Author's response to reviews

Title: Gender differences in the association between adiposity and probable major depression: a cross-sectional study of 140,564 UK Biobank participants.

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Version: 2
Date: 30 January 2014

Author's response to reviews: see over
Dear Dr. Murray,

Research article
“Gender differences in the association between adiposity and major depression: a cross-sectional study of 140,564 UK Biobank participants”.

Thank you for agreeing with Dr. Claire Barnard, Senior Editor BMC Medicine to consider our manuscript for publication in BMC Psychiatry. We have revised the manuscript to take account of the reviewer’s comments and below are our point by point response to these comments.

Reviewer 1
Title: Gender differences in the association between adiposity and major depression: a cross-sectional study of 140,564 UK Biobank participants.
Version: 1 Date: 3 January 2014
Reviewer: Pim Cuijpers

Reviewer's report:

Comment: This paper examines the association between depression and obesity in a large sample, using different measures of obesity. The strength of the study is its large sample size, but there are also several weaknesses.

Comment: One important problem is that the representativeness of the sample is not clear. The sample size is indeed huge, but it is not clear how participants were recruited. I assume that this information is not given in order to keep the paper brief, but it is essential information. Without it, it is not possible to assess the representativeness of the sample.

RESPONSE
We have now added the following paragraph to the Methods, data source, line 2, page 6 and a supplementary figure 1 which shows the schematic of UK biobank invitation and appointment system.

“National Health Service (NHS), UK maintains the records of almost all individuals of the general population through general practitioners. Based on these records, about 5 million primary invitations were sent to the eligible participants who were living within a reasonable travelling distance from the assessment centres (see online supplementary figure 1). UK Biobank recruited 502,682 participants, aged 40-69 years, via 22 assessment centres across the United Kingdom between 2006 and 2010”.

Comment: What worries me is that the mean age is 57 years, with a SD of 8. That does not suggest that this is a very good representation of the population, because young people (<30) and very old people (>75) are
underrepresented. I am sure whether this is a true problem (because the numbers in other age groups are still large enough), but it should be described clearly by the authors.

**RESPONSE**
We have now added to our limitations, page 15, last paragraph;
“UK Biobank recruited middle and old aged individuals (aged 40 to 69 years) from the general population and so young people or very old people are underrepresented”.

**Comment:** The other main problem is the method to measure depression. Too bad that they did not use a normal standardized diagnostic interview to assess the presence of major depression. The measure they now use is clearly not adequate. Many people who are depressed never seek treatment for it. Furthermore, many people who seek treatment for nerves or anxiety also have a low mood, without meeting criteria for major depression. So, this measure is not adequate. It does give an indication of depression, but it is not the best way to assess depression. If they would have used the full PHQ-9 would have been better.

**RESPONSE**
This is a reasonable point and throughout the text (and within the title) of the revised manuscript we have used the term ‘probable major depression’ rather than ‘major depression’. We have also provided more detail on the criteria for probable major depression as well as possible limitations, as follows.

**On pages 8 and 9 of the revised manuscript:**
“Our classification of probable major depression was based on criteria published previously by our group [31]. We convened a series of meetings of Biobank-approved researchers focusing on mental health and cognition (membership DJS, JPP, DM, NC, JG, MH, BC, BN, DM, JE, ID and BR) and, after a number of iterations of proposed criteria, a definition for probable major depression was agreed. It should be noted that this approach represented a pragmatic synthesis of the data which was available to us as part of the UK Biobank baseline assessments and that the validity of this diagnosis is in part supported by differences between the probable depression group and controls in terms of gender distribution, socioeconomic status, self-reported health rating, current depressive symptoms and smoking status [31]. Probable major depression and current depressive symptoms were therefore defined using information from specific questions on the severity and duration of both depressed mood and anhedonia, questions on past help-seeking behaviour for mental health and answers to the Patient Health Questionnaire (PHQ) [32]. Participants were then classified as having probable major depression if they reported a lifetime history of having ever had either depressed mood for a period of at least two weeks or a period of at least two weeks of being unenthusiastic/disinterested (anhedonic); plus they had reported ever having seen a general practitioner or psychiatrist for ‘nerves, anxiety, depression” in the past. We included participants who reported one or more eligible episodes but participants with probable bipolar I or II disorders were excluded from this study.”

**On page 15, line 8 of the revised manuscript (limitations), we have added:**
“We also acknowledge that our definition of probable major depression is a pragmatic approach based on the data which were available to us rather than a formal structured diagnosis. As such, it is possible that we may have missed out some participants with a lifetime history of major depression who have never sought treatment for it. Further, a proportion of people who seek treatment for “nerves or anxiety” may also have had low mood and anhedonia without meeting full diagnostic criteria for major depression. For these reasons, we have been careful to classify participants in this study with significant depressive features as ‘probable major depression’ rather than formally diagnosed ‘major depressive disorder’.

**Comment:** Has the current method been validated and are data on sensitivity and specificity available?

**RESPONSE**
As noted above, our definition of probable major depression is a pragmatic approach to identifying individuals with clinically significant depressive symptoms rather than a formal diagnosis of major
depressive disorder derived from a structure diagnostic interview. To some extent, there is support for our definition in terms of sociodemographic variables, as published previously by our group (Smith, et al., (2013) Prevalence and characteristics of probable major depression and probable bipolar disorder within UK Biobank: Cross-sectional study of 172,751 participants. PLoS ONE, 8(11): e75362) but we acknowledge that the criteria we have used have not validated in terms of having data on sensitivity and specificity. However, this is likely to be possible in the future as Biobank participants are linked to routine medical records both retrospectively and prospectively.

**Smaller issues:**

**Comment:** p.5: none of the included studies were conducted in the UK: why is this relevant?

Plos Med is not a UK journal.

**RESPONSE**
This is now deleted from the manuscript.

**Comment:** p.8, third line: what is the difference between Asian and Chinese?

**RESPONSE**
We have now changed the text to;
“Ethnic group (white, mixed, Asian/Asian British [Indian, Pakistani, Bangladeshi], black/black British, Chinese and other)

**Comment:** p.9: a p-value of 0.05 does not seem adequate in such a large sample size.

**RESPONSE**
We have now changed the text to
“For the descriptive analysis the statistical significance was defined as p<0.001”.

**Comment:** p.10: it is not clear why information on depression was not available for almost 20% of the participants. Any systematic missings?

**RESPONSE**
We have addressed this point within our limitations section as follows (page 15, line 1):

“Inclusion in our study was limited to the participants who provided complete information on mood. Approximately 20% of participants provided some but not all of the answers to questions about depression, anhedonia, duration of symptoms and previous help-seeking behaviour and could not be classified with confidence as having a lifetime history of probable major depression or not. These individuals were more likely to be of normal-weight, men, younger, in employment, had a history of more alcohol use, were more socially deprived, more likely to be non smokers and did not report medical comorbidity as often as those participants who did not provide complete information.”

**Comment:** p.11, line 8: with evidence of a linear relationship. This is important information that can not be described as brief as this. How was this examined, and what were the exact outcomes?

**RESPONSE**
We have now added to page11, line 14;
“Nonetheless, participants classified as overweight or obese (class I, II or III) based on BMI still had significantly higher odds of having major depression, compared to normal weight participants, with evidence of a linear relationship. The odds ratios of major depression were; 1.09, 1.12, 1.21, and 1.39 (all p-value <0.001) for overweight, class I, II and III obese, respectively”.
Comment: p.13, line: being underweight was not associated with major depression. This worries me, as eating less than normal is one of the main symptoms of depression. Could this be the results of the method to define depression? Or maybe the selection of participants?

RESPONSE
We have mentioned in our limitation:
“Previously, we reported an association between being underweight and poor mental health, particularly in women. The lack of an association with underweight in this study may reflect a lack of statistical power due to smaller numbers in this sub-group, or may be due to the previous study using the General Health Questionaire (GHQ-12) which is a short screening instrument rather than a detailed assessment of mental health”.

Comment: p.13: here the authors refer to a study (Wiltink et al) who also used several methods to define obesity, while the main reason for the current study was that no earlier studies were conducted using several methods. This study should be described in the introduction and it should be made clear why the current study still is needed.

RESPONSE
We have now mentioned this study in our introduction;
“One recent, comparatively smaller German study (N=4907) examined the association between obesity and depression, using the continuous measure of BMI, WC and WHR but not the direct measurement of BF% (ref). Overall, there is a paucity of larger studies which used other than BMI measures in exploring this association”.

Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: I declare that I have no competing interests

Reviewer's 2 report
Title: Gender differences in the association between adiposity and major depression: a cross-sectional study of 140,564 UK Biobank participants.
Version:1 Date:22 January 2014
Reviewer: George P Chrousos
Reviewer's report:
This manuscript is well written and the data are from a very large population. The study reveals an association of obesity with major affective disorder. The data are compatible with findings of smaller studies.

Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: No competing interests

RESPONSE
Thank you very much for the favourable comments.
Supplementary Figure 1. Schematic of UK biobank invitation and appointment system