Statins Reduce Mortality After Non-severe but Not After Severe Pneumonia: A Systematic Review and Meta-Analysis

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Abstract - PURPOSE: The objective of this study was to perform a systematic review and meta-analysis of the effects of statins on mortality for patients with non-severe pneumonia or severe pneumonia. **METHODS:** PubMed, EMBASE, Cochrane Database of Systematic Reviews, Cochrane central register of controlled trials and Clinicaltrials.gov were searched for the association between statins and non-severe/severe pneumonia. Eligible articles were analyzed in Stata 12.0. **RESULTS:** The database search yielded a total of 566 potential publications, 24 studies involving 312,309 patients met the eligibility criteria. Pooled unadjusted data showed that statin use was associated with lower mortality after non-severe pneumonia (odds ratio [OR] 0.70, 95% confidence interval [CI], 0.66-0.73), but not severe pneumonia (OR 1.05; 95% CI, 0.86-1.28). However, this protective effect of statins was weakened using adjusted estimates (OR 0.78, 95% CI, 0.75-0.82). Besides, protective effect of statins was attenuated by confounders in a subgroup analysis, especially when accounting for pneumonia severity indicators (OR 0.88; 95% CI, 0.80-0.96). **CONCLUSIONS:** Statin use was associated with reduced mortality after non-severe pneumonia but not severe pneumonia and this protective effect was weakened in subgroups.

INTRODUCTION

Pneumonia is one of the highest mortality diseases [1]. In United States, nearly 4 million adults had community-acquired pneumonia (CAP) per year [2], which caused almost 50,000 deaths and 1.1 million hospital admissions [3, 4]. The incidence of pneumonia was almost 3.3 per 1000 patients for hospitalized patients [5] and the annualized total medical costs reached 14,038 dollars per patient [6]. Although great progress had been made in antimicrobial treatment, mortality of pneumonia was still high, especially for severe pneumonia, mortality rate of which was as high as 50% [7].

Statins, as one of the inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA), are able to lower the level of blood cholesterol and used in patients with cardiovascular diseases or to prevent cardiovascular events [8-10]. Stains have potential immunomodulatory and anti-inflammatory effects in CAP [11, 12]. An earlier retrospective cohort study showed that, in bacteremia patients, in-hospital mortality was significantly reduced after using statins [13]. Since 2005, researchers have focused more attention on statins in the treatment of infections [14-16]. Most of these studies argue that statins are advantageous to outcome and prognosis of patients with infectious diseases. However, Fernandez et al demonstrated that hospital mortality was significantly higher after statin therapy [17]. Majumdar et al reported that statins were not associated with reduced mortality in a prospective cohort study of 3415 patients with pneumonia [18]. Whether statin use was associated with reduced mortality for patients with pneumonia is still in debate.

In this study, we performed systematic review and meta-analysis to address the roles of statins in non-severe and severe pneumonia. Further, subgroup analysis was conducted taking pneumonia severity, propensity score, comorbidity and smoking status as important confounders.

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MATERIALS AND METHODS

Information Sources and Search Strategy

This meta-analysis was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) recommendations [19, 20]. PubMed, EMBASE, Cochrane Database of Systematic Reviews, Cochrane central register of controlled trials and Clinicaltrials.gov were searched using the following key terms: (hydroxymethylglutaryl-CoA reductase inhibitors or HMG-CoA reductase inhibitors or simvastatin or lovastatin or pravastatin OR fluvastatin or atorvastatin or rosuvastatin or pitavastatin or statins) and (pneumonia or low-respiratory-tract-infection or lung injury [ALI]or pulmonary injury or acute respiratory distress syndrome [ARDS]). The final date of the literature search was September 31, 2014. There was no publication date, language or status restrictions for searching. “Mortality” was not involved in search strategy for reducing the omission. All studies were downloaded into EndNote 6.0 for further screening. Notably, we successfully contacted Bauer to obtain specific data for this meta-analysis.

Study Selection

Studies were included if they met the following criteria: participants should be above 18 years old; they focused on the association between statin use and pneumonia; they reported mortality after an episode of pneumonia; and involved overall or adjusted mortality. We excluded studies that reported ventilator-associated pneumonia (cannot distinguish it from severe pneumonia) and did not report the mortality rate after pneumonia.

Data Extraction

Data were extracted from all included studies independently by Mingwang Jia and Li Li. Relevant information of each study include study design, sample demographics (i.e., age, gender), type of statins, type of pneumonia, type of statins, outcome measures, association scale (odds ratio [OR] and adjusted OR), and adjusted confounders. When disagreement appeared between the 2 reviewers, a senior reviewer (Wenjie Huang) was consulted for final decision.

Quality Assessment

We used Newcastle-Ottawa Quality Assessment Scale (NOS) [21] to assess the quality of observational studies. NOS include three-part: quality of subject selection, comparability between two groups, and reliability of exposure or clinical outcomes. The full score of NOS is 9 and studies were considered of high-quality when scores ≥ 6. We used Jadad Score [22] to assess the quality of clinical trials. Also, Jadad Score include three-part: randomization, blinding, and withdrawals or dropouts. The full Jadad Score is 5 and studies were considered of high-quality when scores ≥ 3.

Definition of non-severe/Severe Pneumonia And Exposure/Treatment Groups

The Infectious Disease Society of America and American Thoracic Society in 2007 issued consensus guidelines on CAP and SCAP (IDSA/ATS 2007) [23]. Severe pneumonia group was defined as patients need mechanical ventilation or were in the ICU (requiring vasopressors) in our research. Treatment group was defined as patients taking statins (including prior and current users).

STATISTICAL ANALYSIS

We performed all statistical analysis using Stata 12.0 software (StataCorp., College Station, TX). We extracted both unadjusted and adjusted OR for pooling both crude and adjusted risk estimates. OR < 1 indicated that risk of outcome events in the intervention group is lower than that of outcome events in control group, which means that statins reduce mortality of pneumonia. We used I^2 statistic to test heterogeneity of the included studies. An I^2 value of 25%, 50%, and 75% represents low, moderate, and high heterogeneity, respectively [24]. Publication bias was assessed by Begg's test and Egger's test with $P < 0.05$ as indicative of publication bias.

We performed sensitivity analysis to test the robustness of our findings. The study design and participants of each study were considered as possible sources of heterogeneity. Meanwhile, we conducted an influence analysis for knowing the specific ones which cause the heterogeneity.

For a better understanding of the influenced confounders for mortality, we performed a subgroup analysis. We took pneumonia severity, propensity score, comorbidity and smoking status as important confounders and analyzed the relationship between confounders and mortality.

RESULTS

Studies Included in the Systematic Review

The database search yielded a total of 512 potential publications during the initial search. And 24 studies involving a total of 312,309 patients [18, 25-47] met our inclusion and exclusion criteria (Figure 1). The eligible studies included 2 case-control studies [28, 29], 14 respective cohort studies [25, 26, 31, 32, 35-38, 40-44, 46], 5 prospective cohort studies [18, 27, 30, 34, 39] and 3 randomized controlled trials (RCTs) [33, 45, 47] (Table 1, 2). Sample sizes of included studies ranged from 60 to 121,254 patients. Stratified by study locations, populations in the studies were from Europe, Asia, and North America. Eleven studies reported the types of statins received by population [18, 26, 29, 30, 33, 34, 42-45, 47]. Eight studies reported in-hospital mortality [18, 26-28, 33, 36, 38, 43, 46], 1 reported mortality at 28 days [47], 9 reported 30-day mortality [25, 26, 29-31, 35, 40-42], 2 reported 60-day mortality [39, 45], 3 reported 90-day mortality [26, 34, 44], and 1 reported mortality at 6 months [32]. According to our definition of treatment groups, 8 articles [27, 33, 36, 37, 39, 45-47] were classified as severe pneumonia, and the remaining 16 articles [18, 25, 26, 28-32, 34, 35, 38, 40-44] were non-severe pneumonia.

Non-severe pneumonia Group

Unadjusted Mortality

Of the 24 included studies, 11 studies (2 case control studies, 7 respective cohort studies and 2 prospective cohort studies) reported raw mortality after common pneumonia [18, 25, 26, 28, 29, 31, 32, 34, 35, 38, 40]. Pooled meta-analysis revealed that statin would decrease overall mortality after pneumonia (OR 0.70; 95% confidence interval [CI], 0.67-0.73) (Figure 2). A high degree of heterogeneity was observed for the pooled OR of 0.70 (I^2 = 77.9%, P = 0.00). However, neither Begg's test (P = 1.00) nor Egger's Test (P = 0.18) showed evidence of publication bias (Figure 4).

Adjusted Mortality

Of the 24 included studies, 15 studies (2 case control studies, 10 respective cohort studies and 3 prospective cohort studies) reported adjusted mortality after non-severe pneumonia [18, 25, 26, 28-32, 34, 35, 38, 41-44]. Adjustments included social and demographic factors, pneumonia severity, comorbidity indices, smoking status, vaccination status, and propensity to receive statin treatment. Pooling of these data revealed that statin would decrease overall mortality after pneumonia (OR 0.78; 95% CI, 0.75-0.82) (Figure 3). A high degree of heterogeneity was observed for the pooled adjusted OR of 0.78 (I^2 = 74.3%, P =0.001). Egger's test suggested significant publication bias (P = 0.024), but Begg's test did not (P = 0.299) (Figure 4).

Severe pneumonia Group

Unadjusted Mortality

Of the 24 included studies, 8 studies (3 respective cohort studies, 2 prospective cohort studies and 3 RCTs) reported raw mortality after severe pneumonia [27, 33, 36, 37, 39, 45-47]. Pooled meta-analysis revealed that current statin use was not associated with a decreased of mortality after severe pneumonia (OR 1.05; 95% CI, 0.86-1.28). A moderate heterogeneity was observed (I^2 = 41.5%, P = 0.10) (Figure 2). Both Begg's test (P =0.90) and Egger's test (P = 0.68) suggested no significant publication bias (Figure 4).

Adjusted Mortality

Of the 24 included studies, 3 studies (1 respective cohort study and 2 prospective cohort studies) reported adjusted mortality after severe pneumonia [27, 36, 39]. Adjustments included social and demographic factors, pneumonia severity, comorbidity indices, smoking status and vaccination status, and propensity to receive statin treatment. Pooling of these data revealed that statin use was not associated with a decrease of mortality after severe pneumonia (OR 0.92; 95% CI, 0.53-1.60). A moderate heterogeneity was observed (I^2 = 41.0%, P = 0.18) (Figure 3). Both Begg's test (P = 1.00) and Egger's test (P = 0.76) suggested no significant publication bias (Figure 4).

Subgroup Analysis

We performed subgroup analysis to determine whether clinical factors influenced the mortality of pneumonia after statins using (Table 3).We took pneumonia severity, propensity score, comorbidity and smoking status as important confounders. In the non-severe pneumonia group, no statistically significant differences were observed. But we found that the protective effect weakened when studies were analyzed according to the inclusion of important confounders in their models, especially the adjusted pooled OR for pneumonia severity (0.88, 95% CI 0.80-0.96) and for propensity score (0.86, 95% CI 0.80-0.94), and the more confounders were considered, the weaker the protective effect was. In the severe pneumonia

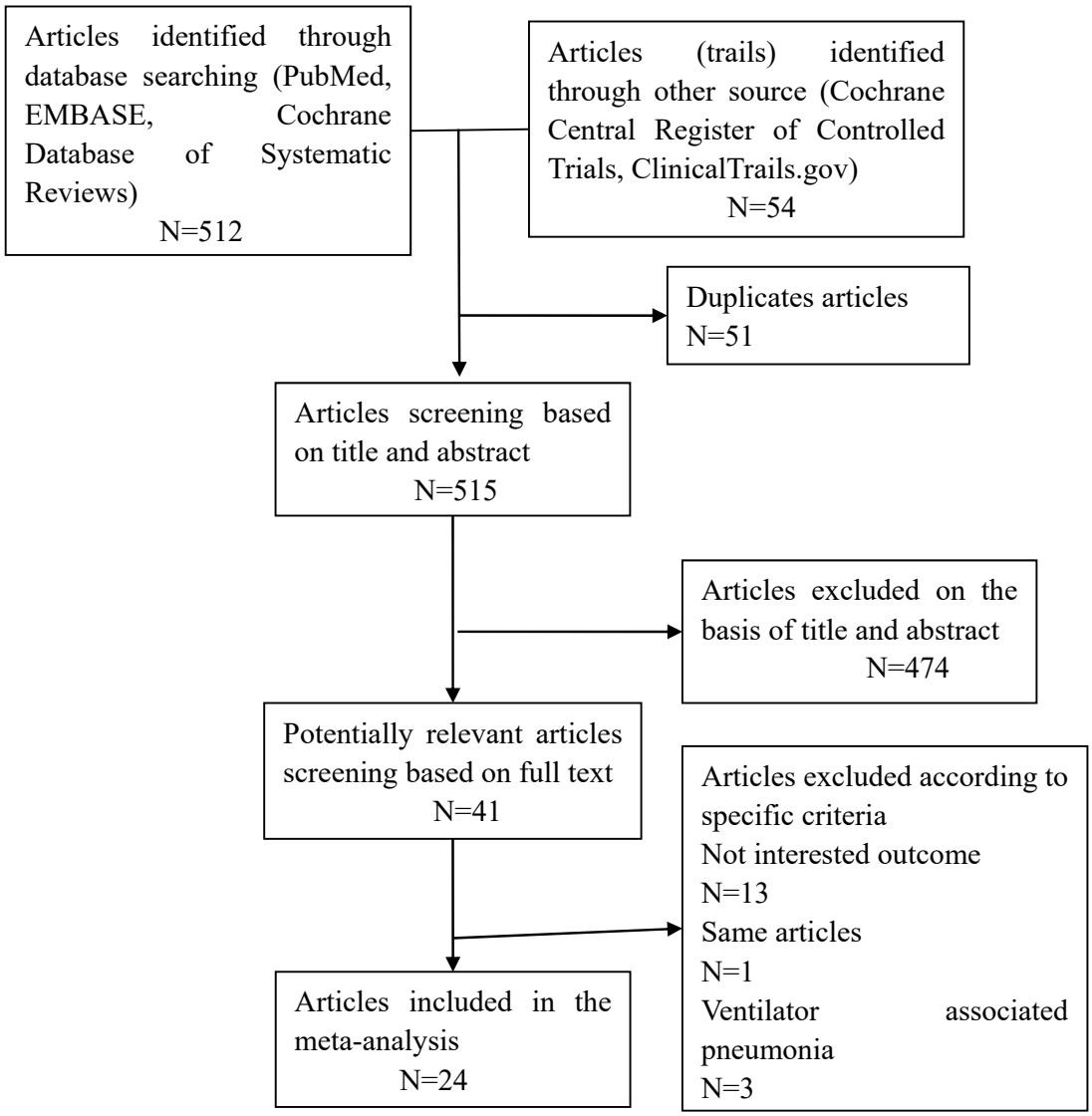

Figure 1. Flowchart of search selection.

group, though OR was lower in the adjusted data, nonetheless, there was no association between statins users and non-statin users.

Sensitivity analysis

There was a substantial degree of heterogeneity in both unadjusted and adjusted analysis, especially in the non-severe pneumonia group. We performed several sensitivity analyses (Table 4). The I^2 statistic was as low as 0% and 51.5% for non-severe pneumonia (unadjusted) and non-severe pneumonia (adjusted) in prospective cohorts; 28.6% and 53.2% in case-control cohorts, respectively; 0.0% for severe pneumonia in a RCT. The I^2 statistic was as low as 0.0% for severe pneumonia (unadjusted) in North America, 63.7% and 0% for non-severe pneumonia (adjusted) and severe pneumonia (unadjusted) in Europe, respectively. Meanwhile, we performed an influence analysis (Figure 5), which found that, in the unadjusted group, when excluded Kwong's article (only provided the OR value but does not provide a specific number of patients), the I^2 statistic changed into moderate heterogeneity (I^2 = 49.4%, P = 0.04) but didn't change result (OR 0.64; 95% CI, 0.61-0.68). In the adjusted group, we excluded Kwong and Rothberg's articles. The I^2 statistic changed to moderate heterogeneity (I^2 = 41.1%, P = 0.06) but didn't change result (OR 0.69; 95% CI, 0.65-0.74).

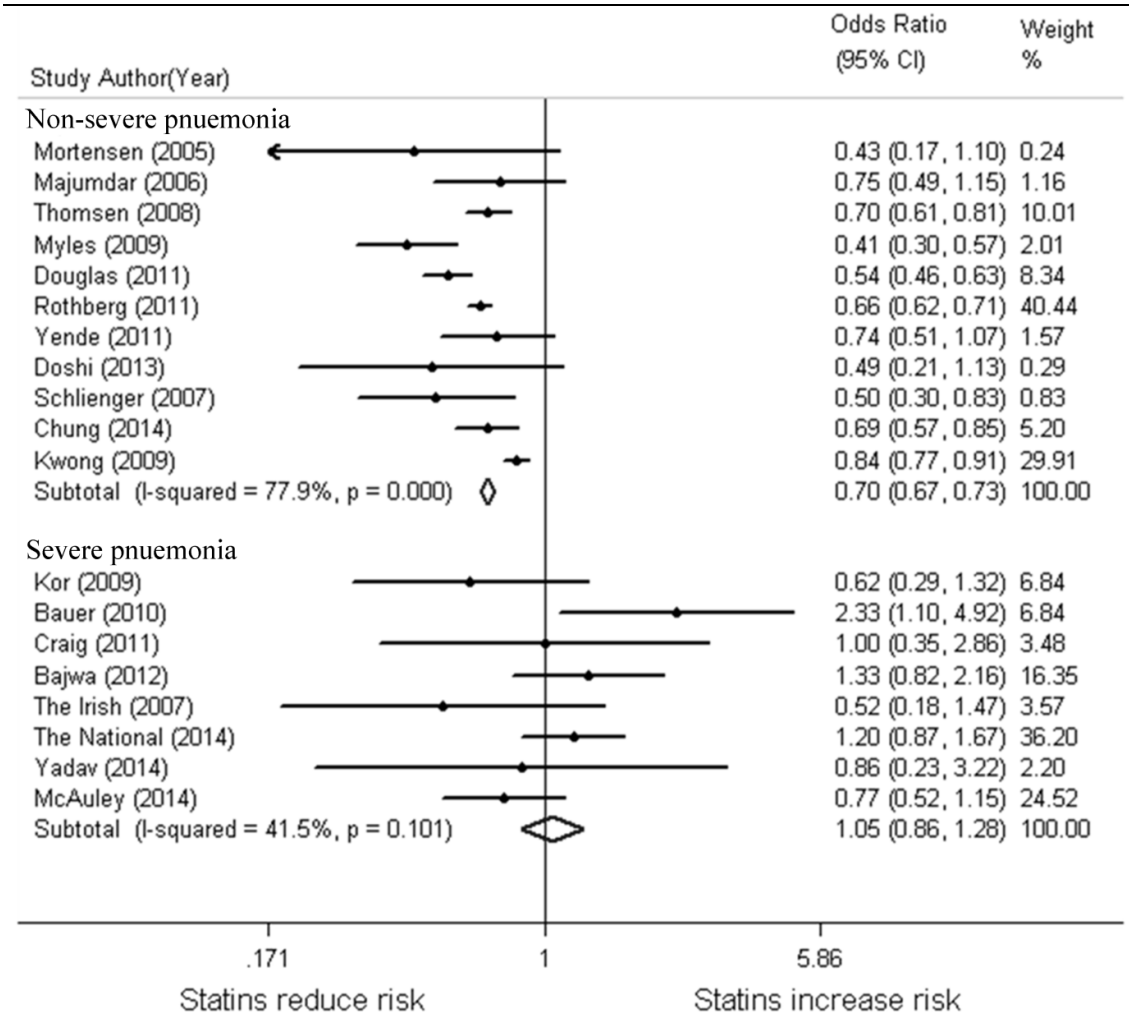

Figure 2. Forest for the pooled unadjusted association between statin use and mortality. Forest plot showed that statin users were less likely to die after an episode of non-severe pneumonia compared with nonstatin users in unadjusted estimates, but in the severe pneumonia group, there was no obvious difference in mortality.

DISCUSSION

This meta-analysis of 24 studies showed that statin users were less likely to die after non-severe pneumonia compared with non-statin users, but in the severe pneumonia group, there was no obvious difference in mortality. In the non-severe pneumonia group, statins was associated with reduced mortality using both unadjusted and adjusted estimates. However, this protective effect was weakened in subgroups.

In non-severe pneumonia group, statin reduced the mortality using adjusted and unadjusted estimates but there was no association in severe pneumonia group using either adjusted estimates or unadjusted estimates. Kwok's meta-analysis did not find an association between pneumonia and statins using unadjusted data but found an association using adjusted data [48]. Chopra's meta-analysis found an association between pneumonia and statins using both unadjusted data and adjusted data [49]. These results suggested the severity should be considered when using statin for pneumonia treatment. In a subgroup analysis, we obtained similar results to Chopra [49].

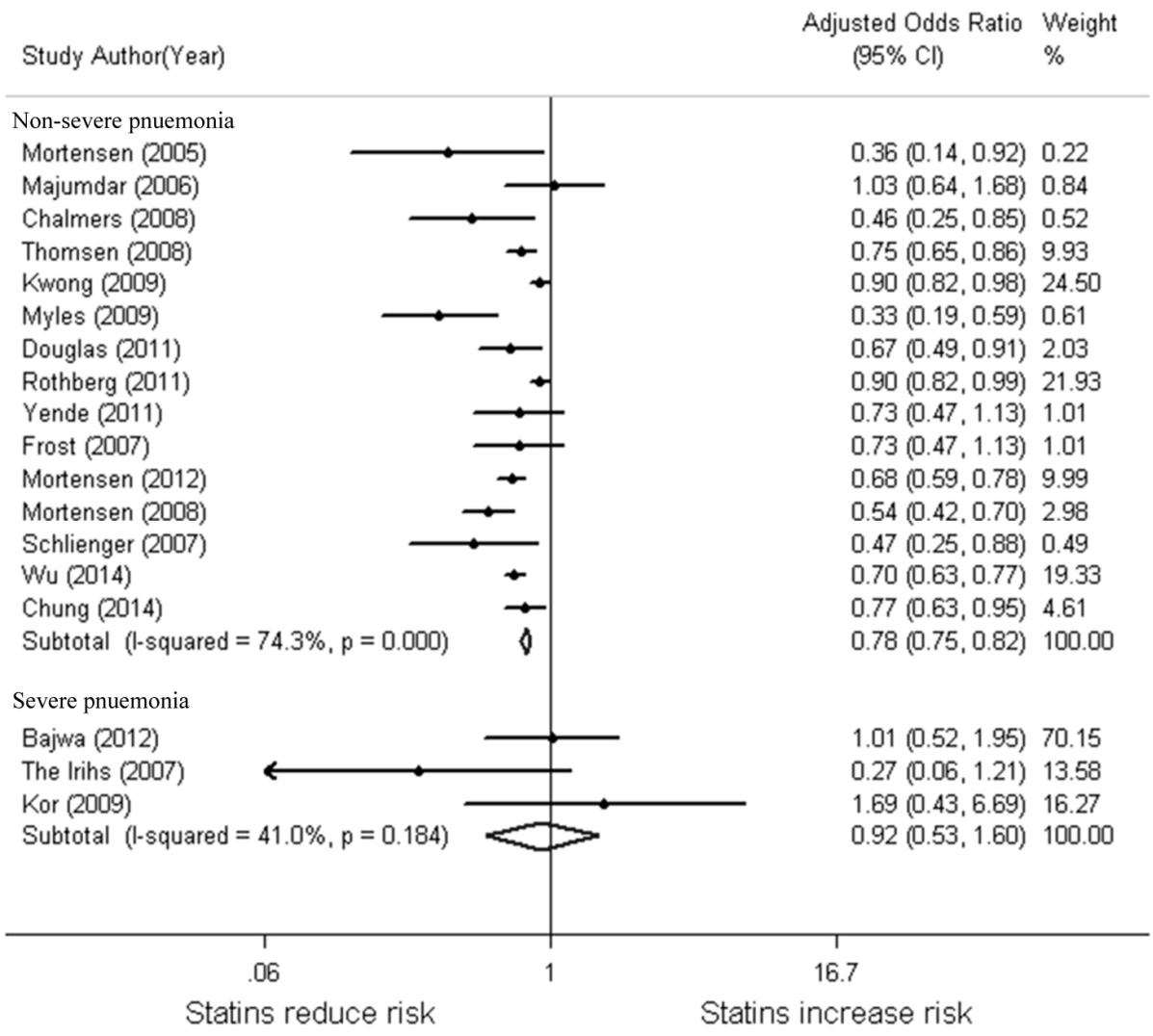

Figure 3. Forest for the pooled adjusted association between statin use and mortality. Forest plot showed that protective effect of statins was weakened in non-severe pneumonia when accounting for adjusted estimates, and there was no obvious difference in mortality in adjusted severe pneumonia group.

The protective effect we found was weakened when accounting for patient differences through the use of propensity scores, pneumonia severity indicators, smoking status and comorbidity in non-severe pneumonia group.

There were several limitations for this Systematic Review and Meta-analysis. First, the definition of severe pneumonia has flaws. We define patients who need mechanical ventilation or in the ICU (requiring vasopressors) as the severe pneumonia group in our research, and we may have missed severe pneumonia patients who did not use mechanical ventilation or vasopressors or did not mention these parameters in the papers. Additionally, not all ALI/ARDS were caused by pneumonia. However, considering that pneumonia is the main reason of ALI/ARDS and that there must be lung inflammation after developing ALI/ARDS, we define ALI/ARDS as severe pneumonia in our paper. Second, few papers discussed the adjusted OR in severe pneumonia, which may lead to an obvious bias. Thus, we performed a subgroup analysis and analyzed an unadjusted group for better understanding of severe pneumonia.

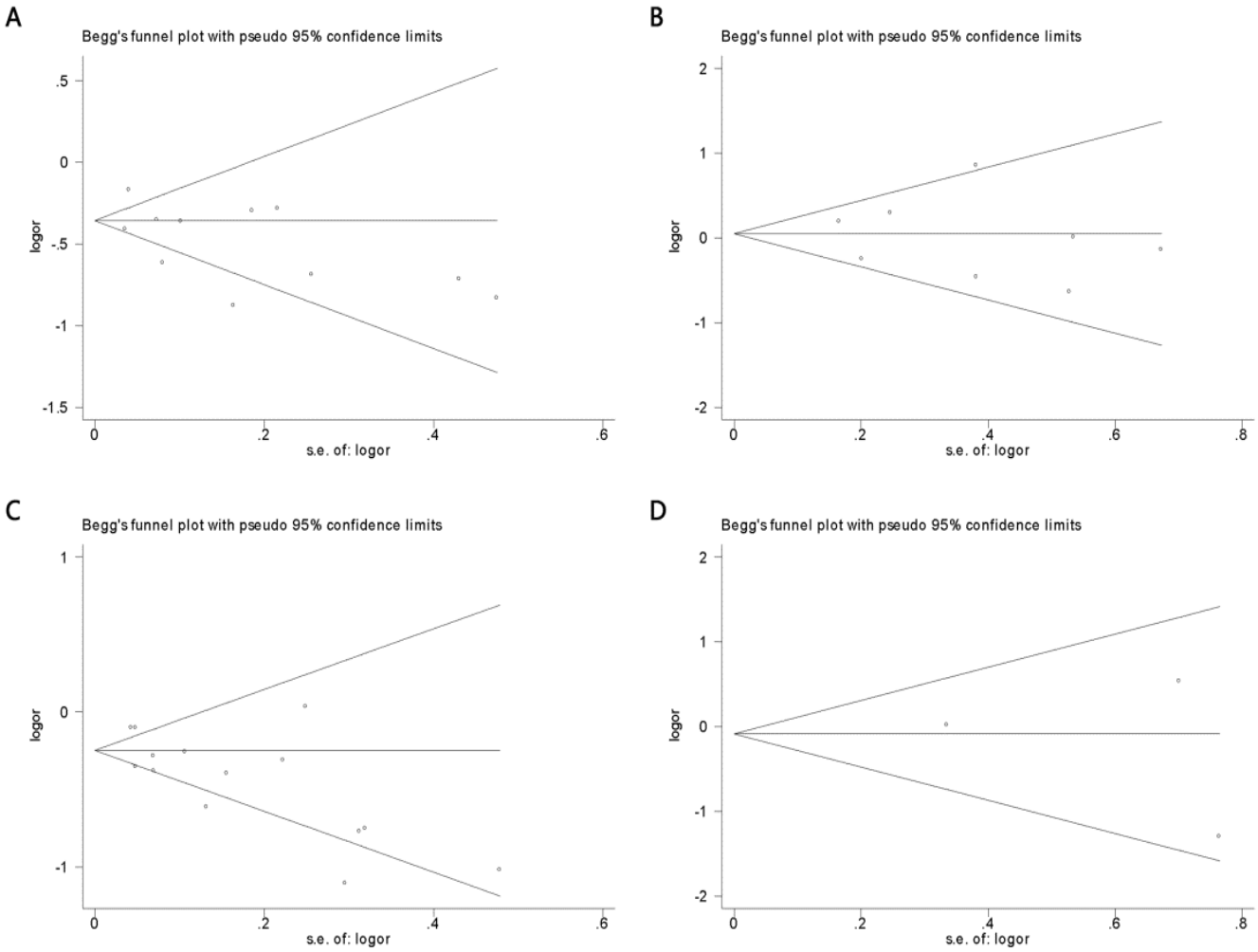

Figure 4. Begg's test for Publication bias. Begg's test for unadjusted non-severe pneumonia (A), unadjusted severe pneumonia (B), adjusted non-severe pneumonia (C) and adjusted severe pneumonia (D).

Third, although we conducted adjusted measures and performed subgroup analysis, residual confounding and healthy-user bias remain threats to our conclusions. However, our analysis has important strengths. We divided pneumonia into non-severe pneumonia and severe pneumonia and performed a subgroup analysis to determine whether methodological or clinical factors influenced the meta-analytical estimates of statins on pneumonia mortality.

Statin use is associated with a reduction in mortality in non-severe pneumonia, but because this association in attenuated in studies with a better adjustment for confounders, it is likely that this association is at least partly explained by a healthy user effect. The protective effect of statin was weakened in a subgroup analysis by confounders in non-severe pneumonia, especially when accounting for patient differences through the use of pneumonia severity indicators. In future work, a double-blind, randomized, large sample experiment is necessary considering pneumonia severity as an important element.

FUNDING SOURCE

No sponsorship from institutions or pharmaceutical industry was provided to conduct
this study.

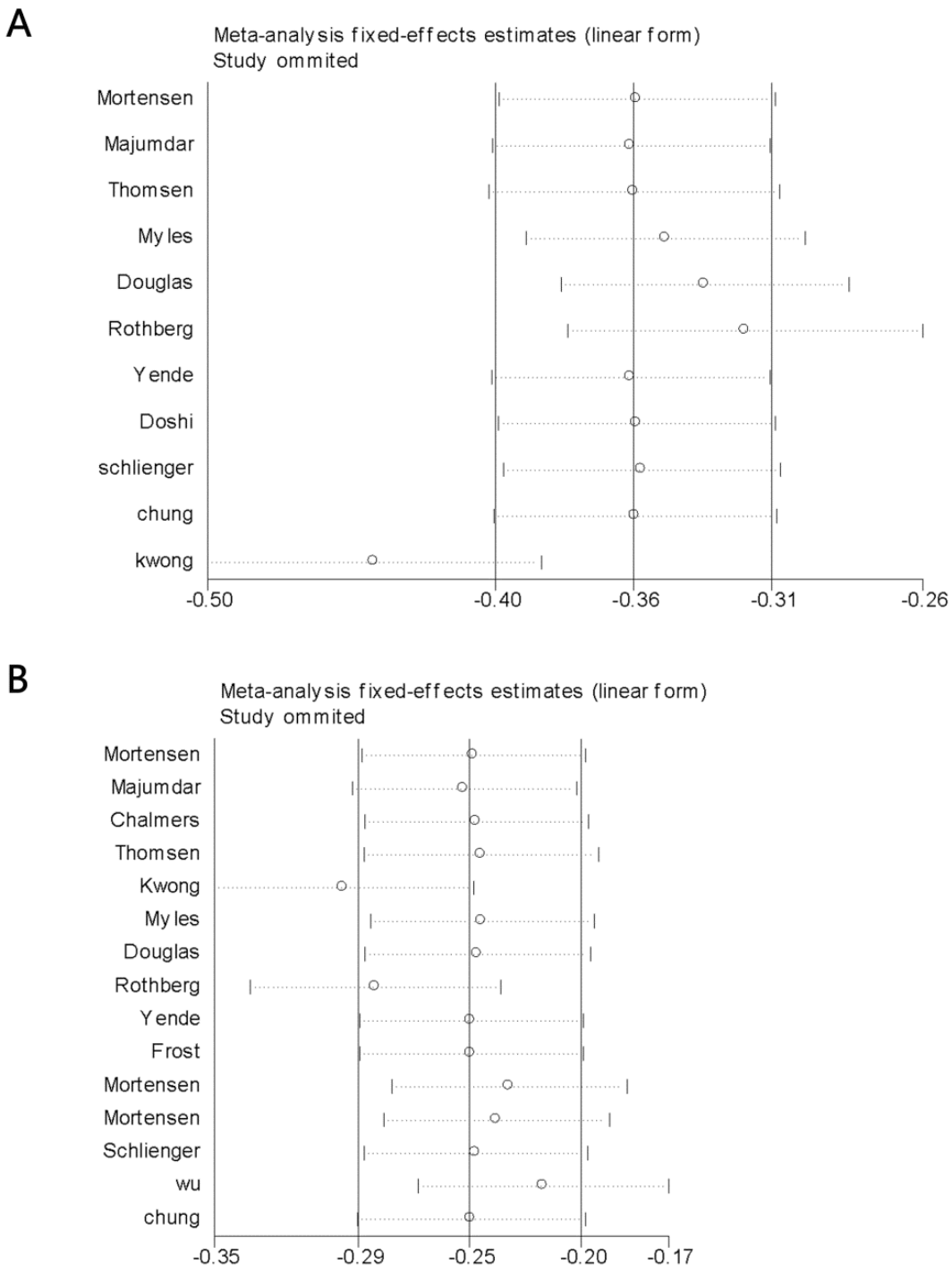

Figure 5. Sensitivity analysis for unadjusted non-severe pneumonia (A) and adjusted non-severe pneumonia (B).

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Table 1. General Characteristics of Included Studies

Study (First author; year)	Country	Study Design	Mean Age (Y)	% Male	Statin Type(s)	Sample Size (n)		
						Statin	Nonstatin	Total
Majumdar; 2006 [18]	Canada	PC	75	53	Simvastatin, Pravastatin, Atorvastatin accounted for 90%	325	3,090	3,415
Kwong; 2009 [25]	Canada	RC	74	45	Not reported	N/A	N/A	13,027
Thomsen; 2008 [26]	Denmark	RC	73	53	Simvastatin(61%),Pravastatin(15%), Atorvastatin(15%),other(9%)	1,372	285,28	29,900
The Irish Critical Care Trials Group; 2007 [27]	Ireland	PC	58	62	Not reported	24	164	188
Chung; 2014 [28]	Taiwan	CC	N/A	53.7	Not reported	2,894	8,682	11,576
Schlienger; 2007 [29]	United Kingdom	CC	N/A	54.4	atorvastatin, fluvastatin, lovastatin, pravastatin, or simvastatin	141	1,112	1,253
Chalmers; 2008 [30]	United Kingdom	PC	66	49.7	Simvastatin(72%), Atorvastatin(21.4%), Pravastatin(6.6%)	257	750	1,007
Myles; 2009 [31]	United Kingdom	RC	N/A	N/A	Not reported	357	3,324	3,681
Douglas; 2011 [32]	United Kingdom	RC	N/A	N/A	Not reported	1,789	6,542	8,331

Table 1 continued…

Craig; 2011 [33]	United Kingdom	RCT	52.3	73	simvastatin	30	30	60
Yende; 2011 [34]	United States	PC	68.8	53	Atorvastatin(47.7%), Simvastatin(39.4%), Pravastatin(7.7%), Lovastatin(3.5%), Fluvastatin(1.6%)	426	1,469	1,895
Mortensen; 2005 [35]	United States	RC	60	79	Not reported	110	677	787
Kor; 2009 [36]	United States	RC	64.8	51.7	Not reported	45	133	178
Bauer; 2010 [37]	United States	RC	57.6	46.5	Not reported	37	150	187
Rothberg; 2011 [38]	United States	RC	74	44	Not reported	23,285	97,969	121,254
Bajwa; 2012 [39]	United States	PC	59.7	62	Not reported	75	663	738
Doshi; 2013 [40]	United States	RC	64.3	N/A	Not reported	90	257	347
Frost; 2007 [41]	United States	RC	N/A	N/A	Not reported	19,058	57,174	76,232
Mortensen; 2012 [42]	United States	RC	74.8	98.2	atorvastatin, cerivastatin,fluvastatin, lovastatin, pravastatin, simvastatin	7,763	15,233	22,996
Mortensen; 2008 [43]	United States	RC	75.2	98.6	atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, simvastatin	1,567	7,085	8,652
Wu; 2014 [44]	United States	RC	74.6	N/A	atorvastatin, cerivastatin,fluvastatin, lovastatin, pravastatin, and simvastatin	N/A	N/A	5,301
The National Heart, Lung and Blood Institute; 2014 [45]	United States	RCT	52.4	49	rosuvastatin	379	366	745

Table 1 continued…

Yadav; 2014 [46]	United States	RC	67.9	66	Not reported	52	68	120
McAuley; 2014 [47]	United Kingdom	RCT	53.8	57	simvastatin	259	280	539

OR= odds ratio; PC= prospective cohort; RC= retrospective cohort; RCT= randomized controlled trial; CC= case-control; N/A= not available.

Table 2. Outcomes and Quality of Included Studies

Study (First author; year)	Key Variables Adjusted in Regression Models	Clinical Outcomes	OR (95% CI)	Adjusted OR (95% CI)	Quality score
Majumdar; 2006 [18]	Demographic variables, nursing home status, comorbidities, medications taken, vaccination status, smoking status, pneumonia severity score, propensity score	In-hospital mortality	0.75 (0.49-1.15)	1.03 (0.64-1.68)	6
Kwong; 2009 [25]	Demographic variables, hospitalizations in the past three years, current medications prescribed, influenza-related risk factors , type of statin prescribed	30-day mortality	0.84 (0.77-0.91)	0.9 (0.82-0.98)	7
Thomsen; 2008 [26]	Demographic variables, comorbidity, alcoholism-related disorders, urbanization of place of residence, type of hospital, current medications prescribed, calendar period	30-day mortality, 90-day mortality	0.70 (0.61-0.81)	0.75 (0.65-0.86)	8
The Irish Critical Care Trials Group; 2007 [27]	Demographic variables, SOFA score, PaO2/FiO2 ratio, plateau pressure, Vt/kg, arterial carbon dioxide tension and use of statins	In-hospital mortality	0.52 (0.18-1.47)	0.27 (0.06-1.21)	7
Chung; 2014 [28]	Demographic variables, CCI score, propensity score, monthly income, residential urbanization and residential region	In-hospital mortality	0.69 (0.57-0.85)	0.77 (0.63-0.95)	7
Schlienger; 2007 [29]	Smoking status, body mass index, influenza or pneumococcal vaccination, current medications prescribed, chronic comorbid conditions	30-day mortality	0.50 (0.30-0.83)	0.47 (0.25-0.88)	6

Table 2 continued…

Chalmers; 2008 [30]	Age, pneumonia severity score; comorbidity, smoking, aspirin, β-blockers, ACE inhibitor use	30-day mortality	N/A	0.46 (0.25-0.85)	7
Myles; 2009 [31]	Demographic variables, current smoking ,socio-economic status, comorbidity	30-day mortality	0.41 (0.30-0.57)	0.33 (0.19-0.59)	8
Douglas; 2011 [32]	Demographic variables, propensity score(body mass index, socioeconomic status, consultation rate, prescribing rate, smoking status, etc.	6-month mortality	0.54 (0.46-0.63)	0.67 (0.49-0.91)	7
Craig; 2011 [33]	RCT	ICU mortality, Hospital mortality	1.00 (0.35-2.86)	N/A	5*
Yende; 2011 [34]	Demographics and comorbidities, severity of illness, treatments received, healthy user indicators	90-day mortality	0.74 (0.51-1.07)	0.73 (0.47-1.13)	7
Mortensen; 2005 [35]	Propensity score, use of statin at presentation, process of care measures	30-day mortality	0.43 (0.17-1.10)	0.36 (0.14-0.92)	7
Kor; 2009 [36]	Statin administration, propensity score, APACHE III predicted ICU LOS, DNR code status on admission to the ICU, and postoperative state	ICU mortality, Hospital mortality	0.62 (0.29-1.32)	1.69 (0.43-6.69)	7
Bauer; 2010 [37]	Statin group, gender, and fluid balance during ARDS episode, use of corticosteroids, propensity score, age, APACHE II score, and tidal volume	ICU mortality	2.33 (1.10-4.92)	N/A	7
Rothberg; 2011 [38]	Demographic variables, comorbidities, early non-pneumonia treatments, physician specialty, medications associated with statin use, severity of pneumonia, propensity scores	In-hospital mortality	0.66 (0.62-0.71)	0.90 (0.82-0.99)	6
Bajwa; 2012 [39]	Demographic variables, severity of illness, vasopressor or corticosteroid use, presence of shock, liver or renal failure, history of diabetes, aspirin, propensity score	60-day mortality	1.33 (0.82-2.16)	1.01 (0.52-1.95)	9
Doshi; 2013 [40]	Age, sex and preexisting conditions and alcohol use, disease severity scores	30-day mortality	0.49 (0.21-1.13)	N/A	6

Table 2 continued…

Frost; 2007 [41]	Duration of enrollment before initiation of statin therapy, the CCI, the number of different medications taken, receiving influenza vaccinations after initiation of statin therapy.	30-day mortality	N/A	0.73 (0.47-1.13)	6
Mortensen; 2012 [42]	Demographic variables, receipt of guideline concordant antibiotics, comorbid conditions, other medications.	30-day mortality	N/A	0.68 (0.59-0.78)	7
Mortensen; 2008 [43]	Demographic variables, VA means test, classes of medications and the Charlson composite score	In-hospital mortality	N/A	0.54 (0.42-0.70)	8
Wu; 2014 [44]	Demographics, intensive care unit admission, need for mechanical ventilation and/or vasopressors, prior comorbid conditions, and other outpatient medications.	90-day mortality	N/A	0.70 (0.63-0.77)	9
The National Heart, Lung and Blood Institute; 2014 [45]	RCT	60-day mortality	1.20 (0.87-1.67)	N/A	5*
Yadav; 2014 [46]	Demographic variables, comorbidities, treatments received; smoking, alcohol abuse, BMI, other medications.	In-hospital mortality	0.86 (0.23-3.22)	N/A	7
McAuley; 2014 [47]	RCT	28-day mortality	0.77 (0.52-1.15)	N/A	5*

N/A, not available

Table 3. Subgroup Analysis

	Non-severe pneumonia OR (95% CI)		**Severe pneumonia OR (95% CI)**	
Subgroup	**Unadjusted Data**	**Adjusted Data**	**Unadjusted Data**	**Adjusted Data**
Adjustment for pneumonia severity	0.67 (0.62-0.71) [18, 34, 35, 38, 40]	0.88 (0.80-0.96) [18, 30, 34, 35, 38]	1.33 (0.82-2.16) [39]	1.01 (0.52-1.95) [39]

Table 3 Continued…

Adjustment for propensity score	0.65 (0.61-0.69) [18, 28, 32, 38]	0.86 (0.80-0.94) [18, 28, 32, 38]	1.25 (0.88-1.77) [36, 37, 39]	1.11 (0.61-2.02) [36, 39]
Adjustment for comorbidity	0.66 (0.62-0.70) [18, 26, 28, 29, 31, 34, 38]	0.76 (0.72-0.80) [18, 26, 28-31, 34, 38, 42, 44]	N/A	N/A
Adjustment for smoking status	0.55 (0.48-0.62) [18, 29, 31, 32, 34]	0.65 (0.53-0.79) [18, 29-32, 34]	N/A	N/A
One confounder	0.69 (0.60-0.79) [26, 35, 40]	0.70 (0.66-0.76) [26, 35, 42, 44]	1.20 (0.71-2.05) [36, 37]	1.69 (0.43-6.69) [36]
Two confounders	0.51 (0.45-0.59) [29, 31, 32]	0.55 (0.43-0.71) [29, 31, 32]	1.33 (0.82-2.16) [39]	1.01 (0.52-1.95) [39]
Three confounders	0.67 (0.62-0.71) [34, 38]	0.88 (0.80-0.96) [30, 34, 38]	N/A	N/A
Four confounders	0.75 (0.49-1.15) [18]	1.03 (0.64-1.08) [18]	N/A	N/A

CI= confidence interval; OR= odds ratio; N/A= not available.

Table 4. Sensitivity Analysis

	Non-severe pneumonia OR (95% CI) I^2		**Severe pneumonia OR (95% CI) I^2**	
Subgroup	**Unadjusted Data**	**Adjusted Data**	**Unadjusted Data**	**Adjusted Data**
Study design				
Retrospective cohort	0.69 (0.66-0.73)86.7% [25, 26, 31, 32, 35, 38, 40]	0.79 (0.75-0.82) 81.1% [25, 26, 31, 32, 35, 38, 41-44]	1.11 (0.69-1.80)67.6% [36, 37, 46]	N/A*
Prospective cohort	0.75 (0.56-0.98)0.0% [18, 34]	0.75 (0.56-0.99)51.5% [18, 30, 34]	1.10 (0.71-1.69) 61.2% [27, 39]	0.71 (0.46-1.10)43.0% [27, 39]
Case-control	0.66 (0.55-0.80)28.1% [28, 29]	0.73 (0.60-0.89)53.2% [28, 29]	N/A	N/A
Randomized controlled trial	N/A	N/A	1.01 (0.79-1.28) 31.2% [33, 45, 47]	N/A
Study location				
North America	0.73 (0.69-0.77) 75.1% [18, 25, 34, 35, 38, 40]	0.80 (0.76-0.84) 78.9% [18, 25, 34, 35, 38, 41-44]	1.21 (0.96-1.53) 36.9% [36, 37, 39, 45, 46]	1.11 (0.61-2.02) 0.0% [36, 39]

Table 4 Continued…

Europe	0.59 (0.53-0.65) 74.5% [26, 29, 31, 32]	0.69 (0.61-0.77) 63.7% [26, 29-32]	0.76 (0.54-1.08) 0.0% [27, 33, 47]	N/A
Asia	N/A*	N/A*	N/A	N/A

I= confidence interval; OR= odds ratio; N/A= not available.
*Contain one study, can't get I^2.