A SYSTEMATIC REVIEW OF THE EFFECTS OF OBESITY ON OUTCOMES IN PATIENTS WITH HEART DISEASE

PROTOCOL INFORMATION

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Conflict of interest
None

Founding sources/sponsor
University of Leicester

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10 July 2015

Anticipated completion date
30 September 2015

Type of review
Epidemiologic; Intervention

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English

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United Kingdom

Keywords
Systematic review; body mass index; obesity; obesity paradox; heart failure; cardiovascular disease; acute coronary syndrome; myocardial infarction; percutaneous coronary intervention; angioplasty; coronary artery bypass grafting, cardiac surgery; mortality.
BACKGROUND

Key points
Over the last decades, improvement in socioeconomic conditions has led to an increase of the overweight population worldwide, and studies in diverse patient groups have demonstrated strong associations between increased body mass index (BMI) and favourable outcomes. This phenomenon termed the “obesity paradox” is at odds with the well-recognised causal association between these factors and cardiovascular disease. However, these studies were biased by the small sample size and their nonadjusted methodology due to the effects of unmeasured confounders. More recent studies have attempted to establish whether the obesity paradox can be simply explained by bias or whether there are important underlying mechanisms that may be harnessed to improved prognosis in patients with cardiovascular disease. This systematic review will summarise recent developments to identify areas of uncertainty or gaps in knowledge that need to be addressed by future studies.

The clinical problem
Cardiovascular disease remains the leading cause of death in the UK (73,000 deaths per year, 200 deaths per day). The total cost of premature death, lost productivity, treatment and prescriptions for cardiovascular disease in the UK is £19 billion per year (www.bhf.org). Multiple clinical studies have demonstrated that patients with heart disease who are overweight, or obese have improved long-term survival when compared to normal weight, underweight or severely obese patients [1,2]. This is a controversial finding; diabetes, pre-diabetes, hyperlipidaemia and obesity, all manifestations of the metabolic syndrome, are key risk factors for the development of cardiovascular disease, and multiple observational analyses have demonstrated an increase in premature cardiovascular death in these patients [3,4]. Furthermore these conditions are rapidly increasing in prevalence and are predicted to consume a significant and increasing proportion of all healthcare expenditure in the coming years [5]. However, if obesity or being overweight is associated with improved outcomes in specific clinical settings this may have important implications for a number of reasons. i) It may help tailor strategies or the use of interventions in underweight and very obese patients that may improve outcome; ii) it may challenge current assumptions that patients with these conditions should lose weight acutely, particularly prior to surgery; iii) it may deliver new treatments that can target specific processes underlying these observations; iv) it may provide new insights into the pathogenesis of diabetes and the metabolic syndrome that will lead to better outcomes and reduced healthcare expenditure in general.

Study bias
There are however significant limitations in the existing evidence. Firstly these observations have been made in non-randomised studies that included relatively small cohorts of selected patients, typically suffering from multiple sources of bias that relate either to the limitations of the study design, or the effects of unmeasured confounders [6,7]. Specific sources of bias include:
1. **Selection bias:** observational analyses are normally conducted in retrospective cohorts of patients who have already been selected for specific interventions or diagnostic groups by clinicians. Obese or overweight patients may be preferentially selected because they are younger. Similarly, ‘fitter’ obese or overweight patients may have been selected for these interventions (percutaneous coronary intervention, cardiac surgery), excluding the less fit obese or overweight patients from analyses [8].
Alternatively, ‘survival bias’ may lead to more obese patients dying from cardiovascular disease before they present for treatment, interventions or the diagnosis of heart failure [8].

2. **Treatment bias:** Overweight and obese patients may be considered more suitable for aggressive or multiple interventions than other patient groups, particularly those with low body weight, increasing the likelihood that they will have better clinical outcomes.

3. **Study Power:** the assumptions that must be met to ensure the accuracy of regression analyses, the most common type of analyses in these studies, are not necessarily met in smaller samples where multiple covariates are considered alongside the effects of obesity. Conversely, large analyses may detect very small effects that are highly statistically significant, leading to an over-interpretation of their importance.

4. **Reverse epidemiology:** this is a limitation of all epidemiologic studies, which by design can never demonstrate causality. Rather than demonstrating that increased BMI improves survival these studies may instead demonstrate that factors that lead to low BMI also lead to poor survival. For example smoking, poverty and malnutrition, or cachexia attributable to other diseases is likely to lead to low BMI and also to high mortality [9, 10].

**Unmeasured Confounders**

1. **Body mass index:** BMI is the main exposure of interest in many of these studies, not necessarily delineating a homogeneous group of patient who for example have or do not have the metabolic syndrome. BMI may be elevated by visceral adiposity that is thought to promote insulin resistance and the metabolic syndrome, or by subcutaneous adiposity or increased muscle mass, that may counter the pathological effects of the metabolic syndrome [11,12].

2. **Race and geographical setting:** for example the relationship between BMI and the metabolic syndrome are different between ethnic groups [13].

3. **Association between obesity (measured as BMI) and outcome:** this association may be spurious. The result may be attributable to other key covariates including the presence or absence of atherosclerosis, smoking, socioeconomic group, dietary fat or sugar content, serum lipid levels, glucose levels or insulin levels, all of which have different exposures in obese and non-obese patients [13-16].

**The knowledge gap**

Although obesity has been implicated as one of the major risk factors for hypertension, heart failure, and coronary artery disease, evidence from clinical cohorts of patients with cardiovascular diseases indicates that obesity is associated with favourable survival in leaner patients, especially in those affected by heart disease (defined as patients with heart failure, heart valve disease or symptomatic coronary artery disease). More recent evidence has suggested that these findings may be attributed to bias attributable to study design or to confounding factors. In this review we will assess the contribution of methodological bias, or unmeasured covariates such as lean body mass, visceral adiposity, impaired glucose tolerance, smoking or exercise tolerance on the obesity paradox. Better understanding of this phenomenon may assist with the risk stratification and management of existing patients and also help develop new treatment strategies for patients with cardiovascular disease.

**Why it is important to do this review**

Obesity, diabetes and the metabolic syndrome are currently reaching epidemic proportions and have significant implications for health services and national economies [5]. These are important risk
factors for most cardiovascular diseases, the most common cause of death in the UK and elsewhere. Improved understanding of how the metabolic syndrome affects clinical outcomes, or how these patients may be better risk stratified or treated, may ultimately improve clinical outcomes. This review will define the knowledge gap in our understanding of the “obesity paradox”, identify areas of uncertainty and identify areas for further research.

OBJECTIVES
The overarching aim of the review is to assess the interaction between obesity and related clinical syndromes and clinical outcomes in patients with heart disease.

HYPOTHESIS
It is our hypothesis that the association between obesity, currently defined by the World health Organisation as an elevated Body Mass Index, and improved survival in patients with heart disease is likely to represent the effects of methodological bias or residual confounding.

AIMS
1. To summarise published studies that have considered the associations between obesity and death in patients with heart disease.
2. To assess the quality and potential sources of bias in these studies.
3. To estimate the associations between obesity and death in patients with heart disease.
4. To explore our main hypothesis we will then assess the effects of likely sources of bias and unmeasured confounders on our estimates.
5. To conduct sensitivity analyses to assess potential sources of heterogeneity; study type (cohort, case control, propensity scoring, analysis), cohort size, study quality.

METHODS
Criteria for selecting studies for this review
Types of studies
We will consider clinical studies that have evaluated the effect of the primary exposure of interest (BMI) on mortality in patients with heart disease.
We will included include studies with quantitative, qualitative and mixed-methods approaches in order to obtain a comprehensive overview of the existing evidence based literature.
The following types of studies will be analysed and included:

- Clinical randomised trials;
- Controlled before-and-after studies;
- Prospective and retrospective cohort studies;
- Cross-sectional studies;
- Case-control studies.

Study exclusion criteria
Exclusion criteria will include:
• Studies where BMI is expressed only as a continuous variable;
• Repeat publications of the same analysis or dataset;
• Conferences abstracts;
• Editorials & opinion pieces;
• Books or grey literature.

**Types of participants**
Adult patients with heart failure, stable coronary artery disease (stable angina), acute coronary syndrome or acute myocardial infarction, or those undergoing percutaneous coronary interventions or cardiac surgery.

**Exposures of Interest**
The primary exposure of interest is obesity stratified into BMI groups according to the classification system of the World Health Organisation (WHO): Underweight (<18.5/20 kg/m²), Normal weight (18.5/20 to 24.9 kg/m²), Overweight, (25 to 29.9 kg/m²), Obese Class I (30 to 34.9 kg/m²), Obese Class II (35 to 39.9 kg/m²) and Obese class III (≥40 kg/m²).

Secondary exposures of interest will include the following:
2. Geographic setting by continent.
3. Measures of obesity other than BMI; defined as measures of visceral adiposity (waist circumference, hip waist ratio, CT assessment of visceral adiposity, hepatic steatosis, fat mass index) or subcutaneous adiposity (triceps skin fold thickness), or Gallagher Body fat categories.
4. Socioeconomic deprivation: Charlson Comorbidity Index.

**Types of outcome measures**
• Primary outcome measure will be: all-cause mortality in hospital or within 30 days.
• Secondary outcome measures will include:
  a. Hospital morbidity/complications (postoperative or perioperative)
  b. Early late cardiovascular mortality (at 1 year)
  c. Long-term all-cause mortality

**Search methods for identification of studies**

**Electronic searches**
We will search the following databases (from inception to 30 June 2015):
- Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 1, 2014).
- MEDLINE (OvidSP, 1946 to 30 June 2015).
- Embase (OvidSP, 1974 to 30 June 2015).
- PubMed (e-publications only: searched 30 June 2015).
- SCOPUS (1960 to 30 June 2015)
No language restriction will be applied.

**Searching other resources**
We will check references of all identified trials, relevant review articles, and current treatment guidelines for further literature. These searches will be limited to the “first generation” reference lists.

**Search term**
The following search terms will be used: (((obesity OR body mass index OR anthropometry OR adiposity OR body weight[MeSH Terms])) AND (mortality OR death OR survival[MeSH Terms])) AND (heart failure OR cardiac surgery OR acute coronary syndrome OR myocardial infarction OR angioplasty OR stent OR coronary artery bypass OR heart valve[MeSH Terms])) NOT surgery, laparoscopic[MeSH Terms].

**Results of the scoping search**
A preliminary electronic search (PUBMED) using the above search terms has identified 6122 titles of studies conducted in human subjects.

**Data collection**

**Selection of studies**
Four authors (GM, AD, FS, SP) will screen all titles and abstracts of papers identified for relevance to the review aims. Studies clearly not meeting the eligibility criteria will be excluded at that stage. Remaining studies will be assessed on the basis of their full text for inclusion or exclusion using the criteria indicated above. At this stage, three authors will independently assess eligibility. Disagreements will be resolved by consensus in discussion with a fifth reviewer (GJM). Numbers of studies assessed, included and excluded will be recorded. Duplicate reporting of studies will be carefully assessed and indicated.

**Qualitative analysis**
A qualitative analysis will help to explore questions such as how patient selection, treatment and type of study may have influenced the primary effect estimate. The following questions will be considered for a qualitative analysis:

1. Was the study population well described?
2. Were the outcomes of interest clearly defined?
3. Were the exposures of interest (primary and secondary) well defined?
4. Does the article state both inclusion and exclusion criteria?
5. Were the analysed variables clearly defined?
6. How was missing data managed?
7. Were more than 10 events per variable included?
8. Were criteria used to determine indication for treating postoperative complications?
9. Was the follow-up for following variables of interest well stated?

**4.3.3 Data extraction and management**
Aside from details relating to included study quality the following groups of data will be extracted:

- **Study characteristics:**
citation (author/year), study design, place of publication, date of publication, inclusion/exclusion criteria.

- **Population characteristics:**
total patient number, population enrolment period (years), geographic location, and clinical characteristics (age, gender) including risk factors (proportions) for heart disease (hypertension, diabetes, hyperlipidaemia, smoking, cerebrovascular accident, coronary artery disease), and treatment (number of vessels stented, surgical procedures).

- **Exposures:**
number of intervention groups, detailed nature of intervention and detailed nature of comparator; analysed cofounders.

- **Outcomes:**
outcome definition, outcome measures.

- **Results:**
number of participants allocated to each group, sample size, summary data. Reasons why an included study did not contribute data on a particular outcome will be carefully recorded and the possibility of selective reporting of results on particular outcomes will be considered.

Four authors (GM, AD, FS, SP) will perform data extraction independently. Data will be extracted onto study specific data extraction form. Disagreements will be resolved by consensus between the authors or by discussion with a fifth author where necessary (GJM). Once disagreements will be resolved, the consensus data extracted will be recorded onto a third data extraction form. One reviewer will transcribe this into the systematic review computer software RevMan 5 (v. 5.3). Another reviewer will assess all data entry for discrepancies. Missing data will be requested from study authors. If data are unclear, missing, or presented in a form that is unable to be reliably extracted, authors will be contacted to assist in the process. The corresponding author will be initially contacted by email, with the first author (if not the corresponding author) copied into all correspondence. If email addresses are not available, authors will be contacted by phone. Authors will be given seven days to respond to emails, after which they will be followed up with a phone call and an additional email. If no responses are received after an additional seven days, another phone call will be made to contact the author. Attempts to reach authors will occur for an additional seven days and if authors are unable to be contacted, the authors will be classified as uncontactable.

**Risk of bias assessment**
Four authors (GM, AD, FS, SP) will independently assess the risk of bias in included studies by considering the following:

- Randomised trials will be assessed using the Cochrane Collaboration’s Risk of Bias tool [18], assessing randomization, sequence generation, concealment of allocation, blinding of patients, health care providers, data collectors, and outcome assessors; incomplete outcome data, selective reporting of outcomes, and reporting of adherence to study protocol.

- Observational studies will be assessed using the Newcastle-Ottawa Scales (NOS) for cohort and case-control studies, which consist of 3 parameters for: selection (maximum 4 points), comparability (2 points), and exposure/outcome assessment (3 points) [19]. A maximum score of 9 points thus reflects the lowest risk of bias (highest quality). In addition, because of the quality scoring is controversial in reviews/meta-analyses of observational studies, all
observational articles will be appraised according to the critical review checklist of the Dutch Cochrane Centre proposed by MOOSE [20].

Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a fifth review author (GJM) if necessary.

**Measures of treatment effect and data analysis**

A narrative synthesis of the included studies will be provided, focusing on the impact of obesity on early and late outcomes. Detailed tables of the findings from the included studies will be provided, with reference to the type of study (i.e. randomized, cohort studies, case control studies...), the study period, the inclusion/exclusion criteria, type of analysed outcomes. In addition, additional tables will be provided listing salient characteristics of each study, with reference to population age, gender proportions (male vs. female), comorbidity proportions (i.e. hypertension, diabetes), number of treatment or control subjects, proportions of periprocedural/postoperative complications (i.e. stroke, renal dysfunction, perioperative myocardial infarction, respiratory failure...), and length of hospital stay. Additional tables will summarize the attributable study (randomized or observational) points obtained by the Cochrane Collaboration’s Risk of Bias tool, Newcastle-Ottawa Scales (NOS) for cohort and case-control studies, and the checklist of the Dutch Cochrane Centre proposed by MOOSE. We will provide summaries of intervention effects for each study by calculating risk ratios (for dichotomous outcomes) or standardised mean differences (for continuous outcomes). Pooled adjusted odds ratios (OR) and (95% CI) will be estimated using both fixed-effects and random-effects models. Separate analyses for observational studies and/or randomized controlled trials will be conducted. Subgroup analyses will be performed by study design and type of outcomes. Heterogeneity will be assessed by Cochrane Q statistic, which will give a qualitative value and will be considered statistically significant for heterogeneity if a P value of less than 0.10 is obtained, and the I2 statistic, which gives a quantitative measurement; I2 values higher than 50% will be considered a reflection of severe heterogeneity. Sensitivity analyses will be conducted to explore the robustness of our results. To identify any study that may have exerted a disproportionate influence on the summary treatment effect, we will perform an exclusion sensitivity analysis where studies will be deleted one at a time. Results obtained with a fixed-effects model will be compared with those obtained with a random effects model. All calculations and graphs will be performed with the meta-analysis software Review Manager version 5.

**Subgroup Analysis**

*Our sub-group analyses will specifically consider bias attributable to the following:*

  a. **Selection bias:** our review will consider multiple clinical settings where selection or survivor bias may be less or more evident.
  b. **Treatment Bias:** our review will consider differences in the interventions used in obese and non-obese patients.
  c. **Study Power:** our review will compare effect estimates in large versus small cohorts.
  d. **Reverse epidemiology:** our analysis will assess the effect of inclusion or exclusion of those with low body weight (BMI <18kg/m²) from the analysis.

*We will also consider the effects of the following potential sources of confounding:
e. **Metabolic Syndrome**: we will assess the interaction between visceral adiposity, versus subcutaneous adiposity or increased muscle mass on the main effect estimate.

f. **Race and geographical setting**: we will assess the interaction between geographical location and the main effect estimate.

**COMPETING INTERESTS**
The authors declare that they have no competing interests.

**AUTHORS’ CONTRIBUTIONS**
GM, GJM had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: GM, GJM.
Acquisition of data: GM, AD, FS, SP.
Analysis and interpretation of data: GM, AD, FS, SP, GJM.
Drafting of the manuscript: GM, AD, FS, SP, GJM.
Statistical analysis: GM, AD, FS, GJM.
Study supervision: GJM.
REFERENCES
