Author's response to reviews

Title: The incidence of co-morbidities related to obesity and overweight: A systematic review and meta-analysis

Authors:

Daphne P Guh (daphne@sm.hivnet.ubc.ca)
Wei Zhang (wzhang@cheos.ubc.ca)
Nick Bansback (nbansback@cheos.ubc.ca)
Zubin Amarsi (zamarsi@arthritisresearch.ca)
C. Laird Birmingham (clbirm@interchange.ubc.ca)
Aslam H Anis (aslam.anis@ubc.ca)

Version: 3 Date: 5 February 2009

Author's response to reviews: see over
February 5, 2009

BMC Health Services Research

Dear Editorial Team:

RE: MS: 2435043332086033

Thank you for your recent letter inviting us to revise and resubmit the above manuscript. In the current version of paper, as per your suggestion, we have responded to all of the reviewers’ comments and the appropriate changes to the manuscript have been made. Our responses below are according to the comment number of each reviewer.

Responses to Comments
Reviewer: John Broom
Reviewer's report: Minor Essential Revisions:
1. The authors use only 2 databases to collect published papers in the field and are therefore liable to have missed additional papers in their field. Other databases such as CINHAL, HealthSTAR, AMED, BIOSIS, etc. should also have been addressed. In addition no specific hand-searching of appropriate obesity related journals was carried out again leading to possible missing data. Some explanation as to why there was this restricted search of published work needs to be addressed in the text of the paper. On major systematic review of obesity and its comorbidities is certainly missing from the references, ie. Health Technology Assessment 2004, Vol 8: no 21. by Avenell, A et al.

Precise rules for how far to search to produce a systematic review have not been universally agreed. (Stevens A (2001) Consensus, reviews and meta-analysis. In Stevens A, Abrams K, Brazier J, Fitzpatrick R and Lilford.R (eds) /Methods in Evidence Based Healthcare./ Sage publications, London, pp. 367) We spent considerable time in developing, testing and re-testing the review search strategy to ensure that it captured all of the relevant studies. Given the sizable literature and that we were searching for non RCT studies for which search filters are more complex, we determined that complementing the search with checking reference lists and thorough searching the internet as suggested by Peersman (Peersman, (2001) Learning from research. In Oliver, A. and Peersman, G. (eds) /Using Research for Effective Health Promotion./ Oxford University Press, Buckingham, pp. 3243) was more useful rather than searching another electronic database.

We do not believe the reviewers concern is simply the number of electronic databases we searched, but whether any bias might have occurred due to our search strategy. We agree this is an important point, but given the nature of the studies we are looking for e.g. mainstream studies with no reason to publish in non healthcare journals, we consider our search strategy sufficient. We addressed this as one limitation in our discussion section (last paragraph, page 17).
The reference to Health Technology Assessment 2004, Vol 8: no 21. by Avenell, A et al. which the reviewer has kindly provided was on the effect of reduced BMI rather than the absolute level of BMI on long-term health outcomes and therefore excluded from the meta-analysis.

2. The authors quote the definition of obesity according to WHO for a Caucasian population only. The studies included in this meta-analysis were carried out in "Western Countries", but these countries have significant non-Caucasian populations. Some discussion of this needs to appear since the definition of obesity relative to both BMI and waist circumference differs in these populations.

About 55% of the studies were US studies and 20% of them reported ethnicities of the sample. There was one study which focused on the black women (endometrial cancer) while the proportion of Caucasian ranged from 81% to 95%. Ethnicity was seldom reported on the other non-US studies. We have now added the information on ethnicities reported by the studies in the result section. Our final result on endometrial cancer did not include the black cohort (last paragraph, pages 8).

3. In their comorbidities the authors use the term "heart disease" to include various pathologies not related to or classified as heart disease, ie. Pulmonary embolism, stroke, and hyperlipidaemia. The term "heart disease" should be replaced with "cardiovascular disease risk".

As suggested, the term “heart disease” has been replaced with “cardiovascular disease risk” in the last paragraph on page 5. This did not affect our search strategy.

4. The term "hyperlipidaemia" is meaningless and is no longer in use. This should be replaced by the term "dyslipidaemia".

We re-conducted the search by replacing “hyperlipidaemia” (Subject Heading and Explode (using the selected term and all of its more specific terms)) by “dyslipidaemia” (Subject Heading and Explode (using the selected term and all of its more specific terms)). In Medline, we identified additional 108 articles that captured under “dyslipidaemia” but not under “hyperlipidaemia”. In Embase, we identified additional 1819 articles. After reviewing these articles, we found that 716 studies were not with prospective cohort design, 51 did not have generalizable population, 218 were with irrelevant subjects and 941 were review, commentary, editorial articles etc. We only found 1 prospective study that measured the association between obesity and dyslipidaemia (Metabolism, Vol 50, No 6 (June), 2001: pp 696-702 by Srinivasan SR et al.). However, this study has 4 different definitions of dyslipidaemia and it did not provide the required information on incidence of dyslipidaemia among young adults with 25<BMI<30kg/m² (overweight).

During the search, we found many studies focused on hyperlipidemia/dyslipidemia and obesity as risk factors or measured the cross-sectional relationships between obesity and hyperlipidemia/dyslipidemia. However, no prospective cohort was designed to look at the association between the incidence of hyperlipidemia/dyslipidemia and baseline overweight and obesity status.
5. All of the tables are difficult to follow in their current presentation and impossible for the non-expert in meta-analyses. These tables need further extensive descriptors.

We have now provided heading and footnotes on each figure to describe the figures for meta-analysis results. On each figure, we put subtitles including reference, obesity criteria, sex, age criteria, length of study follow-up, country, sample size.

6. There are a number of errors of syntax which need to be checked and corrected and I’m not clear what the authors mean by "post endometrial cancer" on p7.

The typo “post endometrial cancer” has been corrected with “endometrial cancer” (3rd paragraph, page 9).

I also find it difficult to believe that no studies relating to dyslipidaemia risk relating to obesity were found.

Please refer to our responses to the comment #4.
Reviewer: E Atlantis
Reviewer’s report:
This report describes findings of a systematic review and meta-analysis of prospective cohort studies investigating the risk of an extensive range of non-fatal disease outcomes associated with baseline exposure to general and central overweight and obesity, by sex and length of study. This report is a comprehensive and substantial contribution to the topic of obesity-related morbidity. I present several issues to be addressed and suggestions for improvement.
Title: I suggest a title that’s better reflects the report’s content; eg “systematic review and meta-analysis...” risk of non-fatal diseases incidence”... etc.

The title has been changed to “The incidence of co-morbidities related to obesity and overweight: A systematic review and meta-analysis”.

Abstract:
The abstract (and the main text in general) is somewhat bland and not well-written. I suggest the authors’ look at recent systematic reviews for suggestions on how to improve their writing. I suggest using “incidence“ in the abstract and throughout. The conclusion should not be used to highlight study strengths. It should summarise findings, and include implications, ie make policy recommendation.

We have revised much of the manuscript, in particular the abstract, introduction, result and discussion sections. We have also, as suggested, used the term “incidence” throughout the manuscript.

Introduction:
First sentence requires refs of some good quality prospective cohort studies, or previous reviews of cohort studies.

For the first sentence (page 3), we have added 3 systematic reviews that summarized the co-morbidities associated with obesity based on the existing evidence.

Cite most recent systematic reviews on the topic, highlight shortcomings to then justify the present review. One justification is that if additional studies have been published since the most recent review, etc.

We justified our present systematic review by three points (pages 3-5). First, WC has been reported to be an even better predictor of many cardiovascular diseases and type II diabetes than BMI. However, most recent reviews only focused on obesity defined by BMI instead of WC. Secondly, there is inconsistency in the definitions for BMI and WC in previous reviews – many have combined studies estimating the incidence of co-morbidities by per unit change of BMI (kg/m²) and WC (cm). We wanted to measure the incidence by categorization of overweight and obesity defined by BMI and WC measurements. Last, we prefer using a standardized and consistent definition for overweight and obesity across all diseases, a consistent inclusion criteria and consistent methodology for performing a meta-analysis. This could ensure the review quality and also enable the comparisons of the size of effect across co-morbidities.
Methods:
Use exposure variables for subheadings for obesity
Use Disease outcomes subheading for diseases

Done. We have used “Exposure variables” and “Disease outcome” as the subheadings (page 5)

The selection of co-morbidities requires further justification than “reviewed by an eating disorder and obesity expert”. Perhaps selecting the top 10 diseases that accounts for say 90% of total global disease burden would be better justification (see WHO reports).

Possible co-morbidities of overweight and obesity were first identified from a preliminary search reviewed by an eating disorder and obesity expert and previous systematic reviews that summarized the co-morbidities associated with obesity. We also reviewed the leading causes of global burden of disease and included the diseases reported with burden attributable to overweight and obesity (last paragraph, page 5).

Why weren’t search terms for central obesity selected?

In Medline and Embase, there is no subject heading for ‘central obesity’. However, our search strategy used the MeSH term based on the subject heading for obesity, which was exploded (using the selected term and all of its more specific terms). We believe that the term ‘central obesity’ have been included under the subject headings of ‘Adipose Tissue’, ‘Obesity’, ‘Body Mass Index’, or ‘Body Composition’.

“not mortality rate” is not clear.

We have clarified this in the last paragraph on page 6.

“Data extracted included.....” should say “for study characteristics”.
Report the work conducted by authors’ names, search, inclusion/exclusion, data extraction etc.

This has been done in the last paragraph on page 6.

It isn’t appropriate to pool central obesity (WC) effect measures with general obesity (BMI) effect measures, because they are different independent variables (regionally vs generally specific).

We pooled WC effect measures separately from BMI effect measures. We clarified this in the last paragraph on page 7.

Why test for significant heterogeneity, and then use random effect modeling regardless of Q statistic?
We used random effect models to estimate the pooled RR. The Q-statistic was provided to indicate the degree of homogeneity across the studies. We have now re-worded the sentences to make it clearer (1st paragraph, page 7).

Please conduct sensitivity analyses to determine systematic differences in summary effects between studies by age, ethnicity and country of study (most from US) subgroups. This will provide a more population-specific understanding of RR of disease incidence associated with obesity. And tests the robustness of your findings!

Sensitivity analyses based on duration of study follow-up, age, country of study and ethnicity were conducted (1st paragraph, page 7) and presented in result section (last paragraph, page 15) and the figures.

Results:
Stick to consistent decimal places.

Done.

Figures:
The figures need more information. Titles for % weighting, n’s, effects etc.
I have no idea what the values represent that appears to be for summary effects.

We have re-done and clarified all the figures. Please also see our response to comment #5 from reviewer John Broom.

I hope these comments are helpful.
1. Is the question posed by the authors well defined? yes
2. Are the methods appropriate and well described? not quite
3. Are the data sound? yes
4. Does the manuscript adhere to the relevant standards for reporting and data deposition? not quite
5. Are the discussion and conclusions well balanced and adequately supported by the data? no
6. Are limitations of the work clearly stated? no
7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? unsure
8. Do the title and abstract accurately convey what has been found? no
9. Is the writing acceptable? no
Reviewer: Jeremy Miles

Reviewer's report:

Discretionary revisions

Were any language restrictions placed on the searches or the papers?

We searched papers published in English. We have now clarified this in the 1st paragraph on page 6.

Were any attempts made to rate the quality of the included studies?

Quality of the included studies was assessed by the length of follow-up and identification of exposure and outcome variables. We have now added this in the last paragraph on page 8.
Reviewer: Adriana Perez

Reviewer's report:

Minor essential revisions:

This manuscript presents a meta-analysis estimating the risk of twenty co-morbidities related to obesity and overweight. The authors provided two forms of risk assessment using incidence rate ratios and ratio of proportions depending of the data available for the meta-analysis. No major concerns were found.

This is very well written paper, the design, methods and results are very well presented and clear to researchers. There is a large benefit for this paper for the result provided. The authors are encourage to add a note in the discussion section to the readers, informing about the reasons why they did not report any publication bias results or informing the readers about the results of the publication bias analyses.

We have now added the assessment of potential publication bias in the method (1st paragraph, page 7), result (2nd paragraph, page 15) and discussion sections (1st paragraph, page 18). Potential publication bias was visually inspected by funnel plots and tested by asymmetry tests. However, for many co-morbidities, there were not enough studies to examine publication bias. Specifically, potential publication bias was assessed for post-menopause breast cancer, endometrial cancer, ovarian cancer, colorectal cancer, and prostate cancer. There was some evidence of funnel-plot asymmetry for prostate cancer.

We believe that we have revised the manuscript in accord with the reviewers’ comments. We are also grateful to the reviewers for their insightful comments which have resulted in an improved manuscript. I hope that you will find our responses satisfactory and agree to publish our paper.

Regards,

Aslam H. Anis, PhD
Centre for Health Evaluation and Outcome Sciences
620-1081 Burrard Street
Vancouver, B.C., Canada, V6Z 1Y6
Phone: 604-806-8712
Fax: 604-806-8778
E-mail: aslam.anis@ubc.ca