

## Review Article

# Effects of statins on short and long-term cognitive impairment in patients with critical illness: a systematic review and meta-analysis

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**Abstract:** Purpose: The aim of the current study was to determine whether statins are effective in prevention of delirium and cognitive impairment in critically ill patients. Methods: A systematic search was performed of MEDLINE, EMBASE, the Cochrane Central Register, and all available Chinese databases to identify publications from inception to February 2018. Adults with no history of cognitive dysfunction, treated with statins in intensive care units, were included from observational studies and high-quality randomized controlled trials (RCT) after formal bias assessment. Results: Nine studies were included in the quantitative synthesis. Short-term trials included 2 RCTs, 5 prospective studies, and 2 retrospective studies. Pooled data demonstrated no reduction in delirium prevalence (RR, 0.93; 95% CI, 0.71-1.22). Long-term cognition studies included only one RCT, with a follow-up duration of 12 months. Results revealed no reduction of impaired cognition in statin-treated patients (OR, 1.07; 95% CI, 0.53-2.19). Conclusion: Despite some encouraging observational studies, present data shows no benefit for statins in reducing delirium for intensive care and long-term cognitive impairment.

**Keywords:** Statins, delirium, critical illness, cognitive dysfunction, meta-analysis

## Background

Delirium is a form of acute brain dysfunction, with a prevalence between 60% to 80% in critically ill patients requiring mechanical ventilation [1]. Delirium is associated with prolonged hospitalization [2], excessive healthcare costs [3], increased mortality [4], and even persistent cognitive impairment [1]. Delirium is independently associated with a 3-fold increased risk of mortality at 6 months. For survivors, a 10-fold increased risk of cognitive impairment exists at 12 months [5]. Long-term cognitive impairment after critical illness reduces quality of life, increases healthcare costs, and leads to institutionalization [6]. Researchers have examined interventions that may prevent and/or treat delirium during critical illness. However, no interventions, to date, have been proven consistently efficacious [7]. In addition to reducing formation and entry of low-density lipoprotein

(LDL) cholesterol into the circulation and lowering serum fatty acid concentrations, statins have other cholesterol-independent effects, including antithrombotic and anti-inflammatory effects, reduction of apoptosis, and cell death [8]. These pleiotropic effects make statins promising candidates for treatment of delirium during critical illnesses, since they might interrupt the neuroinflammatory cascade hypothesized to contribute to delirium [9]. Although the pathogenesis of delirium remains poorly understood, Page and co-workers reported that ongoing neuroinflammation may cause oxidative damage and apoptosis, leading to development of cognitive impairment [10]. Some observational studies have shown that statin administration has positive effects on reduction in the duration of delirium, while discontinuation of statins has been associated with an increased risk of delirium [11, 12]. However, some randomized controlled trials, focusing on the effects of st-

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atins and their neurological benefits, have reported no differences in the prevalence of delirium in intensive care or on cognitive impairment at 6 months and 12 months after discharge from intensive care [13, 14].

Several excellent meta-analyses of observational studies have been published on the potential influence of statins on brain dysfunction (delirium, dementia, and cognitive impairment). However, these studies did not focus on critically ill patients and showed conflicting results [11, 12]. The most recent report was published in 2017, but new high quality RCTs studies have been released that were not included in either of these meta-analyses [13]. The objective of this meta-analysis was to review current studies and estimate any benefit of statins in preventing delirium in short-term and cognitive impairment in long-term for critical ill patients with no history of cognitive dysfunction.

### Methods

#### *Search methods for identification of studies*

*Electronic search:* A systematic search of MEDLINE, the Cochrane Central Register, and EMBASE was conducted from inception to February 25, 2018. This search was augmented by hand, searching of relevant articles and making inquiries among colleagues, collaborators, and experts in the field. This study also searched Chinese Biomedical Database (CBM) (1975 to February 28, 2018), China National Knowledge Infrastructure (CNKI) (1917 to February 28, 2018), and VIP Database (1989 to February 28, 2018). No language restrictions were applied. This optimal search strategy was according to previous literature [14] with the aid of an expert. The following search terms were used: statins or statin or simvastatin or lovastatin or pravastatin or fluvastatin or atorvastatin or rosuvastatin or cerivastatin and dementia or cognition disorders or delirium or amnesic and follow-up studies or longitudinal studies or prospective studies or random control studies and critical ill or intensive care unit.

#### *Study characteristics*

*Types of studies:* For both delirium and cognitive impairment, studies were required to be randomized controlled trials, high-quality prospective studies, and retrospective cohort

studies of any statin using validated objective measures of delirium and cognitive impairment as end points. Studies comparing two different statins without a placebo were excluded.

*Types of participants:* Critical ill patients with no history of cognitive dysfunction were included. Patients in ICU after surgery were included, especially coronary surgery.

*Types of interventions:* Any member of the statin family was given, within the licensed dose range, with a parallel concomitant placebo.

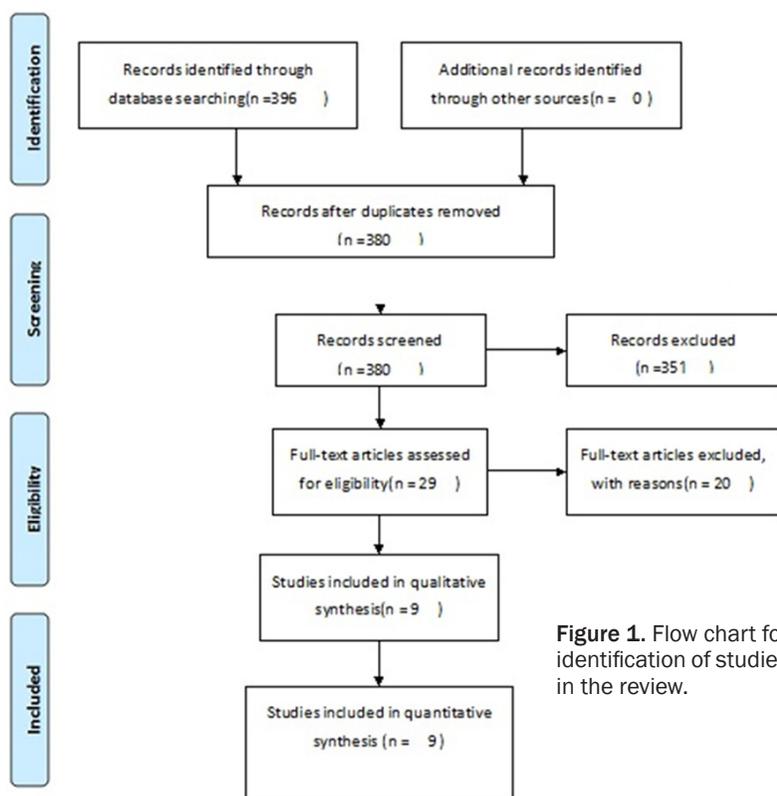
*Types of outcome measures:* Primary outcome was the daily delirium status in intensive care, up to 28 days, in the intention-to-treat population. Delirium status was assessed daily by researchers or clinical personnel with the validated and reliable Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) [15]. Secondary outcomes were cognitive function at 6 months and 12 months. Immediate memory and delayed memory were assessed with Logical Memory I and II age-adjusted scaled scores (range 1-19; higher is better) from the Wechsler Memory Scale (Third Edition). Attention and working memory were assessed with Digit Span age-adjusted scaled scores (range 1-19; higher is better) from the Wechsler Adult Intelligence Scale (Third Edition) [16].

#### *Data collection and analysis*

*Selection of studies:* Two authors, independently, searched and screened publications. The two authors agreed upon and tested the MeSH terms and search strategy. They screened citations and independently selected trials for relevance against the defined inclusion criteria. This study excluded trials that did not fulfil the criteria from further analysis. Any disagreements, in the selection of studies, were resolved by discussion.

*Data extraction and management:* Available data on demographics of participants (age, gender, lipid values at baseline), statin regimen (type of statin, daily dosage, starting time, duration), and follow-up duration was extracted. The number of participants in each treatment group and the number of participants experiencing the outcome of interest was also extracted. This study reported results of dichotomous outcomes as an odds ratio (OR) with 95% CI. Data

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**Figure 1.** Flow chart for identification of studies in the review.

### Assessment of risk of bias in included studies

Methodological quality of RCTs was examined using Cochrane's tool for assessing risk of bias using the following domains: selection bias, detection bias, performance bias, attrition bias, reporting bias, and other bias. For observational studies, the Newcastle-Ottawa Scale was adopted for exposures and outcomes of interest in this review. Highest risk of bias contained self-reported methods, record linkage (generally taken from pharmacy databases on filled prescriptions) compared with in-person clinical assessment of dementia, and studies that did not adjust for known confounders or a propensity score [17].

### Results

A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram is shown in **Figure 1**. The initial search identified 396 records. After screening, 29 were considered potentially eligible. These 29 full-text articles were assessed for eligibility. Nine met eligibility requirements for qualitative synthesis and for quantitative synthesis (8 short-term and 1 long-term cognition studies). The 9 remaining studies underwent bias assessment. Twenty were excluded, as their risk of bias was higher than that of the remaining group (**Figure 2**), primarily due to outcome measurement and appropriate consideration of confounders. Results showed high heterogeneity ( $I^2=95\%$ ) for all studies and moderate heterogeneity ( $I^2=41\%$ ) for perspective studies. A total of 269,278 patients were included in this analysis. Statins were used in 23,856 (8.3%) patients. In the total cohort, 4,382 (1.4%) patients underwent cardiac surgery. Statin use was noted in 2,321 (53.0%) of these patients (**Figure 4**).

#### Prevention of delirium

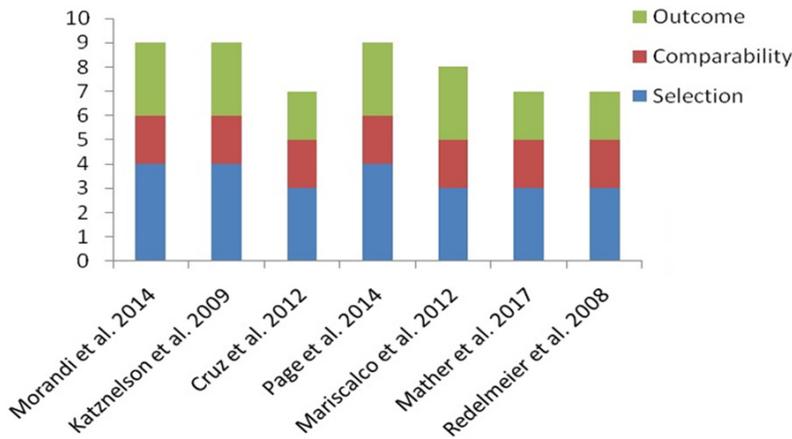
Short-term trials included one randomized controlled trial, 5 prospective studies, and 2 retro-

was applied using RevMan version 5.1 software (Cochrane Collaboration).

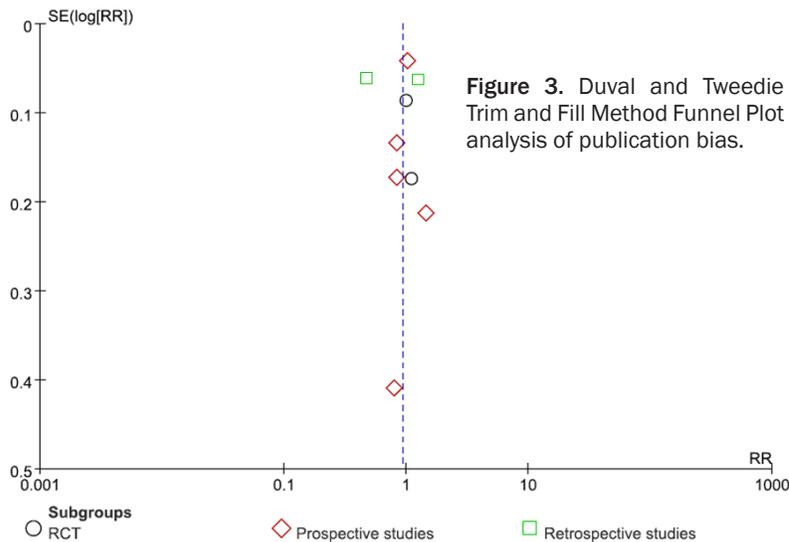
**Dealing with missing data:** If intention-to-treat data were not available in the publications, 'on-treatment' or the data of participants that completed the trial was sought.

**Assessment of heterogeneity:** The impact of heterogeneity was assessed for each pooled analysis by Cochran's Q test and  $I^2$  statistic. Low, moderate, and high degrees of heterogeneity corresponded to  $I^2$  values of 25%, 50%, and 75%. Furthermore, a random or fixed effects model was chosen based on heterogeneity. A random effects model was selected when the  $I^2$  was  $> 50\%$ . Publication bias was estimated by visual inspection of the funnel plot. Duval and Tweedie Trim and Fill Method was used to assess publication bias if visual inspection of the funnel plot suggested an asymmetrical distribution of the studies. If heterogeneity still existed with any model, sensitivity analysis was carried out (excluding studies with conflicting results from the rest), thereby assessing the robustness of results of fixed-effects versus random-effects models [13].

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**Figure 2.** Bias summary for observational studies, rated by the Newcastle-Ottawa Scale, with 9 total possible points (4 for selection, 2 for comparability, and 3 for outcome). More points indicate a higher-quality study.



**Figure 3.** Duval and Tweedie Trim and Fill Method Funnel Plot analysis of publication bias.

pective studies, showing inconsistent effects. Pooled data demonstrated no reduction in delirium prevalence (risk ratio, 0.92; 95% CI, 0.68-1.26). Characteristics of these studies are summarized in **Table 1**. In total, the studies did not show any consistent effects of statin therapy on delirium end points. Monitoring varied between 6-12 hours, based on study/institution protocols. Delirium was identified using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) in four studies. International classification of disease code was used in one study, while both CAM-ICU and intensive care delirium screening checklist were used in the remaining study. Delirium was noted in 936 (3.8%) and 4,218 (1.5%) of the patients in statin and non-statin groups, respectively. Overall

heterogeneity was 95%, reflecting high heterogeneity among included studies. Therefore, a random effects model was adopted. The overall risk of delirium in the nine studies was not significantly different in the statin and non-statin groups, while two retrospective studies demonstrated contrary results (RR, 0.76; 95% CI, 0.29-1.99). Since the two retrospective studies contributed most of the patients, exclusion sensitivity was performed. Exclusion of each or both studies did not alter results (RR, 0.88; 95% CI, 0.60-1.30) or (RR, 1.00; 95% CI, 0.87-1.14). Visual inspection of the funnel plot suggested asymmetry. Duval and Tweedie trim and fill plots did not alter the above results significantly, not necessarily indicating publication bias (**Figure 3**).

### *Prevention of long term (12 months) cognitive impairment*

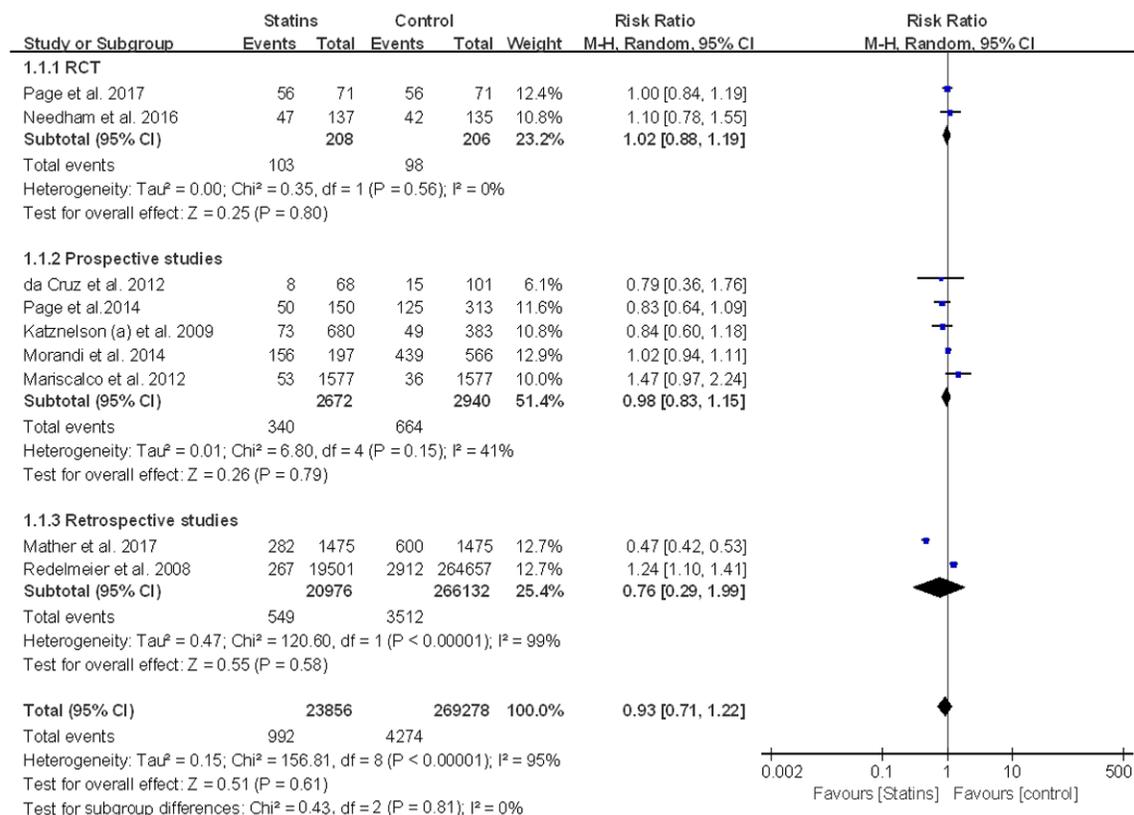
Only one RCT focused on cognitive decline as the primary outcome and it did not concern dementia. This

study (148 patients) had a follow-up duration of 12 months. Results revealed no reduction of impaired cognition in statin-treated patients (odds ratio, 1.07; 95% CI, 0.53-2.19) (**Figure 5**).

### Discussion

The present systematic review evaluated studies regarding statin interventions on short-term and long-term cognitive impairment in intensive care patients without a history of cognitive dysfunction. Overall, 2 RCTs [13, 14], 5 prospective cohort studies [11, 12, 22-24], and 2 retrospective cohort studies [18, 19] were evaluated. Strengths of the present study include a clear taxonomy for short- vs long-term effects of statin therapy, use of a priori eligibility crite-

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**Figure 4.** Forest plot of quantitative synthesis for short-term cognition showing incidence of delirium in the statin vs placebo groups (constructed using Cochrane RevMan version 5.1 software).

ria, focus on objective outcome measures, formal assessment of bias, and quantitative synthesis.

Regarding statins and short-term cognition, studies including RCT and observational studies varied from its amount. This review provides the first quantitative synthesis of digit symbol substitution test scores. This review strengthens the findings of two recent systemic reviews by incorporating several additional publications, focusing on delirium studies defined by formal risk of bias assessment [13, 20]. Current data demonstrated contradicting impact of statins in delirium prevention. However, contradictions are subject to individual study bias. The largest data for this analysis emanated from the study by Redelmeier and colleagues. It had methodological weaknesses of restriction of ages and property of statins (non-lipophilic) [18]. Mariscalco [22, 24], Cruz [21], and Katznelson [22] evaluated patients regarding different types of surgery, duration of statin use, and intra- and post-operative management. Statin withdrawal was associated with

higher postoperative cardiovascular events and troponin release and worsening delirium [23]. However, the effects of statins in the peri-operative population for prevention of post-operative delirium remain unclear. Results of observational studies of statins and delirium in the intensive care unit (ICU) are contradictory [18, 19]. RCT results do not support simvastatin administration in the management of delirium.

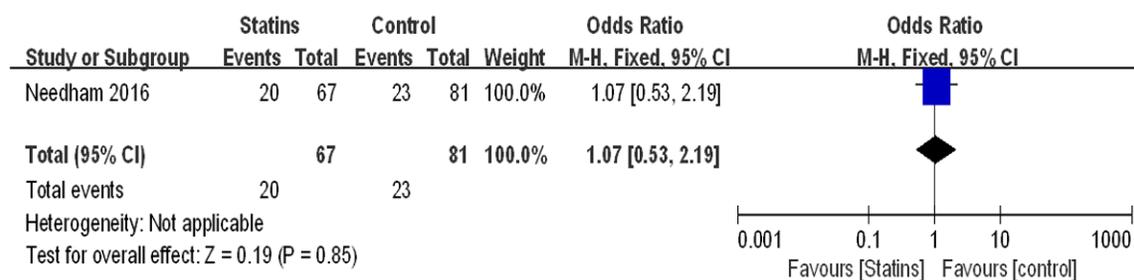
Regarding statins and long-term cognition, one high quality RCT [24] evaluated the effects of statins on delirium in ICU. Moreover, a long-term follow-up was performed to evaluate the impact of delirium treatment on cognitive and functional impairment. There was no benefit of rosuvastatin in reducing delirium in intensive care or cognitive impairment at 6 months and 12 months in this trial, consistent with a separate patient cohort from ARDSNet's EDEN trial (36% at 6 months, 25% at 12 months). In that cohort of patients with respiratory failure or shock, they were assessed at 3 months (40%) and 12 months (34%) with a different set of cognitive tests. In the present review, the im-

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**Table 1.** Characteristics of studies meeting the inclusion criteria

Parameter/Studies	Cruz et al. 2012	Katznelson et al. 2009	Mariscalco et al. 2012	Moradi et al. 2014	Page et al. 2014	Redelmeier et al. 2008	Mather et al. 2017	Page et al. 2017	Needham et al. 2016
Country				United states	United Kingdom	Canada	United states	United Kingdom	United states
Design	Prospective	Prospective	Prospective	Prospective	Prospective	Retrospective	Retrospective	RCT	RCT
Study period	01/2011-06/2011	05/2005-06/2006	10/2004-12/2010	03/2007-05/2010	08/2011-02/2012	04/1992-0/42002	09/2012-09/2015	02/2013-07/2016	2010-2014
Number (entire)	169	1063	3154	763	463	284158	2950	142	272
Female N (%)		304 (30%)	859 (22%)	372 (49%)	219 (47%)	142718 (50%)	1319 (44%)	60 (42%)	136 (50%)
Non-stain users	68	383	2474	444	319	264657	1475	71	135
Age			67.8	61	70	72.9		62	52.5
Population	Cardiac surgery	Cardiac surgery	Cardiac surgery	ICU	ICU	Cardiac and non-cardiac surgery	ICU	Receiving invasive mechanical ventilation	Receiving mechanical ventilation
Inclusion criteria	Cardiac surgery	First cardiac surgery with CPB	Use of CPB	ARF, shock	All ICU	> 65 years, elective surgery	All ICU	Receiving invasive mechanical ventilation	Receiving mechanical ventilation
Exclusion criteria		Circulatory arrest, CHD, re-do surgery	Alcohol use, Psychiatric illness	Recent ICU stay*, IMV < 2 months, dementia, CPR with ABI, no long-term follow-up		Emergent or day surgery, major vascular diseases	Richmond Agitation Sedation Scale (RASS) assessment of -4 or -5	Younger than 18 years old, pregnant or breastfeeding	Acute respiratory distress syndrome for more than 48 h
Statins used	Simvastatin (92.6%) Atorvastatin (5.9%) Rosuvastatin (1.5%)		Simvastatin Lovastatin Rosuvastatin Fluvastatin	Simvastatin (54.0%) Atorvastatin (20.0%) Lovastatin (12.0%) Rosuvastatin (8.0%) Pravastatin (6.0%)		Atorvastatin Pravastatin Simvastatin Lovastatin Rosuvastatin Fluvastatin Cerivastatin	Atorvastatin (74.6%), pravastatin (12.6%), rosuvastatin (4.4%), and simvastatin (8.4%)	Simvastatin	Rosuvastatin
Prehospital duration	≥ 2 months		5.0±4.5 days						
Delirium criteria	CAM-ICU, ICDSC	CAM-ICU	CAM-ICU	CAM-ICU	CAM-ICU	ICD codes	CAM-ICU	CAM-ICU	CAM-ICU
Primary outcome	Delirium	Delirium	Delirium	Delirium	Delirium	Delirium	Delirium	Delirium-free and coma-free in the first 14 days	Delirium status in intensive care up to 28 days
Secondary outcome								Delirium-free and coma-free in the first 28 days	Cognitive function at 6 months and 12 months
Risk/Newcastle ottawa scale	7	9	8	9	9	6	6	Low	Low

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**Figure 5.** Forest plot of quantitative synthesis for long-term cognition showing incidence of dementia in the statin vs placebo groups (constructed using Cochrane RevMan version 5.1 software).

pact of statins varied significantly across different studies, but no interventions were effective. This can partially be ascribed to the fact that resolution of delirium was evaluated using different assessment tools. All types of delirium are not the same, varying according to specific characteristics, duration, and persistence. Therefore, it is of great significance to evaluate the effects of statins that attenuate intensive care and post-intensive care cognitive impairment.

The present systematic review had some limitations. First, different types of studies, including RCTs, retrospective studies, and perspective studies, may have been responsible for the observed heterogeneity. Second, because of high heterogeneity and the small number of studies, publication bias could not be properly assessed. Third, some studies did not have the same end points or the same data available for synthesis. Therefore, the authors were contacted. More data, however, was not always available.

### Conclusion

In critically ill patients without baseline cognitive dysfunction, results of this meta-analysis revealed no significant short-term cognitive detriments related to statin therapy. Long-term data also suggests no beneficial role in the prevention of dementia. Future studies investigating statins and cognition should use a clear taxonomy, establish protocols a priori, and focus on objective outcome measures. More studies regarding mechanisms, outcomes, individual drugs, and dosages are warranted to evaluate statins as a potential therapy for critically ill patients.

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### Disclosure of conflict of interest

None.

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