Author's response to reviews

Title: Obesity survival paradox in pneumonia: a meta-analysis

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Author's response to reviews:

Reviewer: Thomas TJ marrie

Comments to the Author:

This is a timely report that uses meta analysis to examine the obesity paradox in pneumonia.

Minor essential revisions

1. Abstract - "... conducted a dose response meta-analysis ..." this is confusing - yes a meta analysis was conducted but what is a dose response meta analysis. I know what the authors mean - suggest this be reworded.

Response:

Thank you very much for your valuable comments on our manuscript.

We revised this sentence and the title in this revision. We deleted “dose response” before meta-analysis.

2. The study in ref 12 involves patients on peritoneal dialysis and as such it will include patients with health care associated pneumonia. Why did you include this study?

Response:

Thank you very much for your constructive comments.

We agreed with the reviewer that patients with health care associated pneumonia would not be included in this study. Thus, we deleted this study (ref 12) in this revision.

3. Figure 5 - would be useful to present this as percent mortality at the various BMI categories.

Response:

Thank you very much for your enlightening comments.
We agreed with the reviewer that it would be more useful to present this as percent mortality at the various BMI categories. We sought to find a authoritative paper which described the percent mortality at BMI of 20-22 kg/m2. However, we did not find out this paper. Thus, Fig. 5 was not revised as the reviewer requested.

Quality of written English: Needs some language corrections before being published.
Response:
This manuscript has been edited and proofread by Medjaden Bioscience Limited. Thank you very much again for your time on our manuscript.

Reviewer: Carl Lavie
Comments to the Author:
This is a nice study and well-written meta-analysis on an important topic. The authors show that overweight/obese develop more pneumonia, but once pneumonia is present, overweight and obese have a lower mortality. There are many obesity paradoxes (Lavie CJ Progress in Cardiovascular Disease 2013, published on-line November), and this situation with pneumonia (more disease but lower mortality) is quite similar to the situation seen in coronary heart disease (De Schutter A et al Progress in Cardiovascular Disease published on-line October 2013) and Heart Failure (Lavie CJ et al JACC/HF 2013;1:93-102) which could be referenced. Also, it is unclear how the authors could use Leptin as both a mechanism for more pneumonia but lower mortality? – this needs to be better explained or deleted. Also, as with many diseases, (cancer, HIV, rheumatoid arthritis, etc), obesity may allow for greater metabolic reserve to fight a severe illness – couldn't this be the same with pneumonia? Response:
Thank you very much for your valuable comments on our manuscript. We have read the interesting papers published by Dr. Lavie CJ and colleagues. In addition, we quoted these papers in this revision [1-4]. We also re-wrote the reasons for the inverse relationship between obesity and the risk of pneumonia mortality.
Thank you very much again for your time on our manuscript.
References


Reviewer: Darren C Greenwood

Comments to the Author:

Major compulsory revisions:

1. Text that uses any causal language should be avoided because the meta-analysis is only based on observational studies. So, for example, the final sentence in the abstract must be changed or removed. Text referring to “effect size” must be changed.

Response:

Thank you very much for your valuable comments on our manuscript. We agreed with the reviewer that we should tune down the conclusions, because the conclusions were based on observational studies. We thus revised the final sentence in the abstract. We also deleted “effect size” in this revision.

2. Retrospective cohorts should not be excluded. Include them. The exposure is still prospectively recorded; the term “retrospective” only refers to the formation of the cohort in history, hence the alternative name “historical cohorts”. This adds a substantial number of good studies to the meta-analysis.

Response:

Thank you very much for your enlightening comments. We added the retrospective cohorts studies in this revision. There were seven retrospective cohort studies and fifteen prospective cohort studies in this meta-analysis.

3. The search strategy is not sufficiently detailed. The MOOSE guidelines cited specify that the exact search strategy should be provided. For example, there are no terms referring to the mortality outcome, nor to the study design.

Response:

Thank you very much for your suggestion. The detailed search strategy has been presented in the Additional File 1.

4. Use of the Newcastle-Ottawa scale needs improvement. The purpose is not to arrive at a score, but to inform risk of bias. Therefore the criteria on which each dimension is judged need to be provided in the methods, e.g. what was considered adequate follow-up, and the score for each dimension provided, rather than just the overall summary score.
Response:
Thank you very much for your constructive comments.
The detailed criteria of methodological quality assessment has been provided in the Additional File 2.

5. We need the PRISMA checklist, as required for all meta-analyses.
Response:
The PRISMA checklist for present meta-analysis is provided in the Additional File 3.

6. I found the methods and results confusing in that there appear to be three sets of meta-analysis. First, using the reported groupings of normal, overweight and obese. Second linear dose-response. Third non-linear dose-response. The exclusion of studies using unusual categorisations of BMI (foot of page 6 / top of page 7) is unnecessary for the dose-response meta-analyses. If a dose-response trend is used then it doesn’t matter how BMI is categorised. That’s the point of it. Similarly there is no reference “group” for the dose-response meta-analyses (as suggested on top of page 7), but a reference point, which you could choose to be 20kg/m² or 25kg/m² or whatever you want. This needs clarification, and explanation why a meta-analysis using the reported categorisations is needed.
Response:
Thank you very much for your comments on our manuscript. In this revision, we re-wrote the Statistical Analysis section.
We agreed with the reviewer that the exclusion of studies using unusual categorisations of BMI is unnecessary. In fact, we wanted to included all these studies using unusual categorisations of BMI, and we thus wrote “In order to avoid eliminating studies with important information, we considered BMI levels within 4 kg/m² of standard categories to be acceptable” in the previous version.
We also agreed with the reviewer that there is no reference “group” for the dose-response meta-analyses, but a reference point. We performed dose-response meta-analysis of the relationship of a 5-unit increase in the BMI and pneumonia or mortality risk using generalized least-squares trend estimation analysis based on the methods developed by Orsini et al. [1]. This method requires the distribution of case and person-years and median level of BMI in each category to the corresponding relative risk for each study (the relative risks with estimates for at least 3 quantitative exposure categories are known). This could explain why a meta-analysis using the reported categorisations is needed.

References

7. More detail is required for the “polynomial models” fitted. What polynomials were used? Quadratic? Cubic? Fractional polynomials? If the latter, what powers were considered? How was the best fitting model arrived at? How was the test
for nonlinearity performed? The results are not replicable without these details. The coding of all this in Stata is quite involved, and there is great scope for difference of approach.

Response:
In this revision, we re-wrote the Statistical Analysis section.

We tested for a potential nonlinear relation between BMI, pneumonia risk, and mortality using a two-stage random effects dose-response meta-analysis. This was done by modeling BMI with the use of restricted cubic splines with three knots at fixed percentiles (10%, 50%, and 90%) of the distribution [1]. First, a restricted cubic spline model was estimated with a generalized least-squares regression taking into account the correlation within each set of published RRs as described by Orsini et al. [2]. At a second stage, we combined the study-specific estimates using the restricted maximum likelihood method in a multivariate random effects meta-analysis [3]. A P value for nonlinearity was calculated by testing the null hypothesis that the coefficient of the second spline was equal to zero.

References

8. Discussion should include that meta-analysis of cohorts is prone to the same weaknesses as cohorts, e.g. confounding, etc.

Response:
Thank you very much for your valuable and constructive comments.

We revised the manuscript as the reviewer suggested: “A meta-analysis of observational studies inherits the limitation of the original studies. Because this meta-analysis was based on data from cohort studies, selection and recall bias cannot be excluded. Although most studies adjusted for potential confounders, such as age, gender, smoking, and underlying diseases, the possibility of residual confounding cannot be ruled out. Because this meta-analysis investigated only BMI, we cannot exclude the possibility that the observed associations may be confounded by other lifestyle factors, such as lower physical activity or dietary factors.”

9. The methods say that I-squared is used to quantify heterogeneity, but they haven’t used it in the text. It should be. Heterogeneity is high, and this needs (a) more exploration in the analyses, and (b) more acknowledgement in the discussion. Random effects models don’t mean it can be ignored.
We added I-squared data in this revision. We examined the role of several potential sources of heterogeneity by subgroup analyses according to study design, gender, ascertainment of case, pneumonia type, assessment of anthropometry, and duration of follow-up. Meta-regression was also performed to find the sources of heterogeneity. However, we did not determine the primary sources of heterogeneity (please see Additional Files 6 and 9). We acknowledged this limitation in this revision: “caution with interpretation of the results is necessary, and these results should be confirmed by future studies”.

Minor essential revisions:

1. Grammar needs improving throughout the manuscript. Response: This manuscript has been edited and proofread by Medjaden Bioscience Limited.

2. No meta-analysis is going to resolve the problem of the paradox, but it can describe whether it exists for pneumonia. The introduction and aims should be changed to clarify this. Response: We have revised this part: “To date, no meta-analysis has described whether an “obesity survival paradox” exists for pneumonia. The aim of this meta-analysis is to investigate the relationships between elevated BMI, pneumonia risk, and mortality.”.

3. The forest plots need to be tidied up. The horizontal axis needs a better scale and labelling. Response: We revised the forest plots as the reviewer requested.

4. The dose-response plot needs the 2 in kg/m2 to be superscript. Response: We revised this issue as the reviewer requested.

5. Some p-values are quoted to 3 significant figures, when 1 or 2 should suffice to avoid giving a false sense of precision. Response: We revised this issue as the reviewer requested.

6. The authors describe results from sensitivity analyses as being “Statistically similar”, but the estimates are sometimes quite different. It could well be chance, but statistical significance is not everything. Response: We agreed with the viewpoint of the reviewer. In this revision, sensitivity analysis was conducted by excluding one study at a time.

7. Asymmetry in the funnel plot is evidence of a small-study effect. One example of this is publication bias, but there are other explanations, such as the smaller studies being carried out better. Or worse. So refer to them using the more general term of “small-study effects”. Tests of small-study effects will have low
power with the sort of numbers included, so I would prefer the focus to be on the funnel plot rather than the test. Response:
We used “small-study effects” in this revision and used funnel plot but not other tests to assess small-study effects (please see Additional Files 4, 5, 7, and 8). Thank you very much again for your time on our manuscript.