Author's response to reviews

Title: Impact of Adiposity on Cardiac Structure in Adult Life: the Childhood Determinants of Adult Health (CDAH) Study

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Author's response to reviews: see over
Title: Impact of Adiposity on Cardiac Structure in Adult Life: the Childhood Determinants of Adult Health (CDAH) Study

Reviewer: Anthony Staines

General comments

1. The analysis is a follow up to what seems to be a large cross-sectional survey of child health. The overall presentation of the paper is hard to follow. I accept that these are complex studies, and not particularly easy to present, but this paper is still very hard to follow. A quote from the paper cited by the authors is apposite “To achieve robust conclusions, more than one analytical approach should be adopted, with the results compared and inconsistencies investigated, thus carrying out sensitivity analyses in the broader sense”(1). This has not been done here. A deeper analysis is needed, looking at several possible models for what is going on here, and taking account, in particular, of the variation in age at first measurement.

A sensitivity regression analysis was undertaken, in which both age at baseline and age at follow-up were included in the analysis. This did not alter the findings. A further analyses stratified by age group (7 to 10 years of age & 11 to 15 years of age) was undertaken, this also did not alter the associations shown, except for change in skin fold thickness and change in fat mass in females aged 11 to 15 years. A comment has been added in text. Page 12 – ‘This association did not change with adjustment for both age in childhood and adulthood or stratification by age group, with the exception of change in skinfold thickness and fat mass in females aged 11 to 15 years and BMI change in males aged 7-10 years, which were no longer significant.' The analyses are shown below.
<table>
<thead>
<tr>
<th>Body Mass Index (BMI)</th>
<th>Males</th>
<th></th>
<th>Females</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1 - Prior to further adjustment for child age</td>
<td>Model 2 – Adjusted for both child and adult age</td>
<td>Model 1 – Prior to further adjustment for child age</td>
<td>Model 2 – Adjusted for both child and adult age</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Regression Coefficient</td>
<td>95% CI</td>
<td>P</td>
<td>Regression Coefficient</td>
<td>95% CI</td>
</tr>
<tr>
<td>LVM (g)</td>
<td>Childhood BMI</td>
<td>0.41</td>
<td>0.14 to 0.67</td>
<td>0.003</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Change in BMI</td>
<td>0.27</td>
<td>0.04 to 0.51</td>
<td>0.023</td>
<td>0.25</td>
</tr>
<tr>
<td>Waist circumference (WC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVM (g/m$^2$)</td>
<td>Childhood WC</td>
<td>0.04</td>
<td>-0.02 to 0.09</td>
<td>0.213</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Change in WC</td>
<td>0.04</td>
<td>-0.01 to 0.08</td>
<td>0.088</td>
<td>0.04</td>
</tr>
<tr>
<td>Fat mass (FM)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVM (g/m$^2$)</td>
<td>Childhood FM</td>
<td>0.04</td>
<td>-0.02 to 0.10</td>
<td>0.223</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Change in FM</td>
<td>0.03</td>
<td>-0.02 to 0.08</td>
<td>0.237</td>
<td>0.03</td>
</tr>
<tr>
<td>Skin fold thickness (SFT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVM (g/m$^2$)</td>
<td>Childhood SFT</td>
<td>0.01</td>
<td>-0.06 to 0.07</td>
<td>0.827</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Change in SFT</td>
<td>0.01</td>
<td>-0.05 to 0.06</td>
<td>0.844</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Model 1 - adjusted for confounding factors in adulthood: age, fitness, triglycerides and total cholesterol). LVM - Left ventricular mass. BMI, FM and LM data are ranked by age (separately in males and females) to account for the impact of age on growth among children. Model 2 – as per model 1, with further adjustment for child age.
Analysis method 2

**BMI & LVM – Model 3 Prior to stratification by child age group**

**Males**

Childhood BMI Regression coefficient 0.46 (0.23 to 0.70) \( p<0.001 \)

Change in BMI Regression coefficient 0.30 (0.08 to 0.52) \( p=0.009 \)

**Females**

Childhood BMI Regression coefficient 0.44 (0.30 to 0.58) \( p<0.001 \)

Change in BMI Regression coefficient 0.29 (0.15 to 0.44) \( p<0.001 \)

**BMI & LVM - models stratified by child age group**

**Males - 7 to 10 years of age**

Childhood BMI Regression coefficient 0.70 (0.29 to 1.12) \( p=0.002 \)

Change in BMI Regression coefficient 0.37 (-0.02 to 0.75) \( p=0.060 \)

**Females - 7 to 10 years of age**

Childhood BMI Regression coefficient 0.41 (0.24 to 0.58) \( p<0.001 \)

Change in BMI Regression coefficient 0.34 (0.14 to 0.54) \( p=0.001 \)

**Males - 11 to 15 years of age**

Childhood BMI Regression coefficient 0.38 (0.07 to 0.69) \( p=0.016 \)

Change in BMI Regression coefficient 0.29 (0.01 to 0.56) \( p=0.042 \)

**Females - 11 to 15 years of age**

Childhood BMI Regression coefficient 0.53 (0.29 to 0.76) \( p<0.001 \)

Change in BMI Regression coefficient 0.32 (0.10 to 0.55) \( p=0.007 \)

**Waist Circumference & LVMI – Model 3 Prior to stratification by child age group**

**Males**

Childhood Waist Circumference Regression coefficient 0.04 (-0.01 to 0.09) \( p=0.100 \)
Change in Waist Circumference Regression coefficient 0.04 (-0.01 to 0.08) p=0.072

**Females**

Childhood Waist Circumference Regression coefficient 0.10 (0.06 to 0.14) p<0.001
Change in Waist Circumference Regression coefficient 0.08 (0.04 to 0.13) p<0.001

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**Waist Circumference & LVMI - models stratified by child age group**

**Males - 7 to 10 years of age**

Childhood Waist Circumference Regression coefficient 0.05 (-0.03 to 0.14) p=0.198
Change in Waist Circumference Regression coefficient 0.03 (-0.5 to 0.11) p=0.451

**Females - 7 to 10 years of age**

Childhood Waist Circumference Regression coefficient 0.11 (0.05 to 0.16) p<0.001
Change in Waist Circumference Regression coefficient 0.11 (0.05 to 0.16) p<0.001

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**Males - 11 to 15 years of age**

Childhood Waist Circumference Regression coefficient 0.03 (-0.03 to 0.09) p=0.322
Change in Waist Circumference Regression coefficient 0.04 (-0.01 to 0.09) p=0.140

**Females - 11 to 15 years of age**

Childhood Waist Circumference Regression coefficient 0.11 (0.05 to 0.18) p=0.001
Change in Waist Circumference Regression coefficient 0.08 (0.01 to 0.15) p=0.021

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**Fat mass & LVMI – Model 3 Prior to stratification by child age group**

**Males**

Childhood Fat mass Regression coefficient 0.04 (-0.01 to 0.10) p=0.109
Change in Fat mass Regression coefficient 0.03 (-0.02 to 0.07) p=0.462

**Females**

Childhood Fat mass Regression coefficient 0.11 (0.06 to 0.16) p<0.001
Change in Fat mass Regression coefficient 0.07 (0.03 to 0.12) p=0.002
Fat mass & LVMI - models stratified by child age group

**Males - 7 to 10 years of age**
Childhood Fat mass Regression coefficient 0.08 (-0.02 to 0.17) p=0.100
Change in Fat mass Regression coefficient 0.05 (-0.04 to 0.14) p=0.264

**Females - 7 to 10 years of age**
Childhood Fat mass Regression coefficient 0.12 (0.05 to 0.19) p=0.002
Change in Fat mass Regression coefficient 0.13 (0.06 to 0.20) p<0.001

**Males - 11 to 15 years of age**
Childhood Fat mass Regression coefficient 0.03 (-0.04 to 0.09) p=0.427
Change in Fat mass Regression coefficient 0.02 (-0.04 to 0.07) p=0.562

**Females - 11 to 15 years of age**
Childhood Fat mass Regression coefficient 0.12 (0.04 to 0.19) p=0.003
Change in Fat mass Regression coefficient 0.05 (-0.02 to 0.11) p=0.167

Skin fold thickness & LVMI – Model 3 Prior to stratification by child age group

**Males**
Childhood Skin fold thickness Regression coefficient 0.02 (-0.03 to 0.07) p=0.462
Change in Skin fold thickness Regression coefficient 0.01 (-0.04 to 0.05) p=0.901

**Females**
Childhood Skin fold thickness Regression coefficient 0.09 (0.04 to 0.15) p<0.001
Change in Skin fold thickness Regression coefficient 0.06 (0.02 to 0.11) p=0.009

Skin fold thickness & LVMI - models stratified by child age group

**Males - 7 to 10 years of age**
Childhood Skin fold thickness Regression coefficient 0.07 (-0.03 to 0.17) p=0.181
Change in Skin fold thickness Regression coefficient 0.05 (-0.03 to 0.15) p=0.242
**Females - 7 to 10 years of age**

*Childhood Skin fold thickness Regression coefficient 0.12 (0.05 to 0.19) p=0.002*

*Change in Skin fold thickness Regression coefficient 0.13 (0.06 to 0.19) p<0.001*

**Males - 11 to 15 years of age**

*Childhood Skin fold thickness Regression coefficient 0.01 (-0.06 to 0.07) p=0.869*

*Change in Skin fold thickness Regression coefficient -0.02 (-0.07 to 0.04) p=0.562*

**Females - 11 to 15 years of age**

*Childhood Skin fold thickness Regression coefficient 0.09 (0.01 to 0.17) p=0.022*

*Change in Skin fold thickness Regression coefficient 0.03 (-0.04 to 0.10) p=0.453*

Overall I think you need to redo this work, think much more carefully about your message, and how it is to be presented. I think this is really worth doing. I entirely take your point that the question is important, and that your work represents a great opportunity to answer the question in a new way. However, I can't understand what you are doing well enough to see what the answer is.

*The document has been updated throughout, to reflect the suggested changes by the reviewers. We hope that these changes have clarified the analyses and findings sufficiently.*

**Specific comments**

**Abstract**

2. The abstract should make clear that this is a study of measurement on two occasions – once in childhood aged 9, 12 or 15, and once in adult life, aged 26 to 36.

*The text has been amended. ‘The measures were taken once when the children were aged 9 to 15 years, and once in adult life, aged 26 to 36.’*
Methods

3. The authors write “In order to provide a graphical illustration of the associations between adiposity measures and LVMI, separate categorical variables describing pattern of change between childhood and adulthood in adiposity status were created for each of BMI, waist circumference, fatmass and skinfold thickness. Those in the highest quartile (age and sex specific) were defined as overweight/obese. The resulting categories of change were: (1) normal weight as child and normal weight as adult; (2) overweight/obese as child and normal weight as adult; (3) normal weight as child and overweight/obese as adult; (4) overweight/obese as child and overweight/obese as adult. We present means on the LVMI outcome for each adiposity change category”. This is very confusing. There are quite standard ways of defining overweight/obesity in terms of BMI for adults and children. I can see no justification for redefining these well understood terms. Please stop using the term overweight/obese to refer to the highest quartile of 4 different measures, and use a more neutral and less confusing term, like top quartile. When analysing change it would make more sense to use quartiles of change, not of initial and starting position. As all your measures are continuous why not just use graphs of the raw data? These would be unambiguous.

The text has been updated. Table 2 has used the categories of overweight and obese calculated using age and sex specific cut-points in childhood as is standard practice (Cole TJ, Freeman JV, Preece MA. British 1990 growth reference centiles for weight, height, body mass index and head circumference fitted by maximum penalized likelihood. Statistics in medicine. 1998;17:407-429) and according to the international standard definition in adulthood (overweight BMI ≥25 and obese ≥30). Refer to page 6 and page 19.
For Figure 1, to provide estimates that could be compared across adiposity measures (BMI, waist circumference, fat mass and skin fold thickness) the highest quartile of each measure was used to define overweight/obese. Refer to page 10.

4. Modelling approach – it is hard to make sense of your description of your models. Presumably these are linear regression models, with normal errors. How are the included variables defined? How did you define the change variables – directly, in terms of quantiles, or what? An equation, or two, would be worth several hundred words here.

The text has been updated, page 10, paragraph 3. Adiposity and change in adiposity were modelled as continuous predictors in the regression models. Change is based on taking the difference of continuous scores.

5. How do you account for the fact that the measurements at the two time points are on the same people?

There is only one record (i.e., one row of data) for each participant. We are merely using predictors that are measured at baseline and follow-up to predict an outcome at follow-up.

6. How do you account for the fact that some people were measured before and others during puberty?

Unfortunately, no data was collected at the baseline survey on pubertal stage of the participants. In the absence of information on pubertal staging, age was used which is considered a reasonable proxy in the absence of pubertal stage. As detailed in our reply to comment #1, we undertook a series of sensitivity analyses which showed no effect modification by age status (<11 years vs. >11 years), with the exception of change in skinfold thickness and fat mass in females aged 11 to 15 years, which was no longer significant.
7. How did you assess goodness of fit of the models?

Regarding goodness of fit we should point out that the main aim of the analysis is to examine the relationship between adiposity and cardiac structure rather than to derive a prediction model for cardiac structure. We have adjusted for key established confounders.

8. Why and how did you select the variables you chose to include?

We selected variables on the basis that they were: (a) predictors of interest – adiposity; (b) potential confounders or (c) potential mediators. Each variable has a theoretical role and they were not selected for the model on the basis of statistical tests.

9. Did you use any other methods of model criticism? All of this needs to be described to the same level of detail as the Echoardiographic measures. You describe a variable named fatmass as one of your measures of adiposity in

Concerning “model criticism”, we are unsure what the reviewer is requesting. If they would like to specify, we will be happy to accommodate. Concerning the variable fatmass, we reviewed our text in the methods and identified that we did not specifically mention the creation of this variable from the skinfold measures in earlier versions of this manuscript. In the revised version (page 7) we have specifically mentioned fat mass and believe this will amend any confusion caused by this variable being first mentioned in the results.

10. Table 3 – I'm no sure what this is, nor am I sure how you calculated it. Is it the percentile of body fat derived from the skinfold thickness?
Table 3, is a regression analysis of echocardiographic measures in adulthood on measures of adiposity in childhood and change in adiposity from childhood to adulthood, as stated in the table title.

The reviewer is correct. As stated in the methods section ‘Percent body fat at baseline and follow-up were estimated from established regression equations that incorporate four measures of skin fold thickness’. Page 5, paragraph 2.

Results

11. You ought to report all 4 adiposity variables, and the 4 change variables too. Table 3 is problematic. I’m not sure what, exactly, your various measures of adiposity are. For example you report coefficients of 0.46 for Childhood BMI and 0.30 for change in BMI for males, as the effects on LVM. Does this mean that LVM goes up by 0.46g for every unit change in childhood and adult BMI, and by a further 0.3 g for every unit difference between childhood BMI and adult BMI? I think presenting predicted values would make more sense here.

This has been described in great detail in the methods section, page 11. ‘In these models the regression coefficient for the child adiposity variable is the difference in the mean cardiac outcome between subjects who are one unit apart in their adiposity level at both childhood and adulthood (e.g. subject A is one unit higher in BMI than subject B at both time points). If the association were causal it would represent the effect of an increase of 1 unit in adiposity at both childhood and adulthood. The coefficient for the change in adiposity variable quantifies the mean increase in the cardiac outcome associated with a one unit difference in change (e.g. comparing cardiac outcome between two children whose changes in adiposity are 1 unit apart, say an increase of 2 units versus an increase of 1 unit).’
I think you need to present more basic results. Your graphical presentation is quite insufficient. The key point you are making, I think, is that bigger children have bigger hearts as adults. How does heart size relate to change in size over time? How does it relate to the age at first measurement? Is there an indication that there is any difference in this relationship for pre-pubertal and pubertal children?

The reviewer correctly identifies that the main results of our research suggest that bigger children do indeed go on to have larger hearts as adults. Because we did not have echocardiography data from childhood, we were unable to determine if those children with increased adiposity had larger hearts already in childhood. We have added text to this effect to the limitations on page 16. Concerning the reviewer's comments on age at first measurement and pubertal status, please refer to our response to comments #1 and #6 (above).

Conclusions

For me, as a non-cardiovascular epidemiologist, the two really striking things about your results are the huge differences between males and females, and the lack of consistency in the trends shown in your Figure 1. You don't seem to consider the former very much. I wonder what an outcome variable of LVMI would look like for males and females, with BMI as the explanatory variable? I accept that there were very few obese/overweight children in the original sample, which makes the trends unreliable, but I am struck by the varying patterns between the first two groups (normal child/normal adult) and (normal child/obese, overweight adult), across your four adiposity measures.

As the reviewer has acknowledged, the sample size is quite small to make strong conclusions about differences between the gender groups. However, in the discussion (page 14) we do refer to differences by sex and provide reasoning for these apparent
differences. We do not, however, draw strong conclusions because of the aforementioned sample size issue and because confidence intervals shown for males and females often overlapped considerably and magnitudes of the effects observed were not so marked that we considered comment as essential. In the revised manuscript, we acknowledge in the limitations that further work is needed to identify any substantial effect modification by sex (page 16). Concerning using continuous (non-categorised) BMI as an explanatory variable for the outcome of LVMI among males and females, these data are already shown in Table 3.