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)	EFFECTOR: Effect of Bariatric Surgery Before Pregnancy on the Vascular Function in the Offspring – Protocol of a cross-sectional follow-up study
AUTHORS	Van De Maele, Karolien; Gies, Inge; devlieger, roland

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Peter Flom Institution and Country: Peter Flom Consulting Competing interests: None
REVIEW RETURNED	07-Nov-2018

GENERAL COMMENTS	I confine my remarks to statistical aspects of this paper. I note that this article is a proposal and that no data have been collected or analyzed yet; my comments are only about the proposed methods. The authors write: <<< RHI will be assessed both as continuous variable and dichotomized (cutoff 1.67 for defining low and high RHI). >>> Arbitrary cutoffs are rarely useful. There seems to be little reason to do it that way. I can't say it's absolutely wrong, but without some substantive reason, there's little to recommend it. The authors write: <<< As continuous outcome, a linear regression model will be used, after assessing the need for transforming the RHI into a symmetric distribution (Box-Cox transformations). >>> This is not correct. First, linear regression makes no assumptions about the distribution of any variable - it makes assumptions about the errors, which are estimated with the residuals. Second, if the residuals are not normal, it is better to use a method that does not make those assumptions. Here, I recommend quantile regression. In fact, I recommend quantile regression regardless of whether the assumptions of linear regression are met, because it allows examination of the extremes of the distribution, not just the mean, and these are likely to be of clinical significance. I also suggest splines as a tool for examining the relationship between the continuous IVs and the DV. I am a little concerned about the inclusion of child's BMI - it seems likely to be highly correlated with the DV and therefore leave little variance to be explained. Are the authors really interested in the relationship between RHI and group after controlling for child BMI? Perhaps they are (I am not a substantive expert) but I wanted to raise the point.

REVIEWER	Reviewer name: Allegaert, Karel Institution and Country: KU Leuven, development and regeneration Competing interests: none
REVIEW RETURNED	07-Dec-2018

GENERAL COMMENTS	The study design is very relevant since aims to further explore the impact of maternal obesity and its management on subsequent vascular function. The authors hereby took the decision to only use 'home' assessment tools, and this is somewhat unfortunately, since the 'vascular' function assessment is overall very limited to a single vascular reactivity test. perhaps retinal vascular structure, or sublingual assessment, or biomarkers (vit D, functional vit K equivalents like carbocylation of matrix Gla protien) can be considered. At best, vascular ultrasound and cardiac ultrasound could have been added. The authors should at least reconsider these limitations.

VERSION 1 – AUTHOR RESPONSE

ANSWERS TO REVIEWER 1 (Peter Flom, USA)

We thank the reviewer for the thorough check of the statistical methodology of our research protocol. It is correct that this is a statistical plan and none of the analysis have yet been performed.

 The authors write: “RHI will be assessed both as continuous variable and dichotomized (cutoff 1.67 for defining low and high RHI).” Arbitrary cutoffs are rarely useful. There seems to be little reason to do it that way. I can't say it's absolutely wrong, but without some substantive reason, there's little to recommend it.

The use of the cutoff values to dichotomize the variables was formulated by analogy with what is used in adult research. However, literature in children and adolescents describe continuous values. Therefor we chose to delete the passage since we agree this does not add substantially to the data analysis. (p7 – main document)

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This is not correct. First, linear regression makes no assumptions about the distribution of any variable - it makes assumptions about the errors, which are estimated with the residuals. Second, if the residuals are not normal, it is better to use a method that does not make those assumptions. Here, I recommend quantile regression. In fact, I recommend quantile regression regardless of whether the assumptions of linear regression are met, because it allows examination of the extremes of the distribution, not just the mean, and these are likely to be of clinical significance. I also suggest splines as a tool for examining the relationship between the continuous IVs and the DV.

Please note the study was powered to show a difference in means. Examinations of the extremes of the distribution might not be feasible due to the sample size. Therefore, we have put linear regression as 1st method (if Gauss-Markov assumptions can be met). Otherwise, the data will be explored with quantile regression. The association between the continuous explanatory variables and the outcome variable will be assessed with splines or loess smoother functions. We changed the main document as can be consulted on page 7 of the main document.

 I am a little concerned about the inclusion of child's BMI - it seems likely to be highly correlated with the DV and therefore leave little variance to be explained. Are the authors really interested in the relationship between RHI and group after controlling for child BMI? Perhaps they are (I am not a substantive expert) but I wanted to raise the point.

Since this will be the first follow-up study of this kind performed in the original cohorts, we are not yet sure whether the children's BMI will be strongly correlated with the original maternal cohort. We are however aware of the raised point and will take it into consideration when analyzing the data.

ANSWERS TO REVIEWER 2 (Editorial Board)

 the study design is very relevant since aims to further explore the impact of maternal obesity and its management on subsequent vascular function. The authors hereby took the decision to only use 'home' assessment tools, and this is somewhat unfortunately, since the 'vascular' function assessment is overall very limited to a single vascular reactivity test. Perhaps retinal vascular structure, or sublingual assessment, or biomarkers (vit D, functional vit K equivalents like carbocylation of matrix Gla protien) can be considered. At best, vascular ultrasound and cardiac ultrasound could have been added. The authors should at least reconsider these limitations.

Response: We consider the limitation of the choice of assessments due to the choice for home visits. However, this choice is substantiated. We know the follow-up research in the offspring of mothers with obesity during pregnancy is extremely difficult for different reasons. Firstly, follow-up studies have low response rate because of difficulties of contacting the people again (changing of address, telephone number etc.) and secondly there is a taboo on the weight problems in the offspring of mothers suffering from obesity. We know home visits provide higher response rates and can be the decisive factor for inclusion. We might be able to have a larger group of children compared to assessments in the hospital. We had to limit however the number of performed tests since all the measurements are performed after an overnight of fastening and the combination of assessments as provided in the protocol now already take 60 to 90 minutes.