Reviewer's report

Title: Obesity survival paradox in pneumonia: a dose-response meta-analysis of prospective cohort studies

Version: 1 Date: 15 January 2014

Reviewer: Darren C Greenwood

Reviewer's report:

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.

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.

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.

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.

5. We need the PRISMA checklist, as required for all meta-analyses.

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.

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

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.

Minor essential revisions:
1. Grammar needs improving throughout the manuscript.
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.
3. The forest plots need to be tidied up. The horizontal axis needs a better scale and labelling.
4. The dose-response plot needs the 2 in kg/m² to be superscript.
5. Some p-values are quoted to 3 significant figures, when 1 or 2 should suffice to avoid giving a false sense of precision.
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.
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.

Discretionary revisions:
1. I’m personally not convinced by the clever mechanisms suggested to explain the paradox. I think it’s probably just an artefact of data collection. People who are normal weight must be more frail to succumb to pneumonia, but those who are obese are more likely to get pneumonia in the first place, so are otherwise fitter. No amount of adjustment for confounding can fully correct for this. It’s much the same as smoking after a heart attack. Smokers have better survival. But that’s because they’re more likely to have the heart attack in the first place. Those who quite after the heart attack still have even better survival than those who continue. There is no “paradox”.

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
I declare that I have no competing interests.