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
Thank you for the opportunity to revise and resubmit this manuscript. In addition to responding to the review comments we have had the echocardiographs re-reported. We discovered, a potential problem with the initial grading of the echocardiographs and as a precaution had all the images re-graded. The data analyses have all been re-undertaken with the new reported echocardiographs. This overall had a limited impact on main finding of the manuscript relating to LVM, it did however bring out some sex differences for other measures of adiposity, which are addressed in the discussion. We felt it necessary to undertake these precautions to ensure the integrity of the data and study findings.

Reviewer 1:

Impact of adiposity on cardiac structure in adult life: the childhood determinants of adult health (CDAH) study This paper explores the association among measures of adiposity (BMI, waist circumference, skin fold thickness determined fat mass and sum of skin fold thickness) and left ventricular mass measured in adulthood by two dimensional M mode echocardiography. The design of this substudy which measures 180 children from a cohort of 8498 (<2%) has children aged 7 to 15 years and therefore 26 to 36 years as adults. There is huge variability within this sample. I am not a statistician but have wrestled with the problem of measuring growth and change in children. A statistician with an understanding of the analytical and practical problems as the authors quote themselves is essential. De Stavola BL, Nitsch D, dos Santos Silva I, McCormack V, Hardy R, Mann V et al (2006). Statistical issues in life course epidemiology. American journal of epidemiology 163: 84-96. The paper needs severe editing and revision to remove contradictions, inconsistencies and to be more readable.

Major comments and compulsory revisions

1. The growth of children is difficult to monitor as change in physical parameters is rapid and not linear. The measurement of children in this study took place when they were between 7 and 15 years of age. This age span includes puberty. When modeling change in children, age should be a very accurately measured variable, yet it appears in Table 1 to be measured to the nearest year which completely negates the complexity of the subsequent modeling. A difference in 1cm of height makes a very large difference to subsequent conclusions and a child may change many cm within a year. Height is squared for both the LVM index and body mass index.

   • Thank you for these comments. To clarify, the variable age is calculated by subtracting the date of birth from the study visit date, as is standard practice. We have presented the mean age and standard deviation of participants in childhood and adulthood in table 1 and reported the age range in text.

   • We used the exact age of the child on the date of the study visit and have accurate measures of height and cardiac structure all taken on the same day, these measures are what we have presented in table 1.

   • We have used standard internationally accepted measures of body mass index and left ventricular mass index. Childhood overweight and obesity for BMI were defined using age and sex specific cut-points.

   • The reviewer raised some interesting points and this led to a discussion around the definition we had used to define childhood BMI. We have subsequently reviewed the definition of childhood BMI and re-defined it using the UK reference population because it was collected in 1990, which is closer, and may be more relevant, to the time our baseline data were collected (1985), than the US reference population from 2000. This has led to an increase in the number catgorised as overweight and obese in table 2.

2. The use of indices as continuous variables rather than raw data should be considered carefully Packard GC, Boardman TJ (1999). The use of percentages and size-specific indices to normalize physiological data for variation in body size: wasted time, wasted effort? Comparative
We have used standard internationally accepted measures of adiposity (weight, height, BMI, waist circumference and skin fold thickness) and cardiac structure.

3. I cannot follow the argument presented – The overall conclusion is that adiposity and adiposity from childhood to adulthood appear to have a detrimental effect on cardiac structure (in adulthood) either expressed as LVM or LVMI. Childhood BMI is not standardized for age and gender i.e. a continuous variable as a z score? Adult ventricular mass is reported in g and is divided by height in m² as an index – this also is problematic.

- To clarify the data in table 3 are shown separately for males and females and are adjusted for confounding factors in adulthood: age, fitness, triglycerides and total cholesterol.
- It is standard practice to report LVMI.
- The childhood BMI has been calculated using the UK reference population and accounts for the age and sex of the child.

4. Bigger people have bigger hearts and other organs. Athletes also have larger hearts. The more mass to circulate blood to the more work the heart does. Why is a larger heart deleterious?

- The reviewer is correct and it is known for example that high fitness is associated with increased LVM.
- In the more general population, an increase in LVM accounting for ones size has a detrimental effect on health. In the introduction on page 3, we have tried to highlight some of these effects. Cross-sectional studies of children and youth have demonstrated elevations in left ventricular mass (LVM) in association with elevated blood pressure, type 1 diabetes and increased body mass index (BMI). This association is of major interest as it is well established that adults with left ventricular (LV) hypertrophy, a consequence of increased LVM, are at an increased risk of myocardial infarction, congestive heart failure and cardiovascular disease (CVD) mortality.

5. The definition of overweight and obesity varies – initially for children the criteria of Cole are used and for adults in the statistics section it states that the highest quartile in males and females were defined as overweight/obese. The criteria for adults usually are BMI 25 and 30 kg/m². In table 2 more than 50% are classified as overweight or obese – what criteria were used?

- The text has been updated. The criteria for adults used in table 2 are BMI 25 and 30 kg/m², for overweight and obese respectively.

6. On 10 children were classified as overweight or obese out of 180. Yet in figures 1a to 1d there 10 children are shared between two categories overweight child and normal weight adult, and overweight child and overweight adult. Numbers in each category are not provided. These figures need more explanation.

- The children are only included in one of the four categories. We now report the age and sex specific quartiles, rather than predicted means, to simplify the analyses.
- Refer to question 1, point 4.

7. Figure 2 is similarly confusing – in statistical methods low fit category is #20% fitness (how as % fitness defined?) and fit was 20% in 20 to 100% separately my male and female. In figure 2 children are referred to unfit (rather than low fit) This needs clarification and justification.

- As recommended by the reviewer, the figure has been removed.

8. Both Figures 1 and 2 need to be considered carefully for how they add to the flow of argument.

- We agree with the reviewer, that figure 2 adds little to the flow of the argument presented in this manuscript and so we have removed the figure.
- We are happy to be guided by the editor for figure 1. Figure 1 graphically shows the
important association between child and adult obesity and changes in cardiac structure. Particularly showing the impact of childhood overweight and obesity. Often a figure is a good way to reinforce a message.

9. More justification of why an increased LVM is deleterious is required; is there a cut off? What are the deleterious effects the authors refer to? What is the range of “normal?” Blood pressure was controlled for so this is not the effect?
   - Refer to response 4.

**Minor essential points and revisions**

10. Throughout the manuscript measures are stated without the unit of measurement.. e.g. LVM, LVMI
   - The units have been added to table 2 and 3.

11. Page 7 what does the d stand for in the equation by Devereux?
   - diastole

12. Was the variable skinfold thickness reported in table 1 the sum of four skinfolds – this should be clarified.
   - That is correct. Refer to page 5, para 2.

13. Why was the fitness index calculated as Watts divided by lean mass? Presumably the lean mass was determined from the skinfold equations?
   - Cardiorespiratory fitness is expressed in relative terms as watts per kg (W/kg) of lean body mass. A standard way to present the fitness index.

14. % Fat is stated on page 9 and in discussion referral is to fat mass – which variable was used and why?
   - The text has been updated. The word % fat has been replaced with fatmass.

15. Table 3 – was child age and adult age accounted for in the modeling and if so how? BMI trajectory in children is not linear – in fact BMI may fall with age up to about 7 years and then rises in a sigmoid fashion with very rapid change in adiposity during puberty for girls.
   - The study did not assess growth trajectories.
   - The models in table 4 adjusted for both mediating and confounding factors. As stated: Model 1 - contains childhood adiposity and change in adiposity as predictors. Model 2 - as Model 1 but adjusted for confounding factors in adulthood: age, fitness, triglycerides and total cholesterol). 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.

16. No note is made if the women have had children or not. This does make a difference to BMI.
   - The study has not analyzed whether women have had children or not. The sample size is small and we limited adjustment for confounding to established factors.

**Reviewer 2:**

Impact of Adiposity on Cardiac Structure in Adult Life: the Childhood Determinants of Adult Health (CDAH) Study Context The modifiable determinants of cardiovascular disease continue to constitute an area of study which holds potential to inform interventions to prevent, ameliorate, and treat disease. Recognising that exposures and their pathophysiologic effects are often spread over decades rightly
raises the profile of a life course approach to risk assessment. This manuscript presents incremental findings in this area by analysis of cohort data based on a large childhood cohort whose members are now young adults. The study in essence adds to the examination list cardiorespiratory fitness, glucose metabolism and longitudinal changes in size and body composition which operate over some two decades. The findings add to the literature and so reinforce already described relationships between size/adiposity in earlier life, as well as change in body composition and size over time, and left ventricular structure, held to be a proxy for future CVD risk. Within this context the authors add information on a very small subset (a convenience sample constituting less than half of one percent of the cohort) who had physical fitness tests and cardiac echos.

Major Comments
1. The great weakness of the study relates to sampling. The authors indicate a random sample of 204 was selected but that only 180 of these had complete examinations.
   - It is usual for there to be a loss of a few participants due to poor imaging and incomplete data. We have reported this accordingly. Page 8, ‘Two hundred and four (204) participants underwent cardiac imaging and of these 181 had complete data available and acceptable echocardiography images.’
2. It is unclear what the hypotheses were that drove the sample selection. In addition, one fears that the 180/204 actually measured might have proven post hoc to be a convenience sub-sample of the already very small (<0.5%) set of individuals selected for additional investigations. Given this, it is worrisome that there are no power calculations to inform the level of confidence, a priori, one might place on observed differences across subcategories.
   - The sample for cardiac imaging was small to limit the burden on study participants of lengthy clinical examinations which were already of about 3 hours’ duration without cardiac imaging. One in three of the adult participants who had more extensive measurements in childhood, including blood pressure and blood biochemistry (9, 12 and 15 year-olds), were randomly selected for cardiac imaging i.e. approximately 1 in 9 participants overall. This has been clarified in the manuscript, page 4.
   - The question addressed in this paper is a secondary data analysis. A power calculation is only relevant for the main study question for which data were collected, not for secondary data analysis.
   - Although there is no power calculation the 95% confidence intervals for the estimates give clear indication of the precision with which we have answered our study questions.
   - Our study has clearly detected some relationships. Power calculations would have been useful had we found NO evidence of a relationship which then could have been due to lack of power.

Other Comments
3. The aim/objective of this observational study appears to be to evaluate the particular relationship between body composition and body size over time and cardiac structure and function. This is stated clearly enough in a non hypothetical style. The methods used for making anatomical and physiological measurements are appropriate. The sampling methodology as above seems to lack power calculations.
   - Our study has clearly detected some relationships. Power calculations would have been useful had we found no evidence of a relationship.

4. The statistical approach is appropriate for life course data. The discussions seem muted in relation to the metabolic determinants of cardiac structure/function, blood glucose, serum lipids. In addition, an opportunity was lost or rejected to explore fully potential mechanisms linking adiposity with cardiac structure and function.
   - The discussion has a section on mechanisms. Page 11 para 2.

5. The limitations of the study are stated baldly and restricted to sample size and potential bias due to incomplete recruitment. For example…It is odd that adiposity is currently the leading pathophysiological candidate for inducing cardiac structural and functional changes in the setting of
overweight/obesity. Yet the discussion is silent on the weakness demonstrated by the analyses of
the relationship of measures of fat mass (skinfolds and BMI) and cardiac anatomy. Is this
weakening related to measurement error?

- The reviewer has not explained what they meant by 'study limitations are stated badly'.
  The key limitations of the study are clearly stated.
- This study has for the first time assessed the association of several measures of adiposity
  with cardiac structure and function and each has shown a similar association. The strongest
  associations (largest regression coefficient) were observed for BMI.

6. Is it that both BMI and skinfold assessment of body composition are proxies for some other
anatomic or pathophysiological process? Is the pathway for the effect of fitness through modulation
of body composition or is it metabolic or physiological?

- There are several possible mechanistic pathways that may account for the associations shown
  in this study. In the discussion we mention that it is well acknowledged that central fat is
  metabolically active and leads to the activation of a series of pathophysiologic processes
  including activation of the renin-angiotensin system and development of insulin resistance

Editorial comments:

As you will see, concerns have been raised regarding the statistical aspect of your study. On
resubmission we will seek additional advice to assess this point.

Please include a 'Competing interests' section between the Conclusions and Authors’ contributions. If
there are none to declare, please write 'The authors declare that they have no competing interests'.

- A competing interests section has been added in text, page 12.

The questions that are asked of authors are:

Financial competing interests:
- In the past five years have you received reimbursements, fees, funding, or salary from an
  organization that may in any way gain or lose financially from the publication of this
  manuscript, either now or in the future? Is such an organization financing this manuscript
  (including the article-processing charge)? If so, please specify.

- Do you hold any stocks or shares in an organization that may in any way gain or lose financially from
  the publication of this manuscript, either now or in the future? If so, please specify.

- Do you hold or are you currently applying for any patents relating to the content of the
  manuscript? Have you received reimbursements, fees, funding, or salary from an organization
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Non-financial competing interests: are there any non-financial competing interests (political, personal,
religious, academic, ideological, intellectual, commercial or any other) to declare in relation to this
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Please include an 'Authors' contributions' section before the Acknowledgements and Reference list.
For the Authors' contributions we suggest the following format (please use initials to refer to each
author's contribution): "AB carried out the molecular genetic studies, participated in the sequence
alignment and drafted the manuscript. JY carried out the immunoassays. MT participated in the
sequence alignment. ES participated in the design of the study and performed the statistical analysis.
FG conceived of the study, and participated in its design and coordination. All authors read and
approved the final manuscript." An "author" is generally considered to be someone who has made
substantive intellectual contributions to a published study. To qualify as an author one should 1) have
made substantial contributions to conception and design, or acquisition of data, or analysis and
interpretation of data; 2) have been involved in drafting the manuscript or revising it critically for
important intellectual content; and 3) have given final approval of the version to be published. Each
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• A authors contribution section has been added in text, page 12.