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Review Article

Body mass index is associated with the risk of ICU admission and death among patients with pneumonia: a systematic review and meta-analysis

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Abstract: Introduction: The aim of this study was to examine the association between body mass index (BMI) and the risk of intensive care unit (ICU) admission and death among patients with pneumonia. Method: A systematic literature search of the PubMed, EMBASE and the Cochrane Library was conducted by using the searching strategy as "pneumonia" AND ("death" OR "mortality" OR "Intensive Care Unit admission" OR "ICU admission") AND ("BMI" OR "body mass index" OR "obese" OR "obesity" OR "overweight" OR "underweight"). Studies evaluating the risk of ICU admission or death among patients with pneumonia stratified by BMI were included. Result: A total of six studies with 132,465 patients were finally included in this meta-analysis. Patients with higher BMI were associated with reduced risk of ICU admission or death (odds ratio: 0.86, 95% confidence interval: 0.80-0.92, $P<.001$) compared with those with normal BMI. However, underweight patients had increased risk of ICU admission or death (1.23, 95% CI: 0.83-1.63, $P<.001$) than normal weight patients. Conclusion: This meta-analysis indicated that underweight was associated with poor outcomes of patients with pneumonia while obesity was related to better outcomes inversely.

Keywords: Body mass index, death, ICU admission, pneumonia, obesity, underweight

Introduction

Pneumonia is a common infectious disease related to high morbidity and mortality in both developed and developing countries despite the development of effective antibiotic therapy. The 2010 Global Burden of Disease Study reported that lower respiratory tract infections, including pneumonia, are the fourth most common cause of death globally and the second most frequent reason for years of life lost [1]. The incidence of pneumonia was found higher in the elderly, male, people with unhealthy lifestyles like smoking, alcohol abuse, being underweight and those who had comorbid conditions [2].

The influence of Body mass index (BMI) on the risks or the outcomes of many diseases has been a hot topic in recent years [3-5]. The BMI-pneumonia association has also been studied by researchers. Some studies suggested a reduced risk of pneumonia among overweight patients [6, 7], while other studies showed a reverse results [8, 9]. In a recent meta-analysis, obesity was reported as a protective factor of pneumonia while underweight was found to be a significant risk factor of pneumonia in contrast [10]. The relationship between BMI and the outcomes of pneumonia has also been investigated by several studies. Fezeu and his colleges reported that obesity was associated with higher risk of intensive care unit (ICU) admission and death in influenza A patients [11]. Other studies, however, showed different results in the patients with community-acquired pneumonia [12-14]. So the purpose of our analysis was to investigate the relationship between BMI and the risk of ICU admission and death among patients with pneumonia.

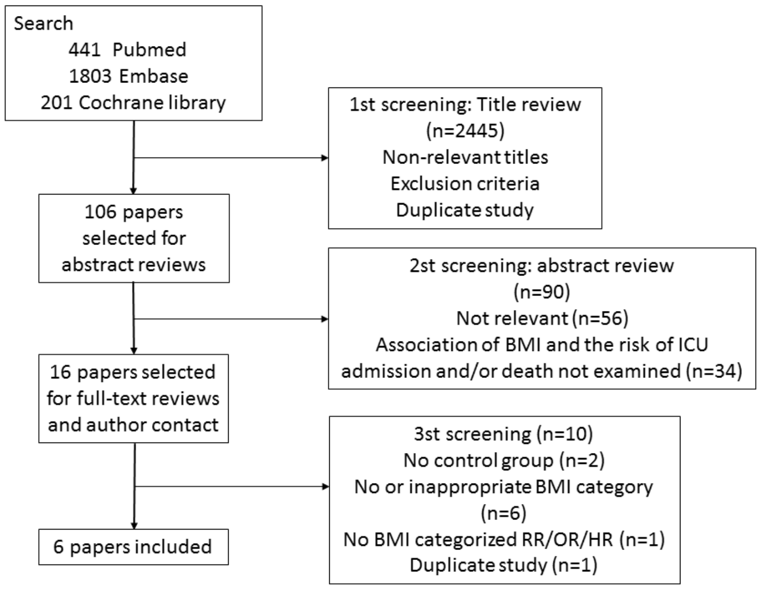

Figure 1. Flow diagram for inclusion and exclusion of studies. BMI, body mass index.

Methods

Literature search and study selection

We conducted a systematic literature search in PubMed, EMBASE and the Cochrane Library for relevant studies published before November 2015 by using a following combination of free keywords and MeSH terms: "pneumonia" AND ("death" OR "mortality" OR "Intensive Care Unit admission" OR "ICU admission") AND ("BMI" OR "body mass index" OR "obese" OR "obesity" OR "overweight" OR "underweight"). Two authors (Feng Cai and Xiaodong Wu) independently screened the titles and abstracts and performed a full-text review of the eligible literatures.

Studies were included if they met the following inclusion criteria. First, they had to be human studies written in English language. Second, the studies should investigate the association between BMI categories and the outcomes of pneumonia including mortality or ICU admission. Third, BMI values needed to be categorized by the WHO classification (underweight, <18.5; normal weight, 18.5-24.5; overweight, 25-29.9; obesity, ≥30) or using specific cut-off points. At last, these studies must provide effect sizes like odds ratio (OR), or hazard ratio (HR) with its corresponding 95% confidence interval (CI), otherwise provide data available to calculate the effect size. Studies were excluded if they focused on the association of viral pneumonia and BMI.

Quality assessment and data extraction

Quality of all included studies was assessed independently by two authors according to the Newcastle-Ottawa Scale. For each study, one author (Feng Cai) extracted the following data: author, publication year, country, the number of participants, baseline characteristics of participants including age and gender, study design, obesity definition categorized by BMI, outcome of the study, and the effect size with 95% confident intervals (CIs) for each BMI category compared with normal weight or original data which could calculate the effect size and its 95% CI. A second author (Xiaodong Wu) rechecked the accuracy and any disagreements should be resolved by consensus.

Data synthesis and analysis

All statistical analyses were performed using Stata 12.0 (Stata Corporation, College Station, TX, USA). We used ORs that were published or provided by the researcher in each study, if available, including approximations to OR such as HR or risk ratio (RR); otherwise, OR for abnormal BMI versus normal BMI was estimated from the number of patients in each group. We performed the analyses of the association between higher BMI and risk of ICU admission or death for two different BMI cut-offs: ≥25 and ≥30, when obtainable. Pooled effect sizes were computed using a random effects model approach that accounts for inter-study variation, presenting with 95% CIs overall, and within subgroups. Heterogeneity between studies was estimated using the I^2 statistic. We also conducted a stratified analyze evaluating the risk of ICU admission or death among patients with pneumonia by BMI.

The sensitivity analyses were performed by using fixed effects models and excluding stud-

Table 1. Characteristics of the studies reporting the association between BMI and the risk of ICU admission or death among patients with pneumonia

First author, year, country	Sample size (n)	Women (%)	Mean age (years)	Obesity definition (BMI, kg m^{-2})	Outcomes	Study design	Effect size	Quality assessment
King, 2013, USA	18 746	3	67.5	≥30	Death, ICU admission	Retrospective study	OR	6
Inoue, 2007, Japan	110,792	58	58	≥25*	Death	CH	HR	6
Corrales-Medina, 2011, USA	266	N	65.5	≥30	Death	Retrospective study	OR	4
Kahlon, 2013, Canada	907	52	68	≥30	Death, ICU admission	Retrospective study	OR	6
Singanayagam, 2013, UK	1079	50	66	≥30	Death	Retrospective study	HR	6
Takata, 2007, Japan	675	60.7	N	≥25$^{\Delta}$	Death	Retrospective study	HR	6

N, not provided in the study; BMI, body mass index; ICU, intensive care unit; CH, cohort study; OR, odds ratio; HR, hazard ratio; *,$^{\Delta}$These two studies from Japan combined obese subjects with overweight subjects because the obese patients was minor.

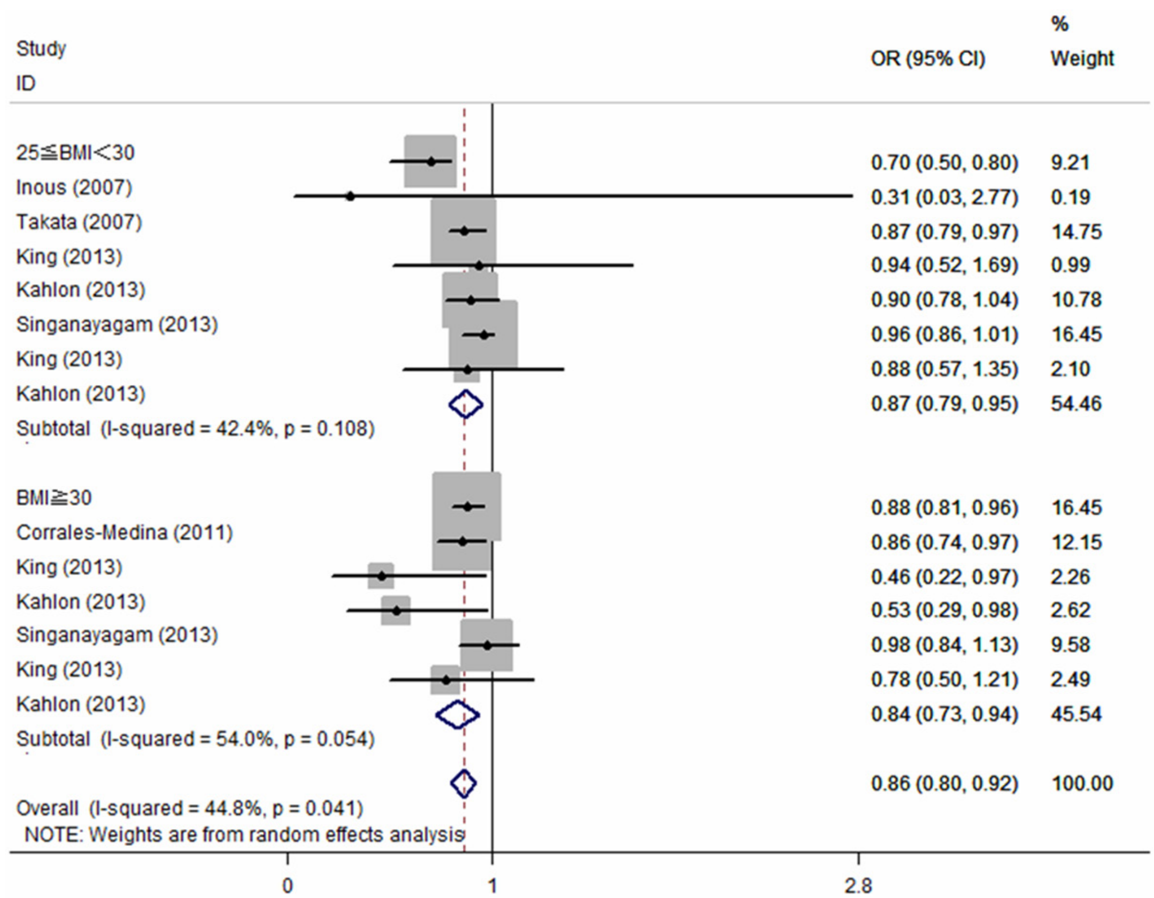

Figure 2. Association between higher BMI (25≤ BMI <30 or BMI ≥30) and risk of intensive care unit (ICU) admission and/or mortality among patients with pneumonia. BMI, Body mass index; ES (95% CI), effect size and 95% confidence interval.

ies of which the ES was not provided or adjusted [15]. We used the I^2 statistic to estimate heterogeneity between combined studies: low (<25%), moderate (25-75%) and high (>75%). Both the Begg's funnel plots and Egger's test were performed to assess publication bias.

Results

Study characteristics

Figure 1 summarized the study selection process for the analysis. Of 2486 literatures identi-

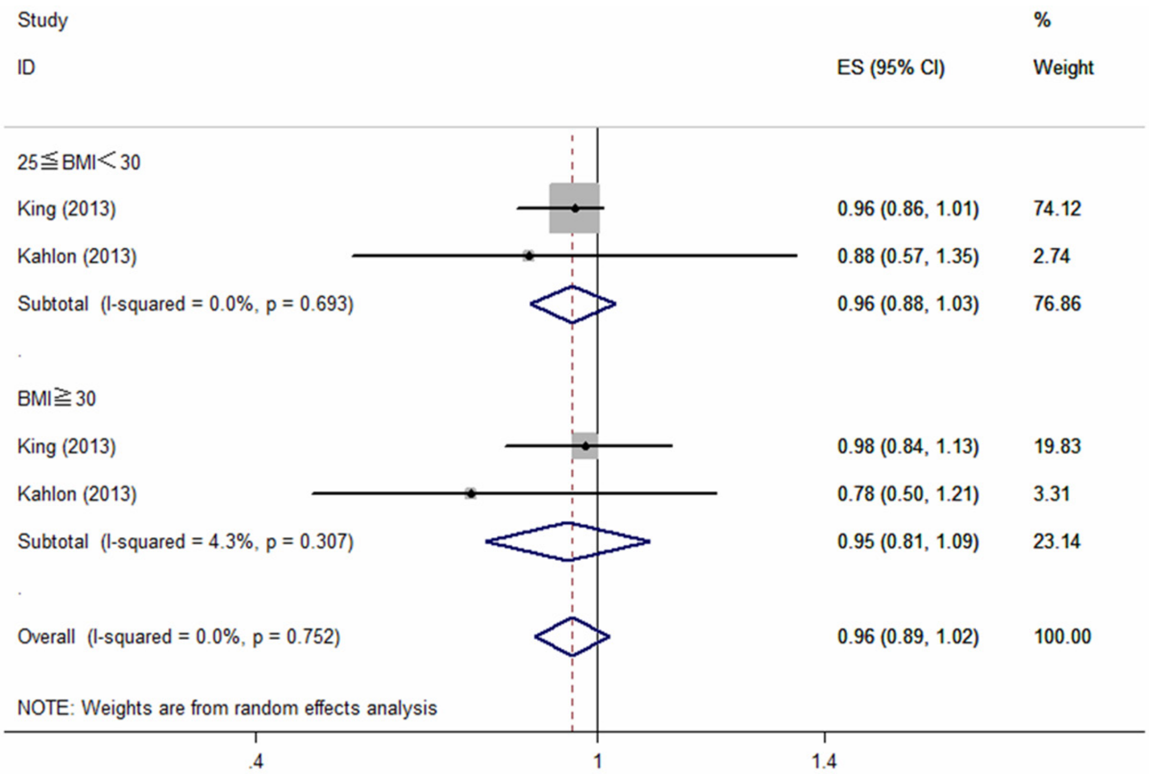

Figure 3. Association between higher BMI and the risk of ICU admission among patients with pneumonia stratified by BMI. BMI, Body mass index; ES (95% CI), effect size and 95% confidence interval.

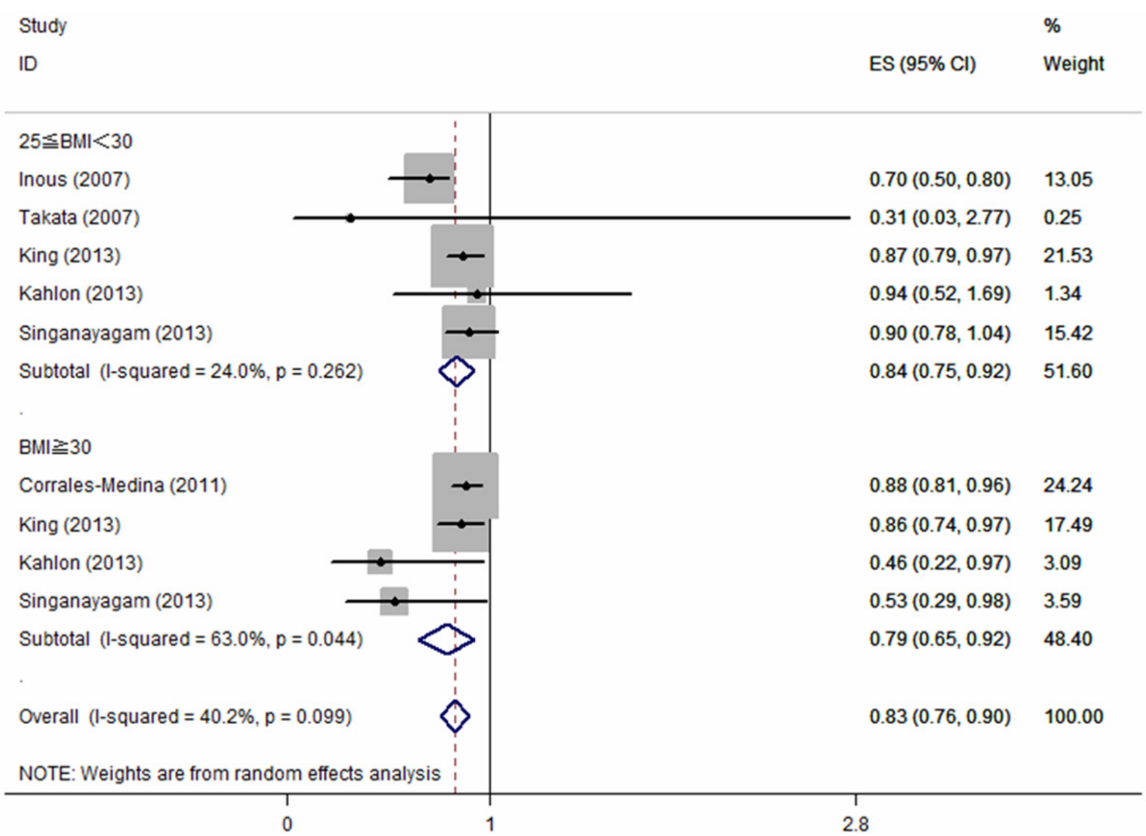

Figure 4. Association between higher BMI and the risk of death among patients with pneumonia stratified by BMI. BMI, Body mass index; ES (95% CI), effect size and 95% confidence interval.

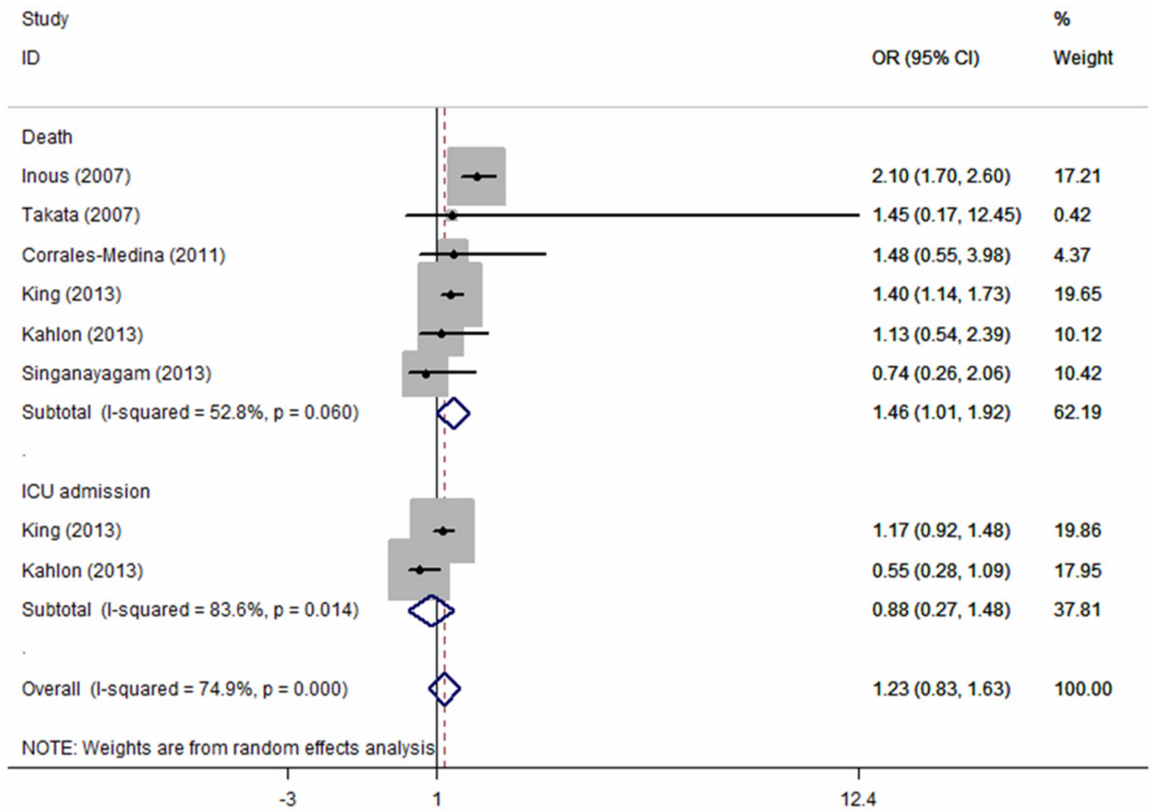

Figure 5. Association between underweight and the outcome (ICU admission or mortality) among patients with pneumonia. BMI, Body mass index; ES (95% CI), effect size and 95% confidence interval.

fied from our initial systematic search, 6 were finally included (**Figure 1**). Geographically, two studies had been done in the USA [12, 16], two in Japan [7, 17], one in Canada [13] and one in the United Kingdom [14]. A total of 132,465 participants were included in this analysis, and the sample size of each study ranged from 266 to 110,792 patients. The mean age of the subjects in these 6 studies ranged from 58 to 68 years, with one study from Japan investigated patients over 80 years old [17], and the proportion of women ranged from 3% to 60.7%. BMI was categorized according to the WHO definition (underweight, <18.5; normal weight, 18.5~24.5; overweight, 25~29.9; obesity, ≥30) in four studies. And the two Japanese studies categorized the participants as underweight (10~18), normal (18~23) , mildly overweight (23~25), or overweight (≥25) on account of the characteristics of the population [7]. The outcomes were death only and 'death and ICU admission' in combination (**Table 1**). All of the articles were assessed according to the Newcastle-Ottawa Scale in **Table 1** [12].

Association between BMI and the risk of death or ICU admission

Pooled estimates of effect sizes (ES) for the association between higher BMI and risk of ICU admission or mortality were showed in **Figure 2**. Six estimates from four studies examined on the association between obesity (BMI ≥30) and risk of ICU admission or death while seven estimates from five studies reported the ES of the overweight (25≤ BMI <30) group (two studies included separately ICU admission and deaths for both obesity and overweight). The pooled ES was 0.87 (95% CI: 0.79-0.95, P<.001) for overweight and 0.84 (95% CI: 0.73-0.94, P<.001) for obesity, with moderate heterogeneity among studies (underweight: I^2 = 42.4%, P = .11; obesity: I^2 = 54%, P = .05). In general, the pooled

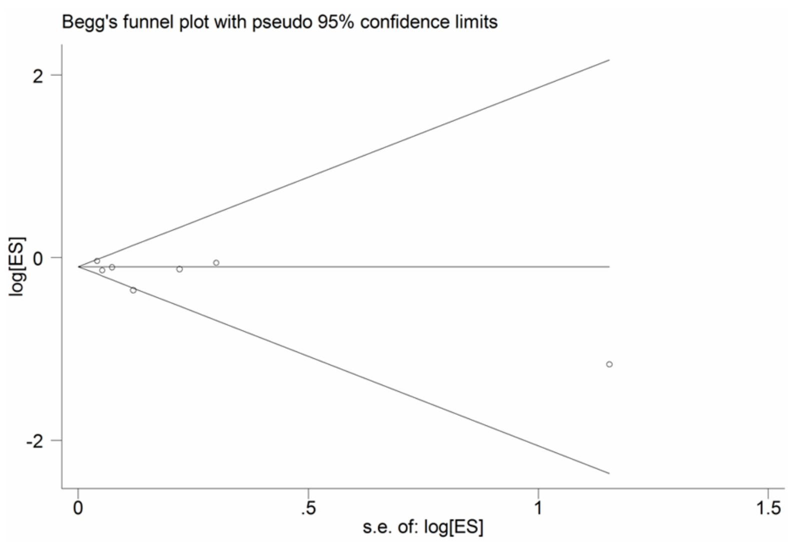

Figure 6. Begg's funnel plots for assessing publication bias of studies included in the meta-analysis of the association between overweight and the risk of ICU admission and death among pneumonia patients. P = .55. s.e. standard error; ES, effect size.

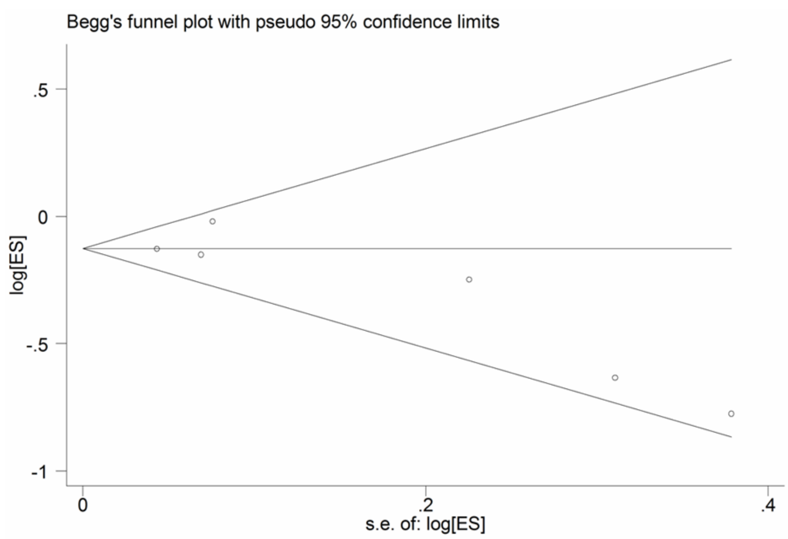

Figure 7. Begg's funnel plots for assessing publication bias of studies included in the meta-analysis of the association between obese and the risk of ICU admission and death among pneumonia patients. P = .06. s.e. standard error; ES, effect size.

summary estimate indicated that higher BMI was associated with lower risk of ICU admission or death (ES: 0.86, 95% CI: 0.80-0.92, *P*<.001; heterogeneity: I^2 = 44.8%, *P*<.05).

We separately evaluated the risk of ICU admission and the risk of death among patients with higher BMI stratified by BMI categories. As shown in **Figures 3** and **4**, elevated BMI was significantly associated with lower risk of death (ES: 0.83, 95% CI: 0.76-0.90, *P*<.001; I^2 = 40.2%, *P* for heterogeneity <.01) or risk of ICU admission (ES: 0.96, 95% CI: 0.89-1.02, *P*<.001; I^2 = 0%, *P* for heterogeneity = .75) and the relationship was more obvious in the obese category (ES for the risk of death: 0.79, 95% CI: 0.65-0.92, *P*<.001, I^2 = 63%, *P* for heterogeneity <.05; ES for the risk of ICU admission: 0.95, 95% CI: 0.81-1.09, *P*<.001, I^2 = 4.3%, *P* for heterogeneity = .307).

The **Figure 5** showed a stratified analysis of underweight-pneumonia relationship by outcomes of pneumonia. The summary ES for pneumonia mortality or the risk of ICU admission among underweight patients was 1.23 (95% CI: 0.83-1.63, *P*<.001; I^2 = 74.9%, *P*<.001) while the respective ESs were 1.46 (95% CI: 1.01-1.92, *P*<.001; I^2 = 52.8%, *P* for heterogeneity = .06) for the death and 0.88 (95% CI: 0.27-1.48, *P* = .05; I^2 = 83.6%, *P* for heterogeneity <.05) for the risk of ICU admission.

Sensitivity analyses

Since moderate heterogeneity was generated during the calculation of pooled ES for the analysis of **Figure 2** with significant heterogeneity for the analysis of **Figure 5**, we performed a sensitivity analysis to explore the potential source of heterogeneity. In a methodological sensitivity analysis, we repeated the analysis of **Figures 2** and **5** using fixed effects models instead of random effects models, and the pooled estimates for the risk of ICU admission or death were 0.89 (95% CI: 0.85-0.94, *P*<.001) (I^2 = 35.7%, *P* for heterogeneity = .11) for overweight, 0.87 (95%

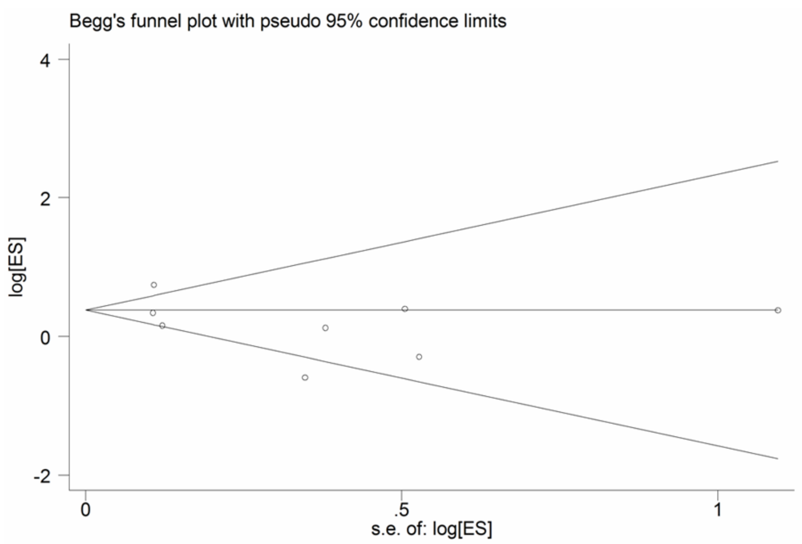

Figure 8. Begg's funnel plots for assessing publication bias of studies included in the meta-analysis of the association between underweight and the risk of ICU admission and death among pneumonia patients. P = 1. s.e. standard error; ES, effect size.

CI: 0.81-0.92, *P*<.001) (I^2 = 30.7%, *P* for heterogeneity = .05) for obesity and 1.25 (95% CI: 1.09-1.41, *P*<.001) (I^2 = 74.9%, *P* for heterogeneity <.001). Also, after excluding the two studies from Japan in which the BMI category was different from others, the pooled ES was 0.92 (95% CI: 0.87-0.97, *P*<.001) (I^2 = 0%, *P* for heterogeneity = .66) in overweight (25≤ BMI <30) category, presenting no alteration in the association between overweight and the outcomes of pneumonia but a significant decrease in magnitude of heterogeneity comparing with the original analysis.

Assessment of publication bias

No publication bias was identified when analysis was performed for overweight (Begg's funnel plots in **Figure 6**, P = .55; Egger's test, P = .20) and underweight (Begg's funnel plots in **Figure 8**, P = 1; Egger's test, P = .28) but obesity (Begg's funnel plots in **Figure 7**, P = .06; Egger's test, P = .11).

Discussion

Our meta-analysis of six studies with a large sample of 131,790 patients is to evaluate the relationship between body mass index and the risk of ICU admission or death among patients with pneumonia. We found that higher BMI (overweight or obesity) was likely a predictor of better outcomes in patients with pneumonia. The association were more obvious in obese patients and in the analysis of death. In contrast, the risk of ICU admission and mortality in underweight patients were increased 23% comparing with that in normal weight patients. However, this relationship was not statistically significant. Because of the limited number of studies using the risk of ICU admission as the outcome, the relativity between BMI and the risk of ICU admission has not been well established.

The relationship between underweight and worse outcomes of pneumonia in this meta-analysis was plausible since underweight has always been reported as a risk factor of pneumonia as well as other diseases. Underweight is almost always connected to malnutrition and commonly reflects a debilitating status [18]. Besides, underweight may contribute to the increased mortality due to an inability to meet the energy demands which is crucial in the immune responses against infection [19].

The association between obesity and pneumonia was always obscure. Obesity has been found by some studies as a protective factor from death in a variety of diseases, known as a phenomenon called "obesity survival paradox" [20-22]. A recent meta-analysis showed that this obesity survival paradox also existed in pneumonia [23]. Our analysis conformed to this result. A possible explanation for this phenomenon may be that the body mass index is not an accurate evaluation for obesity because it does not always represent true fat [24]. Agarwal et al. reported the low negative predictive value of BMI for obesity among patients with Chronic Kidney Disease [25]. Nevertheless, a study conducted by CJ. Lavie and his colleagues showed that the obesity paradox was still present in patients with stable coronary heart disease by using different body composition metrics such as lean mass index (LMI) and body fat

(BF) [26]. But unfortunately, there were not any researches investigating the association between body composition and pneumonia. Furthermore, Martín-Ponce et al. mentioned in their article that obese patients had better nutritional status, with less anorexia, less weight loss and more muscle mass with better handgrip strength and thus suffered less advanced co-morbidities [27]. Also, changes of the immunological function in patients with elevated BMI may provide an explanation of this phenomenon. Stapleton et al. found in their study that the inflammatory response may be altered in patients with acute lung injury and an increasing BMI with lower levels of key biomarkers of inflammation and injury, particularly IL-6, IL-8, and SP-D, suggesting that obese patients with ALI may have a reduced alveolar epithelial injury and consequently help protect against further lung injury and increased mortality [28]. However, a recent review included that the anti-inflammatory adipocytokines such as adiponectin, omentin, and SFRP5 were reduced in obesity, which is associated with increased inflammation and possible lung injury. But it also emphasized that there were controversial reports [29]. Finally, obese subjects have higher serum leptin concentrations than normal-weight subjects and leptin enhances CD4 lymphocyte response towards T helper type 1 cells [13].

However, when comparing with the study of Fezeu [11], we found that the obesity-pneumonia relationship was indeed different from the obesity-influenza relationship. Morbidity and mortality of the influenza A infection predominantly affected children and young adults, while the patients included in our analysis were mainly middle-aged and older people [30]. We were unable to examine the association of obesity and the outcomes of pneumonia by age for the reason that we could not found any studies included in these two analyses providing the prevalence of obesity according to age classes. This remarkable difference in age may lead to the inconsistency between these two analyses. So, we need to investigate if the effect of obesity on ICU admission or death among influenza or pneumonia is age-dependent.

Our analysis has several limitations. First, our searches were confined to literatures written in English, so this may increase the risk of publication bias in our analysis. Second, we didn't take into account of the detailed classifications of pneumonia because of the limited number of studies. Finally, the adjusted effect sizes extracted from the study were not identical and one of the studies failed to provide adjusted ES for the respective categories of underweight, overweight and obesity [12]. However, after a stratified analysis by effect sizes, we found no alternation in the association between BMI and the outcomes of pneumonia (data not shown).

In conclusion, our analysis showed underweight was associated with an increased risk of ICU admission and death in patients with pneumonia, while higher BMI might relate to better outcomes. The reason of obesity paradox in the prognosis of pneumonia has not been clarified. Furthermore, in clinical work, underweight patients with pneumonia need more monitoring.

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Disclosure of conflict of interest

None.

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