Original Article

Overview the effect of statin therapy on dementia risk, cognitive changes and its pathologic change: a systematic review and meta-analysis

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Background: Many studies have reported on the role of statin therapy in dementia, but its efficacy remains controversial. We aimed to search for reliable and meaningful articles to assess the efficacy of statin therapy for dementia risk, cognitive items, and pathologic markers.

Methods: Related literature for this study was published in the period from January 1, 1987 to January 1, 2018. Odds ratio (OR) and 95% confidence interval (95% CI) estimates were pooled in either fixed or random effects models.

Results: A total of 23 relevant studies were included after the application of the search strategy. The pooled results showed that statin therapy would downregulate dementia risk according to an analysis of 1,314,431 dementia patients and 1,836,539 healthy controls (OR: 0.64, 95% CI: 0.50, 0.81). In addition, specific changes in mini-mental state examination (MMSE) score were observed in individuals with dementia with statin therapy (OR: 0.46, 95% CI: 0.17, 0.74). However, the results of this meta-analysis showed that statin therapy did not significantly modify the Alzheimer's Disease Assessment Scale (ADAS-cog) score (OR: −0.26, 95% CI: −1.13, 0.62). No significant association was found between statin therapy and activities of daily living performance (OR: −0.69, 95% CI: −4.12, 2.74). When investigating pathological markers, our results indicated a significant influence of statin therapy on plasma amyloid β_{40} ($A\beta_{40}$) (OR: 9.27, 95% CI: 0.71, 17.84), plasma $A\beta_{42}$ (OR: 2.60, 95% CI: 1.07, 4.13), plasma low-density lipoprotein (LDL) cholesterol (OR: −16.95, 95% CI: −25.54, −8.37), plasma lathosterol (OR: −0.11, 95% CI: −0.14, −0.07), plasma 24s-hydroxycholesterol (OR: −10.41, 95% CI: −15.57, −5.25), and cerebrospinal fluid (CSF) lathosterol (OR: −0.07, 95% CI: −0.12, −0.01).

Conclusions: The available data indicate that statin therapy may reduce dementia risk, altering cognitive items and pathologic markers.

Keywords: Statin; dementia; risk; cognitive function; pathologic markers; meta-analysis

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Introduction

Dementia is a complicated process, including the loss of synaptic connections, cell death, gliosis, and inflammation, as well as disruptions in functional networks, underlying cognition, behaviour, personality, and sensorimotor functions, eventually influencing an individual's autonomy (1). With the global population ageing rapidly, dementia has become a major public health problem. It affected approximately

46.8 million people worldwide in 2015, and the number of individuals with dementia will reach 131.5 million by 2050 (1). Considering the prevalence of dementia, it is critical to discover a useful method to diagnose and treat dementia.

A growing body of evidence suggests a close association between lipids and vascular changes in dementia. The beta-hydroxy-beta-methylglutaryl-CoA (HMGCoA) reductase inhibitor may reduce intracellular cholesterol/protein ratios and markedly inhibit beta-secretase cleavage of newly synthesised amyloid precursor protein in human HEK cells (2); in addition, the low-density lipoprotein (LDL) receptor-related protein receptor has been proven to play a possible role in Alzheimer's disease (AD) (3). Lipid-lowering agents (LLAs), particularly HMGCoA-reductase inhibitors (statins), may be helpful for certain arterial disorders (4-7), and these arterial factors are linked closely to dementia. Hence, LLAs may be a promising method to treat dementia. Current studies indicate that modulating lipid levels may influence dementia in elderly individuals; for example, two epidemiologic studies first reported that statin users may reduce the risk of dementia (4,8). Furthermore, many research groups have begun to explore the effects of statins on dementia risk and pathologic changes (9-14). However, the U.S. Food and Drug Administration has asserted that there are several adverse effects of statin therapy, for example, confusion and memory loss in elderly people (15,16).

Currently, statin therapy is a thriving area of research. However, as mentioned above, the current conclusions about statin therapy in dementia are incompatible. Although numerous studies have discussed the effects of statins on dementia, there is still a lack of studies providing an overview of their roles in dementia risk, cognitive changes, and pathologic changes. The existing articles discuss the role of specific statin therapies in specific types of dementia. Our study is the first to provide an overview of the various statin therapies in various types of dementias. We hope our study will provide investigators with more information about the progress of research on statin therapy for dementia. This paper is intended to review the currently available evidence to assess via meta-analysis the efficacy of statins for the treatment of dementia, including the effects of statin therapy on dementia risk, cognitive changes, and pathologic changes.

Methods

Search strategy

To assess the efficacy of statins for the treatment of dementia, including the effects of statin therapy on dementia risk, cognitive changes, and pathologic changes via meta-analysis, we searched for related literature in MEDLINE, EMBASE, the Cochrane Library, and BIOSIS previews for studies published in the period from January 1, 1987 to January 1, 2018. The search terms used are "dementia", "Alzheimer", "AD" and "statin" with Boolean operators as appropriate. We also obtained other relevant studies from meta-analyses and reference lists.

Study selection

Eligible studies for this meta-analysis met the following criteria: (I) the cohorts in the study were subjected to a period of statin therapy. Since the duration of most studies is inconsistent, we did not select specific durations; (II) the patients were diagnosed with dementia, AD, vascular dementia (VaD), or another type of dementia; (III) a variety of outcome measures for dementia were included, such as cognitive function, as measured by the assessments that follow. The mini-mental state examination (MMSE) is one of the most extensively and most frequently used cognitive tests, with high precision and accuracy. The total score for the MMSE is 30, and a higher score indicates better cognitive function. In addition, when a patient received a score of 23 or less, he or she was considered to suffer from cognitive impairment (17). The cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) is a testing method to measure cognitive changes in dementia-related drug trials (18). The ADAS-cog includes three items: descriptions, administrative procedures, and scoring. A higher score indicates better cognition function. The activities of daily life (ADL) scale is scored out of 100 and assesses basic self-care and mobility abilities. A higher score reflects greater independence (19). We also examined some pathological biomarkers, including plasma $A\beta_{40}$, plasma $A\beta_{42}$, cerebrospinal fluid (CSF) $A\beta_{40}$, CSF $A\beta_{42}$, CSF total tau, CSF phosph-tau; plasma total cholesterol; plasma high-density lipoprotein (HDL) cholesterol; plasma LDL cholesterol; plasma triglycerides; plasma lathosterol; plasma 24S-hydroxycholesterol; CSF lathosterol, and CSF 24S-hydroxycholesterol. The included studies were required to contain the statistical information necessary to compute our results.

Data extraction and quality assessment

Zhu, Dai and Ma reviewed all appropriate articles according

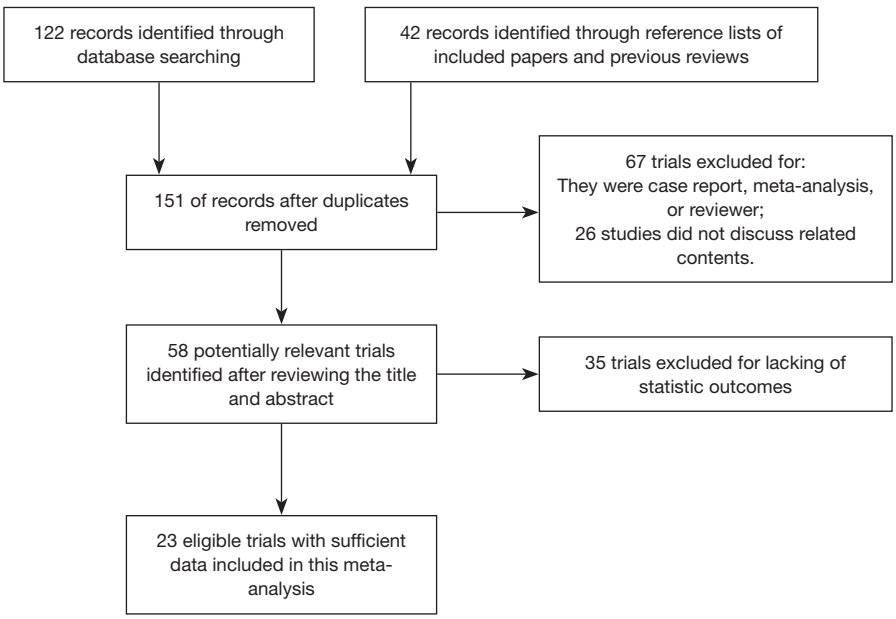

Figure 1 Flow diagram of study identification process.

to predefined criteria. We recorded the final valid statistics of each outcome by the mean, SDs, the number of patients at the time closest to the endpoint of the statin intervention, or the number of patients and controls with/without statin therapy. In addition, we also extracted the author name, data for country of study origin, published year, characteristics of participants (number, age, and number of males/females), and intervention details. When conflicts appeared in inclusion, exclusion, or data extraction, the conflicts were solved via discussion.

Quantitative data synthesis

Review Manager (version 5.2.3 for Windows, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) was used to estimate the overall effects of statin therapy on dementia risk, cognitive changes, and pathologic markers by combining the results of each trial. Statistical heterogeneity was assessed using the I^2 statistic. The results were considered heterogeneous when I^2 was more than 50% (20). In this study, we chose a priori a random effects model for the outcome measures, sample characteristics, and heterogeneity of intervention types (21). When the number of methodologically sound studies was relatively small (less than 10), it was not necessary to use funnel plots to investigate publication bias. We evaluated publication bias only when the number of studies was more than ten (22).

Results

Literature search and characteristics of included studies

As the search strategy shows in *Figure 1*, a total of 23 relevant studies were included after the application of the search strategy. In total, 13 articles were included to explore the effects of statin therapy on dementia risk (4,23-34), and 11 studies were included to evaluate the effects of statin therapy on cognitive changes and pathologic changes (31,35-44). The details of the treatment methods were summarized in *Table 1*; specifically, these therapy methods are statin therapy (no mention of specific statin type) (4,23-26,28-35,41, 43-46), atorvastatin therapy (4,27,40), fluvastatin therapy (4,27), lovastatin therapy (27,37), pravastatin therapy (4,27,37), simvastatin therapy (4,27,36-38,42,44), rivastigmin therapy (39), and cerivastatin therapy (4). We included general dementia patients (no mention of specific dementia type) (4,23-28,31-34), AD patients (24-26,29,30,35-38, 40-44), and VaD patients (26,39) in this study.

Effects of intervention

Dementia risk

To reveal the effects of statin therapy on dementia risk,

Table 1 Characteristics of the included studies for the meta-analysis

No.	Author	Location	Year	Dementia type	Case				Control			PMID
					Treatment	Age [n]	Sex (M/F)	N	Age [n]	Sex (M/F)	N	
1	Jick H	USA	2000	Dementia	Statins	50–59 [7]	113/171	284	50–59 [29]	421/659	1,080	11089820
					Simvastatin	60–69 [30]			60–69 [131]			
					Pravastatin	70–79 [108]			70–79 [407]			
					Atorvastatin	80–89 [139]			80–89 [513]			
					Fluvastatin							
					Cerivastatin							
2	Peter P	USA	2005	Dementia AD	Statins	73.0±5.4	138/154	292	75.7±7.2	1,948/2,624	4,572	15699299
3	Thomas D	USA	2005	Dementia; AD; VaD	Statins	Age >80 y; 728 (56.7)	420/864	1,284	Age >80 y; 7,199 (54.5)	5,384/7,825	13,209	16009757
4	Benjamin Wolozin	USA	2007	Dementia	Atorvastatin	73.5±5.3		53,869				17640385
					Fluvastatin	74.2±5.6		5,136				
					Lovastatin	74.8±5.6		54,052				
					Pravastatin	73.5±5.3		1,778				
					Simvastatin	74.5±56		727,128				
5	Cramer C	USA	2008	Dementia	Statins	69.6±6.2	187/265	452	70.4±7.00	511/711	1,222	18663180
6	Sparks DL	USA	2008	AD	Statins	74.5±3.6	297/462	759	74.9±3.9	648/661	1,309	18690839
7	Haag MD	Netherlands	2008	AD	Statins	69.4±9.1	2,797/4,195	6,992				18931004
8	BBenito-León J	Spain	2010	Dementia	Statins	73.4±4.4	52/85	137	73.3±5.1	168/243	411	20413854
9	Chuang CS	Taiwan	2014	Dementia	Statins	54.6±12.4	30,296/31,354	61,650	54.1±12.8	30,296/31,354	61,650	24635778
10	Wu CK	Taiwan	2015	Dementia	Statins	72.9±5.8	991/1,012	2003	72.9±5.8	1,008/995	2,003	24766342
11	Chao TF	Taiwan	2015	Dementia	Statins	73.2±7.4	25,490/25,763	51,253	73.2±7.4	101,960/81,448	205,012	26080283
12	Chitnis AS	USA	2015	Dementia	Statins	78.23±8.53	513/622	1,135	73.85±9.17	3,273/3,654	6,927	26363909
13	Hendrie HC	USA	2015	Dementia; AD	Statins	78.7±5.5	17/48	65	76.4±4.8	278/631	909	26673814

Table 1 (*continued*)

Table 1 (*continued*)

No.	Author	Location	Year	Dementia type	Case				Control			PMID
					Treatment	Age	Sex (M/F)	N	Age	Sex (M/F)	N	
14	Tokuda T	Japan	2001	AD	Statins	64.3±7.6	15/7	22	60.0±13.3	15/8	23	11310640
15	Simons M	Germany	2002	AD	Placebo or simvastatin	68.0±9	9/15	24	68.5±8	9/11	20	12205648
16	Vega GL	Germany	2003	AD	Lovastatin (40 mg/d)	66±8	6/4	10				12707064
					Simvastatin (40 mg/d)	70±8	7/3	10				
					Pravastatin sodium (40 mg/d)	74±9	4/7	11				
					Extended-release nicotinic acid (1 g/d)	68±7	4/6	10				
17	Sjögren M	Sweden	2003	AD	Simvastatin 20 mg/day for 12 weeks	73.1±5.0	11/8	19				12714796
18	Moretti R	Italy	2016	VaD	Rivastigmine 3–6 mg/day	68–81		208				14569643
19	Sparks DL	USA	2005	AD	Atorvastatin calcium tablets, 40 mg, and identical placebo	78.15±1.3	20/12	32	78.9±1.2	20/11	31	15974900
20	Winblad B	Europe, Canada and the US	2007	AD	Statin, galantamine 24 mg/day or placebo	74.0±7.8	29/21	50	75.2±8.2	229/390	619	17233547
21	Serrano-Pozo A	USA	2010	AD	12 Week of treatment with simvastatin	65.6±8.6	4/8	12				20473136
22	Padala KP	USA	2012	AD	Statin	76.7±6.6	7/11	18				22921881
23	Geifman N	UK	2017	AD	Simvastatin Arm, Original placebo arm	73.3±9.8	72/99	171	74.5±8.9	67/102	169	28212683
					Continual use of statins (trials from the integrated dataset)	76±7.5	301/299	600	76.7±8.4	321/472	793	
					Continual use of statins (ROS/MAP dataset)	81.8±6.6	89/257	346	82.5±6.7	159/354	513	

AD, Alzheimer's disease; VaD, vascular dementia.

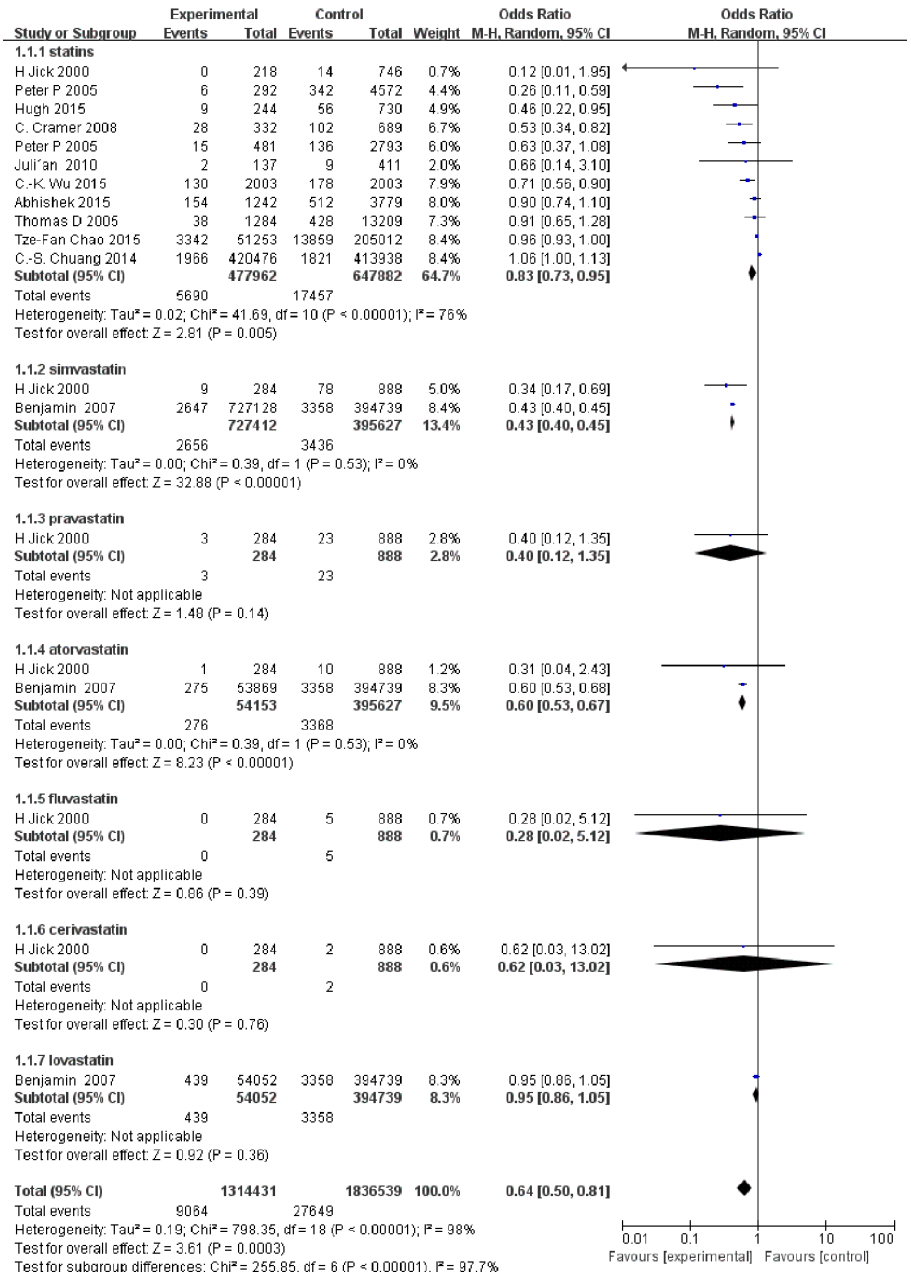

Figure 2 Forest plots show the effects of statin therapy on dementia risk.

we conducted a meta-analysis to assess the function of statin intervention on dementia risk, and the odds ratio (OR) represented the modified ratio of incident dementia compared to the controls (*Figure 2*). Since the heterogeneity is 98%, we used random effects model. In *Figure 2*, the pooled results show that statin therapy reduces dementia risk after analysing 1,314,431 dementia patients and 1,836,539 healthy controls [OR: 0.64, 95% confidence interval (CI): 0.50, 0.81]. When assessing specific types of statins, only two drugs, simvastatin and atorvastatin, have consistent results (OR: 0.43, 95% CI: 0.40, 0.45; OR: 0.60, 95% CI: 0.53, 0.67). The other four drugs mentioned, pravastatin, fluvastatin, cerivastatin, and lovastatin, showed no significant influence on dementia risk (OR: 0.40, 95% CI: 0.12, 1.35; OR: 0.28, 95% CI: 0.02, 5.12; OR: 0.62, 95% CI: 0.03, 13.02; OR: 0.95, 95% CI: 0.86, 1.05).

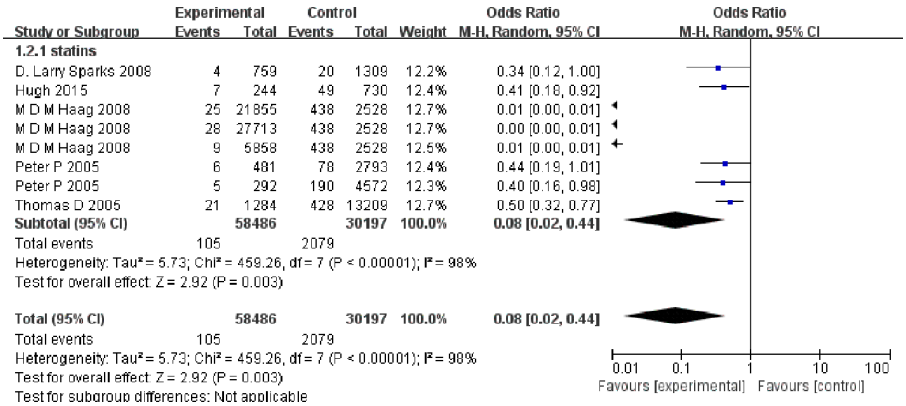

Figure 3 Forest plots show the effects of statin therapy on AD risk. AD, Alzheimer's disease.

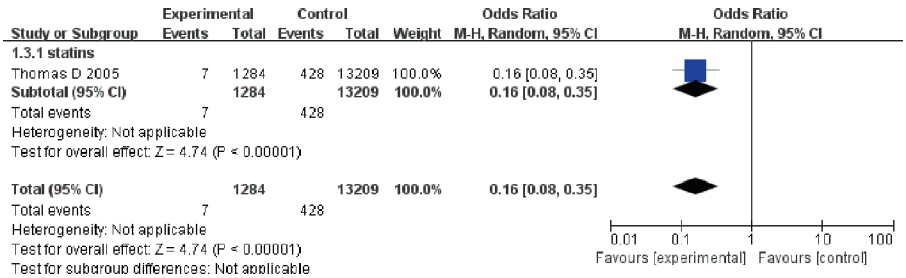

Figure 4 Forest plots show the effects of statin therapy on VaD risk. VaD, vascular dementia.

The results of our meta-analysis revealed statin therapy would reduce AD risk (OR: 0.08, 95% CI: 0.02, 0.44) (*Figure 3*) in the random model used when heterogeneity is more than 50%. VaD is another common dementia type. However, only one study of our included studies has concrete data to assess the pooled effect of statin therapies on VaD prevalence. This study indicated that statin therapy resulted in lower VaD prevalence (OR: 0.16, 95% CI: 0.08, 0.35) (*Figure 4*). These results may indicate that statin therapy meaningfully reduces the prevalence of the onset of dementia.

Cognition

Since MMSE score is a common measure to assess cognition function, our study tested the influence of statin therapy on cognition changes on the MMSE. Finally, our study indicated specific changes in MMSE score of individuals with dementia as a result of statin therapy (OR: 0.46, 95% CI: 0.17, 0.74) (*Figure 5A*). The results indicated statin therapy may improve cognitive function. Of note, simvastatin intervention did not significantly alter MMSE score (OR: 0.70, 95% CI: −2.23, 3.63); however, atorvastatin therapy increased MMSE score (OR: 0.57, 95% CI: 0.23, 0.91).

ADAS-cog score is another common measure method to evaluate cognitive changes. However, inconsistent with MMSE score changes, the results of this meta-analysis showed statin therapy may not significantly alter the ADAS-cog score (OR: −0.26, 95% CI: −1.33, 0.62) (*Figure 5B*).

Activities of daily living (ADL)

Only two studies were included to test the effects of statin therapy on ADL performance (40,43), and the final results are shown in *Figure 5*. No significant association was observed between statin therapy and ADL performance (OR: −0.69, 95% CI: −4.12, 2.74) (*Figure 5C*). Moreover, atorvastatin therapy significantly altered ADL performance (OR: −2.40, 95% CI: −3.33, −1.47) (*Figure 5C*).

Pathological biomarkers

A total of 16 items [plasma amyloid β_{40} ($A\beta_{40}$), plasma $A\beta_{42}$, CSF $A\beta_{40}$, CSF $A\beta_{42}$, CSF total tau, CSF phosph-tau, plasma total cholesterol, plasma HDL cholesterol, plasma LDL cholesterol, plasma triglycerides, plasma lathosterol, plasma 24S-hydroxycholesterol, plasma

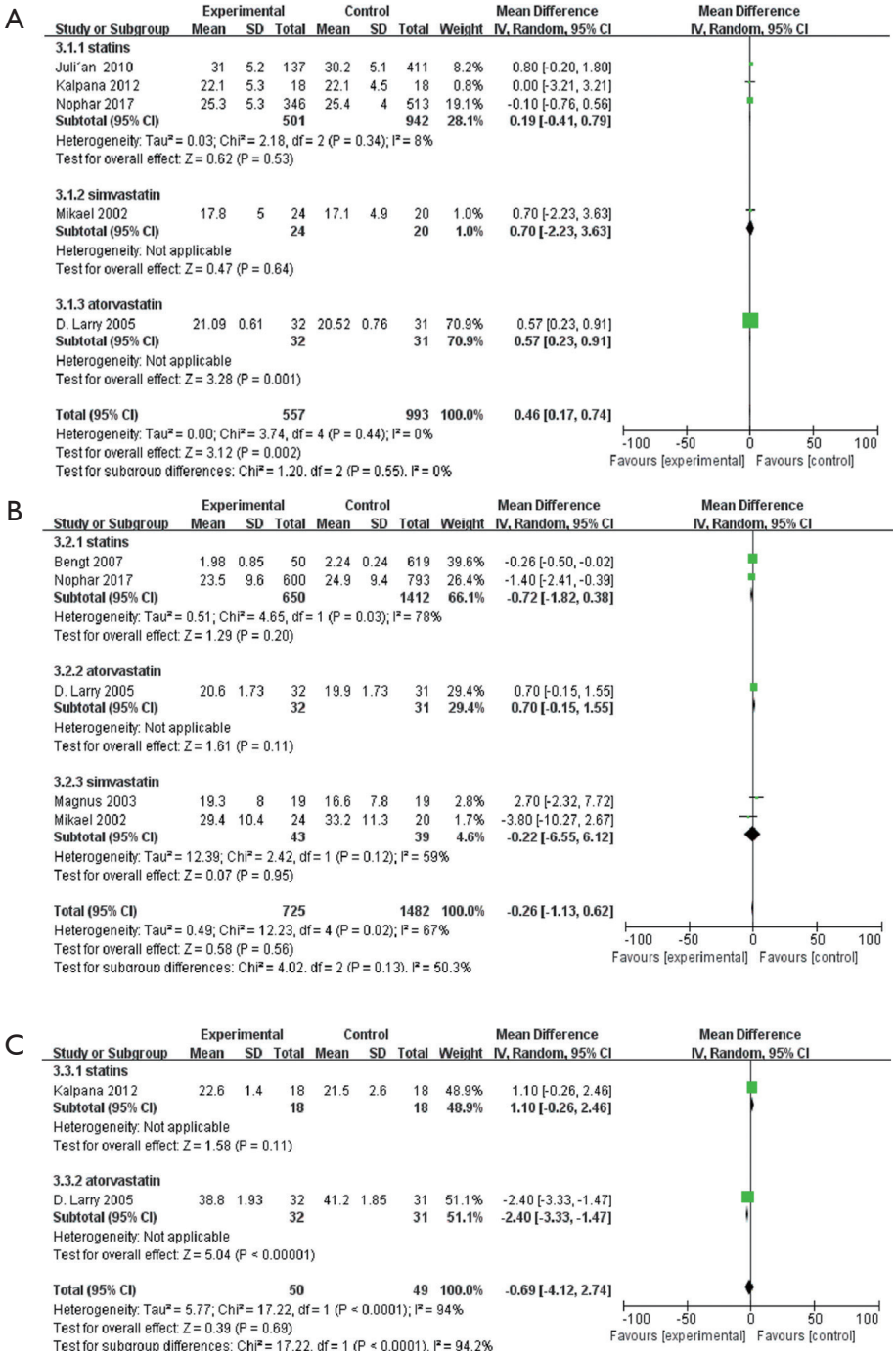

Figure 5 Forest plots show the effects of statin therapy on cognitive changes in dementia samples.

campesterol, plasma sitosterol, CSF lathosterol, and CSF 24S-hydroxycholesterol] were utilized to assess the effects of statin interventions on pathological biomarkers in dementia patients. As shown in *Figure 6*, the results indicate significant effects of statin therapy on plasma $A\beta_{40}$ (OR: 9.27, 95% CI: 0.71, 17.84) (*Figure 6A*), plasma $A\beta_{42}$ (OR: 2.60, 95% CI: 1.07, 4.13) (*Figure 6B*), plasma LDL cholesterol (OR: –16.95, 95% CI: –25.54, –8.37) (*Figure 6E*), plasma lathosterol (OR: –0.11, 95% CI: –0.14, –0.07) (*Figure 6G*), plasma 24s-hydroxycholesterol (OR: –10.41, 95% CI: –15.57, –5.25)

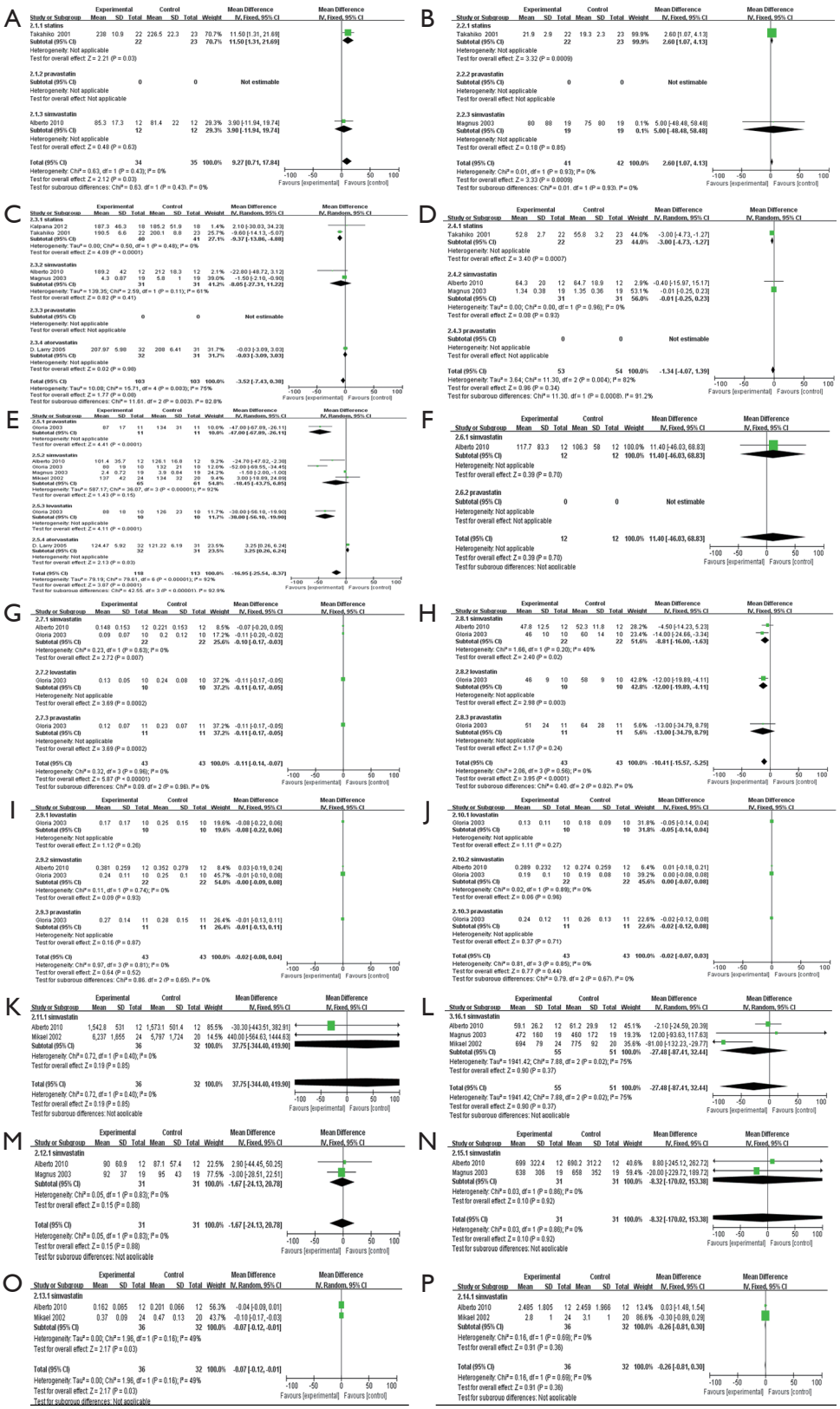

Figure 6 Forest plots show the effects of statin therapy on pathological markers in dementia samples.

(*Figure 6H*), and CSF lathosterol (OR: –0.07, 95% CI: –0.12, –0.01) (*Figure 6O*). No significant results were observed for plasma total cholesterol (OR: –3.52, 95% CI: –7.43, 0.38) (*Figure 6C*), plasma HDL cholesterol (OR: –1.34, 95% CI: –4.07, 1.39) (*Figure 6D*), plasma triglycerides (OR: 11.40, 95% CI: –46.03, 68.83) (*Figure 6F*), plasma campesterol (OR: –0.02, 95% CI: –0.08, 0.04) (*Figure 6I*), plasma sitosterol (OR: –0.02, 95% CI: –0.07, 0.03) (*Figure 6J*), CSF $A\beta_{40}$ (OR: 37.75, 95% CI: –344.40, 419.90) (*Figure 6K*), CSF $A\beta_{42}$ (OR: –27.48, 95% CI: –87.41, 32.44) (*Figure 6L*), CSF phospho-tau (OR: –1.67, 95% CI: –24.13, 20.78) (*Figure 6M*), CSF total tau (OR: –8.32, 95% CI: –170.02, 153.38) (*Figure 6N*), and CSF 24S-hydroxycholesterol (OR: –0.26, 95% CI: –0.81, 0.30) (*Figure 6P*).

Publication bias

Since the number of methodologically sound studies is relatively small (less than 10), it was not necessary to use funnel plots to investigate publication bias. In this study, we assessed publication bias via Begg's test. Accounting for the number of studies, we only explored publication bias as relating to the effects of statins on modulating dementia risk. Our results indicated no publication bias in for these studies overall in the meta-analysis.

Discussion

Higher cholesterol levels in mid-life are reported to increase the risk of developing AD, and statin therapy may exert a protective influence against AD or dementia (16). Although these included articles showed inconsistent results about the effects of statin therapy on dementia, our study is an updated meta-analysis that evaluates the effects of statin therapy on dementia risk and pathological changes. Our study revealed that statin interventions would reduce dementia risk, especially decreasing AD and VaD prevalence. Statin interventions may improve MMSE score, and a significant role of statin therapy was observed in plasma $A\beta_{40}$, plasma $A\beta_{42}$, plasma LDL cholesterol, plasma lathosterol, plasma 24s-hydroxycholesterol, and CSF lathosterol.

Vascular risk factors play critical roles in dementia progression; hence, modifying related factors may be a promising method to treat dementia. Interestingly, our study indicated that statin therapy may reduce dementia risk via modulating related pathologic biomarkers. Of note, statin therapy improves MMSE score, while not significantly altering ADAS-cog score. MMSE and ADAS-cog scores are two common cognitive assessments, but several differences exist between the two assessments. MMSE score is divided into two sections: the first part requires vocal responses and then covers orientation, memory, and attention; the second part tests the ability to name, follow verbal and written commands, write a sentence spontaneously, and copy a complex polygon (47). The ADAS-cog was designed as a rating scale to assess the severity of dysfunction in cognitive or non-cognitive behaviours in dementia patients. In addition, cognitive items and memory items account for approximately 60% of the total points (18). After comparing the two assessments, it is apparent that an ADAS-cog score reflects more abilities of memory. Consistent with the U.S. Food and Drug Administration's discovery, statin therapy may induce memory loss in elderly people. Therefore, statin therapy may increase abilities such as orientation, attention, naming, following verbal or written commands, and memory.

When discussing specific therapies, our results showed different results for different statin therapies. In this meta-analysis, six specific statin types were included, and they are simvastatin, pravastatin, atorvastatin, fluvastatin, cerivastatin, and lovastatin. In (online: http://atm.amegroups.com/public/system/atm/supp-atm.2018.06.43-1.pdf), we provide the current research progress on these drugs in dementia. In addition, early biomarkers are crucial, and they may help to improve the diagnosis of dementia (48-50). These biomarkers include proteins in Aβ metabolism (51), tau metabolism (52,53), and lipid metabolism (54). Hence, we also evaluated the effects of statin therapy on dementia-related biomarkers in *Figure 6*. Our results may be helpful in revealing the role of statin therapy in diagnosis and treatment of dementia.

As shown in (online: http://atm.amegroups.com/public/system/atm/supp-atm.2018.06.43-1.pdf), simvastatin is a well-studied type of statin in dementia therapy. A dozen studies were carried out to explore its effect on dementia in clinical, *in vivo*, and *in vitro* studies. However, the results of clinical studies were inconsistent. After pooling these data, the results of our meta-analysis showed simvastatin may decrease dementia prevalence (OR: 0.43, 95% CI: 0.40, 0.45), which indicated simvastatin therapy may alleviate related pathologic process. Although our group failed to find a close association in Aβ or tau metabolism, according to (online: http://atm.amegroups.com/public/system/atm/supp-atm.2018.06.43-1.pdf), the *in vivo* and *in vitro* studies showed that simvastatin therapy may modulate Aβ (55-58) or tau metabolism (55,59) by enhancing the phosphorylation of NR2B and Akt (60), altering the level of HIF-1α and

BACE (61), α7nAChR-cascading the PI3K-Akt pathway, increasing BDNF (61,62), decreasing oxidative stress (63), blockading retinoblastoma protein phosphorylation, and inhibiting cyclin E/cyclin-dependent kinase (CDK) 2 activity associated with increased levels of the CDK inhibitors p21(Cip1) and p27(kip1) (64). Concerning lipid metabolism, we discovered that simvastatin therapy could downregulate the level of plasma 24s-hydroxycholesterol (OR: −8.81, 95% CI: −16.00, −1.63) and CSF lathosterol (OR: −0.06, 95% CI: −0.10, −0.02). Moreover, the role of simvastatin therapy on lipid metabolism was proven *in vivo* and *in vitro* (65,66). Considering the above studies, simvastatin therapy may be a promising method to treat dementia.

However, other statin therapies still lack sufficient data to prove their influence on dementia. Our group has even devoted our attention to lovastatin therapy. Our data indicate that statin-regulated sAPP secretion occurs via activation of the PI3K pathway and inhibition of ROCK signalling. Statins may modulate neuronal excite protection through both cholesterol-dependent and -independent mechanisms and maybe linked to calpain-mediated neuronal death (67). Our group demonstrated that lovastatin suppressed the aberrant tau phosphorylation both from frontotemporal dementia and Parkinsonism linked to a chromosome 17 (FTDP-17) mutation and okadaic acid induction in cultured rat primary neurons. The protective effect of lovastatin occurred at multiple pathological sites of tau protein, such as Tyr^{181}, Tyr^{231} Ser^{202}/Tyr^{205}, Tyr^{212}/Ser^{214} and Ser^{396}/Ser^{404} (68). In addition to our findings, a major study group also revealed similar results about the effects of lovastatin therapy on dementia-related pathologic changes, such as related to Aβ (69-71). However, these current studies did not show its effects on dementia patients. It remains for more experimental groups to discover its true effects.

In summary, our meta-analysis offered some evidence of potential benefits of statin therapy on dementia. However, the major question is whether the current improvements are of clinical value. In addition, our study explored all types of study. In fact, there is low evidence in comparison to those based only on randomized controlled trials (RCTs). Therefore, further RCT trials with larger samples and longer interventions are needed to evaluate whether our findings are truly significant.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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