PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Is arterial stiffening associated with adiposity, severity of obesity and other contemporary cardio-metabolic markers in a community sample of adolescents with obesity in the United Kingdom?
AUTHORS	Hudson, Lee; Kinra, Sanjay; Wong, Ian; Cole, Tim; Deanfield, John; Viner, Russell

VERSION 1 - REVIEW

REVIEWER	Latini, Robert IRCCS - Istituto di Ricerche Farmacologiche Mario Negri Dept of Cardiovascular Res. Competing interests: NONE
REVIEW RETURNED	23-Jun-2017

GENERAL COMMENTS	Authors of ms 2017-000061 report the baseline characteristics of a cohort of 174 adolescents enrolled to the HELP interventional trial. Out of a large set of measures related to adiposity, circulating biomarkers, pulse wave velocity (the variable of interest) was found to be related only to age and adiposity with a large overlap between groups of zBMI. The Authors question the validity of PWV as a marker of cardiovascular risk in adolescents. Several limitations of the study are correctly listed at the end of the Discussion. However, the possibility that the study is underpowered is not considered. The Authors should attempt to assess the statistical power of their study in 174 subjects to detect an predefined increase in cardiometabolic risk markers for defined increments of PWV. In other words, the Authors should let the reader appreciate the probability of a false negative result when they conclude on the lack of relevance of PWV. Last, since the study is based in single measurements, the within-subject between-time variability of the variables of interest and of PWV in particular cannot be assessed. Can the Authors provide at least 1 more measurement in each child? This data would substantially enrich the present ms.

VERSION 1 – AUTHOR RESPONSE

Reviewer's comments

- …the possibility that the study is underpowered is not considered. The Authors should attempt to assess the statistical power of their study in 174 subjects to detect an predefined increase in cardiometabolic risk markers for defined increments of PWV. In other words, the Authors should let the reader appreciate the probability of a false negative result when they conclude on the lack of relevance of PWV.

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Thank you to the reviewer for raising the important issue of power in our study, specifically the question of whether there is sufficient power to capture associations and the possibility of type 2 errors. We have inserted a section in the limitations section of the discussion on this.

We were grateful to the editor for highlighting the importance of using our data for other purposes other than the original obesity intervention study. This does though come with the issue that the original study's sample size was calculated and collected based on power calculations to detect a difference in the original intervention, and not for our analyses as a primary objective.

Our numbers do meet the usual "rules of thumb" (for example 50+8k, where k is the number of independent variables, which would be 58 for univariable analyses)(1) However, we have now referred and referenced more robust sample size calculations as per Cohen(2) using derived graphs considering numbers of variables, power, sample size and effect sizes to capture in regression analyses provided by Miles and Shelving.(3) Reference to these graphs show that our study is adequately powered for univariable analyses to capture associations in regression analysis where effects size are large or medium at the 0.8 level (as per convention). However, we have power at 0.4 level to capture a small effect, so acknowledge we could have seen type 2 errors in reporting no associations between a number of variables – we have been clear about this in our limitations.

We haven't commented on the multivariable models, because in these models the majority of the adiposity markers remained associated at $p<0.05$, and had medium effect sizes (now stated in the results section); thus type 2 errors are less relevant.

We hope that the editor and the reviewer will be sympathetic to this issue of sample size and power in our study, which after all is a major issue for many cross-sectional studies require participants to undergo measurements such as PWV and blood testing (not withstanding the "big data sets"). In univariable analyses, the required sample size at 0.8 power to detect small effect sizes in all such studies require > 400, and for 3 variables in models > 600; sample sizes which are very difficult, if at all possible, in these settings to collect.

As an extension to these comments, we have also added in a measure of effect size for the associations we found in univariable analyses in the main results section, and for the multivariable models. We elected to do this in the text rather than the tables because so few associations were found, it seemed unhelpful to put R2 into the table (2 and 3) for each regression model, and would have detracted from the key information the main tables.

- Last, since the study is based in single measurements, the within-subject between-time variability of the variables of interest and of PWV in particular cannot be assessed. Can the Authors provide at least 1 more measurement in each child? This data would substantially enrich the present ms.

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We take this point. Again this relates to the nature of our data, which is taken from a bigger obesity trial where multiple measurements were taken and set time points. As the reviewer and editor will appreciate, recruitment and retention into an RCT is very challenging, especially in adolescents with obesity. This was a major challenge for our original study. We were very mindful then to reduce burden, and did not repeat PWV measures, only collecting one measure that met the manufacturer's quality indices. We can reassure that it was a single, trained operator, and that quality indices used by the manufacturer are robust and adhered too. We don't however have repeated measures, and so can't take action on this point; though we have been clear about it as a limitation in our discussion.

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