Protocol for Systematic Review: Association of All-Cause Mortality with Overweight and Obesity Using Waist Circumference, Waist-to-Hip Ratio, and Waist-to-Height Ratio

June 2013

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Study Team

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Background

The association of adult overweight and obesity with mortality is of considerable clinical, epidemiological, and public health importance. While there is a general consensus that extreme levels of obesity and underweight are associated with increases in mortality, the relationship of overweight and moderate levels of obesity with mortality remains controversial with some studies finding a lower mortality risk in these groups and others finding an increased mortality risk. Establishing the risk associated with intermediate levels of adiposity has important implications for preventative strategies, as population-level approaches may not be appropriate under certain exposure-outcome scenarios.

In order to help clarify the relationship, a recent systematic review has been published investigating the relationship between body mass index and all-cause mortality. Consistent with the research team's previous work, a reduction in the all-cause mortality risk was observed in the overweight and grade 1 obese categories in meta-analyses of 97 studies. The authors considered whether included studies were adequately adjusted (for age, sex and smoking status) or over-adjusted (if including variables, such as hypertension, on the causal pathway). Analyses were stratified by age group (over 65 years and adults under 65 years) but there was limited investigation of age or period effects, which may arise as cardiovascular mortality has reduced and obesity has risen over time.

In addition to the above, a number of other relevant systematic reviews have been conducted. A systematic review of the relationship between obesity and mortality in the elderly (over 65 years) was recently conducted. This included a meta-analysis of three studies, which showed an increased mortality rate with obesity (assessed using body mass index) in women but less convincingly in men. Chang et al conducted a systematic review with a narrative synthesis of the effects of body fat distribution (assessed using body mass index (BMI), waist-to-hip ratio (WHR), waist circumference (WC)) on a broad range of outcomes in older adults. Like Flegal et al, they found that most literature suggest a reduced mortality rate with moderate levels of obesity in this population group. A systematic review and narrative synthesis of the relationship between physical activity, obesity, and morbidity/mortality (requiring information on all three variables) found a lower risk of all-cause mortality in individuals with high BMI but good fitness. Ashwell and colleagues assessed how waist-to-height ratio compared to body mass index and waist circumference as screening tools for cardiometabolic risk factors. Another systematic review compared the impact of including both waist and hip circumference on risk models for cardiovascular prediction for cardiovascular diseases, diabetes and mortality, finding hip circumference (but not necessarily waist-to-hip ratio) provides valuable information for risk prediction.

Although a systematic review that retrieved some relevant literature to investigate measurement methods was performed in 2008, at present, no systematic review establishing the relationship between waist-circumference (WC) and/or waist-to-hip ratio (WHR) and all-cause mortality has been conducted. All of these anthropometry measures appear to be limited in their ability to accurately measure adiposity but are easy to use for clinical and epidemiological purposes. An investigation of the relationship between anthropometric measures and all-cause mortality may be informative. Consistency in the relationship between different anthropometric measures and all-cause mortality adds weight to the hypothesis that being overweight may reduce all-cause mortality risk. In contrast, a dose-response relationship observed with either WC or WHR may suggest that the finding of a lower mortality rate with overweight may reflect the limitations of BMI as a measure. Unfortunately, in contrast to BMI, there is no clear agreement on the best cut-off points.
for WC- or WHR-based risk assessment, with the WHO and IDF suggesting two different sets of cut-offs\textsuperscript{12} (Table). In addition, measurement methods (such as the location of bony markers to be used to assist in measurement) are also variable but there is systematic review evidence to suggest that this may not affect the estimation of relative risks in studies\textsuperscript{11}.

Table: A Summary of Published Cut-Offs for Waist Anthropometry

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Cut-offs</th>
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<tbody>
<tr>
<td>WHO – WC</td>
<td>&gt;94 (M), &gt;80 (F)</td>
</tr>
<tr>
<td>WHO – WC (v. High risk)</td>
<td>&gt;102 (M), &gt;88 (F)</td>
</tr>
<tr>
<td>WHO – WHR</td>
<td>≥0.9 (M); ≥0.85 (F)</td>
</tr>
<tr>
<td>IDF Europids</td>
<td>&gt;94 (M); &gt;80 (F)</td>
</tr>
<tr>
<td>IDF S Asians, Chinese, Japanese</td>
<td>&gt;90 (M); &gt;80 (F)</td>
</tr>
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However, it is noteworthy that many studies have not used the above cut-offs (which were first published in 2000) but instead report findings on the basis of quintiles.
Review Aims

This review aims to investigate the association (allowing for non-linearity) between waist-related measures of adiposity and all-cause mortality in adults.

The criteria for the systematic review, in terms of the PICOS statement, are as follows:

- Population: General adult population (aged 16 years and over)
- Intervention: None
- Comparator: Waist-circumference, Waist-to-hip ratio, Waist-to-height ratio
- Outcome: All-cause mortality
- Study design: Prospective studies (including cohort studies, cross-sectional studies with mortality follow-up using administrative data etc.)

Methods

Search strategy
A comprehensive search strategy has been developed in conjunction with an information scientist for searching the Medline and Embase databases (see Appendix 1) from inception. References will be imported into Endnote to facilitate screening.

Two reviewers will independently screen the initial list of retrieved article titles and abstracts. A longlist will be created for full-text articles to be retrieved. The reviewers will then independently identify articles for inclusion with any discrepancies resolved by consensus and discussion with a third member (LG) of the research team if necessary. Reference lists and cited articles (using google scholar) will be scrutinised and experts known to the authors will be contacted to check the comprehensiveness of the identified articles for inclusion.

Inclusion/Exclusion Criteria
The inclusion criteria are identical to criteria described above in the PICOS statement. Articles published at any time and in any language will be considered for inclusion.

Articles that meet any of the following criteria will be excluded:

1. Not prospective studies
2. Study population limited to persons with specific medical conditions or undergoing medical procedures (since relative risk estimates may not be representative of the general population)
3. Studies restricted to only overweight or obese people (since these studies will not allow investigation of the risks associated with different exposure levels)
4. Studies of children only (defined on the basis of most participants in the study being aged under 16 years)

5. Do not report all-cause mortality by exposure(s) of interest (i.e. waist circumference, waist-to-hip ratio, waist-to-height ratio)

6. Total study sample size of 50 or less

Data Extraction
Data will be extracted from the papers into Microsoft Excel by two reviewers independently. Information to be abstracted will include:

- Publication details: author(s), title, journal, date, stated aims

- Study characteristics: country and region of study conduct, year(s) of baseline fieldwork, follow-up period, sampling frame, baseline response rate, population exclusion criteria, sample size, attrition, number of outcome events, age/sex/ethnicity characteristics

- Information related to study quality: exposure measurement methods, analytical sample restrictions, covariate adjustment (including adjustment of body mass index)

- Key data: method of classification of exposure i.e. waist circumference/waist-to-hip ratio/waist-to-height ratio, self-report or objective measurement, number/ratio of events in different exposure groups in as much detail as possible (e.g. means with 95% confidence intervals, p values)

Study Quality assessment
Studies will be classified as high, medium, or low risk of bias for the purposes of this systematic review by the two reviewers independently based on the below criteria:

Low risk of bias – Collects measurements according to a standardised protocol and addresses potential confounding from age/sex, smoking and pre-existing disease but not for mediating variables and/or BMI.

Medium risk of bias – Relies on some self-reported measures and/or adjusts for BMI.

High risk of bias – Does not address potential confounding factors adequately or adjusts for BMI.

While a number of quality appraisal criteria exist, there remains no established consensus on the most important indicators of quality within observational epidemiological studies and some experts have argued that quality indicators should be determined in relation to the specific research question. Separate meta-analyses of high quality studies only will be conducted to investigate the influence of study quality on the findings.
Synthesis

Given the variability in the population samples, measurement methods and cut-off points, meta-analysis will be challenging. Three main approaches to synthesis will be considered, dependent on data availability. First, data reported according to the WHO cut-off points (as described earlier), will be meta-analysed in a random-effects model. A random-effects model is more appropriate for the analysis since it allows for the effect of the exposure to vary between studies. Second, a meta-regression model treating the exposure as continuous will be calculated. Third, a narrative synthesis of studies will be performed in addition to the above two methods if heterogeneity precludes adequate exploration of the data quantitatively. Statistical heterogeneity will be quantified by calculating $I^2$ statistics and detailed investigation of the causes of heterogeneity will be pursued if the statistic exceeds 50%15.

For both quantitative synthesis approaches, analyses will be stratified by measurement (WC, WHR, WHtR). The primary analysis will be limited to studies at low and medium risk of bias, with a secondary analysis limited to low risk of bias studies only. Following this, a number of sub-group analyses will be considered to explore heterogeneity including: sex (male, female, both sexes combined), age group (age 65 years and over, under 65 years, mixed age group), ethnic group (Asian, Black, White) and adjustment for BMI (adjusted, unadjusted). Adiposity is known to vary across age, sex, and ethnicity and therefore relationships may vary across these groups. BMI is known to be highly correlated with other anthropometric measures and therefore establishing if other measures show independent associations once adjusted for BMI would be of interest. In addition, separate analyses will be considered for high-quality studies only and studies that are representative of the general population from which they are drawn. Lastly, period effects will be sought by allowing for statistical interaction between associations and year(s) of study conduct since the effect of overweight may be affected by the dominant causes of mortality (in particular, being affected by secular trends in cardiovascular mortality).

Meta-Analysis using WHO Cut-Off Points

Studies that report hazard ratios in comparison to a reference group (as per the WHO statement) will be synthesised in the initial stage of analysis. Authors of individual studies will be contacted for additional necessary results when not available. Random-effects models (for the analyses as described above) will be performed.

Meta-Regression

Meta-regression that allows for a non-linear relationship between WC/WHR and all-cause mortality will be performed. This may require making some assumptions in order to convert extracted data into a format that is suitable for modelling (further considerations outlined below).

Narrative Synthesis

Given the likely heterogeneity described above, narrative synthesis (privileging studies ranked as high quality) will also be conducted. This will focus on exploring the relationship between overweight and all-cause mortality, based on grouping studies as indicated in the meta-analysis section described above. In addition, the narrative synthesis will investigate whether findings from the meta-analysis are reflected in the wider literature.
Statistical Issues
A number of potential statistical difficulties in conducting meta-analysis have been identified and the approaches planned to deal with each of these issues are outlined below.

Dealing with differential cut-off points
We shall be dealing with data from different studies with different cut-offs for WC/WHR. We shall use estimates for the mean WC/WHR for each category within each study as proxies for that category. This involves making assumptions about the distributions of the WC/WHR values within categories. Where possible we shall base our assumptions on population-specific sources of continuous data – e.g. NHANES, Health Survey for England.

Dealing with correlation of within-study relative risks and hazard ratios
The standard approach to trend estimation of exposure-response relations when only published category-specific relative risks (or hazard ratios) and their confidence intervals are available is to fit a weighted least squares linear regression through the origin, in which the dependent variable is the estimated log relative risk, the independent variable is the exposure level to which the dependent variable corresponds, and the weights are the estimated inverse variances of the log relative risks. In the first instance, we may use this method which assumes that the log relative risks are not correlated. However, the assumption of independence of the estimates is generally violated because the estimates for separate exposure levels depend on the same reference group. It has been shown that wrongly assuming zero correlation among a series of log relative risks estimated using a common referent group leads to a biased estimate for the variance of the trend. Therefore, Greenland and Longnecker proposed a method to derive estimated cell counts of the 2X2 table adjusted for confounding, then derive the asymptotic correlation between the adjusted log odds ratio estimates for each exposure level relative to the referent level, from which we can get the estimated covariance matrix for these study-specific estimates. More recently, Hamling et al developed an alternative to the GL method, with the apparent advantage of being able to adjust for a loss of precision due to confounding.

For assessment of linear association, the relative risk estimates are first combined to approximate the logistic coefficient within each study and used to obtain an overall pooled meta-analytic estimate.

Allowing for non-linearity of association between WC/WHR and mortality (prepool method)
A more flexible method for meta-analysis of association involves pooling of data across studies prior to trend analysis, which can be extended to fitting and testing non-linear logistic models (studies must report dose-specific odds ratios or rate ratios to be included). Non-linearity can be explored by way of polynomial models, fractional polynomials or splines.

SAS will be used to implement inverse-variance-weighted and correlation-corrected prepool methods to fit flexible meta-regression models, accommodating random-effects models.
**Individual-Person Meta-Analysis**
Ideally, individual-person meta-analysis would be the best method of overcoming the above statistical issues. Depending on the number of studies identified for inclusion, we will explore the potential for conducting such an analysis in collaboration with authors of included studies.

**Deviation from Protocol**
Given the heterogeneity in reporting within this area, it is anticipated that deviations from the protocol are likely within the analysis phase of this systematic review but this protocol has been produced (and made publically available) to allow others to review deviations from the *a priori* systematic review plan and independently assess their appropriateness.
We would like to thank the following colleagues at the MRC/CSO Social and Public Health Sciences Unit for their advice: Candida Fenton, Information Scientist, for assistance in developing the search strategy; Dr. Geoff Der for statistical advice; Dr. Hilary Thomson and Dr. Matt Egan for providing comments on the protocol.
References


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Medline 1946 to March Week 3 2013

1 Adiposity/ 4046
2 Adipose Tissue/ 57392
3 Body Height/ph [Physiology] 2926
4 Body Size/ph [Physiology] 1168
5 Body Weight/ph [Physiology] 14087
6 Overweight/ 9331
7 Skinfold Thickness/ 5373
8 Obesity/ 113370
9 exp Obesity, Abdominal/ 995
10 Body Mass Index/ 69781
11 Thinness/ 3101
12 Adipose.ab. or Adipose.ti. or Adiposity.ab. or Adiposity.ti. or BlA.ab. or BlA.ti. or "bioelectric impedance analysis".ab. or "bioelectric impedance analysis".ti. or "Body Height".ab. or "Body Height".ti. or "Body Mass Index".ab. or "Body Mass Index".ti. or "Body size".ab. or "Body size".ti. or "body Weight".ab. or "body Weight".ti. or Fat.ab. 575113
13 Waist*.ab. or Waist*.ti. or Girth*.ab. or Girth*.ti. 19482
14 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 630861
15 13 and 14 15484
16 exp Abdominal Fat/ 3758
17 Anthropometry/ 29843
18 Body Fat Distribution/ 1286
19 Intra-Abdominal Fat/ 2182
20 Metabolic Syndrome X/ 16506
21 exp Obesity, Abdominal/ 995
22 Subcutaneous Fat, Abdominal/ 378
23 exp Waist Circumference/ 3295
24 exp Waist-Hip Ratio/ 2515
25 "Abdominal Adipose Tissue".ab. or "Abdominal Adipose Tissue".ti. or "Abdominal Fat".ab. or "Abdominal Fat".ti. or "Abdominal Obesity".ab. or "Abdominal Obesity".ti. or "Abdominal Subcutaneous Adipose Tissue".ab. or "Abdominal Subcutaneous Adipose Tissue".ti. or "Abdominal Subcutaneous Fat".ab. or "Abdominal Subcutaneous
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28 Life Expectancy/ 13097
29 exp Mortality/ 259685
30 Survival Rate/ 115384
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31 32 27 or 28 or 29 or 30 or 31 1271544
33 Adolescent/ 1516292
34 Adult/ 3718804
35 "Aged, 80 and over"/ or Aged/ 2178006
36 Frail Elderly/ 6054
37 Middle Aged/ 3098034
38 Young Adult/ 270659
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40 26 and 32 and 39 2849
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1 obesity/ 214299
2 adipose tissue/ 50870
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5 body weight/ 170391
6 obesity/ 214299
7 skinfold thickness/ 7675
8 obesity/ 214299
9 body mass/ 154657
10 body weight/ 170391

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11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 911104
12 Waist*.ab. or Waist*.ti. or Girth*.ab. or Girth*.ti. 30654
13 12 and 13 24491
14 exp abdominal fat/ 8458
15 anthropometry/ 34857
16 Body Fat Distribution/ 3600
17 Intra-Abdominal Fat/ 5801
18 Metabolic Syndrome X/ 39212
19 exp abdominal obesity/ 4435
20 Subcutaneous Fat, Abdominal/ 825
21 waist to height ratio/ 116
22 waist circumference/ 17938
23 waist hip ratio/ 5696
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26 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 109748
27 "cause of death"/ 61406
28 life expectancy/ 26713
29 exp mortality/ 582675
30 survival rate/ 131736

Death.ab. or Death.ti. or Fatal.ab. or Fatal.ti. or Fatality.ab. or Fatality.ti. or "life expectancy".ab. or "life expectancy".ti. or Mortality.ab. or Mortality.ti. or Survival.ab. or Survival.ti.

32 27 or 28 or 29 or 30 or 31 1785245
33 adolescent/ 1225322
34 adult/ 4372605
35 aged/ 2109888
36 frail elderly/ 4842
37 middle aged/ 1098046
38 33 or 34 or 35 or 36 or 37 5679868
39 26 and 32 and 38 3961

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