Author's response to reviews

Title: The role of increased body mass index in outcomes of sepsis: A systematic review and meta-analysis

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Responses to Reviewer 1:

Abstract:

1. Consider defining overweight, obese and morbidly obese when you first mention them in lines 6-9. You can then save the space later in the abstract.

Response: Thank you very much for the suggestion. We have defined overweight, obese and morbidly obese when we first mention them in the abstract (Page 4, lines 6-9). The details are as follows:

“We aimed to evaluate the associations between overweight (25 kg/m2 < BMI ≤ 29.9 kg/m2), obese (30 kg/m2 < BMI ≤ 39.9 kg/m2) and morbidly obese (BMI > 40 kg/m2) BMIs and outcomes in septic patients.”

2. In your conclusion paragraph, lines 56-59, consider adding “Overweight, but not obesity or morbid obesity, was associated with lower mortality.

Response: We greatly appreciate your suggestion. We have added the sentence in the conclusion of the abstract (Page 5, lines 1-3). The details are as follows:

“Conclusions: In sepsis cases, overweight, but not obesity or morbid obesity, was associated with lower mortality. Further prospective studies are needed to clarify this relationship.”
Background:

3. Page 6, Line 12: Saying "a survey" is very vague. Can you say who did the survey, how big it was, what the response rate was?

Response: Thank you very much for your helpful suggestions. We have described "a survey" concretely (Page 6, lines 5-9). We hope that this change improves our work, and the details are as follows:

“Walkey et al conducted a nationwide retrospective cohort study that identified 53.9 million adult infection hospitalizations from 2003 to 2009 and found that in the USA, the sepsis incidence rate has increased to 535 cases per 100,000 person-years and continues to rise.”

4. Page 6, Lines 44-50: Can you be more specific about which critical illnesses this paradox relates to? Is it just sepsis?

Response: We greatly appreciate your valuable comments. The obesity paradox was first described in 1999 in overweight and obese people undergoing haemodialysis (Fleischmann E, et al. Kidney Int. 1999;55:1560-7.). The authors demonstrated that compared with that of patients with a normal weight BMI, the one-year survival rate was significantly higher in the overweight patients. With a one-unit increase in BMI over 27.5, the relative risk for death was reduced by 30% (P<0.04). Subsequently, the paradox was found in patients with heart failure (Sharma A, et al. Am J Cardiol. 2015;115:1428–34.) and acute coronary syndrome (Niedziela J, et al. Eur J Epidemiol. 2014;29:801–12.). Furthermore, Ni YN et al conducted a meta-analysis of all recently published trials and found that obesity and morbid obesity are associated with lower mortality in patients with Acute Respiratory Distress Syndrome (Ni YN, et al. Crit Care. 2017;22;21:36.).

We have given examples to specify the critical illnesses to which the obesity paradox relates in page 6, lines 19-20. The details are as follows:

“Notably, certain clinical studies addressing the effects of obesity on critical illnesses (such as heart failure, acute coronary syndrome and acute respiratory distress syndrome) have revealed an "obesity paradox" in which obesity is not harmful and can even be protective, including for patients who have already become sick.”

5. Page 6 lines 53-59. This sentence is unclear. What associations are you referring to?

Response: We thanks for pointing out the unclear sentences. We have rewritten the sentence (Page 6, lines 53-59). The details are as follows:

“The role of obesity in patient outcomes in specific ICU populations, such as septic patients, has been paid much attention; however, extant clinical data on this topic remain controversial.”

6. Page 7 line 1-6: "Certain study has" should be Studies have.
Response: Thank you very much for your correction. We have replaced "certain study has" by "studies have" (Page 7, line 3-5). The details are as follows:

“Studies have indicated that obesity is correlated with an increased risk of death, whereas other investigations have reported inverse or null associations between obesity and risk of death.”

7. Page 7 lines 23-25: No need to say you are interested in the topic, would drop this sentence.

Response: Following the suggestion, we have dropped the sentence “We are interested in this topic.”

Methods:

8. Page 8 line 9: If you are going to list only some of the types of studies that were excluded you should give the full list somewhere, even if in a supplemental index.

Response: We greatly appreciate your constructive suggestions. In the revised manuscript, we rewrote the sentence in page 8, lines 4-6. The details are as follows. And we provided a full excluding list in an additional file, APPENDIX B.

“Two investigators independently screened all articles that satisfied our inclusion criteria. Studies were included in our analysis if they (1) utilized prospective or retrospective observational study designs (excluding systematic reviews, letters, editorials and so on. The full excluding list is given in additional file, APPENDIX B);”

9. Page 8 line 48: There should be a space between day and mortality

Response: Thank you very much for your correction. We have added a space between day and mortality (Page 8, line 48). The details are as follows:

“Different statistical approaches were used to assess mortality in the included studies; in order of preference, we used ICU mortality, hospital mortality, 28-day mortality and 60-day mortality.”

Discussion:

10. Page 12 lines 17-18: Is this comparable to the obesity paradox or is this an example of the obesity paradox?

Response: Thank you very much for your comments. The “obesity paradox” is a medical hypothesis that holds that overweight (25 kg/m2 < BMI ≤ 29.9 kg/m2) patients or obese (BMI > 30 kg/m2) patients have better clinical outcomes than normal weight patients (Antonopoulos AS, et al. Obes Rev. 2016;17:989-1000.).
Our meta-analysis showed that patients with BMI ≥ 25kg/m2 exhibited decreased mortality compared with that of normal-weight patients. We hold that this phenomenon is an example of the “obesity paradox”. To reduce confusion, we have rewritten the sentence you noted in the revised manuscript (Page 12, lines 15-19). The details are as follows:

“This meta-analysis showed that patients with BMI ≥ 25 kg/m2 exhibited decreased mortality compared with that of normal-weight patients, which is an example of the “obesity paradox” and can be explained in several ways.”

11. Page 12 lines 36-37: Not sure what you mean that leptin is the most representative as well as anti-inflammatory. I would drop the “most representative” part.

Response: Thank you for your suggestion. We have dropped the "most representative" part and rewrote the sentence in Page 12, lines 36-37. The details are as follows:

“Second, adipose tissue can also regulate immunity by excreting proteins such as leptin, which is an anti-inflammatory adipokine.”

12. Page 13 lines 15-20: What does it mean that adiponectin levels were higher in surviving overweight patients compared with surviving normal weight patients? If they both survived wouldn't this suggest the adiponectin level doesn't matter?

Response: Thank you very much for your helpful comments. It is true that comparing the concentration of adiponectin in obese patients and normal patients cannot account for the role of adiponectin in sepsis. After a careful reading of related literature, we found that the authors demonstrated that "compared with patients who survived sepsis, we found lower preseptic adiponectin concentrations in the subgroup of patients dying during the course of sepsis", which could better express our viewpoint. We also have access to the relevant literature on "adiponectin and sepsis" (Teoh H, et al. Am J Physiol Endocrinol Metab. 2008;295:E658–64; Konter JM, et al. J Immunol. 2012;188:854–63.), and the results suggested that adiponectin may play a lung protective role in the setting of sepsis. Thus, we rewrote the sentence in our revised manuscript (Page 13, lines 11-20). The details are as follows:

“Levels of adiponectin, an anti-inflammatory adipokine, change during the course of sepsis. In sepsis, higher adiponectin levels before sepsis and decreasing adiponectin levels after sepsis are associated with survival. Additionally, compared with patients who survived sepsis, O'Brien et al found lower adiponectin concentrations before sepsis in the subgroup of patients who died during the course of sepsis.”

13. Page 13 lines 20-28: What do you mean obesity is treated earlier by nurses? When and how are nurses treating obesity and what is it being treated earlier than?

Response: We greatly appreciate your helpful comments. We apologize for making an incorrect expression that led to confusion. We thought that obese patients had received more aggressive care and treatment from doctors and nurses. In the revised manuscript, we rewrote this sentence (Page 13, lines 29-31). The details are as follows:
“Finally, obesity may be treated more aggressively than other diseases, in part because it is associated with high risks of cardiovascular disease, insulin resistance, hypertension, and other comorbidities.”

14. Page 14 lines 34-29: I think you mean to say that an unmeasured confounding variable COULD also explain the results. Could you give an example?

Response: Thank you very much for your suggestion. We used “smoking” as an example in our revised manuscript (Page 14, lines 15-17). The details are as follows.

“Second, an unmeasured confounding variable in our meta such as smoking, which has been identified to be associated with mortality after severe sepsis, may also explain the aforementioned results.”

Conclusion

15. Page 16 lines 45-50: Would add that obesity and morbid obesity were not associated with increased mortality

Response: We greatly appreciate your suggestion. We have added the sentence in our conclusion (Page 17, lines 3-7). The details are as follows.

“Compared with normal-weight patients, patients with BMI ≥ 25 kg/m2 exhibited decreased mortality. Overweight BMI is associated with lower mortality in patients with sepsis; moreover, obesity and morbid obesity were not associated with increased mortality.”

Responses to Reviewer 2:

First, we thank you for your positive and constructive comments and suggestions. We summed up two points from the comments you wrote to us, and responded, point-by-point, to the comments as listed below.

1. Can you demonstrate how your study is significantly different from this study that is published so recently with similar results?

Response: We greatly appreciate your comments. We compare our research with the study (Pepper DJ, et al. Crit Care. 2016;20:181.) and summarize the significant differences in three aspects.

First, Pepper et al used the adjusted odds ratios (aOR) of mortality to perform the meta-analyses and showed that overweight or obese BMIs reduce adjusted mortality in adults admitted to the ICU with sepsis. In our study, we used the odds ratios (OR) of mortality to perform the meta-analyses and then extracted available data and analysed the adjusted effects of BMI on the OR for mortality relative to normal BMI (additional file, APPENDIX D). These two analyses both
demonstrated that overweight, but not obesity or morbid obesity, was associated with lower mortality.

Second, we performed further analysis. Before we performed the subgroup analysis, we pooled data from the eight included studies and compared the mortality between patients with BMI ≥ 25 kg/m² and normal-weight patients and found that relative to normal BMI, patients with BMI ≥ 25 kg/m² exhibited decreased mortality (OR 0.81; 95% CI 0.74-0.89, P < 0.0001) (Fig. 2). Two [16, 21] of eight studies meet our inclusion criteria of combined underweight and normal weight together as BMI < 25. We could not extract the data of normal patients as a reference group. Thus, we removed these two studies, conducted the same comparison again, and found that the trend of decreased mortality among patients with high BMI remained statistically significant (OR 0.83; 95% CI 0.75-0.92, P = 0.0003) (Fig. 3). We then performed a subgroup analysis to determine the extent of obesity that is associated with lower mortality. Additionally, we examined hospital and ICU LOS, while Pepper et al only performed a subgroup analysis of adjusted mortality with relatively limited data.

Third, the eight studies included in our work are significantly different from the six studies in the meta-analysis of Pepper et al. We did not incorporate three studies due to the reasons. Two studies (Wurzinger B, et al. Win Klin Wochenschr. 2010;122:31–6; Sakr Y, et al. Crit Care Med. 2015;43:2623–32.) are in accord with our inclusion criteria. Unfortunately we could not extract the valuable data even though we have sent emails to the authors. Another study (Adamzik M, et al. Anesthesiology. 2011;114:912-7) is a nice work, in which Adamzik et al showed that the C-allele of the AQP51364A/C polymorphisms associated with increased 30-day survival in patients with severe sepsis. The result suggested the importance of variations in the expression of AQP5 channels in severe sepsis. However, the study does not meet our criteria because it does not attempt to show any association between obesity and sepsis.

In addition to the same three studies, we included five additional studies that followed our strict standard and received detailed introductions in our meta-analysis (Table 1, Table 2). Among these, the study of Pisitsak et al is rigorously designed and is the most recently published. This study compared 28-day and 90-day mortality rates between BMI greater than or equal to 25 kg/m² and BMI less than 25 kg/m²; they also defined visceral obesity by a high visceral adipose tissue-to-subcutaneous adipose tissue ratio and found that visceral obesity contributes to adverse outcome in sepsis patients. We sent emails to the author (Keith R. Walley, MD) to obtain the number of deaths as well as the sample of sepsis patients in each group. They replied with data. In our initial analysis comparing the mortality between septic patients with BMI ≥ 25 kg/m² and other subjects, data from this study helped us reach the conclusion that patients with BMI ≥ 25 kg/m² exhibited decreased mortality (Fig. 2).

We have summarized the answer to your question and added it to our discussion to better present our work in page 15, lines 12-22. The details are as follows.

“Our study included more valuable studies and performed further analyses. We found that patients with BMI ≥ 25 kg/m² exhibited decreased mortality. Additionally, the subgroup analysis demonstrated that overweight was associated with lower mortality. Although we failed to observe a significant association between obese or morbidly obese BMI and decreased mortality,
we also did not find obese or morbidly obese BMI to be correlated with worse outcome. Furthermore, we extracted available data, analysed the adjusted effects of overweight BMI on the OR for mortality relative to normal BMI, and showed that overweight BMI reduced adjusted mortality (additional file, APPENDIX E). What’s more, we looked at hospital and ICU LOS.”

2. Also, in the discussion, could you provide clarification as to what it means to treat obesity earlier and how that pertains to patients admitted for sepsis?

Response: We greatly appreciate your helpful comments. We apologize for making an incorrect expression that led to confusion. We thought that obese patients had received more aggressive care and treatment from doctors and nurses. In the revised manuscript, we rewrote this sentence (Page13, lines 29-31). The details are as follows.

“Finally, obesity may be treated more aggressively than other diseases, in part because it is associated with high risks of cardiovascular disease, insulin resistance, hypertension, and other comorbidities.”