Author's response to reviews

Title: Association of Body Mass Index, Sagittal Abdominal Diameter and Waist-Hip Ratio with Cardiometabolic Risk Factors and Adipocytokines in Arab Children and Adolescents

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Author's response to reviews: see over
1. While this version of the manuscript is much improved over previous versions, it still remains that the vast majority of children tested in this study are normal weight and healthy. Only 28.4% of the population was overweight or obese. They had normal glucose, lipids, and insulin levels. It is difficult to determine how these data might be useful in a high risk population. It is mentioned that MetS is higher in the region, but what risk factors are present in these children? Obesity is an obvious risk factor, but only around 1/4 of the subjects tested was obese. Do the children have significant family history of cardiometabolic disease? This was not delineated, but would be helpful to the case. Although the sub-classes were removed due to small numbers, recruitment of more overweight and obese subjects to compare with the normal weight healthy controls would strengthen the paper.

Response:
The authors acknowledge this comment. We emphasize that the aim of the paper was to associate SAD to anthropometric and metabolic parameters in an apparently healthy cohort of children. To have a prevalence of 28.4% of overweight and obese children at random selection should also not be overlooked as that would translate to 1 out of 5 Saudi children having increased body mass index. Analysis was done collectively and not in subgroups as previously suggested during the 2nd round of review.

2. In the Abstract, Results section, the sentence is not complete. Perhaps consider adding the work "and" after WHR.

Response:
This comment is well noted. The sentence was revised which now reads: "BMI was superior to SAD as well as WHR, and had the highest number of significant associations to MetS components ..."

3. In the last sentence of the Background, the primary aim of the study was not to correlate SAD with indices of cardiometabolic risk and adipocytokines. While this was a secondary aim, the primary aim of the paper was to compare the 3 anthropometric measures in regard to which had the most associations cardiovascular disease and adipocytokines. Please revise.

Response:
This comment is well noted. The last paragraph of the background was revised which now reads "Thus, the present study aims to determine the superior marker of obesity through comparisons of SAD, BMI, WHR in terms of association strength with metabolic risk factors and levels of circulating adipocytokines in a cohort of Saudi children"
4. In the Methods section under anthropometry, please define Cole and colleagues’ definition of BMI, and remove the last sentence of the paragraph.

Response:
Reviewer request is appreciated. Cole and colleagues’ definition of BMI was added and the last sentence of the paragraph was removed.

5. In the discussion section, last paragraph, the sentence beginning with "Furthermore" needs to be removed as it no longer applies since no groupings were included in this version of the paper.

Response:
This comment is well noted. The sentence for subject grouping was removed.

Minor Essential Revisions

1. In the Abstract, Methods, Components should be added after MetS as MetS was not diagnosed in this study, but the components were assessed individually for associations with the anthropometric measures.

Response:
Reviewer request is appreciated. The abstract and methods sections was revised and the word components was added after MetS

2. In the Background, second paragraph, visceral fat is predictive of cardiometabolic risk, but does not indicate the degree of cardiometabolic risk. Please revise.

Response:
This comment is well noted and corrected in the revised version.

3. In the Methods section, KSU is used in the first sentence, but not defined until the third. Please correct.

Response:
This comment is well noted and corrected in the revised version.

4. In Methods, last sentence, again add components after MetS.

Response:
Reviewer request is appreciated. Methods sections was revised and the word components was added after MetS

5. In Methods, Blood Chemistry, seventh sentence, after Luminex please add Multiplex Assay.

Response:
This comment is well noted and corrected in the revised version.
6. In the Results section, first paragraph, next to last sentence, please reword as follows"... and retained blood pressure, lipids, glucose, and leptin after adjustment for age and gender."

Response:

This comment is well noted. The first paragraph of the results section was revised which now reads "BMI z-score on the other hand, had the highest number of significant associations, and retained blood pressure, lipids, glucose, and leptin after adjustment for age and gender."

7. In the Results section, second paragraph, last sentence, please reword as follows "...waist-hip ratio was significant in glucose, 2 or more components of MetS and MetS itself."

Response:

This comment is well noted. The first paragraph of the results section was revised which now reads "Lastly, waist-hip ratio was significant in glucose, two or more components of MetS and MetS itself."

8. In the Discussion section, second paragraph, it would be helpful to address the associations that were different between BMI and SAD. SAD had more associations with the adipocytokines, so may have a different predictive value than BMI.

Response:

The comment was noted and the discussion was revised accordingly.

9. In the Discussion section, second paragraph, in the sentence starting with "Furthermore" please clarify that those statistics were from adult studies not children.

Response:

This comment is well noted and data from adult studies were clarified.

10. In the Conclusion, please remove the words "predictive power" as no long terms studies have been done to base predictive power on.

Response:

This comment is well noted . The word predictive power was removed

Discretionary Revisions

1. In Table 3, consider bolding the significant values in the Asymptotic Significance category.

Response:

The significant values were highlighted as suggested.
Reviewer # 2

The specific primary concerns about the manuscript in present form are the following:

1. There are several statements in the Introduction and Discussion that have improper references. It is unclear if there was a technical problem with selecting specific references (for example, reference software), or if this reflects a fundamental misinterpretation of the literature. Specific examples that require attention are:

1a. Page 3: “Furthermore, SAD was recently suggested to be a superior predictor of MetS than the visceral fat area (VFA) [13]. The latter, measured at the level of the umbilicus, is the current gold standard for the determination of obesity-related cardiovascular risk [4, 14].” While I generally agree with the ideas proposed in these lines, the references cited do not support these statements. Specifically, the authors have erroneously listed the date of publication for Ref 13 (Kvist) as 1998 instead of 1988. In either case, this is not recent. More importantly, in Ref 13 the SAD measurement was compared to other anatomical assessments of abdominal fat made with computed tomography, but there are no metabolic outcome measurements presented in that paper to support the authors’ statement. The problem with citing Ref 4 (Rexrode) is that neither SAD nor visceral fat was reported in that study. The data analyses presented in Ref 4 are based on correlations between either BMI or waist-hip ratio and the risk for coronary heart disease in 40-82 year old men only. The relevance to children in the current study is questionable. The problem with citing Ref 14 (Van Der Kooy) is that the primary focus of that study was comparing various anthropometrical surrogates, including SAD, for abdominal fat measured by MRI in adults, but there was not any rigorous comparison of SAD to cardiovascular risk. There was a table of correlations between lipid concentrations and indices of central adiposity but these data are all from healthy men and women and no other CV risks were reported. The authors of Ref 14 concluded that SAD was a better predictor of visceral fat in men than it was in women. (The implication of that finding was never explored in the current paper - it seems like a missed opportunity to analyze boys and girls separately).

Response:

This comment was well noted by the authors. The introduction part was revised accordingly and several references were updated including #13. The study of Kvist was removed from the revised references section and was replaced accordingly by a more recent study done by Pimentel et al. (see reference 13).

1b. On Pages 3 and 4 are these statements: “To date, very few studies have correlated SAD to other metabolic abnormalities, especially in children,” and “very few studies have examined whether SAD in children and adolescents is superior to other anthropometric parameters in predicting cardiometabolic risk factors.” The problem with these statements as written is that there are no supporting references provided. Of the three citations that appear at the end of the second sentence, only one included children in their study and none included the SAD measurement that is the topic of the current study. As a reader, when I see statements like these the natural question to ask is, even if there were only a few studies in children, “what were the findings?” because it sets the expectations for the current paper. The authors should mention briefly that other investigators either did or did not find value for SAD measurements in
children (example, Ref 26), and could still promote the novelty and significance of their study in Saudi children because of the current health concerns cited in the last part of the second sentence.

Response:

This comment is well noted. The 3 references mentioned in the sentence concerned actually refers to the increased prevalence of MetS in both Saudi adults and children. The sentence has been revised accordingly to emphasize that the references do not refer to the limited studies done on SAD. Furthermore, reference #26 was included in the introduction as one of the few studies done on SAD in children.

1c. Page 7: “The results are in agreement with similar earlier studies done among children of European and Turkish descent [21-22].” As written, this statement implies that those prior studies reported that BMI was superior to SAD as a predictor for MetS. This unnecessarily undermines the value of the current study. In fact, SAD was not included in Ref 22 and in Ref 21 SAD values were reported but only as a correlate to BMI; the relative predictive power of BMI versus waist and WHR were presented in Ref 21, but a comparison of SAD versus BMI was not. The authors may want to rephrase to specifically note the BMI was shown to be a better predictor of skin folds and WHR in those studies.

Response:

This comment was well noted and the discussion was changed accordingly as found in page 8, 1st paragraph.

1d. Page 8, Line that begins, “Furthermore, in terms of identifying patients with MetS.” The way this is written overstates the value of SAD. Although it is noted the that data come from studies that were performed in adults with severe obesity and CVD risk, predictive utility is clearly less in normal patients and in the present study of children.

Response:

Again this comment is well noted and we have added another sentence "It is noted however that predictive power of SAD among normal adults, and in this case, children, will be clearly less as compared to those who harbor known CVD risk factors such as obesity", to emphasize that results of the present study should be interpreted with caution.

1e. Page 8: “When the same person lies supine the fat mass shifts cranially, causing anterior projection of the abdomen (abdominal height) which is measured by the SAD [22].” This is the wrong reference. SAD was not measured in that study.

Response:

This comment was well noted. The authors changed the reference accordingly to one of our previous studies (reference 19) and is now appropriately cited.

Each of the examples cited above need be corrected so that the cited references actually
support the statements.

2. Statistical Methods: There were no general statistics or figures that show how SAD or the other variables vary with age, etc. The authors acknowledge that they did not record pubertal status, which is an unfortunate limitation. However, given this limitation, it is still appropriate to comment about the effect of age. More importantly, it is difficult to determine if application of a linear regression approach to address the primary question is correct. There was no mention of whether the data are normally distributed and whether it would be appropriate to reanalyze the data after transformation procedures were used. In the Methods and/or Results the approaches used to assure normality, or the steps taken to account for departures from normality, should be acknowledged.

Response:

We have added an additional figure demonstrating the linear trend between SAD and age in both boys and girls. This has been included in the revised manuscript. Furthermore we have revised the statistical part of the methods section, stating in detail assumptions of normality and distribution prior to analysis.

Minor concerns

Page 8, Line that begins, “Furthermore, the big discrepancy in the sample sizes of groups after classification” refers to groupings that were not part of the current analysis. Rephrase accordingly.

Response:

This sentence has been removed.

Page 9, Authors state “excess adiposity during childhood could advance puberty in girls and delay onset in boys.” Since one of the key outcomes in the study is insulin, which is included in the classification of insulin resistance (HOMA-IR) and MetS, it should be acknowledged that insulin resistance is affected by puberty. The wide range in age in this study almost assures that there is also a wide range in developmental stages, although that was not measured, and this may contribute to weakening the proposed correlation between measures of adiposity and cardiometabolic risk outcomes. A comment about how the correlation between BMI, SAD or WHR with the components of MetS may be influenced by age or pubertal stage would address this concern.

Response:

The limitations part of the discussion has been revised accordingly.

Ref 15 (Al-Daghri, 2010): Recheck title. Published version title begins with “Extremely.” This word was omitted in current manuscript.

Response:
The reference has been revised accordingly.

Ref 22 (Agirbasli, 2011): Update with current volume and page number information.

Response:

The reference has been revised accordingly.