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Statins use and risk of dementia

A dose–response meta analysis

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Abstract

Previous studies have indicated that statins use is associated with risk of dementia, but presented controversial results. Medline, Embase, Web of Science, and the Cochrane Database were searched update to November 2017 to identify the potential relationship between statins use and dementia. Thirty-one eligible studies involving a total of 3332,706 participants with 184,666 incident cases were included in this meta-analysis. Statins use was associated with dementia risk decrement (relevant risk [RR]: 0.85; 95% confidence interval [CI], 0.80–0.89). Subgroup analysis showed statins use was associated with Alzheimer disease (AD) (RR: 0.81; 95% CI, 0.73–0.89) and non-AD dementia (RR: 0.81; 95% CI, 0.73–0.89) risk decrement. Furthermore, statins use was associated with dementia risk decrement in female (RR: 0.89; 95% CI, 0.80–0.98) and male (RR: 0.88; 95% CI, 0.83–0.93). In addition, a dose–response showed per 1 year of duration of statins use incremental increase was associated with 20% dementia risk decrement (RR: 0.80; 95% CI, 0.73–0.87), and per 5-mg mean daily dose incremental increase in statins use was associated with 11% dementia risk decrement (RR: 0.89; 95% CI, 0.83–0.96). Statins use was associated with dementia risk decrement. The potency and the cumulative duration of statin utilized played critical roles.

Abbreviations: CI = confidence interval, RR = relevant risk.

Keywords: dementia, dose–response relationship, meta analysis, observational study, statins

1. Introduction

Statins is commonly known 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, and is the first-line drug therapy for the treatment of hyperlipidemia and the first choice for the prevention of coronary heart disease.[1] Statins have been widely used in clinically. In addition to reducing blood lipids, it's prevention and treatment of dementia gradually drawing people's attention.[2] Hypercholesterolemia may be positively correlated with dementia in middle-aged people. Statins may inhibit cholesterol metabolism by regulating cholesterol metabolism in the brain.[3]

According recent data, 93% of United States person use statins as the first choice to lower cholesterol levels, and statin use increased from 17.8% to 25.9% among the population 40 years of age or older, and it is still increasing.[4] Although, statins use has a potential to prevent dementia, there have been safety concerns regarding their effects on statins.[5] Currently, there are continued concerns, partly due to the conflicting results of the association between statins use and dementia.

Considering increasing number of patients being prescribed statins use and clinicians, pharmacists, patients, society, and governments pay more attention to the safety of these drugs; we conducted meta-analysis based on observational studies to determine whether statins use is associated with dementia risk.

2. Methods

Our meta-analysis was conducted according to the meta-analysis of observational studies in epidemiology checklist.[6] There are no ethical issues involved in our study for our data were based on published studies.

2.1. Search strategy

"Dementia" [MeSH] OR "Amentia" [MeSH] OR "Senile Paranoid Dementia" [MeSH] OR "Alzheimer's disease" [MeSH] OR "Parkinson's disease" [MeSH] OR "Huntington's disease" [MeSH] AND "Hydroxymethylglutaryl-CoA Reductase Inhibitors" [MeSH] OR "Statins" [MeSH] OR "Atorvastatin Calcium" [MeSH] OR "Lovastatin" [MeSH] OR "Meglutol" [MeSH] OR "Pravastatin" [MeSH] OR "Rosuvastatin Calcium" [MeSH] OR "Simvastatin" [MeSH] as the retrieval words, the databases such as Medline, Embase, Web of Science, and the Cochrane Database were retrieved from the time of the database established to November 2017.

2.2. Inclusion and exclusion criteria

Literature screening, inclusion, and quality evaluation were conducted independently by 2 researchers. The contents of our

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data extraction include the outcome was dementia. Risk estimates on the association between statins use and dementia risk. For nonrandomized controlled trials (RCTs), quality assessment was used Newcastle–Ottawa scale to score.[7]

2.3. Statistical analysis

Dose–response meta analysis using the method recommended by Greenland, Longnecker, and Orsini et al[8] by using STATA software 14.0 (STATA Corp, College Station, TX).

3. Results

3.1. Literature search results

A total of 2061 articles were screened through database retrieval and manual screening. After reading the topics and abstracts, most animal experiments and no related articles, meta-analyses, reviews, systematic reviews, randomized controls, and other forms of research were excluded and included in 51 articles. Full texts were further read and 21 articles removed. After review reference of studies, 1 article was identified. Finally, 31 studies were used for the final data synthesis.[9–39] The flowchart of literature searching was presented in Fig. 1. The characteristics of the included studies are shown in Tables 1 and 2.

3.2. Statins use and dementia risk

Thirty-one eligible studies including 47 independent reports investigated the association between statins use and dementia risk. Compared with no statins use, statins use was associated with dementia risk decrement (relevant risk [RR]: 0.85; 95% confidence interval [CI], 0.80–0.89; $P < 0.01$) (Table 3). Furthermore, statins use was significantly associated with dementia risk decrement in female (RR: 0.89; 95% CI, 0.80–0.98; $P < 0.01$) (Table 3) and male (RR: 0.88; 95% CI, 0.83–0.93; $P < 0.01$) (Table 3). In addition, statins use was significantly associated with dementia risk decrement in Caucasia (RR: 0.89; 95% CI, 0.83–0.96; $P < 0.01$) (Table 3) and male (RR: 0.92; 95% CI, 0.84–0.97; $P < 0.01$) (Table 3).

Twenty-one eligible studies including 23 independent reports investigated the association between statins use and Alzheimer disease (AD) risk. Compared with no statins use, statins use was associated with AD risk decrement (RR: 0.81; 95% CI, 0.73–0.89; $P < 0.01$) (Table 3). Furthermore, statins use was significantly associated with AD risk decrement in female (RR: 0.88; 95% CI, 0.83–0.93; $P < 0.01$) (Table 3) and male (RR: 0.86; 95% CI, 0.78–0.94; $P < 0.01$) (Table 3). In addition, statins use was significantly associated with AD risk decrement in Caucasia (RR: 0.83; 95% CI, 0.74–0.92; $P < 0.01$) (Table 3) and male (RR: 0.60; 95% CI, 0.36–0.97; $P = 0.03$) (Table 3).

Six eligible studies including 6 independent reports investigated the association between statins use and non-AD dementia risk. Compared with no statins use, statins use was associated with non-AD dementia risk decrement (RR: 0.81; 95% CI, 0.73–0.89; $P < 0.01$) (Table 3).

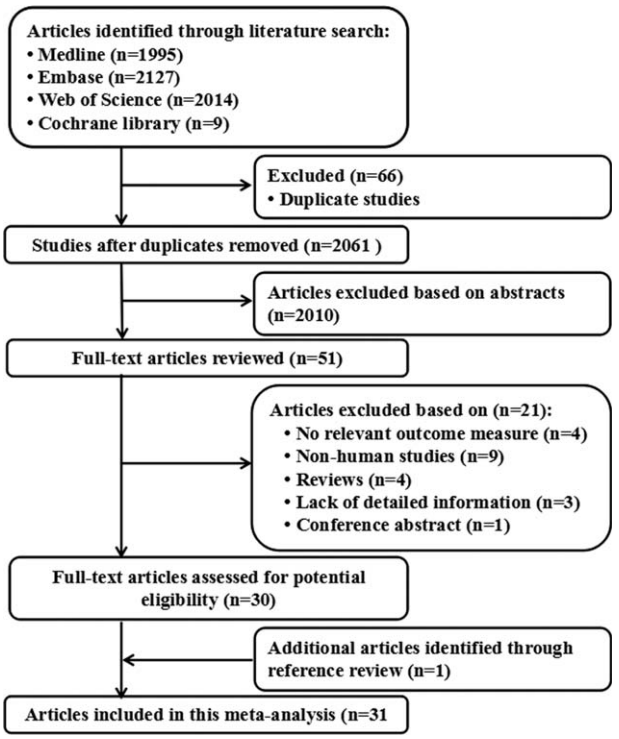

Figure 1. Flow diagram of the study selection process.

3.3. Dose–response between statins use and dementia risk

The test for a nonlinear dose–response relationship was significant (likelihood ratio test, $P < 0.001$), suggesting curvature in the relationship between statins use and dementia risk. Increasing per 1 year of duration of statins use incremental increase was associated with 20% dementia risk decrement (RR: 0.80; 95% CI, 0.73–87; $P < 0.001$) (Fig. 2), and per 5-mg mean daily dose incremental increase in statins was associated with 11% dementia risk decrement (RR: 0.89; 95% CI, 0.83–96; $P < 0.001$) (Fig. 3).

3.4. Publication bias

Results from Egger's tests indicated no evidence of publication bias among these studies (Supplementary Table 1, http://links.lww.com/MD/C337). A funnel plot for publication bias assessment is illustrated in Supplementary Figs. 1 to 3, http://links.lww.com/MD/C337.

4. Discussion

Dementia is a chronic acquired progressive retardation syndrome, and slow onset of intellectual decline is the main feature in clinically, accompanied by varying degrees of personality changes. It is a group of clinical syndromes, rather than an independent disease. Dementia is mainly divided into degenerative dementia and nondegenerative dementia. Degenerative dementia includes AD, fronto-temporal dementia, Louis's dementia, Parkinson's disease, and Huntington's disease, and nondegenerative dementia mainly includes vascular dementia, traumatic brain dementia, and space occupying lesions.[40] There is no specific treatment for degenerative dementia, so as to improve cognitive and symptomatic treatment.[41] Although some of the drugs (such as cholinesterase inhibitors) can improve the ability of patients to accept new things in short term and delay the aggravation of dementia, the long-term curative effect remains to be observed. Antipsychotic drugs can be used to combat psychotic symptoms, agitation, or aggressive behavior.[42] Antidepressants can be used in patients with dementia and

Table 1

Characteristics of participants in included studies of statins use in relation to dementia.

Reference	Study design	Country	No of participants	No of cases	Endpoints	Adjusted effect size (RR 95% CI)	Quality score
Arvanitakis et al[38]	Cohort	USA	929	119	AD	0.91 (0.54, 1.52)	7
Bettermann et al[37]	Cohort	USA	3069	778	Dementia	0.79 (0.65, 0.96)	7
					AD	0.57 (0.39, 0.85)	
Chen et al[39]	Cohort	China	28,321	877	Dementia	0.60 (0.42, 0.88)	7
				720	AD	0.48 (0.30, 0.76)	
				157	Non-AD dementia	1.07 (0.54, 2.12)	
Chou et al[36]	Cohort	China	33,398	16,699	Dementia	0.78 (0.72, 0.85)	7
Corrao et al[35]	Case–control	Italy	28581	1380	Dementia	0.75 (0.61, 0.94)	5
Cramer et al[34]	Cohort	USA	1674	452	Dementia	0.56 (0.37, 0.87)	7
Haag et al[33]	Cohort	Netherlands	6992	466	AD	0.57 (0.37, 0.90)	7
Hajjar et al[32]	Case–control	Columbia	655	113	Dementia	0.23 (0.10, 0.56)	6
					AD	0.37 (0.19, 0.74)	
Hendrie et al[31]	Cohort	India	2629	65	Dementia	0.44 (0.21, 0.92)	7
				56	AD	0.40 (0.18, 0.91)	
Jick et al[30]	Case–control	USA	1364	284	Dementia	0.29 (0.13, 0.63)	6
Li et al[28]	Cohort	USA	2356	312	Dementia	1.19 (0.82, 1.75)	8
				168	AD	0.82 (0.46, 1.46)	
Li et al[27]	Cohort	USA	3099	263	AD	0.62 (0.40, 0.97)	7
Lin et al[26]	Case–control	China	7145	719	AD	0.85 (0.76, 0.95)	5
Mandas et al[25]	Case–control	Italy	987	230	AD	1.70 (1.20, 2.30)	6
				126	Mixed dementia	1.50 (1.00, 2.20)	
				195	Vascular dementia	1.40 (1.00, 2.00)	
Masse et al[24]	Case–control	France	342	170	AD	0.60 (0.34, 1.06)	6
Parikh et al[23]	Cohort	USA	377,838	14,580	Dementia	0.88 (0.85, 0.91)	7
Rea et al[22]	Cohort	USA	2798	428	Dementia	1.08 (0.77, 1.52)	7
				216	AD	1.21 (0.76, 1.91)	
				55	Vascular dementia	1.36 (0.61, 3.06)	
Szwast et al[21]	Cohort	USA	1146	287	Dementia	0.31 (0.10, 1.00)	7
Williams[20]	Cohort	USA	135,536	175	AD	0.39 (0.15, 0.82)	7
Wolozin et al[19]	Cohort	USA	1290,071	3361	Dementia	A:0.91 (0.80, 1.02)	8
						L:0.95 (0.86, 1.05)	
						S:0.46 (0.44,0.48)	
Zandi et al[18]	Cohort	USA	4895	182	Dementia	1.19 (0.53, 2.34)	7
				102	AD	1.19 (0.35, 2.96)	
Zissimopoulos et al[9]	Cohort	Europe	399,979	767	AD (female)	0.85 (0.82, 0.89)	7
				744	AD (male)	0.88 (0.83, 0.93)	
Ancelin et al[29]	Cohort	France	7056	483	Dementia	0.81 (0.53, 1.23)	7
				332	AD	1.09 (0.60, 2.00)	
Benito et al[17]	Case–control	Spain	548	137	AD	1.10 (0.67, 1.76)	6
Beydoun et al[16]	Cohort	USA	2949	259	Dementia	0.41 (0.18, 0.92)	7
				138	MCI	0.71 (0.33, 1.52)	
Glasser et al[15]	Cohort	USA	24,595	7191	Dementia	0.98 (0.87, 1.10)	7
Green et al[14]	Case–control	USA	2378	895	AD	0.61 (0.38, 0.98)	6
Hippisley et al[13]	Cohort	United Kingdom	225922	368	Dementia	S: 0.92 (0.83, 1.02)	7
						A: 0.86 (0.74, 1.00)	
						F: 0.83 (0.53, 1.30)	
						P: 1.23 (0.94, 1.60)	
						R: 0.74 (0.42, 1.31)	
Smeeth et al[12]	Cohort	United Kingdom	729,529	129,288	Dementia	0.81 (0.69, 0.96)	7
					AD	0.81 (0.49, 1.35)	
					Non-AD dementia	0.82 (0.69, 0.97)	
Sparks et al[11]	Cohort	USA	2528	20	AD	0.33 (0.11, 0.98)	7
Zamrini et al[10]	Case–control	USA	3397	309	AD	0.61 (0.42, 0.87)	6

A = atorvastatin, AD = Alzheimer disease, CI = confidence interval, F = fluvastatin, L = lovastatin, MCI = mild cognitive impairment, P = pravastatin, R = rosuvastatin, RR = relevant risk, S = simvastatin.

depression, and help to improve the dementia syndrome. But it must be noted that the anticholinergic side effects of tricyclic drugs can aggravate cognitive impairment.[43] Although benzodiazepines can control the behavior problem of the dementia, it should be specially cautious because it can cause falls and drug dependence. In general, these drugs in treatment of dementia are more or less all kinds of problems, and statins have been widely used in lipid-lowering therapy, and its pleiotropic effects have expanded its clinical value and the potential therapeutic effect of statins on dementia is remarkable.

Statins is commonly known 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, including lovastatin, prava-

Table 2

Outcomes and covariates of included studies of statins use in relation to dementia.

Reference	Endpoints	Data source	Category and relative risk (95% CI)	Covariates in fully adjusted model
Arvanitakis et al[38]	AD and dementia		Mean daily dose (mg) Dementia Non use, 1.0 (reference); >0–<10, 0.53 (0.34, 0.83); >10–<20, 0.68 (0.39, 1.17); >20, 0.80 (0.39, 1.64) AD Non use, 1.0 (reference); >0–<10, 0.38 (0.22, 0.67); >10–<20, 0.57 (0.31, 1.08); >20, 0.74 (0.34, 1.61) Non-AD dementia Non use, 1.0 (reference); >0–<10, 1.20 (0.54, 2.66); >10–<20, 0.96 (0.29, 3.11); >20, 0.73 (0.10, 5.45)	Adjust age group, gender, stroke types, and antidiabetic drugs
Chou et al[36]	Dementia		Duration of statins use (year) Non use, 1.0 (reference); >0–≤1, 1.07 (0.97, 1.19); >1–<3, 0.76 (0.66, 0.87); ≥3, 0.35 (0.28, 0.43)	Adjusted for gender, age, socioeconomic status, and comorbidities
Zandi et al[18]	AD and dementia		Duration of statins use (year) Dementia Non use, 1.0 (reference); >0–≤3, 1.40 (0.49, 3.21); ≥3, 0.71 (0.12, 2.32) Alzheimer Disease Non use, 1.0 (reference); >0–≤3, 1.41 (0.23, 4.70); ≥3, 0.62 (0.03, 2.92)	Adjusted for age, sex, education, the number of ε4 alleles at apoE, a history of hypertension, and a history of diabetes
Zamrini et al[10]	AD		Duration of statins use (year) Non use, 1.0 (reference); >0–≤1, 0.56 (0.34, 0.92); >1, 0.71 (0.42, 1.19)	Adjusted for diabetes, lipid metabolism disorders, hypertension, ischemic heart disease, cerebrovascular disease, and arterial disease where appropriate

AD = Alzheimer disease, CI = confidence interval.

Table 3

Stratified analyses of relative risk of dementia.

Stratification variable	No of reports	Relative risk (95% CI)	Heterogeneity		*P* for test
			P	I^2 (%)	
Dementia	47	0.85 (0.80–0.89)	0.000	65.4	<0.01
Alzheimer disease	23	0.81 (0.73–0.89)	0.000	64.7	<0.01
Non-AD dementia	6	0.81 (0.73–0.89)	0.068	51.2	<0.01
Subgroup analyses for dementia					
Gender					
Female	4	0.89 (0.80–0.98)	0.010	73.4	<0.01
Male	4	0.88 (0.83–0.93)	0.799	0.0	<0.01
Study location					
Caucasia	7	0.89 (0.83–0.96)	0.256	23.7	<0.01
Asia	40	0.92 (0.84–0.97)	0.000	60.5	<0.01
Study design					
Case–control	11	0.79 (0.62–0.98)	0.645	0.0	<0.01
Cohort	36	0.85 (0.73–0.97)	0.011	61.4	<0.01
No of participants					
≥10,000	13	0.94 (0.86–0.99)	0.000	79.8	<0.01
<10,000	34	0.72 (0.62–0.83)	0.705	0.0	<0.01
No of cases					
≥500	20	0.94 (0.87–0.99)	0.000	59.1	<0.01
<500	27	0.80 (0.68–0.90)	0.051	43.8	<0.01
Study quality					
Score ≥7	11	0.79 (0.62–0.98)	0.645	0.0	<0.01
Score <7	36	0.85 (0.73–0.97)	0.011	61.4	<0.01
Subgroup analyses for Alzheimer disease					
Gender					
Female	2	0.88 (0.83–0.93)	0.388	0.0	<0.01

(*continued*)

Table 3

(continued).

Stratification variable	No of reports	Relative risk (95% CI)	Heterogeneity		P for test
			P	I^2 (%)	
Male	2	0.86 (0.78–0.94)	0.099	63.4	<0.01
Study location					
Caucasia	20	0.83 (0.74–0.92)	0.000	64.1	<0.01
Asia	3	0.60 (0.36–0.97)	0.014	76.5	0.03
Study design					
Case–control	6	0.80 (0.73–0.88)	0.808	0.0	<0.01
Cohort	17	0.93 (0.89–0.97)	0.000	70.2	0.02
No of participants					
≥10,000	7	0.90 (0.84–0.96)	0.047	50.8	<0.01
<10,000	16	0.71 (0.50–0.99)	0.161	45.2	0.04
No of cases					
≥500	12	0.80 (0.69–0.91)	0.914	0.0	<0.01
<500	11	0.92 (0.88–0.95)	0.000	83.9	<0.01
Study quality					
Score ≥7	17	0.93 (0.89–0.97)	0.000	70.2	0.02
Score <7	6	0.80 (0.73–0.88)	0.808	0.0	<0.01

AD = Alzheimer disease, CI = confidence interval.

statin, simvastatin, mevastatin, fluvastatin, atorvastatin, cerivastatin, rosuvastatin, and is the first-line drug therapy for the treatment of hyperlipidemia and the first choice for the prevention of coronary heart disease. Recent report presents safety problems between statins use and dementia, and statins use may contribute to the potential of dementia. Currently, there are continued concerns, partly due to the conflicting results of the association between statins use and dementia.

Previous meta-analysis has investigated the association between statins use and dementia risk but presented controversial results. Wong et al[44] based on 20 observational studies found statins use was slight associated with dementia (RR: 0.82; 95% CI, 0.69–97) and AD (RR: 0.70; 95% CI, 0.60–83) risk decrement. However, Rojas-Fernandez et al[45] found statins use was not associated with dementia risk.

This meta-analysis was based on 31 studies (including nine case–control studies and 22 cohort studies) update to November 2017. Our meta-analysis supported statins use was associated with dementia risk decrements, and a dose–response showed per 1 year of duration of statins use incremental increase was associated with 20% dementia risk decrement, and per 5-mg mean daily dose incremental increase in statins use was associated with 11% dementia risk decrement. This meta-analysis included enough studies; these results should be credible.

High-cholesterol diet, elevated serum cholesterol, and high blood pressure are risk factors for coronary heart disease and AD, and hypercholesterolemia in the brain can be deposited in the hippocampus, causing amyloid precursor protein to be degraded intoamyloid precursor protein, which causes degeneration of neurons, resulting in AD. Statins may reduce the formation of β-amyloid peptide by decreasing cholesterol levels. Statins have a stable effect on the homeostasis of the nervous system cholesterol, inhibit the synthesis of cholesterol, lower the cholesterol level, and thus inhibit the beta metabolism of amyloid precursor protein.[46–49] Furthermore, the intermediate product isoprene of cholesterol biosynthesis in dementia

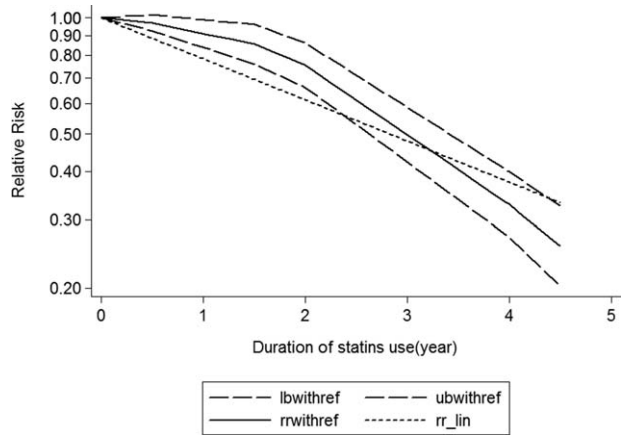

Figure 2. Dose–response relationship between duration of statins use in relation to risk of dementia. The solid line represents point estimates of the association of statins use and dementia risk with the use of a restricted cubic splines model, and the dashed lines indicate 95% confidence intervals.

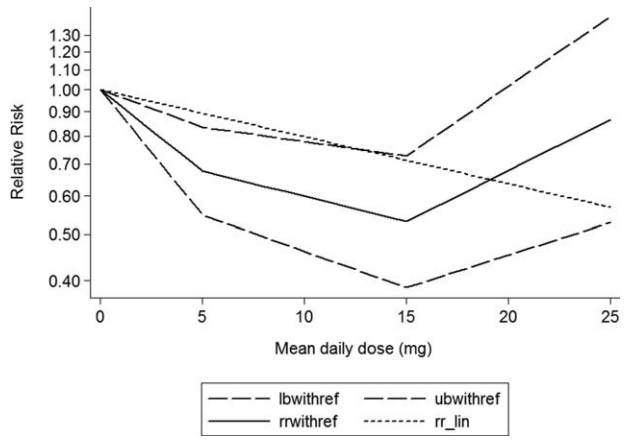

Figure 3. Dose–response relationship between mean daily dose of statins use in relation to risk of dementia. The solid line represents point estimates of the association of statins use and dementia risk with the use of a restricted cubic splines model, and the dashed lines indicate 95% confidence intervals.

patients is often depleted, thus affecting cell growth, mitosis, and signal transduction, while statins have a regulatory role in the above intracellular mechanisms.[50] In addition, commonly known as apoE4, an important cholesterol transporter, is an important risk factor and genetic marker of sporadic and late-onset familial AD and plays an important role in Aβ deposition and the formation of senile plaques. Astrocytes and microglia are the main sources of apoE in the brain. These cells secrete apoE, which requires the isoprenylation of key proteins, while mevalproic acid is the precursor of isoprene derivatives. Statins inhibit the synthesis of mevalonate, inhibit apoE secretion, and reduce extracellular apoE levels, thereby preventing the formation of senile plaques and improving cognitive function.[51]

This meta-analysis also has some limitations. First, we did not included RCTs due to dementia was not a prespecified endpoint in RCTs, and RCTs should be included in the further. Second, study duration was short in these studies and person included in these studies may be different from the real life. Third, the overall sample size of the study was small, which may have a certain impact on the evaluation results.

To sum up, statins use was associated with dementia risk decrement, and it is expected to become an important auxiliary means of dementia treatment. Due to the limitation of the quality and quantity of the inclusion study, more high-quality, large sample, and multicenter RCT are needed to verify the conclusions of this study in the future.

Author contributions

Data curation: Xiaoyu Zhang, Jianzhong Wen, Zhiqiang Zhang.
Formal analysis: Xiaoyu Zhang, Jianzhong Wen, Zhiqiang Zhang.
Project administration: Zhiqiang Zhang.
Software: Xiaoyu Zhang, Jianzhong Wen, Zhiqiang Zhang.

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