Author's response to reviews

Title: Revisiting the J shaped curve, exploring the association between cardiovascular risk factors and concurrent depressive symptoms in patients with cardiometabolic disease: Findings from a large cross-sectional study.

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Author's response to reviews: see over
Dear Editor,

Thank you for considering the aforementioned manuscript for publication in BMC Medicine. We would like to take up the offer of submitting a revised version of the manuscript. We would like to thank the reviewers for their useful reviews and feedback, which we believe have improved our paper. We have now made significant changes to the background and discussion section of this manuscript in response to comments from reviewers. We have also performed additional linear regression analysis as suggested by reviewers. We feel this is an influential piece of work and in its revised version will be of interest to a range of readers across various settings such as cardiologists, primary care physicians, geriatric physicians and mental health specialists; hence it is suitable for a general medical journal such as BMC Medicine. Please find our response below to each of the reviewer comments.

This is a large cross-sectional population study examining the association between cardiovascular risk factors and concurrent depressive symptoms in patients with cardiometabolic disease. Despite the size of the study, I have several problems with it.

The Introduction is unclear and does not lead to a clear research question. The authors say in the first paragraph that depression is an important problem, and then spend the rest of the introduction to describing blood pressure, BMI, etc. But there is a large literature on the association between these problems and depression (see my later comment). The authors should have described this literature and then what this study could add to the knowledge from this earlier research. But they just say that they examine the association between these problems and depression.

Authors’ Response: We would like to thank the reviewer for his comments. We have now made significant changes to the ‘Introduction’ section. We have added an extra paragraph in the introduction section describing the association between cardiovascular risk factors and
depression. We have also shortened the Introduction summary on various guidelines for the treatment of cardiovascular risk factors aimed at primary prevention of cardiovascular events.

Changes to Manuscript (Background>Page5>2nd Paragraph):

The relationship between depression and traditional cardiometabolic disease risk factors such as obesity, hypertension, hyperlipidaemia and raised HbA1c have been studied extensively in general population. Depression is noted to have a significant positive association with obesity in general population, with a stronger association noted in females [12, 13]. In addition, evidence from longitudinal studies show that depression may have a bi-directional relationship with obesity [14]. Results from a meta-analysis of prospective cohort studies shows that depression increases the risk of hypertension incidence in the community [15]. A contradictory relationship has been observed between depression and hyperlipidaemia in elderly men and women in the community; with increased prevalence of depressive symptoms observed with low levels of high density lipoprotein cholesterol (higher atherogenic risk) in women and with low levels of low density lipoprotein cholesterol (lower atherogenic risk) in men [16]. In a prospective study of older adults in a general population, the probability of depression increased with raised HbA1c [17]. However, most of the evidence in this area has come from a general population and there is a paucity of research from patients with diagnosed cardio-metabolic diseases who are likely to be subjected to treatment to reduce these risk factors. The potential effects of lowering these factors with treatment on prevalence of depressive symptoms remain unclear.

Changes to Manuscript (Background>Page 6>3rd Paragraph): (This section was removed from the manuscript).
References have no year and are incomplete, so I cannot verify them.

Authors’ Response: We do apologise for this error, we have identified that there were some references in the bibliography without the information on year of publication. In the revised manuscript, all the reference citations are complete as per journal guidelines for the same.

This study has several more important limitations than the authors mention. No diagnosis of depression was available (only self-report), this was a cross-sectional study making causal assumptions impossible, etc.

Authors’ Response: We agree with the reviewer that the reliability of self-reported symptom scale such as HADS-D in the assessment of depressive symptoms is an important limitation of this study. We have added this to the limitations section. We have also highlighted that it is not possible to make causal assumptions from the findings of this study.

Changes to Manuscript>Discussion>Strengths and Limitations>1st Paragraph>Page15:

This study has a number of key strengths, in that the data came from a large, community based sample, reflecting real life clinical practice. There are several limitations. As the study was based on cross-sectional analysis, it is not possible to make causal inferences from the findings of this study. It is unclear whether the observed association of low levels of cardiovascular risk factors with depressive symptoms is causal or simply an effect of the underlying disease (i.e. reverse causality).

Changes to Manuscript>Discussion>Strengths and Limitations>3rd Paragraph>Page17:

Finally, the overall accuracy of depression screening in our study was reliant on HADS-D which is a self-reported measure and it is not a gold standard measure for assessing depressive symptoms in patients with chronic disease in a primary care setting [56].
In the discussion the authors say that there is little research in the general population on the relationship between cardiovascular risk factors and depression. They have not looked properly in the literature.

Authors’ Response: We agree that this statement is erroneous and we have now removed this from the manuscript.

There is a lot of research on the association between depression on the one hand and obesity, BMI, exercise, smoking and smoking cessation on the other. The authors should have done their homework better.

Authors’ Response: We have now discussed the potential impact of biobehavioural risk factors on the findings of this study and as this information is incomplete in our dataset, we have discussed that as an important limitation.

Changes to Manuscript: >Discussion >Strengths and Limitations >Page16>2nd Paragraph:

Secondly, we did not have complete information on health related behaviours such as smoking status, alcohol intake and amount of physical activity; and no information on disease severity or cardiovascular medications. Biobehavioural factors such as smoking status and participation in smoking cessation interventions, alcohol intake and levels of physical activity are likely to influence the values of clinical measures considered, and also the presence of depressive symptoms is likely to influence these behavioural factors as well as the patient’s likelihood of having depressive symptoms [50–53].

- Major Compulsory Revisions
1. The link between depressive symptoms and cardiovascular disease risk is well known and well documented in the literature. This relation has been observed in community samples and patient populations, with some evidence that the relation actually is stronger in patients. It also is understood that there can be no one “exact physiological mechanism explaining the relationship between depression and cardiometabolic diseases.” Therefore, a more compelling rationale for this study is requested to inform readers more clearly of the unique contributions of these analyses.

Authors’ Response: We agree with the reviewer that the Introduction section did not set a compelling rationale. We have therefore made significant changes to Introduction and justified the need for answering our research question in a better way.

Changes to Manuscript>Background>Page 5>1st Paragraph: Various theories have been hypothesised to explain the link between depression and adverse outcomes, for example, increased platelet activation [8], low heart rate variability [9], higher levels of chronic inflammation[10] and insulin resistance [11], but further research is needed and there may be an overlap between these hypotheses.

Changes to Manuscript>Background>Page5>2nd Paragraph: The relationship between depression and traditional cardiometabolic disease risk factors such as obesity, hypertension, hyperlipidaemia and raised HbA1c have been studied extensively in general population. Depression is noted to have a significant positive association with obesity in general population, with a stronger association noted in females [12, 13]. In addition, evidence from longitudinal studies show that depression may have a bi-directional relationship with obesity [14]. Results from a meta-analysis of prospective cohort studies shows that depression increases the risk of hypertension incidence in the community [15]. A contradictory relationship has been observed between depression and hyperlipidaemia in elderly men and
women in the community; with increased prevalence of depressive symptoms observed with low levels of high density lipoprotein cholesterol (higher atherogenic risk) in women and with low levels of low density lipoprotein cholesterol (lower atherogenic risk) in men [16]. In a prospective study of older adults in a general population, the probability of depression increased with raised HbA1c [17]. However, most of the evidence in this area has come from a general population and there is a paucity of research from patients with diagnosed cardio-metabolic diseases who are likely to be subjected to treatment to reduce these risk factors. The potential effects of lowering these factors with treatment on prevalence of depressive symptoms remain unclear.

2. The authors acknowledge the low uptake of depression screening but I find it troubling that less than 1/3 of those eligible were screened. Per supplementary Table 1, those screened were older, more likely to be male and somewhat healthier than those who were not screened. I would like to see a discussion of how this may have influenced results; e.g., women tend to report more depressive symptoms and score higher than men on HADS-D and similar depression screening instruments. Additionally, is there any information on factors that may have contributed to the low screening rates that could also have influenced the data (e.g., biases at particular clinics in terms of who “needs” screening).

Authors’ Response: We agree with the reviewer that the low uptake of depression screening in our study remains an important limitation. We have now acknowledged that as an important limitation and expanded on possible barriers for depression screening in the primary care setting for patients with chronic disease.

Changes to Manuscript>Discussion>Strengths and Limitations>2nd Paragraph>Page 16: There may be important differences between patients with known depression status and those
whose depression status was unknown, which are not clearly evident from their baseline demographic data. Practitioners may intuitively screen those patients where they are more likely to get a positive result, for instance patients with multimorbidity. Also, there is a possibility of reverse causality with GPs reviewing a patient whom they consider to have depression and offering screening subsequently. Previously reported barriers to discussing depression (or mental health) in patients with chronic disease in primary care, such as stigma associated around the ‘label’ and physicians’ preconception of normalizing depression in patients with chronic disease, could be influencing factors behind low uptake of depression screening in our study [54, 55].

3. Looking at Figure 2, with its 4 panels, it appears the strongest J-shaped relation is for BMI, with a J-shape also evident for SBP but much less of a J-shape for either DBP or total cholesterol. This is not what the text describes, however, which implies a clear and strong J-shape association of each of these 4 CVD risk factors with HADS-D scores. Please clarify.

Authors’ Response: We would like to apologise for this oversight. We have now made changes to the results and discussion section to reflect that the observed non-linear relationship for DBP and total cholesterol with depressive symptoms was weaker.

Changes to Manuscript>Abstract>Results>Page3: SBP and BMI noted to have a non-linear “J-shaped” relationship with the probability of having a positive HADS-D and observed nadirs (levels with the lowest probability) of 148 mm Hg and 30.70 kg/m2, respectively. Total cholesterol and DBP found to have a weaker curvilinear association with concurrent depression symptoms and nadirs of 3.60 mmol/l and 74 mmHg.

Changes to Manuscript>Results>Blood Pressure, Total Cholesterol, Body Mass Index and Depression>Page 12: However, the shape of the J-curve was shallow for DBP when compared with SBP.
The relationships were ‘J-shaped’ with high levels of SBP and BMI associated with greater levels of concurrent depressive symptoms, but with the lowest levels also associated with depressive symptoms. DBP and total Cholesterol had a similar but weaker relationship with depression.

In a general practice sample of patients with CHD, stroke, or diabetes, depressive symptoms were found to have a strong curvilinear association with SBP, DBP, BMI, and HbA1c; and a weaker curvilinear association with total cholesterol and DBP.

4. Please present associations of the CVD risk factors with the continuous HADS score. While “7” may be a typical cut-point used with HADS, it is nonetheless arbitrary. It is important to know if increasing CVD risk is associated with increasing depressive symptoms.

Authors’ Response: We have now performed extra analysis which includes linear regression models with continuous HADS-D scores and each individual cardiovascular risk factor considered in our study. We have given an overview of the model in the methods section and summarised the results. The details of each regression model are presented as supplementary material.

We also performed multiple linear regression analysis with HADS-D as a continuous scale. Five separate regression models were used to examine the impact of each individual clinical risk factor (SBP, DBP, total cholesterol, BMI, HbA1c) on HADS-D as a continuous scale after excluding extreme values for each clinical measure as defined above. Quadratic terms for each clinical measure and other predictor variables, such as age, sex, socio-economic status and number of co-morbid conditions were added to the linear regression model as described above. Cubic terms were tested for each clinical measure. The
turning point or the “nadir” was calculated using the same formula described in the preceding section.

Changes to Manuscript>Results>Supplementary and Sensitivity Analysis>2nd Paragraph>Page 14: The five clinical measures had a non-linear relationship in the respective linear regression models, after adjusting for age, sex, socio-economic status and number of co-morbid conditions. The observed nadirs for SBP, DBP, total cholesterol and BMI were 145 mm Hg, 78 mm Hg, 3.41 mmol/l and 30.25 kg/m2 respectively. The observed nadir for HbA1c in patients with diabetes was 6.21 DCCT (44.4 mmol/mol IFCC). The value for HADS-D increased with increase in value of these clinical measures above their respective nadirs but it increased with decrease in value below these observed nadirs. There were no significant cubic terms. The results of each linear regression are presented in detail in the supplement “S2-Regression Analysis”.

Change to Manuscript>Discussion>Summary of Findings>Page 15: Multiple linear regression analysis with HADS-D as continuous scale showed a similar non-linear relationship between depressive symptoms and these clinical measures.

5. I do not quite follow the logic of the argument urging care with aggressive lowering of CVD risk factors. Perhaps clarifying that an "optimal risk factor level" may need to be considered that is not just the lowest possible value of BP or BMI or cholesterol would help solidify this argument. And what about the case when an "optimal" value differs if the outcome considered is MI, for example, versus clinically manifest depression?

Authors’ Response: We have discussed the need to define optimal risk factor levels in our discussion section which we have revised based on the reviewer’s suggestion.
Changes to Manuscript>Discussion>Implication of Findings>Page 18: There may be a need to define an optimal level of these cardiovascular risk factors below which there is increased risk of adverse clinical outcomes, however such optimal levels could vary depending on individual risk of adverse physical outcomes such as vascular events, death and risk of depressive symptoms.

- Minor Essential Revisions

1. “Incidence” of high depressive symptoms is used erroneously at least twice when prevalence is the correct term; the study did not look at incident depression. But it does raise the question of whether depression history was ascertained for the patients? This would be a strong predictor of future depressive episodes so lack of such information should be an acknowledged limitation.

Authors’ Response: We have changed the term “Incidence” to “Prevalence” as suggested by the reviewer. We have also acknowledged the limitation suggested by the reviewer.

Changes to Manuscript>Methods>Statistical Analysis>Page10: Multiple logistic regression was used with the outcome variable as the prevalence of a positive screening for depression (defined as HADS >7).

Changes to Manuscript>Discussion>Comparison with Existing Literature>2nd Paragraph>Page18: Similarly, increased prevalence of depressive symptoms has been observed with extreme low values of total cholesterol [67, 68] and HbA1c in the general population samples [69].

Changes to Manuscript>Discussion>Strengths and Limitations>3rd Paragraph>Page 17: We also did not have information on history of previous episodes of depression for patients in our study which may influence the prevalence levels for depressive symptoms.
2. Please define "DCCT"

Authors’ Response: We have defined DCCT and added this to the manuscript.

Changes to Manuscript>Methods>Measurement of Clinical Risk Factors and Outcome Variable>Page9: A blood sample was collected by the practice nurse at the time of assessment; the result for total cholesterol was reported in mmol/l and HbA1c was reported in Diabetes Control and Complications Trial (DCCT) units, in other words reported as a comparison to the number obtained by the instruments used to measure HbA1c in the Diabetes Control and Complications Trial [42].

3. "Obese" category should be BMI = or > 30 kg/m2, rather than 35 kg/m2.

Authors’ Response: Thank you for this comment. We have now updated the text in line with the reviewer’s comments.

Changes to Manuscript>Discussion>Comparison with Existing Literature>1st Paragraph>Page 17:

A systematic review of 40 studies in patients with CHD showed that overweight (BMI 25-29 kg/m2) and obese individuals (BMI 30-35 kg/m2) had lower risk of all cause and cardiovascular mortality at 3.8 mean years of follow-up, when compared to those with normal BMI (20-25 kg/m2), underweight BMI (<20 kg/m2), and very obese BMI (>35 kg/m2) [59].

We look forward to hearing your decision on our revised manuscript in due course.
Yours sincerely