Author’s response to reviews

Title: Does Presence of Metabolic Syndrome Impact Anxiety and Depressive Disorder Screening Results in Middle Aged and Elderly Individuals? A Population Based Study

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Author’s response to reviews:

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Dear Editor,

Please find attached the revised manuscript entitled "Does Presence of Metabolic Syndrome Impact Anxiety and Depressive Disorder Screening Results in Middle Aged and Elderly Individuals? A Population Based Study" for publication in BMC Psychiatry and the answers to Editorial and Reviewers comments.

This revision of the manuscript has been approved by all other co-authors of the manuscript.

We look forward to hearing from You.

Yours sincerely,

Jurate Butnoriene, MD, PhD
Editorial Comments:

This generally well-written manuscript investigating if metabolic syndrome (MetS) has an impact on the accuracy of current major-depressive disorder and generalised anxiety disorders using the Hospital Anxiety and Depression scale (HADS). Based on ROC analyses, the authors conclude that the optimal threshold for the HADS-Depression sub-scale is a score ≥9 for individuals with MetS and ≥8 - without MetS. The optimal thresholds for the HADS-Anxiety sub-scale are ≥9 for current GAD in individuals with and without MetS.

Main comments:

There is a debate in literature about the validity of the metabolic syndrome definition criteria. Please refer to this in your paper.

Answer: In Discussion section, final paragraph (page 14), we included a discussion regarding MetS diagnostic criteria and provided recommendations for future studies:

„There is a debate in literature about the validity of the metabolic syndrome definition criteria. We used the MetS definition proposed by the WHO that considers insulin resistance as the cardinal MetS feature and is among the most widely studied MetS diagnostic criteria. However, studies examining potential impact of the MetS diagnosed using other more commonly used sets of diagnostic criteria for mental disorder screening can be attempted. “

The actual message on why we need different thresholds for those with metabolic syndrome and without is not well justified in this manuscript.

Answer: we have restructured the Background section, last paragraph of the paper (lines 84-99), discussing why different threshold of depression/anxiety screening may be needed for patients with metabolic syndromes.
Assuming that one accepts the definition of metabolic syndrome, given that it could simply be just a clustering of risk factors- please discuss the biological mechanisms between these and depression, taking into account the role of commodities in population aged 60+.

Answer: As suggested by the reviewer we have significantly expanded Background section discussing potential overlapping biological/behavioral mechanisms of MetS and Depression:

“An accumulating body of evidence suggests that biological mechanisms underlying the MetS and MDD can overlap. For example, chronic stress, hyperactivity of hypothalamic-pituitary-adrenal (HPA) axis, noradrenergic dysregulation, inflammatory cytokines and endothelial dysfunction were implicated in both MDD and MetS. Furthermore, behavioral changes attributed to MDD, such as smoking, physical inactivity and sleep disturbances, can also contribute towards the development of MetS. On the other hand, metabolic disturbance in MetS patients may contribute to impaired brain functioning and development of GAD, MDD and other affective disorders”.

Abstract

p2. line 32. Please remove the word "current" from the second sentence "We investigated if current..

Answer: the word was removed.

Add a final line emphasising the importance of this work p.2 line 49.

Answer. It was added at the end of the abstract (lines 51-52): “The presence of MetS should be considered when interpreting depression screening results “.

Materials and methods section

p.4 lines 97-100 Move these lines at the end of this section after reference 47 (p.4 line 113).

Answer: the section was moved.

Assessment of the MetS  p.5 line 141

I suggest to use an extra reference for diagnosis (e.g. Kaur, 2014).
Answer: the reference was added:


I suggest to use the word "thresholds" instead of "cutoff scores" everywhere in the manuscript.

Answer: the term was changed throughout the manuscript.

Statistical analyses

ROC curves

The estimate of the area under the ROC curve can be computed either nonparametrically or parametrically using a binegative exponential model. Please include the appropriate details. p.6, line 155

Answer: Details are included on P.6, line 164: “The estimate of the area under the ROC curve was computed nonparametrically”.

Discussion:

P.11 line 222

Please change " were older" with "slightly older" as the difference between 63 and 61 yrs. is rather small.

Answer: were changed.

You may wish to emphasise slightly more the sensitivity and specificity for the proposed thresholds.

Answer: As suggested by the reviewer we emphasized sensitivity and specificity of the proposed thresholds in the Conclusions section (lines 307-310).
Please discuss the role of lifestyle behaviours (alcohol, smoking) and socioeconomic markers (employment status) and urban versus rural area.

Answer: As suggested we have expanded our discussion on lifestyle behaviours and socioeconomic markers in Discussion (new paragraph on Page 13, lines 267-272):

“In the present cohort, patients with MetS were more likely to be retired/disabled, live in urban area, report less physical activity and greater alcohol consumption. These socioeconomic, environmental and behavioral markers were also linked to depressive disorders [68] indicating that common mental disorders and MetS share environmental risk factors. Better understanding of common features underlying common mental disorders and MetS could potentially help to identify vulnerable populations, and to develop more accurate recognition strategies and effective interventions leading to reduced global burden of the two disorders.”

A new reference No.68 was included:


Reviewer reports:

Aradhna Kaushal (Reviewer 1):

General Comments

This paper reports whether screening results for depression and anxiety disorder differ if patients have metabolic syndrome. These findings could have implications for primary care and could reduce false positive screening results. More work is needed on this paper to justify the methods that they use and a deeper discussion on explaining their findings.

Introduction

There is quite a bit in the introduction about how GAD and MDD are under diagnosed in primary care. I can see how this is a public health concern but it needs to identify the research
gap this paper addresses more specifically i.e. will understanding how MetS can impact screening help identification of GAD and MDD?

Answer: We have substantially modified the Background section (page 3, lines 76-83, 85-89) and provided more information and research gaps explaining bidirectional association between the two disorders, by analyzing biological mechanism and co-morbidities underlying the two disorders.

A more comprehensive description of metabolic syndrome is needed. Currently there it is described as "a cluster of cardiovascular disease and type-2 diabetes risk factors". What are these risk factors? How are they diagnosed? What is the prevalence of MetS?

Answer: Discussion section, lines 295-298:

“There is a debate in literature about the validity of the metabolic syndrome definition criteria [72, 73]. We used the MetS definition proposed by the WHO that considers insulin resistance as the cardinal MetS feature and is among the most widely studied MetS diagnostic criteria”.

What are the somatic symptoms which overlap with GAD and MDD? More about the relationship between MetS and depression is needed here, particularly in relation to bi-directional associations. Aside from line 80-81 they are discussed as concurrent and independent health problems.

Answers: on page 3, lines 76-83:

“Significant co-morbidity and bi-directional association of MetS with depressive and anxiety disorders is well-documented [34-39]. An accumulating body of evidence suggests that biological mechanisms underlying the MetS and MDD can overlap. For example, chronic stress, hyperactivity of hypothalamic-pituitary-adrenal (HPA) axis, noradrenergic dysregulation, inflammatory cytokines and endothelial dysfunction were implicated in both MDD and MetS [40]. Furthermore, behavioral changes attributed to MDD, such as smoking, physical inactivity and sleep disturbances, can also contribute towards the development of MetS. On the other hand, metabolic disturbance in MetS patients may contribute to impaired brain functioning and development of GAD, MDD and other affective disorders [41, 42].
New references were added:


And on page 3, lines 85-89.

“However, the MetS is highly co-morbid with other somatic conditions and complaints especially in middle aged and elderly patients [43]. Symptoms of co-morbid cardiovascular disease, diabetes and obesity (such as fatigue and sleep impairment) can overlap with symptoms included in depressive/anxiety self-rating scales leading to impaired recognition of mental disorders and high false positive screening rates by including patients reporting symptoms that are caused by MetS rather than mental disorder.”

What were your hypotheses about how MetS would be related to screening based on previous research? Did you expect different results for GAD and MDD (especially considering reference 40 "Depression but not anxiety associated with metabolic syndrome in primary care")?

Answer: We expected that MetS would “inflate” self-reported depression screening resulting in greater cut-off value in patients with versus without MetS.

We included the study hypotheses, last sentence of the Background:

“We hypothesised that due to overlap of MetS-related symptoms with depression, optimal depression (but not anxiety) screening threshold value would be greater in patients with MetS versus patients without MetS.”
Methods

Methods seem appropriate for research question.

Did you formally test for differences between responders and non-responders? These data could be included in supplementary materials.

Response: As suggested by the reviewer we included a statement about responders and non-responders (Methods section, p. 4, lines 106-108):

“Women who did not respond to the study invitation letter were older when compared to women that were studied (p < 0.05). Other socio-demographic characteristics were similar between responder and non-responders”

Describe in more detail how you determined optimal cut-off score.

Answer: Statistical analyses section, p 6. Lines 164-170:

“The optimal HADS-D and HADS-A thresholds correctly identifying individuals with MDE and GAD, respectively, were determined as the values that gave the closest to the ideal point on the ROC curve, i.e. that made the resulting binary prediction as close to the perfect predictor as possible. [55]. A perfect predictor is represented by a point in the upper left corner in the plot and has 100% sensitivity and 100% specificity. The distance between this optimal point and the ROC curve is estimated using the Euclidean distance. The minimal Euclidean distance indicates the point on the ROC curve with the optimal threshold value”.

Results

You don't report NPVs or accuracy in the results.

Answer: NPVs and accuracy values of each of the examined threshold values are presented in Tables 2 and 3. We did not include these measures in the text as to limit our presentation to key psychometric data.
Discussion

Line 214: Why do self-reported instruments increase probability of false-positive screening result? How this relates to your findings needs to be clearer.

Answer: We have significantly expanded the sections by providing more detailed explanation underlying increased probability of false positive screening results in the Background section (pages 3-4, lines 85-92):

“However, the MetS is highly co-morbid with other somatic conditions and complaints especially in middle aged and elderly patients [43]. Symptoms of co-morbid cardiovascular disease, diabetes and obesity (such as fatigue and sleep impairment) can overlap with symptoms included in depressive/anxiety self-rating scales leading to impaired recognition of mental disorders and high false positive screening rates by including patients reporting symptoms that are caused by MetS rather than mental disorder. Indeed, previous studies indicated stronger association of MetS with depression evaluated using self-rating scales when compared to structured clinical diagnostic interviews [31, 44]. Therefore, different thresholds of depression/anxiety screening may be needed for patients with co-morbid MetS.”

and in Discussion section (page 12, lines 226-234):

“Optimal thresholds of the HADS-D for current MDE screening was higher in participants with MetS, relative to participants without MetS. These findings suggest that somatic symptoms attributed to conditions co-morbid with MetS can overlap with depressive symptoms and consequentially inflate the total HADS-D score. For example, central obesity is among the cardinal MetS features that can cause symptoms similar to depressive disorders, such as general tiredness, fatigue and lower ability to perform physical activity. Consequentially patients with MetS can rate “feeling of slowed down” item of the HADS-D subscale due to obesity rather than depression. From social perspective, obese patients could have lower self-esteem resulting in decreased enjoyment in the social activities [57] and therefore increase rating of the HADS-D subscale items “the ability still enjoy the things, were used to enjoy” and “the loose of interest in personal appearance”.

A limitation of this research is the cross-sectional nature design. There needs to be further discussion about the bi-directional associations between MetS, and GAD and MDD are related to each other.
Answer: The bi-directional associations between MetS, GAD and MDD were discussed in Background section (page 3, lines 76-83) and Discussion section (page 13, lines 227-237 and page 14, lines 261-265):

“Significant co-morbidity and bi-directional association of MetS with depressive and anxiety disorders is well-documented [34-39]. An accumulating body of evidence suggests that biological mechanisms underlying the MetS and MDD can overlap. For example, chronic stress, hyperactivity of hypothalamic-pituitary-adrenal (HPA) axis, noradrenergic dysregulation, inflammatory cytokines and endothelial dysfunction were implicated in both MDD and MetS [40]. Furthermore, behavioral changes attributed to MDD, such as smoking, physical inactivity and sleep disturbances, can also contribute towards the development of MetS. On the other hand, metabolic disturbance in MetS patients may contribute to impaired brain functioning and development of GAD, MDD and other affective disorders [41, 42].”

“These findings suggest that somatic symptoms attributed to conditions co-morbid with MetS can overlap with depressive symptoms and consequentially inflate the total HADS-D score. For example, central obesity is among the cardinal MetS features that can cause symptoms similar to depressive disorders, such as general tiredness, fatigue and lower ability to perform physical activity. Consequentially patients with MetS can rate “feeling of slowed down” item of the HADS-D subscale due to obesity rather than depression. From social perspective, obese patients could have lower self-esteem resulting in decreased enjoyment in the social activities [57] and therefore increase rating of the HADS-D subscale items “the ability still enjoy the things, were used to enjoy” and “the loose of interest in personal appearance”. Similar findings were reported in a systematic review and meta-analysis of epidemiological studies done by Pan et al., [31], showing that the use of self-reported instruments for evaluation of depressive symptom severity among subjects with MetS allows inclusion of patients who do not meet the DSM diagnostic criteria of current MDD and consequentially increase probability of false-positive screening results.”

“These findings suggest that in MetS population, non-CVD related symptoms and other comorbid non-CVD disorders can account for inflation self-reported depressive symptom severity. In patients with diabetes, glucose metabolism impairment can also account for greater self-reported depressive symptom severity because it is known that greater self-perceived depression among patients with MetS is associated with larger waist circumference among women and with elevated plasma glucose concentration among men [67].”
Are there any studies investigating this? Is there a way to tell if somatic symptoms are from MetS or GAD, or both? There also needs to be a discussion about mechanisms.

Answer: To our knowledge this is the first study, evaluating potential impact of MetS for depression screening. Based on our study designs we are unable to exactly clarify which symptoms were due to mental disorders or MetS. Future studies should attempt to elucidate that by performing in-depth interviews and symptom factorial analyses among other potential methods.

Somatic symptoms from both -MetS and MDD were discussed on page 12, lines 228-234:

“For example, central obesity is among the cardinal MetS features that can cause symptoms similar to depressive disorders, such as general tiredness, fatigue and lower ability to perform physical activity. Consequentially patients with MetS can rate “feeling of slowed down” item of the HADS-D subscale due to obesity rather than depression. From social perspective, obese patients could have lower self-esteem resulting in decreased enjoyment in the social activities [57] and therefore increase rating of the HADS-D subscale items “the ability still enjoy the things, were used to enjoy” and “the loose of interest in personal appearance”.

As reported before, the bi-directorial mechanisms between MetS and MDD discussed in Background section (page 3, lines 76-83) and Discussion section (page 13, lines 227-237 and page 14, lines 261-265).

Our findings suggest that: “GAD symptoms do not overlap with symptoms of MetS and MetS related co-morbidities” (page 14, lines 281-282).

Line235-241 Are there any comparable studies looking at just type-2 diabetes and optimal cut-off scores?

Answer: To our knowledge, there are no studies specifically evaluating psychometric properties of the HADS as a function of diabetes, but (page13, lines 263-266):

“In patients with diabetes, glucose metabolism impairment can also account for greater self-reported depressive symptom severity because it is known that greater self-perceived depression among patients with MetS is associated with larger waist circumference among women and with
elevated plasma glucose concentration among men [67]. Studies examining potential impact of co-morbid diabetes on depression screening results should be attempted.”

Tables and Figures

Tables are well presented.

A plot of the final ROC curves in addition to the tables would be useful.

Answer: the ROC curves were added (Figure 1 and Figure 2).

Abstract

Line 32 needs to be re-worded to clarify that these are screening tools.

Answer: clarified.

Readability

There are minor grammatical errors which sometimes obscures meaning. It will need to be carefully proofed and edited.

Answer: the grammar was reviewed and corrected throughout the manuscript.

Luis Miquel Martin Lopez (Reviewer 2):

You only choose 45-year-old population, why?

Answer: We chose this patient population because the prevalence of MetS increases with age which was the study focus.

Why uses only HADS scale and does not add another scale often used in primary care, like PHQ and standar like Hamilton. In this way you could compare
Answer: We selected to evaluate the HADS scale because it is reliable and brief, self-rated scale, composed of statements relevant to both GAD and MDD and is commonly used in primary care for screening purposes.

We agree that the HADS and PHQ are both quick and reliable, patients self-rated screening tools. But we selected to evaluate the HADS, due to it’s advantage be composed of statements relevant to both – either depression and anxiety for primary care patients and for general population.

One study compared HAD-S and PGQ-9 in patients with diabetes: in this study PGQ-9 showed more false-positive results due to diabetes-related symptoms or sleep disorders.


Using the Hamilton Anxiety rating scale or Hamilton Depression rating scale, the patient should be rated by a clinician: it is not self-rating tools. The use of Hamilton scales in primary care takes additional time for GPs and in the reason these scales could not be used as screening instrument for all primary patients visiting GPs.

We included this among the study limitations and recommend that other scales should be investigated in future studies (in Discussion section, page 14, lines 288-301):

“We evaluated psychometric properties of one scale (the HADS) that is commonly used for screening purposes in clinical setting. Psychometric properties of other commonly used depression screening scales, such as the Patient Health Questionnaire, remain to be investigated in patients with MetS.”