Statin Use and Delirium Risk: An Updated Systematic Review and Meta-Analysis

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Abstract

Purpose: Findings on the association of statin use with delirium risk are inconsistent. We performed an up-to-date systematic review and meta-analysis to elucidate this association among critically ill and surgical patients.

Materials and Methods: We searched PubMed, the Cochrane Library, and the EMBASE database, limiting the search to human patients and articles in English published until December 31, 2021. The odds ratio (OR) and 95% confidence interval (CI) were used to indicate the difference in the incidence of delirium between statin use and nonuse groups. A random-effects model was selected in the case of high heterogeneity of study populations. We used funnel plots, Egger's test, Duval and Tweedie's trim-and-fill approach, and the classic fail-safe N to assess publication bias.

Findings: Of a total of 264 identified studies, 13 were selected for the qualitative review—4 RCTs and 9 observational cohort studies. Statin use was not associated with low delirium risk (pooled OR, 0·82; 95% CI, 0·64 to 1·04; p = 0·09). Substantial statistical heterogeneity was observed (I2, 90%). Visual inspection of the funnel plot of ORs from the studies revealed symmetry.

Conclusions: Statin use is not associated with delirium risk. More comprehensive RCTs are required to confirm the results.

Introduction

Delirium is an acute disorder with disturbance in concentration, conscious, or cognition over a short period of time.[1] Approximately 30% of older patients with medical conditions experience delirium at some time during a hospital stay.[2] A relatively high proportion of surgical (10–50%)[3] and critically ill (70%) patients experience delirium.[4] Delirium would make patients extended hospitalization, cognitive impairment and a higher risk of mortality.[5, 6] Delirium has no effective interventions for prevention; however, its incidence could be reduced by multiple interventions for managing risk factors.[7] Using medications for preventing delirium in high-risk settings is not supported by current evidences.[8, 9] Cholinesterase inhibitors,[10] antipsychotic agents,[11] dexmedetomidine,[12] melatonin,[13] and statins[14] have been evaluated for preventing delirium.

Statins have pleiotropic properties, including anti-inflammatory, immunomodulatory, and antithrombotic.[15, 16] Although the pathophysiology of delirium is poorly understood, inflammatory alteration in the central nervous system is known to be a crucial factor.[17] In 2016, Vallabhajosyula et al included six observational studies in a meta-analysis, the results of which indicated that statin use was not associated with a decreased risk of delirium in critically ill and cardiac surgery patients. Recently, inconsistent evidence has been reported, including that from randomized controlled trials (RCTs)[18–21] and observational studies.[22–24] Oh et al performed a retrospective observational study and observed that statin use was associated with a 34% lower risk of delirium than statin nonuse [odds ratio (OR) 0·66, 95% confidence interval (CI) 0·45 to 0·97, p = 0·036].[24] Xu et al performed a RCT in which perioperative rosuvastatin treatment was observed to reduce the incidence of delirium after elective operative surgery under general anesthesia (OR 0·52, 95% CI, 0·31 to 0·89, p < 0·05).[21] However, Page et al conducted a RCT and demonstrated no significant mean difference in the number of days alive without delirium between groups administered simvastatin versus placebo (mean difference 0·4 days, 95% CI, − 1·3 to 2·1; p = 0·66).[19] Because of the inconsistent results of previous studies, we performed an up-to-date systematic review and meta-analysis to elucidate the association between statin use and delirium risk among critically ill and surgical patients.

Methods

This meta-analysis was conducted strictly in accordance with PRISMA guidelines.[25] This study was prospectively registered in the PROSPERO registry, with the registration number CRD42022307045. The PRISMA checklist is provided in Supplementary Table S1.

Search Strategy

We included RCTs and observational studies (either cohort or case–control studies) that evaluated the preventative or treatment effects of statins on delirium in critically ill or surgical patients in an intensive care unit (ICU). We searched PubMed, the Cochrane Library, and the EMBASE database, limiting the search to human patients and articles in English published until December 31, 2021. The details of the search strategy are provided in Box 1. All identified articles were imported into EndNote software (version X8,

Thomson ResearchSoft, CT, USA) to remove duplicate records automatically. Two reviewers (Y. H. C. and J. Y. W.) screened all titles and abstracts independently and evaluated relevant articles. In addition, we searched available bibliographies and review articles for additional potential articles that can be included in this study. Disagreements were resolved through consensus and consultation with a third reviewer (M. J. L.).

Data Extraction and Outcome Measures

By using a standardized data extraction form, we obtained information on the study year, study location, study population, participant characteristics, delirium outcome, and effect sizes and their 95% CIs. For studies that reported only the crude effect size, we contacted authors and requested them to provide data on the adjusted effect size and relevant information. The outcomes assessed were the incidence of delirium as defined using the Confusion Assessment Method (CAM), CAM-ICU, or diagnostic codes from administrative databases. We obtained sufficient published data to calculate the estimates of the crude or adjusted OR with the 95% CI of delirium risk related to statin use in eligible studies. In addition, delirium-free days were counted as an outcome in a few studies.

Risk of Bias Assessment

To examine the quality of the included studies, we used the Cochrane Risk of Bias tool for RCTs[26] and the Newcastle–Ottawa scale for observational studies (Supplementary Appendix 1).[27] The Cochrane Risk of Bias tool assesses the potential sources of bias including selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), and reporting bias (selective reporting).[26] Each study was categorized as having either low risk (green), unclear risk (yellow), or high risk (red) of bias. The risk of attrition bias was considered to be low if the dropout rate was lower than 20% due to the inclusion of few participants in each of the studies. For assessing reporting bias, the protocols for each study were searched on clinicaltrials.gov and biomedcentral.com. The Newcastle–Ottawa scale evaluates three major sources of bias in epidemiological studies by using five items: one for selection bias, two for measurement bias, and two for confounding bias.[27] A study is classified in each domain as having high or low risk in accordance with prespecified criteria. All included studies were evaluated by two pharmacists (Y. H. C. and J. Y. W.) independently; any discrepancies were resolved through discussion.

Statistical Analysis

We conducted a meta-analysis to determine the association of statin use with delirium in RCTs and observational studies. The effect size and 95% CI were defined as the OR and 95% CI to indicate the difference in the incidence of delirium between statin use and nonuse. A random-effects or fixed-effects model was selected to calculate the pooled effect size, and a random-effects model was used if the study population had high heterogeneity. We assessed statistical heterogeneity across studies by using the I^2 statistic.[28] I^2 values of < 50%, 50–75%, and > 75% are deemed to indicate low, moderate, and high heterogeneity, respectively. Exclusion sensitivity analysis was conducted to investigate the effect of individual studies. We performed subgroup analysis on the basis of the study design (RCTs versus other observational studies), country in which the studies were performed, and publication before 2015 versus after 2015. We used funnel plots, Egger's test, Duval and Tweedie's trim-and-fill approach, and the classic fail-safe N to assess publication bias.[29, 30] In addition, we performed meta-regression by adjusting for age and male sex to explore the potential sources of heterogeneity. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach[31] was employed to evaluate the quality of evidence; in this approach, the four grades are high, moderate, low, and very low quality. All statistical analyses were performed using RevMan5 and Comprehensive Meta-Analysis Software.

Box 1

PUBMED on December 14, 2021

MeSH terms

1. "Hydroxymethylglutaryl-CoA Reductase Inhibitors" = 32,147

2. "delirium" = 11,025

Text terms

3. “statin” = 61,940

4. “atorvastatin“ = 10,945

5. “cerivastatin” = 789

6. “fluvastatin” = 2,157

7. “lovastatin” = 12,291

8. “pravastatin” = 4,850

9. “rosuvastatin” = 12,912

10. “simvastatin” = 11,544

11. “deliirum” = 20,886

Search strings (all inclusive):

[(1 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10) =65,927 AND (2 OR 11) = 20,886]=69

Cochrane Library on December 14, 2021

MeSH terms

1. “Hydroxymethylglutaryl-CoA Reductase Inhibitors” = 3,634

2. “delirium” = 898

Text terms

3. “statin” = 7,154

4. “atorvastatin“ = 5,665

5. “cerivastatin” = 196

6. “fluvastatin” = 751

7. “lovastatin” = 987

8. “pravastatin” = 1,967

9. “rosuvastatin” = 2,028

10. “simvastatin” = 3,986

11. “delirium” = 4,290

Search strings (all inclusive):

[(1 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10) =15,510 AND (2 OR 11) = 4,290]=22

EMBASE on December 14, 2021

Emtree term

1. “Hydroxymethylglutaryl-CoA Reductase Inhibitors” = 169,687

2. “delirium” = 36,008

Search strings:

3. (1 AND 2) =424

4. 3. AND 'human'/de = 418

5. 4. AND ('clinical trial'/de OR 'cohort analysis'/de OR 'controlled clinical trial'/de OR 'controlled clinical trial topic'/de OR 'controlled study'/de OR 'cross sectional study'/de OR 'major clinical study'/de OR 'observational study'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial topic'/de OR 'retrospective study'/de) = 173

Results

Search Results and Study Characteristics

A total of 264 database records were screened, and the eligibility of 23 full-text articles was assessed. Eight review articles, three duplicate reports, and one report on cost-effectiveness were excluded from this meta-analysis. Finally, 13 articles were selected for the qualitative review: 4 RCTs and 9 observational cohort studies (Fig. 1). Table 1 summarizes the characteristics of the 13 included studies. The studies included 300,590 participants from eight countries. The mean age of the study participants ranged from 51·0 to 73·9 years across the studies. The percentage of male patients ranged from 7·4–88%.

Table 1
Characteristics of included studies

Author and year	Study Type	Country	Study Population	Statins Use (n)	Age (years, mean ± SD)	Male sex (%)	Outcome Incident delirium: n(%) Delirium free days: mean ± SD	Risk estimate (95% Confidence Interval)
Redelmeier et al. 2008[32]	Retrospective cohort study	Canada	Patients with elective surgery	Statins user 19,501	71.9 ± 4.7	48.2%	273 (1.4%)	aOR 1.28 (1.12 to 1.46)
				Statins nonuser 264,657	73.9 ± 6.1	49.9%	2,912 (1.1%)	
Katznelson et al. 2009[40]	Prospective cohort study	Canada	Patients with cardiac surgery	Statins user 686	Not provided	Not provided	73 (10.6%)	Not provided
				Statins nonuser 383			49 (12.8%)	
Cruz et al. 2012[41]	Prospective cohort study	Brazil	Patients with cardiac surgery	Statins user 68	62.9 ± 10.9	70.6%	8 (11.8%)	aOR 0.63 (0.43 to 0.93)
				Statins nonuser 101	61.5 ± 11.4	59.4%	15 (14.9%)	
Mariscalco et al. 2012[33]	Prospective cohort study	Italy	Patients with cardiac surgery	Statins user 1577	67.4 ± 9.3	79.5%	53 (3.4%)	aOR 1.49 (0.97 to 2.29)
				Statins nonuser 1577	67.5 ± 9.2	79.5%	36 (2.3%)	
Morandi et al. 2014[42]	Prospective cohort study	United States	Patients in Intensive care unit	Statins user 319	65 [58–72]*	60%	253 (79.3%)	Not provided
				Statins nonuser 444	57 [46–68]*	55%	342 (77%)	
Page et al. 2014[43]	Prospective cohort study	United Kingdom	Patients in Intensive care unit	Statins user 151	77 ± 11	57%	50 (33%)	Not provided
				Statins nonuser 319	63 ± 19	52%	125 (40%)	

Author and year	Study Type	Country	Study Population	Statins Use (n)	Age (years, mean ± SD)	Male sex (%)	Outcome Incident delirium: n(%) Delirium free days: mean ± SD	Risk estimate (95% Confidence Interval)
Needham et al. 2016[18]	Randomized controlled trial	United States	Patients with surgery	Rosuvastatin 40 mg/day 137	52 ± 18	53%	4.76 ± 3	Not provided
				Placebo 135	52 ± 16	48%	4.03 ± 2.61	
Mather et al. 2017[22]	Retrospective cohort study	United States	Patients in Intensive care unit	Statins user 1475	< 55:21.3% 55–70:37.8% > 70:40.9%	52.9%	Not provided	aOR 0.47 (0.38 to 0.56)
				Statins nonuser 1475	< 55:20.7% 55–70:33.5% > 70:43.8%	54.6%	Not provided	
Page et al. 2017[19]	Randomized controlled trial	United Kingdom	Patients with Mechanical ventilation in Intensive care unit	Simvastatin 80 mg/day 71	61.9 ± 15.3	63%	66 (93%) 5.7 ± 5.1	Not provided
				Placebo 71	62.1 ± 17.3	52%	67 (94%) 6.1 ± 5.2	
Oh et al. 2018[24]	Retrospective cohort study	Korean	Patients with Total knee arthroplasty under spinal anesthesia	Statins user 922	71.5 ± 6.6	7.4%	35 (3.5%)	aOR 0.66 (0.45 to 0.97)
				Statins nonuser 5028	70.9 ± 6.9	8.7%	269 (5.4%)	
Lee et al. 2018[23]	Retrospective cohort study	Korean	Patients with vascular surgery	Statins user 291	69 [61–75] *	86.3%	25 (8.6%)	aOR 0.74 (0.70 to 0.79)
				Statins nonuser 291	70 [61–74]*	88.0%	39 (13.4%)	
Sohrevardi et al. 2021[20]	Randomized controlled trial	Iran	Patients with delirium	Atorvastatin 40 mg/day 40	51 ± 19	50%	2 ± 1	Not provided

Author and year	Study Type	Country	Study Population	Statins Use (n)	Age (years, mean ± SD)	Male sex (%)	Outcome Incident delirium: n(%) Delirium free days: mean ± SD	Risk estimate (95% Confidence Interval)
				Placebo 50	65 ± 24	30%	1 ± 0.25	
Xu et al. 2021[21]	Randomized controlled trial	China	Patients with elective surgery and general anesthesia	Rosuvastatin 40 mg/day 410	66.3 ± 5.1	41.2%	23 (5.6%)	aOR 0.52 (0.31–0.89)
				Placebo 411	66.5 ± 5.3	45.3%	42 (13.5%)	

* Numbers are median and interquartile range.

Abbreviations: aOR, adjusted odds ratio.

Quality Assessment

Figure S1 presents the results of the quality assessment for the four RCTs. Three RCTs[18, 19, 21] were discovered to have low risk in all the domains of assessment; only one study, which was conducted by Sohrevadi et al,[20] had an unclear risk of random sequence generation, selective-reporting, and other biases. Table S2 summarizes the results of the quality assessment for the nine observational cohort studies. The quality assessment scores ranged from 6 to 8. Five studies did not demonstrate that outcome of interest was not present at start of study. None of the studies described adequacy of follow up of cohorts. All the nine studies adjusted for at least one of the other potentially crucial confounders. Thus, all the studies were evaluated to be of high quality.

Meta-Analysis, Sensitivity Analysis, and Publication Bias

Overall, statin use was not associated with a low risk of delirium (pooled OR, 0·82; 95% CI, 0·64 to 1·04; p = 0·09; Fig. 2). In addition, substantial statistical heterogeneity was noted (I^2, 90%). When we removed any one of the 11 studies at one time, high heterogeneity (I^2, 75–91%) was still observed. When the study by Redelmeier et al[32] was removed, the heterogeneity was 75%. In the sensitivity analysis, the results were inconsistent after each study was individually removed (Figure S2). The association between statin use and delirium risk became significant when we removed the study conducted by Redelmeier et al (OR, 0·76; 95% CI, 0·62 to 0·93; p = 0·009) or that by Mariscalco et al (OR, 0·77; 95% CI, 0·60 to 0·98; p = 0·04)[32, 33]. Visual inspection of the funnel plot of ORs from these studies revealed symmetry (Fig. 3). The result of Egger's regression intercept approach indicated no significant evidence of publication bias (intercept, 0·40, two tailed 95% CI, – 2·69 to 3·48, p = 0·778). The results of Duval and Tweedie's trim-and-fill analysis suggested that the two studies were missing in the right side of the mean effect, and the adjusted OR obtained using the trim-and-fill approach was 0·92 (95% CI, 0·71 to 1·18). The result of classic fail-safe N suggested that 86 nil or null reports would be required to increase the p value associated with the average effect to higher than an alpha level of 0·05. In addition, statin use was also not associated with a reduced delirium-free days (pooled standard mean difference, 0·11; 95% CI, -0·41 to 0·93; p = 0·450; Figure S3). Funnel plot of studies on delirium-free days between statin users and nonusers was also shown in Figure S4.

Subgroup Analysis and Meta-Regression

In the subgroup analysis, the pooled OR from the two RCTs revealed that statin use was associated with a lower risk of delirium (pooled OR, 0·55; 95% CI, 0·34 to 0·90; p = 0·018; Figure S5A). However, in the nine observational cohort studies, statin use was not associated with the risk of delirium (pooled OR, 0·85; 95% CI, 0·66 to 1·10; p = 0·208; Figure S5B). High heterogeneity was still

observed in the observational cohort studies (I^2, 92%). The results of the subgroup analysis focusing on studies published before 2015 indicated that statin use was not associated with delirium risk (pooled OR, 1·07; 95% CI, 0·86 to 1·33; p = 0·543; Figure S6A). However, statin use was associated with delirium risk in pooled studies published after 2015 (pooled OR, 0·60; 95% CI, 0·46 to 0·79; p < 0·001; Figure S6B). The results of the subgroup analysis focusing on studies by location indicated that statin use was not associated with the risk of delirium in the studies conducted in the United States (pooled OR, 0·85; 95% CI, 0·51 to 1·41; p = 0·526; Figure S7A) or Europe (pooled OR, 1·03; 95% CI, 0·61 to 1·74; p = 0·924; Figure S7B). However, statin use was associated with delirium in pooled studies conducted in Asia (pooled OR, 0·74; 95% CI, 0·70 to 0·78; p < 0·001; Figure S7C). The meta-regression models of age and male sex had a poor predictive ability (p = 0·961 and 0·453, respectively). Using the GRADE approach, we provided the evidence of this meta-analysis a rating of low quality and a weak recommendation for this review.

Discussion

In this meta-analysis, we reviewed the association between statin use and the risk of delirium among critically ill and surgical patients, and we did not observe a benefit of statin use for preventing delirium. The results are similar to those of the meta-analysis performed by Vallabhajosyula et al.[14] The overall quality of the evidence, as defined using the GRADE approach, was determined to be low with a weak recommendation, largely due to heterogeneity.

Inflammatory alteration of the central nervous system is a major factor involved in the pathophysiology of delirium.[34, 35] Statins may alleviate delirium through the attenuation of neuroinflammation, deleterious neurotransmitters, cerebral hypoperfusion, and microthrombosis, indicating the potential clinical application of statins for the treatment of delirium. However, the clinical effects of statins for delirium remain a matter of debate.[36] Among critically ill patients, the use of statins in the ICU was associated with a decreased risk of delirium, especially in patients with early-stage sepsis; moreover, discontinuation of a previously used statin was associated with the increased occurrence of delirium. The anti-inflammatory effects of statins may confer neuroprotection, aid memory recovery, reduce the severity of cognitive dysfunction, and attenuate blood–brain barrier injury in critically ill and surgical patients. These pleiotropic effects may contribute to the prevention or mitigation of delirium in critically ill and surgical patients by modifying the process of neuroinflammation and the activation of proinflammatory microglia.[37–39]

The results of the present subgroup analysis focusing on studies published before 2015 indicated that statin use was not associated with the risk of delirium (pooled OR, 1·07; 95% CI, 0·86 to 1·33; p = 0·543; Figure S6A). This result is the same as that of a previous meta-analysis,[14] suggesting that statins may not reduce the occurrence of delirium in critically ill and cardiac surgery patients. However, the aforementioned meta-analysis included and reviewed only six observational studies published before 2015. The strength of our study is that seven more studies, including two RCTs, were included than were in the previous meta-analysis.[14] Additionally, our results indicated that statin use was associated with a decreased risk of delirium in two pooled RCTs, which were published after 2015 and conducted in Asia. We hypothesize that this finding would be associated with racial differences between Asians and other individuals. However, more studies are required to confirm this result and hypothesis.

Our meta-analysis has several limitations. First, few studies were included in our analysis. In addition, heterogeneity among studies in the design and population may have biased the pooled results. Second, our study primarily analyzed observational studies, which have their own limitations. Detailed patients' baseline data, specifically an evaluation of organ dysfunction upon ICU admission and preadmission evaluation of delirium, were not uniformly reported in all studies. In addition, no confirmed information was provided on the timing, dose, duration, or type of statin therapy in these patients. Therefore, subgroup analyses stratified by the statin type could not be performed. Finally, the studies did not provide detailed information on the training of medical staff in the identification of delirium.

In conclusion, the present study conducted a systematic review and meta-analysis of studies published from 1975 to 2021, focusing on the role of statin therapy in reducing the risk of delirium among patients with critical illness or those undergoing surgery; the findings suggest a nonsignificant benefit of statin use in reducing the risk of delirium. Because of the multifactorial nature of delirium, many expected variations among studies were observed in terms of patients, medical providers, and prescribed medications' characteristics. Further research—including the analyses of statins with different lipophilic or hydrophilic nature and half-lives, the timing of preoperative administration, and the timing of reinitiation—are required to clarify the association between statin use and delirium risk immediately after operation.

Conclusion

Statin use is not associated with the risk of delirium. Because of high heterogeneity, studies with better designs, especially RCTs and observational studies, are required to confirm the results of the present study. Statins are a potential therapy for delirium in critically ill patients, and considerable uncertainty remains in this topic.

Declarations

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Availability of Data and Materials: All data generated or analysed during this study are included in this published article.

Author Contributions:

Y.H.C. and W. J. Y. wrote the first draft of the manuscript. Y.H.C. and T. R. P. searched the databases and extracted the data. T.R.P. and M.C.L. evaluated the risk of bias. Y.H.C. and M.C.L. performed the statistical analysis. L.M.C. and C. H. M. critically revised the manuscript. All authors contributed to the final version of the manuscript.

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Figures

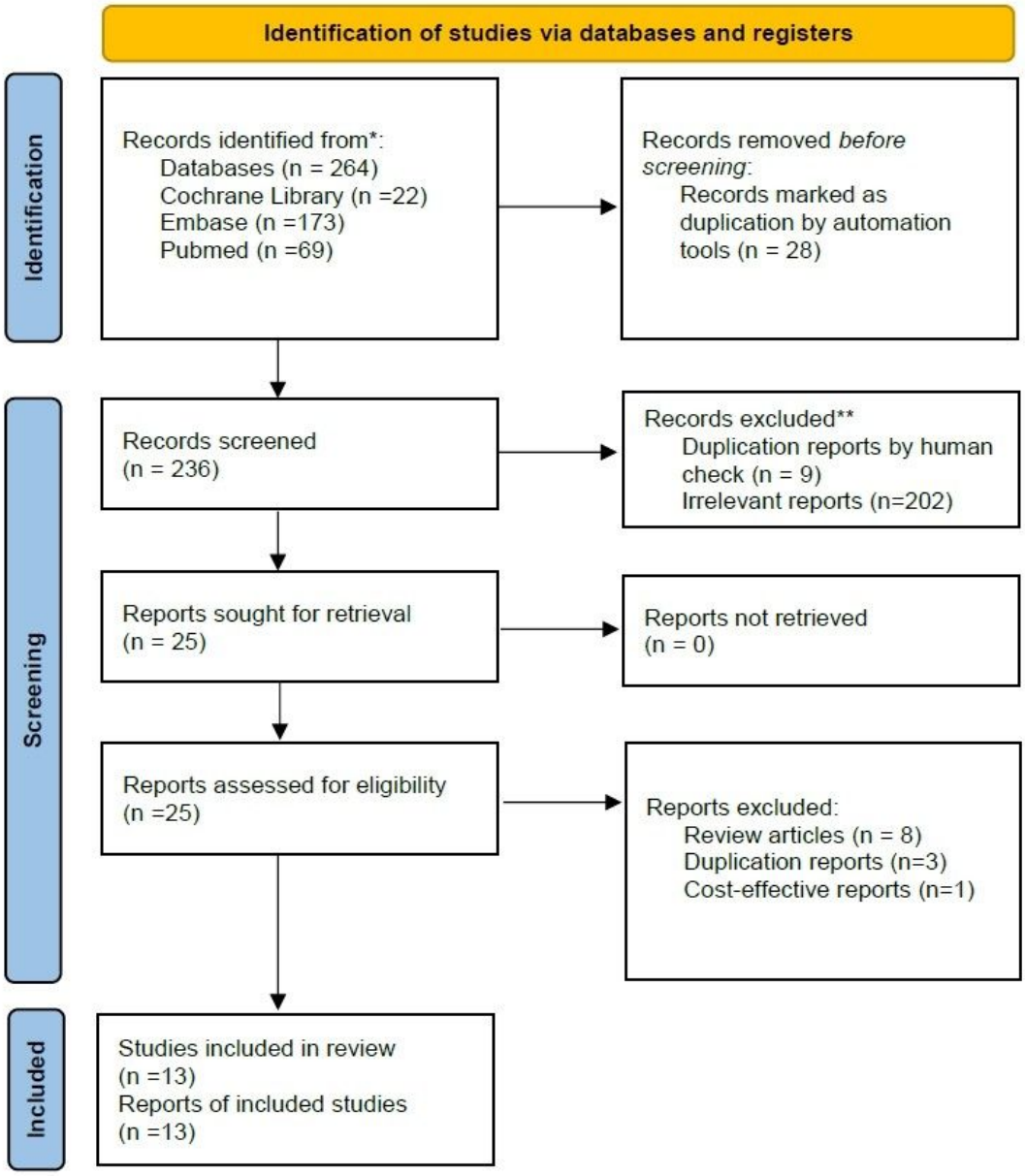

Figure 1

Flowchart of the literature search.

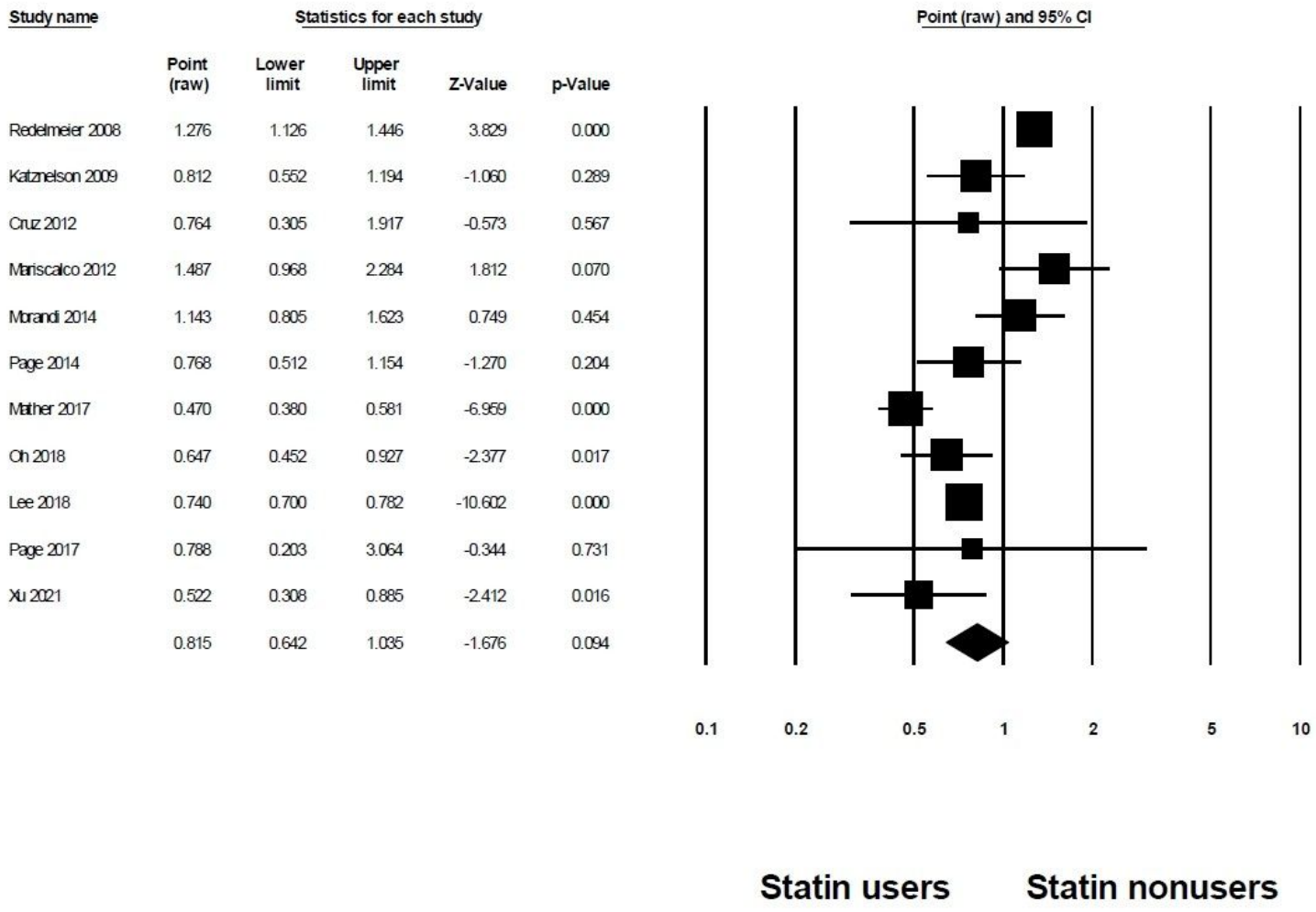

Figure 2

Forest plot of studies investigating statins and delirium.

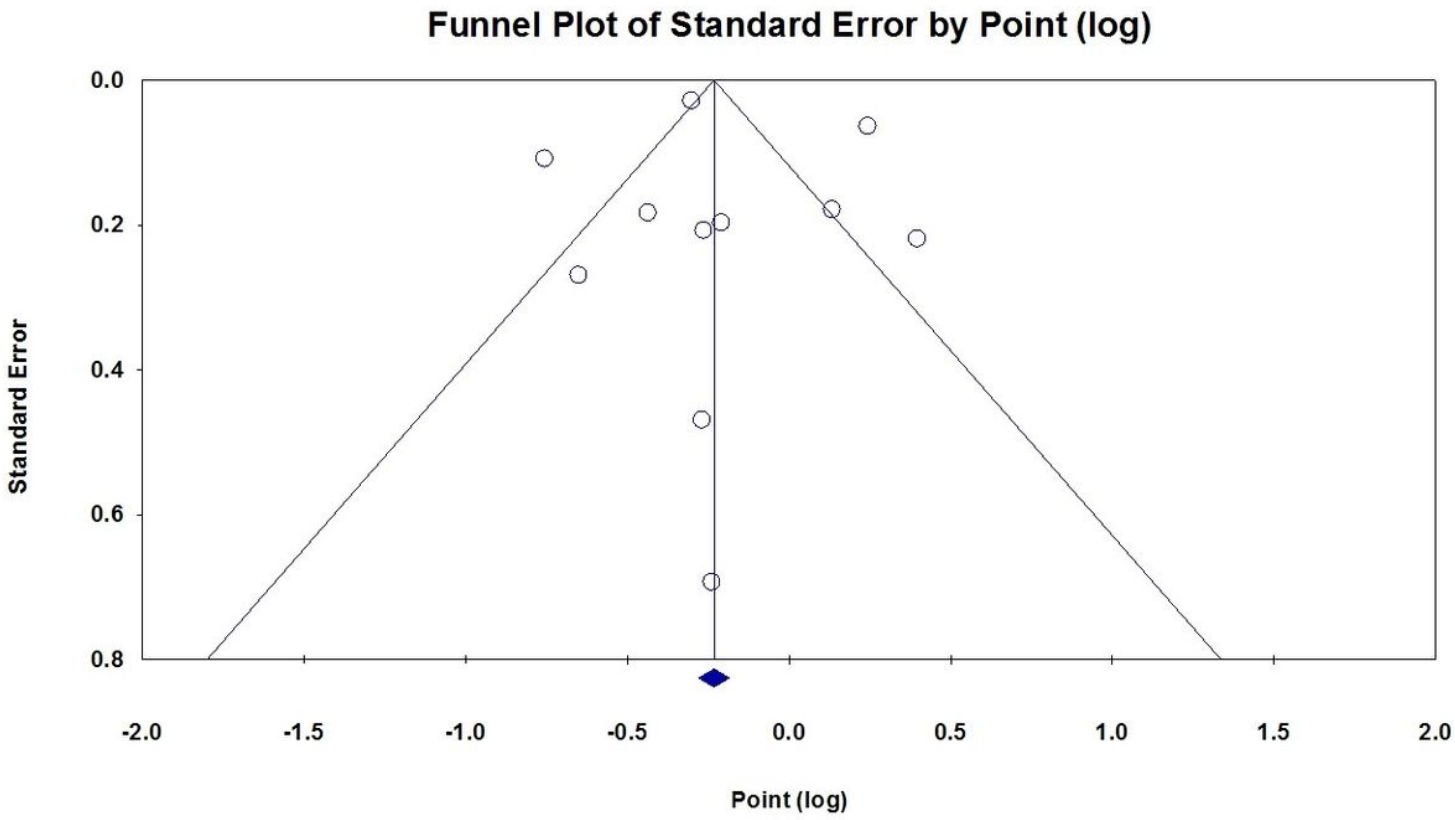

Figure 3

Funnel plot of all studies investigating statins and delirium.

Supplementary Files

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