Author's response to reviews

Title: Multidisciplinary care of obese children and adolescents for one year reduces ectopic fat content in liver and skeletal muscle

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Author's response to reviews: see over
Att. BMC Pediatrics Editorial Board

Please receive this revised manuscript of the original article “Multidisciplinary care of obese children and adolescents for one year reduces ectopic fat content in liver and skeletal muscle”.

Below are the reviewer comments and our answers and alterations of the manuscript:

We have deleted the word ‘here’ from the sentence for (line 84) and we have deleted the part of waist circumference, since this is not a part of the current study (line 132).

Reviewer 1 report:
Major: comments
none
Minor comments
Abstract
Line 33 ‘attempted to elucidate’ Better state ‘evaluated’ Add at the end of this line that factors associated with change in these parameters were also evaluated

These changes have been implemented (line 33).

Line 54 consider removing: ‘as assessed by magnetic resonance spectroscopy measures’. It is redundant

This part of the sentence has been removed.

Background:
No comments
Methods
Line 102-105: Specify whether other liver diseases were excluded. If not shortly address this in the discussion section

This is now specified (lines 101 and 188)

Line 113 Supply some more detail on your program in the text. As the reference to Holm et.al. is not freely accessible: How were children referred, which health care professional saw the patient, approach used during consultations, outpatient setting?

The description of treatment protocol is now more detailed (lines 107-120)

Line 164 Specify ‘how analyze estimations of differences’ was performed, as this is not done using Wilcoxon signed rank test.
The analyses of estimations of differences between the non-normally distributed data at baseline and at follow-up were calculated by the Wilcoxon signed rank test, since it can be used as a paired difference test and is thus applicable in this setting (see statistical papers: [R. Shier, “Statistics,” The Wilcoxon Signed Rank Sum Test, Mathematics pp. 1-3. http://www.lboro.ac.uk/media/wwwlboroacuk/content/mlsc/downloads/2.2_wsrt.pdf] or [I. C. A. Oyeka, “An Introduction to Applied Statistical Methods,” 8th Edition, Nobern Avocation Publishing Company, Enugu, 2009, pp. 496-533.]).

Line 166 Were all determinants tested individually? If so, it is more correct to refer to your analysis as ‘univariate linear regression’ (with adjustment for confounding for 5 covariables)

   It is true that these analyses are univariate and not multiple linear regression analyses. This has now been corrected in the manuscript. (lines 43 and 172)

Line 166: Regression analysis correcting for 5 covariants makes your analysis prone to overfitting. Is it necessary to adjust for all the variables? i.e were these variables confounders/effect modifiers?

   We agree that adjusting for five co-variates make the analyses prone to overfitting. The five co-variates used in the analyses where chosen from a biological point of view, which makes it reasonable to still include all five, even though our statistical analyses do not support that all of the co-variates are confounders/effect modifiers.

Results:

Line 178: Specify how many patients were eligible/treated in the inclusion period in your center. A selection bias could be present as end of treatment measurement are part of the inclusion criteria.

   The number of persons treated is now added (lines 93) as well as the comparison on age and baseline BMI SDS between the total treated group and the included children and adolescents (line 201). The number of eligible children and adolescents and specifications of exclusions have also been implemented (lines 95, 185, 188, and 190) and discussed (line 341).

Line 185. The interval between the scan and blood sampling is up to 60 days. Please also report the time between investigations and the start of the intervention.

   This information is now added to the manuscript (line 197). We have also addressed the fact that most of the MR scans were performed after start of intervention, which may underestimate the fat-reducing effect of the treatment (line 339)

Line 205-2010. It is unclear what this comparison adds. Consider removing.

   This comparison is now removed from the manuscript.
Line 213 and 223: Change heading to this paragraph, as it does not clearly explain its content.

*These headings have now been renamed (lines 224 and 237)*

Line 214-222: The summary given here is difficult to follow for readers. Consider removing all the non-significant p-values mentioned. Put the associated variables in a separate phrase.

*This section has now been rephrased, although we have kept the p-values in order to allow the reader to evaluate the degree of relevance of the non-significant p-values. In example, p-values of 0.06 and 0.07 might inspire others to research such possible association in a setup with more statistical power.*

Line 214 versus 216: In line 214 LFC is not correlated, but in line 216 levels of liver fat are??

*This mistake of contradictory results has now been corrected (line 225).*

Line 224-231: again the summary is difficult to follow and line 224 and 226 are contradictory on the association with MFC.

*The contradictory messages regarding the association with MFC have now been corrected (line 238). As in the previous section, we have rephrased this section and kept the p-values in order to allow the reader to evaluate the degree of relevance of the non-significant p-values (lines 240-245).*

Line 216 versus line 227: How can change in LFC and change in MFC be associated one way but not inversely?

*This is due to the adjustment of the other co-variates: Both changes in LFC and MFC are adjusted for age, sex, treatment duration, baseline degree of obesity, and pubertal developmental stage. On top of this, the change in LFC is further adjusted the baseline level of LFC, while the change in MFC is adjusted for the baseline level of MFC. So taken the given baseline level of LFC into consideration, the changes in LFC associate with the changes in MFC. In contrast, the changes in MFC do not associate with the changes in LFC when you take the given baseline level of MFC into account.*


*The paragraph has been removed from the manuscript.*

Discussion:

Line 224 is a 1% reduction in liver fat biologically important? Or merely statistically significant?
It is still open for discussion which degree of hepatic fat reduction should be considered biologically important, and the answer may also depend on the baseline level of liver fat content. This study reports data of children with a normal liver fat content and children with hepatic steatosis. These two groups have different potentials in liver fat reduction. The mentioned 1% median reduction for all 40 participants is based on LFC reductions in the hepatic steatosis group and maintenance of LFC in the non-hepatic steatosis group. The specific changes in LFC for these two groups have now been added to the manuscript (line 234). This median reduction of 7.8% LFC in the hepatic steatosis group, we find reasonable to consider biologically important. The specific changes in MFC for these groups with/without muscular steatosis have now been added to the manuscript (line 246).

Line 281-289 Also discuss in this section the lack of association between gluc-insulin and LFC/MFC in this study. Discuss that it is remarkable that insulin and glucose did not improve in this study

This has now been added (lines 298-303).

Line 306 in this study LFC and VAT were not associated. So not all findings were in line with previous studies.

This fact has now been corrected (line 317)

Line 311: ‘partly’ could be placed between parenthesis in this phrase

Now implemented (line 322)

Line 321-330: another limitation is that given the sample size and small change in LFC associations in regression analysis might have been missed.

This fact has been added to the Discussion section (line 348)

Reviewer 2 report
This is an interesting study on reduction of ectopic fat in obese children after one year of lifestyle intervention. The results are of interest although not novel and represent an extension of previous findings. The main problem with this study is the very small sample size and the heterogeneity of the study population. Children and adolescents were included, overweight and obese patients were included. This makes it difficult to draw conclusions for the whole population of overweight and obese children. Are overweight children more likely to reduce ectopic fat than obese children, do adolescents act differently as they presumably are more IR than prepubertal children? I think that the study population should be increased and two models one for prepubertal and one for pubertal children.
We most certainly agree to these observations and perspectives. Post hoc analyses (as a result of this comment) showed no difference in the ability to reduce ectopic fat (liver and muscle) when comparing overweight to obese children and adolescents. Further, we found no difference in the ability to reduce ectopic fat when comparing prepubertal to pubertal, prepubertal to postpubertal, or pubertal to postpubertal.

We would like to thank the reviewers for the comments and for contributing to the improvement of this manuscript.

Best regards

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