatin Heart Protection Study,[63] with a 5-year follow-up, reported no impact of simvastatin on cognitive impairment or dementia. However, both studies present methodological limitations that could explain these findings. PROSPER exclusively evaluated pravastatin, a hydrophilic statin with limited BBB penetration, which may inherently restrict its neuroprotective potential. Moreover, the Simvastatin Heart Protection Study did not rigorously control dementia risk factors, and its dementia ascertainment methods fell short of current diagnostic standards. Additionally, the relatively short follow-up period in these trials limits the ability to capture the cumulative effects of statins, which are more likely to be observed in long-term observational studies.

Additional discrepancies become evident when analyzing other RCTs. The HOPE-3 trial,[64] a study using a 2 × 2 factorial design, evaluated the effects of rosuvastatin and a combination of candesartan and hydrochlorothiazide on cognitive decline. It found no significant effects over a median follow-up of 5.7 years. The authors suggested that the failure to observe benefits could be attributed to the relatively short follow-up, reliance on telephone interviews for cognitive assessment, and the healthy volunteer bias. In contrast, another recent study by Hu et al., 2020, demonstrated that telmisartan combined with rosuvastatin significantly reduced cognitive impairment progression and dementia risk over an average 7-year follow-up, particularly in apolipoprotein E (APOE) ε4 carriers.[65] These findings underscore the importance of genetic and cardiovascular context in determining statins' neuroprotective potential.

In line with these observations, our study also identified discrepancies in the protective effects of specific statins. Our subgroup analyses revealed that neither pravastatin nor simvastatin demonstrated significant risk reductions for dementia, aligning with the null findings of the PROSPER and Simvastatin Heart Protection Study trials. This consistency highlights the variability in effectiveness based on statin type, reinforcing the need for future investigations that consider pharmacological differences among these agents.

It is important to note that many RCTs investigating statins and cognitive outcomes, such as those by Sparks et al., 2005, Feldman et al., 2010, and Sano et al., 2011, focused on populations with established dementia. These studies uniformly failed to show significant benefits, likely reflecting the limited ability of statins to reverse existing neurodegenerative pathology.[24–26] By contrast, our study investigates statin exposure and its preventive role against dementia, emphasizing their potential as protective factors rather than therapeutic agents for established neurodegenerative conditions.

The ongoing STAREE trial[66] offers a promising avenue for resolving these discrepancies. This study involves healthy individuals aged 70 years or older treated with atorvastatin or placebo, with dementia among its primary outcomes. With its robust design and extended follow-up period, STAREE has the potential to address many of the methodological limitations observed in prior RCTs, providing more definitive insights into the role of statins in dementia prevention.[67]

These discrepancies between RCTs and observational studies highlight the complementary strengths and limitations of each design. While RCTs are the gold standard for minimizing bias, they often lack the extended follow-up and generalizability of observational studies, which better reflect real-world conditions. However, observational studies may be subject to confounding factors, as further detailed in the Limitations section. Addressing these complexities will require future studies with designs that bridge the gaps between RCTs and observational research, incorporating longer follow-ups, broader populations, and more nuanced analyses of statin pharmacodynamics.

While previous systematic reviews and meta-analyses by Olmastroni et al., 2021, and Poly et al., 2020, identified a protective effect of statins against dementia,[27,28] our study builds upon these findings by incorporating a larger statistical analysis and more refined subgroup analyses, including those exploring duration of exposure and geographic variation. These additions enhance the reliability and broader applicability of our results. Additionally, we employed a dis-

tinct methodological approach by preserving the original effect measures reported in the included studies, thereby ensuring the robustness and accuracy of the pooled analyses. Furthermore, statins, as low-cost medications, hold significant promise in preventing dementia, particularly in low- and middle-income countries where most individuals with dementia reside.[1] The accessibility and affordability of statins, combined with our findings of risk reduction among all dementia, AD, and VaD patients, make them a viable option for large-scale public health interventions aimed at reducing the global burden of neurodegenerative diseases, with the potential to significantly impact the future global health landscape.

5.1 | Limitations

Our study has several limitations. First, the reliance on observational studies: while offering valuable data, the results of long-term analysis are susceptible to several biases and confounding factors that cannot always be adequately controlled. This can impact the robustness of our conclusions. However, we performed a meticulous quality assessment of included studies with the NOS in view of mitigating the biases associated with poor quality studies. Another important issue inherent to observational studies is the "healthy user bias."[68] Patients who take statins may also engage in other health-promoting behaviors that reduce dementia, potentially explaining part of the observed protective effect of statins. To address this bias, we sought to extract the most adjusted effect measure provided by each study. However, it is essential to recognize that behavioral changes related to statin use may introduce additional confounding effects not fully captured in our analysis.

Second, significant heterogeneity was present in many of our results. This issue was anticipated given the pooled analysis of observational studies that varied widely in their diagnostic criteria for dementia, methods of statin use assessment, medication doses, and population characteristics. Notably, the variability in statin prescription, including differences in doses and treatment durations as outlined in Table S5, may have influenced the observed outcomes and contributed to the overall heterogeneity. While subgroup analyses were performed to address some of these variations, the lack of consistently and uniformly reported data on statin doses or concentrations across the included studies remains a significant limitation. This limitation further precluded the possibility of conducting a detailed subgroup analysis based on dosage or concentration. To address overall heterogeneity, we employed several sensitivity analysis methods to identify and reduce heterogeneity, such as funnel plots and Egger tests to visualize heterogeneity in selected outcomes, Baujat plots to investigate the role of each study in the overall contribution to results and heterogeneity, and leave-one-out analysis to assess changes in pooled analysis and heterogeneity when the most divergent studies were excluded.

Third, the variability in diagnostic criteria for dementia across studies represents a key limitation. Many included studies relied on clinical diagnoses or administrative codes (e.g., ICD codes), often without the support of standardized cognitive testing or biomarker validation. This reliance on less rigorous diagnostic methods likely introduced misclassification bias, which could undermine the reliability of the results. Notably, the majority of included AD studies did not utilize biomarker-proven diagnoses, a significant limitation given the evolving consensus on the critical role of biomarkers in accurately defining AD. For transparency, detailed information on the diagnostic criteria used in the included studies is provided in Table 1.

Fourth, the presence of publication bias in one outcome (all-cause dementia HR) identified through the Egger test represents another limitation. This bias, as evidenced by the significant *p*-value and negative bias estimate, suggests that studies reporting null or negative results may be underrepresented in the literature. Although publication bias was not observed for other outcomes, this finding necessitates a cautious interpretation of the results, particularly for this specific outcome.

Fifth, generalizing our findings remains challenging due to the significant heterogeneity in baseline characteristics of included patients and the underrepresentation of certain global populations. Although we conducted comprehensive subgroup analyses, including those stratified by geographic region, our results underscore the lack of representation from Latin America, Africa, and parts of Eastern Europe, as well as the limited data available from Oceania. These gaps, consistent with findings from global epidemiological studies[54] highlighting similar underrepresentation, underscore the urgent need for more diverse and inclusive research efforts. Furthermore, only the study by Zissimipoulos et al., 2017 provided detailed information on the ethnic composition of its participants, which precluded the possibility of conducting subgroup analyses based on ethnicity.

6 | FUTURE RESEARCH

Future research should address several gaps identified in this study. While RCTs have investigated the effects of statins on dementia, limitations such as short follow-up periods, lack of focus on prevention, and variability in diagnostic criteria persist. Ongoing studies like the STAREE[66] trial hold promise for addressing some of these issues, but additional RCTs with robust designs, extended follow-up, and standardized biomarker-based diagnostic criteria are needed to validate our findings and inform clinical practice. Furthermore, the underrepresentation of certain global populations, such as those from Latin America, Africa, and parts of Eastern Europe, emphasizes the need for more diverse, inclusive research. Investigations exploring the relationship between statin use and dementia risk in these populations are critical to improving the generalizability of findings. Similarly, studies examining the effects of statins across different ethnic groups and their interactions with genetic predispositions, such as APOE $\varepsilon 4$ status, are essential for understanding population-specific responses.

TABLE 1 Baseline characteristics of the included studies, encompassing study design, geographic location, population demographics, diagnostic criteria, follow-up duration, reported outcomes, and effect measures.

Study, yr	Design	Country	Age, years (SD)	*N*	Male (%)	Diagnostic criteria	Follow-up	Outcomes	Effect measure	NOS
Ancelin, 2012	Co	France	73.7 (5.24)	6.830	39.7	DSM-IV, NINCDS, ADRDA[c]	7	D, AD	HR	8
Arvanitakis, 2008	Co	USA	74.9 (7.03)	929	31.3	Clinical evaluations following CERAD procedures[c]	12	AD	HR	8
Bettermann, 2012	Co	USA	78.6 (3.3)	3.069	53.8	DSM-IV, NINCDS, ADRDA, NINDS-AIREN, ADDTC[c]	6	D, AD and VaD	HR	7
Beydoun, 2011	Co	USA	57.6 (18.4)	1.604	61.5	DSM-III-R, NINCD-ADRDA[c]	24.9	D	HR	7
Booker, 2016	CC	Germany	80.4 (5.3)	23.912	39.0	ICD-10, Disease Analyzer database (IMS Health)	10	D	HR	7
Caniglia, 2020	Co	Netherland	69.4 (5.58)	6.373	42.9	DSM-III-R, NINCDS–ADRDA, NINDS-AIREN[c]	10	D	RR	8
Chang, 2019	Co	Taiwan	71.7 (8.56)	100.610	46.0	ICD-9-CM	12	D	HR	9
Chao, 2015	Co	Taiwan	73.2 (7.4)	256.265	49.7	ICD-9-CM	10	D	HR	8
Chen, 2014	Co	Taiwan	66.9 (8.63)	18.170	52.3	ICD-9-CM	8	D, AD	HR	7
Chen, 2014 (2)	CC	Taiwan	77.5 (8.1)	27.716	48.8	ICD-9-CM	6	D	OR	7
Chitnis, 2015	Co	USA	74.5 (9.21)	8.062	47.0	ICD-9-CM	3	D	HR	8
Chou, 2014	Co	Taiwan	70–79[a]	33.398	46.1	ICD-9-CM	5	D, AD and VaD	HR	8
Chuang, 2015	Co	Taiwan	54.4 (12.6)	123.300	49.1	ICD-9-CM	12	D	HR	8
Cramer, 2008	Co	USA	70.2 (6.79)	1.674	41.7	DSM-IV, NINCDS-ADRDA[c]	5	D	HR	7
Dufouil, 2005	Co	France	74.2 (5.5)	8.574	39.7	CDR, DSM-IV, NINCDS, ADRDA[c]	NA	D	OR	6
Goh, 2015	Co	United Kingdom	65–74[a]	469.366	52.1	NHS Read Codes	5	D	HR	8
Green, 2006	CC	USA	67.0 (8.58)	2.378	38.6	NINCDS-ADRDA[c]	6	AD	OR	7
Haag, 2008	Co	Netherland	69.4 (9.1)	6.992	40.0	DSM-III-R, NINCDS-ADRDA, NINDS-AIREN[c]	9	AD	HR	7
Hajjar, 2002	CC/Co	USA	78.7 (0.3)	655	26.0	Clinical Diagnosis, MMSE	1	D, AD and VaD	OR	6
Handa, 2021	Co	Japan	77–81[a]	42.024	43.4	NPADM	3	D	HR	6
Hendrie, 2015	Co	USA	76.6 (4.9)	974	30.3	DSM-IV, ICD-10	6	D, AD	OR	8
Hippisley-Cox, 2010	Co	United Kingdom	45.8 (13.5)	2.004.692	49.4	Clinical Record (QResearch Database)	7	D	HR	8

(Continues)

TABLE 1 (Continued)

Study, yr	Design	Country	Age, years (SD)	*N*	Male (%)	Diagnostic criteria	Follow-up	Outcomes	Effect measure	NOS
Jick, 2000	CC	United Kingdom	80–89[a]	1.364	39.5	NINCDS-ADRDA[c]	6	D	RR	7
Jong, 2023	Co	Taiwan	65[b]	52.139	70.9	Dementia ReadCode, TBNHI	5.1	D	HR	8
Khokhar, 2018	Co	USA	81.0 (8.1)	100.515	34.8	CCW Flags	4	D	RR	6
Kim, 2020	Co	South Korea	72.2 (5.35)	143.174	40.3	ICD-10	5	D	HR	8
Kim, 2021	CC	South Korea	75–79[a]	85.860	39.3	ICD-10	NA	AD	OR	7
Lee, 2020	Co	Taiwan	50-54[a]	112.036	48.4	ICD-9-CM	13	D	HR	7
Lee, 2020 (2)	Co	South Korea	66.6 (4.88)	6.182	38.6	ICD-10	12	D, AD	HR	7
Li, 2004	Co	USA	75.1 (6.1)	2.356	40.2	NINCDS-ADRDA, DSM-IV[c]	8	D, AD and VaD	HR	8
Li, 2010	Co	USA	75.4 (6.21)	3.099	40.5	DSM-IV, NINCDS-ADRDA[‡]	6	AD	HR	7
Li, 2020	Co	USA	73.4 (7.1)	733.920	94.9	ICD-9, ICD-10	18.5	AD	HR	9
Lin, 2021	Co	Taiwan	50–59[a]	51.528	28.3	ICD-9-CM	6	D	HR	8
Liu, 2018	Co	Taiwan	75.1 (5.97)	2.012	100	ICD-9-CM	3.5	D	HR	8
Ma, 2014	Co	China	75.3 (5.94)	634	0.0	NINCDS-ADRDA, NINDS-AIREN, DSM-IIIR[c]	5	D	HR	8
Pan, 2018	Co	Taiwan	64.8 (13.16)	9.448	55.0	ICD-9-CM	7.5	D	HR	8
Parikh, 2010	Co	USA	75.5 (6.07)	377.838	98.0	ICD-9-CM	2	D	HR	7
Rajan, 2024	Co	USA	71.9 (NA)	4.807	36.0	NINCDS-ADRDA[c]	10	AD	HR	9
Rea, 2005	Co	USA	75.0 (NA)	2.798	40.8	NINCDS-ADRDA, ADDTC[c]	5	D, AD and VaD	HR	6
Redelmeier, 2019	Co	Canada	76[b]	28.815	38.7	ICD-9-CM	4	D	RR	8

(Continues)

TABLE 1 (Continued)

Study, yr	Design	Country	Age, years (SD)	*N*	Male (%)	Diagnostic criteria	Follow-up	Outcomes	Effect measure	NOS
Ren, 2024	Co	Hong Kong	74.2 (13.6)	104.295	50.3	ICD-9, ICD-10	10	D, AD and VaD	HR	9
Rockwood, 2002	CC	Canada	78.0 (6.84)	1.315	38.0	DSM-III-R, NINCDS-ADRDA, ICD-10[c]	5	D, AD	OR	8
Smeeth, 2009	Co	United Kingdom	60–69[a]	729.529	50.3	ICD-9	4.5	D, AD	HR	8
Sparks, 2008	Co	USA	74.7 (3.79)	2.068	45.7	DSM-IV, NINCDS-ADRDA[c]	3.75	AD	HR	7
Torrandell-Haro, 2020	Co	USA	66.6 (3.51)	288.515	45.1	ICD-9-CM	5	D, AD	RR	9
Wandell, 2018	Co	Sweden	72.3 (10.1)	12.096	54.4	ICD-10	5.5	D	HR	7
Wolozin, 2007	Co	USA	74.6 (5.6)	1.290.071	94.4	ICD-9-CM, NINCDS-ADRDA[c]	2	D	HR	9
Wu, 2015	CC	Taiwan	72.9 (5.8)	4.006	49.9	ICD-9-CM	12	D	HR	8
Yang, 2015	Co	Taiwan	82.24 (5.09)	3.688	33.9	ICD-9-CM	12.5	D	HR	8
Yang, 2022	Co	United Kingdom	74.0 (NA)	33.190	48.1	ICD-10	4	D	HR	8
Zamrini, 2004	CC	USA	73.0 (NA)	3.397	100.0	ICD-9-CM	5	AD	HR	7
Zandi, 2005	Co	USA	75.6 (7.12)	5.092	45.0	DSM-III-R, NINCDS-ADRDA, 3MSE[c]	3	D, AD	HR	8
Zhou, 2021	Co	USA and Australia	74[b]	18.846	43.6	DSM-IV	4.7	D, AD	HR	7
Zingel, 2021	CC	Germany	80.2 (6.4)	24.472	42.3	ICD-10	5.5	D, VaD	OR	8
Zissimopoulos, 2016	Co	USA	75.7 (NA)	399.979	35.8	ICD-9-CM	7	AD	HR	9

Abbreviations: 3MSE, Modified Mini-Mental Sate Examination; ADDTC, Alzheimer's Disease Diagnostic and Treatment Centers; ADRDA, Alzheimer's Disease and Related Disorders Association; AIREN, Association Internationale pour la Recherche et l'Enseignement en Neurosciences; AD, Alzheimer's disease; CC, case–control study; CCW, Chronic Condition Data Warehouse; CERAD, Consortium to Establish a Registry for Alzheimer's Disease neuropsychological assessment battery; Co, cohort study; D, dementia; DSM, Diagnostic and Statistical Manual of Mental Disorders; HR, hazard ratios; ICD, International Classification of Diseases; MMSE, Mini-Mental State Examination; NA, not available; NHS, National Health Service; NINCD, National Institute of Neurological and Communication Disorders; NINCDS, National Institute of Neurological and Communicative Disorders and Stroke; NINDS, National Institute of Neurological Disorders and Stroke; NOS, Newcastle-Ottawa Scale; NPADM, new prescription of antidementia medication; TBNHI, Taiwanese Bureau of National Health Insurance; VaD, vascular dementia.

[a]Studies provided only age ranges.

[b]Studies provided age in median, not mean (average).

[c]Standardized diagnostic criteria.

7 | CONCLUSION

This comprehensive systematic review and meta-analysis demonstrates that statin use is associated with a significant reduction in the risk of dementia, including AD and VaD. Our study, encompassing over 7 million patients across 55 observational studies, provides robust evidence supporting the neuroprotective potential of statins. Our findings highlight the potential role of statins in mitigating dementia risk. Despite inherent limitations such as potential biases and heterogeneity, our analysis strengthens the case for including statins in dementia prevention strategies. The large dataset and detailed subgroup analyses enhance the reliability of our findings, suggesting that statins could play a crucial role in public health interventions, particularly in low- and middle-income countries where the burden of dementia is greatest.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: Fernando Luiz Westphal Filho and Artur Menegaz de Almeida conceived the research question, and elaborated the search strategy; Fernando Luiz Westphal Filho and Fernanda Moraes Tamashiro conducted the study selection; Fernando Luiz Westphal Filho, Paulo Roberto Moss Lopes and Vitor Kendi Tsuchiya Sano contributed to conducting data acquisition. Fernando Luiz Westphal Filho and Artur Menegaz de Almeida conducted the interpretation of the data and Fernando Luiz Westphal Filho and Artur Menegaz de Almeida synthesized the data using statistics software; Fernando Luiz Westphal Filho and Paulo Roberto Moss Lopes assessed the risk of bias; Fernando Luiz Westphal Filho, Paulo Roberto Moss Lopes, Fernanda Moraes Tamashiro, Ocílio Ribeiro Gonçalves, Francisco Cezar Aquino de Moraes and Francisco Cezar Aquino de Moraes drafted the writing. All authors reviewed it for important intellectual content and Francinny Alves Kelly and Pablo Vinícius Silveira Feitoza reviewed it critically as specialists in the field. All authors reviewed and approved the final version for publication and can confirm that they meet the ICMJE authorship criteria.

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CONFLICT OF INTEREST STATEMENT

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. Author disclosures are available in the Supporting Information.

DATA AVAILABILITY STATEMENT

More data can be accessed upon request to the corresponding author.

CONSENT STATEMENT

This study is a systematic review and meta-analysis of previously published data. As such, no new data were collected directly from human participants, and informed consent was not applicable. All included studies in the analysis were conducted in compliance with ethical standards and obtained appropriate informed consent from their participants as stated in their respective publications.

TRANSPARENCY DECLARATION

F.L.W.F., the lead author and manuscript guarantor, affirms that the present manuscript is an honest, accurate, and transparent account of the study being reported. He also affirms that no important aspects of the study have been omitted; and that no discrepancies from the study as planned have occurred.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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