

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Multifactorial correlates of blood pressure in South Asian children in Canada: a cross-sectional study
AUTHORS	Fowokan, Adeleke; Punthakee, Zubin; Waddell, Charlotte; Rosin, Miriam; Morrison, Katherine; Gupta, Milan; Rangarajan, Sumathy; Teo, Koon; Lear, Scott

VERSION 1 - REVIEW

REVIEWER	Dr. Jyoti Ratan Ghosh Visva-Bharati University, India
REVIEW RETURNED	08-Dec-2018

GENERAL COMMENTS	may be accepted as it is.
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REVIEWER	Dr Toby Candler MRC The Gambia @ LSHTM
REVIEW RETURNED	14-Dec-2018

GENERAL COMMENTS	<p>Thank you for the opportunity to read this very interesting paper. The paper is well written, succinct and gives a clear message and implications.</p> <p>I have few comments regarding study limitations in the methodology that I feel should be expanded on:</p> <ol style="list-style-type: none">1. Recruitment from schools with a high % of South Asian enrolment: I wonder if there is a degree of selection bias here. How might those South Asian (SA) children differ if they attend a school with a low % of SA enrollment compared to those who attend a school with high % of SA enrollment? and therefore how are the findings generalisable to the wider population2. Elementary vs. High School questionnaire responses: It is likely that the elementary school children will be unable to complete this with much influence from parents, though potentially the high school children will complete more by themselves. I wonder if this specific limitation could be acknowledged?3. Familial Hypertension: why not asked in all participants? this would be hypertension by recall not measured I assume and therefore you would not pick up those with hypertension that have not sought a medical review to detect the hypertension. As you rightly state in the discussion, BP is highly heritable and therefore I dont think this element of the study design allows us to draw conclusions that a genetic component is less likely.
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	<p>4. Using Fathers Education as a proxy for Socioeconomic score: Is there not a composite score that could be used combining mothers education too? These gender structures are changing and the maternal education is of importance to the socioeconomic status as are other measurable factors e.g. housing, disposable income, combined family income etc not captured by asking just about education. Interestingly in your study, maternal education showed higher % attending college in mothers compared to fathers and therefore maybe mother education has a greater influence on family SES compared than you think. Have you tried adjusting for mothers education - does it influence the outcomes?</p>
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REVIEWER	J.A. de Wilde Leiden University Medical Center, the Netherlands
REVIEW RETURNED	18-Dec-2018

GENERAL COMMENTS	<p>Comments to the author This authors present a relevant study of 'correlates' of blood pressure in South Asian children, which adds to the current knowledge of CVD in South Asians. I have some questions and remarks.</p> <p>A. General comments</p> <ol style="list-style-type: none"> 1. It would be interesting to compare the South Asian group with other ethnic groups, as it is now more difficult to value your findings. Were data of other ethnic groups available? 2. Many parts of the paper are formulated imprecise, and as a result difficult to understand and/or interpret (see below). Please check language / have the paper proofread. Overall language and spelling is acceptable, but could be further improved. 3. I miss an explanatory model/framework on how different factors influence the BP/hypertension. This could improve the readability and relevance of your paper. <p>B. Abstract</p> <ol style="list-style-type: none"> 1. Only one aim has been explicated in the abstract while two aims of your study were explained in the last paragraph of the introduction. I think the readability of the abstract would improve if both would be mentioned as the findings are a result of your aims and methods. 2. Page 3, line 3, "physiological variables...", in my opinion these are not physiological variables. Physiological variables are measures that vary over time and is an indicator of the functioning of a certain bodily system. 3. Page 4 "social risk factors", what factors does this refer to. I believe the words are not chosen correctly. What are social risk factors? Please check the terminology and try to be more precise. <p>C. Introduction</p> <ol style="list-style-type: none"> 4. In the introduction words like 'essential' (line 32) and 'vital' (line 44) are used. I actually don't understand why these words are used. I think these words are too strong for what you want to say. 5. Line 49: 'multifactorial variables', what do you mean by that? Do you just mean 'variables' of 'determinants', or actually variables
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that themselves are multifactorial in origin, because that what these words suggest?

6. Page 5, line 49: 'Using a range of multifactorial variables', can you mention some of the variables known from previous studies, and why these could be relevant?

D. Material and methods

7. Page 6, line 42 'were identified by contacting...', how then?

8. Page 8, line 25: was physical activity assessed by a validated questionnaire. If not, why not? 'expressed in MET', you mean you added MET to the database, based on what was answered?

9. Page 8, line 53, "WHO growth references", Why did you use WHO references and not an ethnic specific equivalent, also for other anthropometrics measures?

10. Page 9, line 32 'BP was transformed to standard deviation scores...', the reference does not give enough information to calculate an exact SDS or percentile. How was that then done?

11. Page 10, line 3 "Socioeconomic status was determined according to father's education, owing to widely reported cultural influences on gender structures in the South Asian population²⁴." I do not understand this sentence, please be more precise or clearer.

12. Why didn't you use the highest educational level or both, and why now only the father's? You refer to an Indian study, but I don't believe this does truly represent the household educational level in a country like Canada.

13. Page 10, line 36 "unadjusted linear regression was used. Usually a distinction is made between univariate and multiple or multivariate regression (as you also do in the results section). You complicate it by adding the term 'adjusted' and 'unadjusted'. I understand what you are doing, but I would like to recommend a more structured setup of the statistical analyses section, for instance in step 1..., in step 2 and in step 3..., and use the same structure to describe the results.

14. Page 10, line 42 "...outcome variable in research studies." What studies? Please add references.

15. Page 11, line 11, "Following linear regression", this small sentence is unnecessary, please remove it, as it is now confusing and superfluous. Also can you explain in more detail how the stepwise regression was performed

16. Page 10, line 54, "multifactorial correlates", what are those?

17. Page 11, line 6, "(i.e., sex was adjusted for age and father's education), while age was adjusted for sex and father's education.", what do you mean? How can you adjust sex for age and father's education while you study BP?

18. Page 11, line 23, you added child's perception of body image to the model, but what theory is behind it to add it to the model? What idea lies behind the correlation with BP? I expect it to strongly correlate with BMI, WC and other body fat measures, and as such does not add anything. I would remove this from the analysis.

19. Why was weight added as variable while other, better measures to capture the level of adiposity, such as BMI and WC, were already in the model?

20. Page 11, line 27, height was added as 'covariate' and not z-scores, while for many other factors, such as BMI, WC, the factor was converted in (standardized) z-scores. Shouldn't this also be done for height? If not, why not?

21. Page 11, line 38, the list of possible covariates was only based on one other study? I find this quite thin. Why only add fast foods,

father's education for diastolic BP models. I find this quite random. Why not use one list of potential 'covariates' for both systolic and diastolic BP? You should have a rationale (etiologic model?) how the factors influence the systolic and diastolic BP.

22. Page 12, line 9 "Patient and public involvement", What does this statement add to the manuscript?

E. Results

23. General comment: it could be more structured and clearer if a structured approach was chosen. Now terms like adjusted, unadjusted, covariate, confounder, univariate, multivariate are intermingled. Please use clear definitions and choose the same term throughout the paper.

24. General: it would be helpful to see how much of the variance is explained by each factor. Please consider adding this as it shows the relevance of each factor.

25. Please add a percentage after the number of boys.

26. Please mention the Table at the first instance a sentence refers to the table, and not at the end.

27. Page 13, line 32, ".....for age by sex", please be more precise, what do you mean?

28. I would like to see the age distribution in more detail in table 1, preferably by age in years, as the numbers will likely influence the findings.

29. Can you summarize the results in the first paragraph, as they now duplicate the table, and do not seem to be all relevant. For instance: All adiposity-measures (BMI-Z, WC-Z etc.) are higher in boys compared with girls.

30. Would it be helpful to differentiate between <10 years and > 10 years of age, as I would expect difference between the found correlates, that might now be obscured by pooling all ages together.

31. Page 13, line 26, "After adjustment for covariates...", which do you mean? Please be precise. It is quite confusing what you consider confounder and what independent variable. Sex, age are now one of the explaining variables instead of confounder?

32. Table 2: what do the numbers represent. I reckon betas and 95% confidence intervals. Please mention this in the table, as well as for what factors/variables the analysis was adjusted for. It should be possible to read a table independently from the text.

33. Page 13, line 46, logistic regression analyses are now introduced for the first time. Add the description of the analysis to methods section, statistical analysis.

34. Page 13, line 46, what do you mean by unadjusted logistic regression? You mean these univariate? It is now difficult to interpret.

35. Page 14, line 10, "...western acculturation score....." and systolic hypertension?

36. Page 14, line 44, "...after adjustment....", again for what? And it would be helpful for a reader to mention only the factors that now were removed instead of mentioning the same list

F. Discussion

37. Generally, the discussion could be better structured. Please consider a clearer structure and the use of subheadings.

38. Your main finding is that body adiposity measures (an already well-known factor in BP) best capture the risk of hypertension, while other factors are likely correlated to these body fat measures, such as lifestyle, acculturation So in your opinion, what does your study add to existing knowledge?

39. How do the statistically significant variables/factors explain BP or hypertension? Can you please elaborate on this. Many variables are likely correlated, such as BMI, WC, so these measure at least in part the same. Is there a general causal model possible in which all factors 'fit'? For instance a distinction is made between systolic and diastolic BP. Are different factors involved, or is the causal pathway similar?

40. Page 16, line 5, based on automated BP measurements it is actually incorrect to speak of hypertension, as a diagnosis should be based on multiple measurements on different occasions etc. Are the methods comparable between your study and the other studies that are referred to, as we know many of the 'raised BP cases disappear after repeated measurements? I don't think it is valid now to make hard statements based on an incomplete BP follow-up.

41. Page 16, line 43. Is grip strength a proxy for overall strength, muscle mass or what? If not, what does it tell you then? I seems to me quite important to know what your variables exactly measure?

42. Page 17, line 32 "...ensuring that the epidemiology ...is captured", Can you rephrase?

43. Page 17, line 25, "development of growth charts...". This implies that these are not yet available, but many studies have been published recommending the use of ethnic specific growth references. Also, this is in contrast with the methods used in your study, as you used WHO references. I would recommend using an ethnic specific references.

44. Page 18, line 9 "the positive....". I still think the body image perception largely mirrors the actual body size. I don't see how stress comes in the equation, as the body size (BMI and WC) would already capture this. I don't see an added value of this variable in the current study.

45. Page 18, line 20 "...disappeared upon adjustment". Did you mean adjustment for sociodemographic confounders such as age and sex in the univariate model, or because in a multivariate model the factor 'fell out' because other factors (such as adiposity measures) already captured the effect of these life style factors?

46. Page 18, line 25 "highlights the links between these....", what do you mean to say? Please rephrase.

47. Page 18, line 44 "it is likely that the subset of parents of child participants who provided...". Can you explain how a non-representative sample would have biased the results? The genetic link still exists between father and his child even if the sample was not fully representative of the population. So even if more or less children with a high BP were sampled an association should still be visible. Could this part be underpowered? Only 10 mothers and 30 father had hypertension.

48. Page 19, line 10 "exposure to second-hand smoking...." I 'think the only reason this was not found significantly associated, was the low numbers of children exposed to smoke (underpowered).

Why was this so low? Of course self-reports could have led to socially desirable answers, but how does it relate to other studies?

49. Page 20, line 35 "physiological variables..", are these physiological variables or just anthropometric measures of adiposity?

In conclusion, a relevant study, but it needs at least a major revision

Good luck!

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Dr. Jyoti Ratan Ghosh

Institution and Country: Visva-Bharati University, India

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
may be accepted as it is.

Reviewer: 2

Reviewer Name: Dr Toby Candler

Institution and Country: MRC The Gambia @ LSHTM

Please state any competing interests or state 'None declared': None Declared

Please leave your comments for the authors below

Thank you for the opportunity to read this very interesting paper.

The paper is well written, succinct and gives a clear message and implications.

I have few comments regarding study limitations in the methodology that I feel should be expanded on:

1. Recruitment from schools with a high % of South Asian enrolment: I wonder if there is a degree of selection bias here. How might those South Asian (SA) children differ if they attend a school with a low % of SA enrollment compared to those who attend a school with high % of SA enrollment? and therefore how are the findings generalisable to the wider population.

Response: We chose the two cities we recruited from because those cities contain a large population of South Asians. While schools were one of the avenues used in recruitment, we did recruit a significant amount of the children sampled in this study from religious centres and through adverts in media outlets. Still, we acknowledge in the limitation section that this is a sample of convenience and as such is not a random sample. However, we do not think this is likely to have an effect on the parameters studied for a myriad of reasons. First, while a convenience sample may not be representative enough to provide accurate prevalence estimates for individual variables, the range of values for each variable in our sample is broad enough that estimation of the relationships between variables should not be biased. Second, results from our study are comparable with studies of South Asian children conducted in other population groups. Our estimates of hypertension at 12% is comparable to estimates from Jafar *et al* (2005) using a nationally representative sample in Pakistan. Additionally, associations observed for anthropometric indicators such as height, weight, BMI, WC, WHtR are also similarly comparable to results in the South Asian children research literature. Also, given that one of the primary outcomes in this study is hypertension, and the definition of hypertension in children is technically different to that in adults, we believe a self-selection bias is unlikely.

References

Jafar TH, Islam M, Poulter N, et al. Children in South Asia have higher body mass-adjusted blood pressure levels than white children in the United States: a comparative study. *Circulation*. 2005; 111(10): 1291-1297. doi:10.1161/01.CIR.0000157699.87728.F1

2. Elementary vs. High School questionnaire responses: It is likely that the elementary school children will be unable to complete this with much influence from parents, though potentially the high school children will complete more by themselves. I wonder if this specific limitation could be acknowledged?

Response: Yes, I agree that you would expect differences in responses from elementary school children vs those in high school. This was anticipated, which is why for all children sampled in this study, especially those in elementary school, a trained research assistant was present to clarify questions that might not be clear to them to avoid the kind of parental influence on child's responses highlighted in your comment.

3. Familial Hypertension: why not asked in all participants? this would be hypertension by recall not measured I assume and therefore you would not pick up those with hypertension that have not sought a medical review to detect the hypertension. As you rightly state in the discussion, BP is highly heritable and therefore I don't think this element of the study design allows us to draw conclusions that a genetic component is less likely.

Response: The RICH LEGACY survey included a short survey assessment of all participants (n=762) and a detailed assessment to explore mechanistic and contextual questions in a subset. Parental health history was only collected as part of the detailed assessment in the subset at a second study visit (n=290). We believe that the number of participants who responded to the question appear significant enough to provide detail into the potential role of the heritability of BP/hypertension in this population of South Asian children. Yet, we are aware that the subset might not be completely representative of the total population and have included the following caveat which can be found in (page 18, line 12-14) "However, it is likely that the subset of parents of child participants who provided this information might not be completely representative of the entire cohort, thereby biasing the results."

4. Using Fathers Education as a proxy for Socioeconomic score: Is there not a composite score that could be used combining mothers education too? These gender structures are changing and the maternal education is of importance to the socioeconomic status as are other measurable factors e.g. housing, disposable income, combined family income etc not captured by asking just about education. Interestingly in your study, maternal education showed higher % attending college in mothers compared to fathers and therefore maybe mother education has a greater influence on family SES compared than you think. Have you tried adjusting for mothers education - does it influence the outcomes?

Response: We agree that gender structures in household are evolving and it would have been better to incorporate a measure of socioeconomic status that takes into account both maternal and parental influence (i.e. household income). However, like the information on familial hypertension, information on household income was only filled by a subset of the participants and thus, using it as a measure of socioeconomic status would have excluded a significant portion of the children in this study. We are also unaware of any composite variable that utilizes data on just maternal and paternal education and merges them into one variable that captures these two items. We adjusted separately for both maternal and paternal education and there was no apparent deviation from the trends in the results reported in the study. This has been included in the limitation section and reads as follows "Fourth, the use of father's education as a measure of socioeconomic status pose limitations. Variables like household income would have been preferred, however only a subset of participants provided data on household income, thus its use would have excluded a significant portion of children in this study. However, as a means to confirm the results, we separately adjusted for mother's education and no deviation in study results was observed."(see page 19, line 10-15).

Reviewer: 3

Reviewer Name: J.A. de Wilde

Institution and Country: Leiden University Medical Center, the Netherlands

Please state any competing interests or state 'None declared': None declared
Please leave your comments for the authors below
Please see attachment.

Comments to the author

This authors present a relevant study of 'correlates' of blood pressure in South Asian children, which adds to the current knowledge of CVD in South Asians. I have some questions and remarks.

A. General comments

1. It would be interesting to compare the South Asian group with other ethnic groups, as it is now more difficult to value your findings. Were data of other ethnic groups available?

Response: The main aim of the RICH-LEGACY study is to better understand predictors of risk in the South Asian population given that they are poorly understood. Just as there are several studies with Caucasian/European only population, this study aimed to explore risk distribution and risk predictors specifically in South Asian children given their predisposition to higher cardiovascular disease risk.

2. Many parts of the paper are formulated imprecise, and as a result difficult to understand and/or interpret (see below). Please check language / have the paper proofread. Overall language and spelling is acceptable, but could be further improved.

Responses: We have made changes to the parts highlighted and also proof read to ensure that your comments are addressed within the manuscript.

3. I miss an explanatory model/framework on how different factors influence the BP/hypertension.

This could improve the readability and relevance of your paper.

Responses: The variables selected in this manuscript were chosen from a recent systematic review of 100 papers that explores correlates of elevated BP and hypertension in children. In this study, we aimed to explore which of these identified variables are relevant within the South Asian children population. For those variables that appear relevant (i.e. those with significant associations), we highlight potential mechanisms linking these variables to BP and hypertension in the discussion section as is common practice in the research literature. As the variables included in this study are extensive, and in most cases the pathways linking the variables to hypertension are divergent, complex and in some cases not well-understood, highlighting potential mechanism linking every single one of them to BP and hypertension will distract from the objectives of this particular manuscript.

B. Abstract

1. Only one aim has been explicated in the abstract while two aims of your study were explained in the last paragraph of the introduction. I think the readability of the abstract would improve if

both would be mentioned as the findings are a result of your aims and methods.

Responses: Changes have been made in the abstract to include the full aims specified in the last paragraph of the introduction (see page 2, lines 4-6)

2. Page 3, line 3, "physiological variables...", in my opinion these are not physiological variables.

Physiological variables are measures that vary over time and is an indicator of the functioning of a certain bodily system.

Responses: The word physiological has been taken out and the line currently reads as “our findings suggest that variables such as age, sex, height, adiposity, and heart rate provide stronger explanatory capacity to BP variance and hypertension risk than other multifactorial variables in South Asian children.” (See page 3, line 3)

3. Page 4 “social risk factors”, what factors does this refer to. I believe the words are not chosen correctly. What are social risk factors? Please check the terminology and try to be more precise.

Response: The word social risk factors is common research terminology used to describe factors relating to conditions in which people live, attend school, grow, and develop. Its use is similar to the term “social determinants”, except determinants denotes a causal relationship and given the cross sectional nature of this study assertions about causal relationships cannot be made, hence the use of the term “risk factors”. We believe this terminology best describes what we aim to communicate in that section of the manuscript.

C. Introduction

4. In the introduction words like ‘essential’ (line 32) and ‘vital’ (line 44) are used. I actually don’t understand why these words are used. I think these words are too strong for what you want to say.

Response: Both “essential” and “vital” were used to denote “important”. They have both been changed to “important” in line with your comment (See page 5, line 13 and 18)

5. Line 49: ‘multifactorial variables’, what do you mean by that? Do you just mean ‘variables’ of ‘determinants’, or actually variables that themselves are multifactorial in origin, because that what these words suggest?

Response: The term multifactorial refers to variables that are multifactorial in origin (i.e. involving a number of factors). As the variables in our study includes physiological variables (factors relating to biology), behavioral (factors relating to lifestyle or individual actions) and social variables (factors relating to conditions in which people live, attend school, grow, and develop), we believe this word appropriately describes what we aim to convey within the manuscript. The term multifactorial has also been defined within the manuscript. (See page 5, line 20-21)

6. Page 5, line 49: ‘Using a range of multifactorial variables’, can you mention some of the variables known from previous studies, and why these could be relevant?

Response: As is currently stated in the introduction, ALL the variables selected and explored in this manuscript were chosen because they were found to be relevant (i.e. previous studies have reported association between these variables with elevated BP and hypertension) as evidenced by the systematic review cited which explored correlates of blood pressure and hypertension in children. This particular systematic review reviewed 100 research papers exploring predictors of elevated BP and hypertension in children. Because, these variables have been identified as variables that are commonly associated with BP and hypertension in other children population, we believe it is worth exploring to see if they are relevant within the South Asian population. We provide a detailed list and description of the variables used in this manuscript in the methods and statistical analysis section of the manuscript.

D. Material and methods

7. Page 6, line 42 'were identified by contacting...', how then?

Responses: Letters were sent to the school boards. We have made changes to the manuscript to reflect that letters were the medium used in the exchange with the school board. It currently reads as "Letters were first sent to school boards to identify elementary schools with a high rate of South Asian enrolment." (See page 6, line 16 and 17)

8. Page 8, line 25: was physical activity assessed by a validated questionnaire. If not, why not?

'expressed in MET', you mean you added MET to the database, based on what was answered?

Response: Yes, physical activity was assessed using a standardized questionnaire. The metabolic equivalent of task (MET) is the ratio of the work metabolic rate to resting metabolic rate and it quantifies the amount of energy expended based on the responses provided on the type of activity, and the amount spent participating in the activity daily.

9. Page 8, line 53, "WHO growth references", Why did you use WHO references and not an ethnic specific equivalent, also for other anthropometrics measures?

Responses: We chose to use the WHO growth reference because we could not find any South Asian ethnic specific reference values for Canadian or North American children. We understand that ethnic specific reference values would have provided useful information, however, in the absence of any, the WHO reference values which includes children from a North American country (USA) country appears valuable. It is important to note that we only used the WHO reference chart for the conversion of our BMI variable. For, WC and WHtR, we utilized recently published LMS values for North American Children (see Sharma et al., 2016). The use of multiple reference values for adiposity metrics allowed for triangulation in results. We are confident that the consistency observed in terms of the association between the adiposity metrics used in this study and hypertension potentially highlights the suitability of the reference values for this population of South Asian children.

Reference

Sharma, A.K., Metzger, D.L., Daymont, C., Hadjiyannakis, S. and Rodd, C.J., 2015. LMS tables for waist-circumference and waist-height ratio Z-scores in children aged 5-19y in NHANES III: association with cardio-metabolic risks. *Pediatric research*, 78(6).

10. Page 9, line 32 'BP was transformed to standard deviation scores...', the reference does not give enough information to calculate an exact SDS or percentile. How was that then done?

Response: Blood pressure was transformed to SDS using the method proposed by The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents (NHBPEP, 2004). The appendix of the NHBPEP (2004) contains adequate information on how this is to be done. The process involved is mathematical and extensive which is why we have referenced it instead.

Reference

National High Blood Pressure Education Program Working Group on High Blood. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004;114(2 Suppl 4th Report):555-576. doi:10.1542/peds.114.2.S2.555

11. Page 10, line 3 "Socioeconomic status was determined according to father's education, owing to widely reported cultural influences on gender structures in the South Asian population²⁴." I do not understand this sentence, please be more precise or clearer.

Response: This sentence implies that father's highest level of education was used as a proxy variable for socioeconomic status. We have rephrased the sentence to improve clarity. We chose father's education because the South Asian family structure has been reported to be patriarchal in nature. We acknowledge the drawbacks in using this variable as opposed to variables such as "household income"; however, only a fraction of the participants recruited for this study provided information on household income, thus utilizing household income as a measure of socioeconomic status would have excluded a significant portion of the children in the study.

12. Why didn't you use the highest educational level or both, and why now only the father's? You refer to an Indian study, but I don't believe this does truly represent the household educational level in a country like Canada.

Response: We acknowledge the drawbacks in using this variable as opposed to variables such as "household income" and we have explicitly stated this in the limitations section (see pages 19, lines 13-18); however, only a subset of the study population provided data on household income, thus, adjusting for this would have excluded a significant portion of the children in the study. However, we also adjusted separately for both maternal and paternal education and there was no apparent deviation from the trends in the results reported in the study. Adjusting for both would have possibly meant adjusting for education in duplicates given how similar the distribution of education were for both mothers and fathers (see table 1).

13. Page 10, line 36 "unadjusted linear regression was used. Usually a distinction is made between univariate and multiple or multivariate regression (as you also do in the results section). You complicate it by adding the term 'adjusted' and 'unadjusted'. I understand what you are doing, but I would like to recommend a more structured setup of the statistical analyses section, for instance in step 1..., in step 2 and in step 3..., and use the same structure to describe the results.

Response: We will stick to the use of the terms "adjusted, unadjusted and stepwise regression" in describing the analysis conducted as they best convey the statistical process in this paper and use them consistently across the board.

14. Page 10, line 42 "...outcome variable in research studies." What studies? Please add references.

Response: References have been added to the sentence (see page 10, line 19).

15. Page 11, line 11, "Following linear regression", this small sentence is unnecessary, please remove it, as it is now confusing and superfluous. Also can you explain in more detail how the stepwise regression was performed

Response: We have taken out the phrase "following linear regression" from the sentence. It now reads as "To address the second study objective, stepwise multiple linear regression analyses were used to identify the combination of risk factors that best explained the variance in BP in South Asian children." (See page 11, line 8-10)

The manuscript has been edited to provide more detail about how stepwise regression was carried out that reads as "Specifically, for this analysis, we utilized the backward method to select the list of multifactorial correlates that provide significant contribution to the outcome (systolic and diastolic BP z-scores) using an entry criterion of $p < 0.05$ and a removal criterion of $p > 0.10$. The specific list of correlates (age, sex, height, weight, heart rate, BMI z-score, WC z-score, WHtR z-score, parental history of hypertension, parental education, exposure to bullying and violence, traditional and western acculturation scores, physical activity in school and outside school, dietary variables and second-hand smoking) considered for introduction in the backward stepwise regression model were chosen *a priori* based on literature evidence¹³ and whether they had a p value < 0.05 in univariate analysis. Using the aforementioned criteria, the following variables were considered in step-wise regression analysis: age, sex, height, weight, BMI z-score, WC z-score, WHtR z-score, heart rate, western acculturation

score, child's perception of body image, and grip strength. In addition to these variables, father's education, daily intake of fast foods and total daily intake were considered in diastolic BP z-score models. The adjusted R squared value for each model provides the combined contribution of the variables in the model to the variance in BP z-scores" (See pages 11, lines 20-23 and 12, lines 1-3)

This information contains adequate detail explaining in a sequential manner how the backward stepwise regression process was carried out.

16. Page 10, line 54, "multifactorial correlates", what are those?

Response: The term multifactorial refers to variables that are multifactorial in origin (i.e. involving a number of factors). To allow for consistency we have changed the use of "multifactorial correlates" to multifactorial variables" which we define in the introduction section of the manuscript.

17. Page 11, line 6, "(i.e., sex was adjusted for age and father's education), while age was adjusted for sex and father's education.", what do you mean? How can you adjust sex for age and father's education while you study BP?

Response: Father's education as we explicitly state in this manuscript was used as a proxy for socioeconomic status. We adjusted for age and father's education on the association between sex and BP because we were trying to eliminate potential confounding effect of age and socioeconomic status which influence behaviors that might have an effect on children's BP. This all feeds back into the idea that the causes of BP are multifactorial and as such when exploring the effect of a physiologically/biologically determined variable like sex, adjusting for sociodemographic variables appears to be good science given their widely documented independent effects on BP.

18. Page 11, line 23, you added child's perception of body image to the model, but what theory is behind it to add it to the model? What idea lies behind the correlation with BP? I expect it to

strongly correlate with BMI, WC and other body fat measures, and as such does not add anything. I would remove this from the analysis.

Response: As we mentioned in the manuscript, the variables included in this paper were carefully pre-selected from a recently published systematic review. Yes, you are right that the Stunkard silhouettes might mirror body weight variables in which case its inclusion is just meant to provide consistency to the relationship between adiposity and BP. It is also possible that due to societal criticism of fatter body types this variable may be more predictive of graded increase in stress levels experienced based on how weight sizes are perceived. This was expressed in detail in the discussion section and provides the underlying rationale for its inclusion in the manuscript.

19. Why was weight added as variable while other, better measures to capture the level of adiposity, such as BMI and WC, were already in the model?

Response: We chose to include weight in the analysis in addition to the other variables because weight is a direct assessment of adiposity, whereas other measures are derived. As you also rightly state in your comment, variables like BMI, WC and WHtR are all measures of adiposity yet we also still included them in linear regression analysis. This is because the aim of the linear regression models is to inform on how these variables individually correlates with BP and hypertension both before and after adjustment for covariates. Whereas in stepwise regression, a more rigorous approach that considers which aggregate set of variables provided more of an explanatory capacity to the models was adopted. Additionally, one of the reasons why we also chose multiple adiposity metrics is to allow for triangulation (convergence) in findings and potentially demonstrate their consistency as correlates of BP and hypertension which is one of the important criteria in the Bradford-Hill model of causation.

It should also be noted that every single variable selected in this manuscript was chosen as we state in the manuscript because they have been previously identified as significant correlates/predictors in studies conducted in other children population.

20. Page 11, line 27, height was added as 'covariate' and not z-scores, while for many other factors, such as BMI, WC, the factor was converted in (standardized) z-scores. Shouldn't this also be done for height? If not, why not?

Response: One of the reasons why z-scores are utilized in the children population is that unlike in adults where variables like BMI<25 and BP<140/90mmhg are considered risk factors for cardiovascular disease risk, cardiovascular disease rarely manifests itself in children and as such defining obesity or hypertension based on these cut-offs appear impractical. As such, the use of z-scores which allows for comparison with a reference population is adopted. Regarding height, the association between height and BP in children is not uniformly consistent in the literature. Some papers have reported positive associations while some have reported negative associations. In fact unlike BMI z-scores or WC z-scores, there is no known cut-off for height that has been shown to be associated with an adverse risk of hypertension in children. Of all the

papers we reviewed in our earlier systematic review (which we used to inform the variables selected in this study) (Fowokan et al, 2018), none converted height to z-scores in their estimation with hypertension.

If the outcome we examined in our study was perhaps stunting or malnutrition then it will perhaps be necessary to convert to z-scores because in both cases low height is known to be a predictor.

Reference

Fowokan, A.O., Sakakibara, B.M., Onsel, N., Punthakee, Z., Waddell, C., Rosin, M. and Lear, S.A., 2018. Correlates of elevated blood pressure in healthy children: a systematic review. *Clinical obesity*, 8(5), pp.366-381.

21. Page 11, line 38, the list of possible covariates was only based on one other study? I find this quite thin. Why only add fast foods, father's education for diastolic BP models. I find this quite random. Why not use one list of potential 'covariates' for both systolic and diastolic BP? You should have a rationale (etiologic model?) how the factors influence the systolic and diastolic BP.

Response: Our manuscript was informed by a systematic review which although is one study combines information in about 100 papers conducted from 2000-2018 (Fowokan et al, 2018). What was meant in the sentence was that while we pre-selected the list of variables included in our research paper using information from the systematic review, the specific variables included in the backward stepwise regression models were based on whether they had a p value <0.05 in unadjusted analysis and their contribution to the stepwise models. This sentence was describing in detail how we went about the statistical process for the stepwise regression and arrived at the variables in the stepwise regression analysis results. This is standard practice when reporting stepwise regression models.

To reiterate, the variables chosen in this manuscript were systematically chosen and we explored their association uniformly for both systolic and diastolic BP/hypertension in this study. As you might have noticed in the introduction section, our objectives were two-fold. What is being referred to in the comment above is the second objective which aims to identify the combined aggregate of factors that provide the most explanatory capacity to BP. To do this, we utilized the stepwise regression method. This analytical method is different to ordinary linear regression because the statistical software

through a process of elimination decides which combination of variables contributes the most to explaining the variance in BP risk.

Reference

Fowokan, A.O., Sakakibara, B.M., Onsel, N., Punthakee, Z., Waddell, C., Rosin, M. and Lear, S.A., 2018. Correlates of elevated blood pressure in healthy children: a systematic review. *Clinical obesity*, 8(5), pp.366-381.

22. Page 12, line 9 “Patient and public involvement”, What does this statement add to the manuscript?

Response: The heading titled “Patient and public involvement” is mandatory for all articles submitted to BMJ open.

E. Results

23. General comment: it could be more structured and clearer if a structured approach was chosen.

Now terms like adjusted, unadjusted, covariate, confounder, univariate, multivariate are intermingled. Please use clear definitions and choose the same term throughout the paper.

Response: Changes have been made to ensure the terms “adjusted” and “unadjusted” are used consistently within the manuscript rather than other synonyms to avoid any potential obscurations. Results reported have been edited to follow a structured approach. We split the results into two sections (i.e. correlates of systolic BP and systolic hypertension and correlates of diastolic BP and hypertension). For each section we first reports results of unadjusted analysis and adjusted analysis for BP (i.e. linear regression models), followed by results from stepwise regression indicating the aggregate combination of variables and their contribution to the variance in BP z-scores. Each section is then capped off by providing results from unadjusted and adjusted models for hypertension (i.e. logistic regression models).

24. General: it would be helpful to see how much of the variance is explained by each factor. Please consider adding this as it show the relevance of each factor.

Response: The stepwise regression analytical outputs only provide the relevance of the combined list of variables included in the final model and not the contribution of individual variables. This is documented by the adjusted R squared variable in the model summary estimates.

25. Please add a percentage after the number of boys.

Response: A percentage has been added to reflect this comment (see page 12, line 16).

26. Please mention the Table at the first instance a sentence refers to the table, and not at the end.

Response: Changes have been made to reflect this comment

27. Page 13, line 32, “.....for age by sex”, please be more precise, what do you mean?

Response: The sentence has been edited to reflect the comment.

28. I would like to see the age distribution in more detail in table 1, preferably by age in years, as the numbers will likely influences the findings.

Response: It is important to note that the conversion of BP to z-scores ensures that resulting z-score variables account for age, sex and height differences (see NHBPEP, 2004). This ensures that standardized comparisons can be made across populations of similar or different ages, sex and height. In addition to this, we also chose to adjust for any possible residual effects of age by also adjusting for age in the adjusted models of the regression analysis. The steps taken ensure that whatever confounding influence age might have on the results are taken into account.

Additionally, we document mean and SD values within the table. For our analysis, age was operationalized as a continuous variable and not as a categorical variable. We have provided a summarized breakdown of ages represented in this study below.

Age groups	N (frequency)	Percentage
5-7years	59	8%
7-9years	469	62%
9-11years	62	8%
11-13years	0	0
13-15years	128	17%
15-17years	44	6%

Reference

National High Blood Pressure Education Program Working Group on High Blood. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004;114(2 Suppl 4th Report):555-576. doi:10.1542/peds.114.2.S2.555

29. Can you summarize the results in the first paragraph, as they now duplicate the table, and do not seem to be all relevant. For instance: All adiposity-measures (BMI-Z, WC-Z etc.) are higher in boys compared with girls.

Response: We have taken out sentences that appear irrelevant such as the mean of non-transformed BP variables and only report statistically significant differences between boys and girls for variables where differences were observed (see page 12, line 16-22).

30. Would it be helpful to differentiate between <10 years and > 10 years of age, as I would expect difference between in the found correlates, that might now be obscured by pooling all ages together.

Responses: We are not aware of any distinction between those age groups not already addressed by converting BP to z-scores (which account for age, sex and height differences in BP, thus allowing for the comparison for children with similar or different ages, sex or height) and adjusting for age in linear and logistic regression models that would provide a sound rationale for dichotomizing children into the age groups you specify.

31. Page 13, line 26, "After adjustment for covariates...", which do you mean? Please be precise. It is quite confusing what you consider confounder and what independent variable. Sex, age are now one of the explaining variables instead of confounder?

Response: We have changed the term covariate to confounders. It is important to note that sex can be an independent variable in its association with BP/hypertension and also be a confounding factor in the relationship between another variable (e.g. age) with BP/hypertension. While we chose age, sex and father's education as the list of confounders, we also wanted to explore the independent association of these variables with hypertension as they were identified by the systematic review that informed the choice of variables we included as relevant correlates of BP and hypertension. To explore the association for age (we only adjusted for sex and father's education while for sex; we adjusted for age and father's education). This is important because it is widely known that blood

pressure fluctuates based on age and sex, and socioeconomic status largely influences health behaviors.

Page 11 line 2-7 which reads as “While age and sex were identified as potential confounders in the association between the other variables assessed in this study with BP and hypertension, we also wanted to examine their independent associations with BP and hypertension. To do this, they were each removed from the list of confounders we adjusted for when exploring their effect on BP z-scores and hypertension (i.e., sex was adjusted for age and father’s education, while age was adjusted for sex and father’s education.)” provides detailed information on this.

32. Table 2: what do the numbers represent. I reckon betas and 95% confidence intervals. Please mention this in the table, as well as for what factors/variables the analysis was adjusted for. It should be possible to read a table independently from the text.

Responses: The tables all include a description that provides information on abbreviations, detail on covariates adjusted for and information presented within the tables. This information for table 2 can be found right at the bottom of the table and it reads as

“Model adjusted for age, sex and father’s education

Values presented are β (95% confidence intervals), and p values

BMI= body mass index, WC= waist circumference, WHtR= waist to height ratio, BP =blood pressure, MET=Metabolic equivalent of task

^aAge was adjusted for sex and father’s education

^bSex was for adjusted for age and father’s education”(See page 30, line)

33. Page 13, line 46, logistic regression analyses are now introduced for the first time. Add the description of the analysis to methods section, statistical analysis.

Responses: This is not the first time we introduced logistic regression analysis in the manuscript. In page 10 line 22, we describe the use of logistic regression analysis as follows: “Similarly, unadjusted and adjusted (age, sex and father’s education) logistic regression analysis was used to explore clinically-relevant associations among the multifactorial correlates with systolic and diastolic hypertension.”

34. Page 13, line 46, what do you mean by unadjusted logistic regression? You mean these univariate? It is now difficult to interpret.

Response: The word univariate and unadjusted were sometimes used interchangeably in the manuscript. The term “univariate” linear regression focuses on exploring the association between a single predictor variable and one outcome variable in the regression model. The term “unadjusted” also means that no other variable (besides the predictor variable) was included in the regression models. These both express same thing, however for consistency of use, we have made changes within the manuscript to reflect the use of unadjusted rather than univariate.

35. Page 14, line 10, “..western acculturation score.....” and systolic hypertension?

Response: Changes have been made to reflect western acculturation score and systolic hypertension.

36. Page 14, line 44, ..after adjustment....., again for what? And it would be helpful for a reader to mention only the factors that now were removed instead of mention the same list.

Response: The list of confounders we adjusted for (i.e. age, sex, father's education) are specified in the statistical methods section.

We have edited both the section on systolic BP/hypertension and diastolic BP and hypertension to emphasize variables that attenuated and became non-significant upon adjusting for confounders and not those that remained.

F. Discussion

37. Generally, the discussion could be better structured. Please consider a clearer structure and the use of subheadings.

Response: The structure has been edited to ensure that the discussion contains a seamless structure. First, we summarize the results, and then highlight the similarities of our results to other published manuscripts. Second, we describe mechanisms linking our reported associations to hypertension. Third, we highlight how results from our stepwise regression suggest the need for more research as a significant amount of the variance of BP remains unexplained. This is finally capped off by the limitations and conclusion section.

38. Your main finding is that body adiposity measures (an already well-known factor in BP) best capture the risk of hypertension, while other factors are likely correlated to these body fat

measures, such as lifestyle, acculturation So in your opinion, what does your study adds to existing knowledge?

Response: The association between adiposity with hypertension wasn't the main finding of the study but just one of the findings we highlight. We document associations between a range of variables (i.e. heart rate, height, age, sex, grip strength) with BP z-score and hypertension in South Asian children and show that the combination of age, sex, BMI z-score, heart rate and weight explain 30% of the variance in systolic BP risk in this population and that age, BMI z-score, heart rate and daily intake of fast foods account for 23% of the diastolic BP variance. This is highlighted in the first paragraph of the discussion and throughout the entire discussion section. We only stress out the impact of adiposity because of its consistency observed across the range of adiposity metrics assessed in this study.

39. How do the statistically significant variables/factors explain BP or hypertension? Can you please elaborate on this. Many variables are likely correlated, such as BMI, WC, so these measure at least in part the same. Is there a general causal model possible in which all factors 'fit'? For instance a distinction is made between systolic and diastolic BP. Are different factors involved, or is the causal pathway similar?

Response: Because of the cross-sectional nature of the study we make no assertions about causality or causal pathways. What is clear in terms of the etiopathogenesis of BP and hypertension in children is that they involve divergent, multiple pathways, especially those involved in BP regulation i.e. renin angiotensin aldosterone system (RAAS), sympathetic nervous system etc. However, much remains to be understood in terms of the specific understanding of how these regulation pathways might link specific variables such as increased adiposity, sex differences, increased height to BP and hypertension. Where we can, we identify potential plausible mechanisms that have been documented in the research literature that explain the links between particular variables and their associations with hypertension. In terms of differences between the mechanistic pathways for systolic and diastolic BP no clear distinctions are made in the literature. This is understandable given that although systolic BP

and diastolic BP measure BP at different stages (at rest and when the heart is pumping blood), they both capture the pressure of the blood flowing through the blood vessels.

BMI, WC, WHtR although have slight distinctions all measure adiposity (body fat). These clearly all fit in the same mechanistic pathway which is discussed in page 17 line 35 and reads as “The consistent association between adiposity and hypertension, including the higher prevalence of hypertension in this population, reinforces their connections through well-established mechanisms. Specifically, the South Asian phenotype of higher body fat—especially the visceral type which has been identified in adults—when compared to their Caucasian peers, could activate the formation of pro-inflammatory cytokines such as Interleukin 6 (IL-6) which results in physiological changes that could lead to endothelial and vascular dysfunction through the development of insulin resistance, resulting in an increased predisposition for hypertension.”

40. Page 16, line 5, based on automated BP measurements it is actually incorrect to speak of hypertension, as a diagnosis should be based on multiple measurements on different occasions etc. Are the methods comparable between your study and the other studies that are referred to, as we know many of the ‘raised BP cases disappear after repeated measurements? I don’t think it is valid now to make hard statements based on an incomplete BP follow-up.

Response: According to (NHBPEP, 2004), “hypertension is defined as average SBP and/or DBP that is greater than or equal to the 95th percentile for sex, age, and height on three or more occasions.” Although the NHBPEP (2004) report suggests that the preferred method be by auscultation, it does not invalidate the use of oscillometric methods in measuring BP or in defining hypertension. It only highlights the discrepancies that have been documented in the algorithms in determining BP by automated devices. To address this we took proper care to ensure that our device was regularly validated as suggested by the NHBPEP report. For this study, BP was measured on three different occasions and in relation to the other studies referred to in the manuscript, they are comparable on those basis.

Reference

National High Blood Pressure Education Program Working Group on High Blood. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004;114(2 Suppl 4th Report):555-576. doi:10.1542/peds.114.2.S2.555

41. Page 16, line 43. Is grip strength a proxy for overall strength, muscle mass or what? If not, what does it tell you then? I seems to me quite important to know what your variables exactly measure?

Response: Grip strength is a proxy for muscle strength (Wind et al, 2010). In our study we observed a positive association between grip strength and hypertension (i.e. higher grip strength was association with increased hypertension risk), suggesting that strength training in children might not be beneficial to hypertension risk in children. In fact, other studies have also documented same results and suggest that aerobic exercise might be more beneficial to muscle strength (as measured by grip strength) in relation to hypertension risk in children (Pescatello et al., 2015). This was highlighted in page 16, line 43 as follows: “Moreover, the positive association between grip strength (a measure of muscle strength) with systolic BP z-score and hypertension upon adjustment in this study raises questions about the benefits of strength training in children. The benefits of physical activity including aerobic exercise in relation to hypertension remain clear; however, the benefits of strength training in relation to hypertension risk, relative to the benefits of aerobic exercise, appear questionable³⁸. It is unclear

what might be responsible for the positive effect observed between grip strength and systolic BP z-score; however, findings from our study appear consistent with studies which have explored this association in Chinese and American children”

Reference

Wind, A.E., Takken, T., Helders, P.J. and Engelbert, R.H., 2010. Is grip strength a predictor for total muscle strength in healthy children, adolescents, and young adults?. *European journal of pediatrics*, 169(3), pp.281-287.

Pescatello, L.S., MacDonald, H.V., Lamberti, L. and Johnson, B.T., 2015. Exercise for hypertension: a prescription update integrating existing recommendations with emerging research. *Current hypertension reports*, 17(11), p.87.

42. Page 17, line 32 “...ensuring that the epidemiology ...is captured”, Can you rephrase?

Response: The sentence has been rephrased.

43. Page 17, line 25, “development of growth charts...”. This implies that these are not yet available, but many studies have been published recommending the use of ethnic specific growth

references. Also, this is in contrast with the methods used in your study, as you used WHO

references. I would recommend using an ethnic specific references.

Response: While certain countries have published ethnic specific growth chart data, we were unable to find any South Asian specific reference growth chart for children living in Canada (or North-America). It should be noted that the WHO growth reference was used only for the conversion of BMI measures to z-scores. We used NHANES values by the recently published Canadian study for the conversion of WC and WHtR to z-scores, as we believe they better capture the growth trajectories of this population of Canadian-South Asian children better than any South Asian ethnic growth chart potentially developed in a country of lesser affluence such as those developed in the Indian subcontinent. The use of multiple reference charts for adiposity metrics allowed for triangulation (convergence) in results. We are confident that the consistency observed in terms of the association between the adiposity metrics used in this study and hypertension potentially highlights the suitability of the reference values used in this study.

It should also be emphasized that although ethnic specific reference curve would have been preferred, the population used in the development of the WHO reference chart comprised of children from North American (USA), thus, making it comparable.

44. Page 18, line 9 “the positive...”. I still think the body image perception largely mirrors the actual body size. I don't see how stress comes in the equation, as the body size (BMI and WC) would already capture this. I don't see an added value of this variable in the current study.

Response:

It is clear that the Stunkard's silhouette although has been shown to be a good assessor of weight status is based on individual perception. It is plausible to theorize based on society's caustic approach to body weight status, especially in kids who are impressionable, that their perception of body weight might fluctuate based on the level of criticism or bullying received. It is important to note that this is just a theory and our inclusion of this variable in addition to other variables of adiposity is to ensure triangulation in findings and establish “consistency” between adiposity and hypertension, which is an important criterion in the Bradford-Hill list for the determination of causality between variable and outcome.

45. Page 18, line 20 "...disappeared upon adjustment". Did you mean adjustment for sociodemographic confounders such as age and sex in the univariate model, or because in a multivariate model the factor 'fell out' because other factors (such as adiposity measures) already captured the effect of these life style factors?

Response: What was meant in that sentence was that after adjusting for age, sex and father's education, most of the associations observed between social and lifestyle variables with BP and hypertension attenuated and became insignificant. The sentence has been rephrased to reflect this.

46. Page 18, line 25 "highlights the links between these....", what do you mean to say? Please rephrase.

Response: The sentence has been rephrased.

47. Page 18, line 44 "it is likely that the subset of parents of child participants who provided...". Can you explain how a non-representative sample would have biased the results? The genetic link still exists between father and his child even if the sample was not fully representative of the population. So even if more or less children with a high BP were sampled an association should still be visible. Could this part be underpowered? Only 10 mothers and 30 father had hypertension.]

Response: The RICH LEGACY survey included a short survey assessment of all participants (n=762) and a detailed assessment to explore mechanistic and contextual questions in a subset. Parental health history was only collected as part of the detailed assessment in the subset at a second study visit (n=290). It is clear that the amount of people who provided data on familial history of hypertension are a fraction of the full RICH-LEGACY sample. As such our claim that the non-representative nature of the subset might bias the sample is based on the fact that we cannot clearly state whether the subset of people were randomly chosen and might accurately reflect the entire study population or whether the missing data might be informative.

Statistical power as we know is chiefly affected by the effect size, sample size and the level of significance (i.e. $p < 0.05$ or $p < 0.01$). Given that statistical significance was set at $p < 0.05$ and the sample size still appears large, we have no reason to believe that the association observed between father and mother's history of hypertension is a false negative one.

48. Page 19, line 10 "exposure to second-hand smoking...." I think the only reason this was not found significantly associated, was the low numbers of children exposed to smoke (underpowered). Why was this so low? Of course self-reports could have led to socially desirable answers, but how does it relate to other studies?

Response: We do acknowledge that there is an inherent bias with reporting self-reported data. However, the results are not unreasonable given strict regulation against public smoking in most Canadian provinces (especially those we recruited from) and aggressive social marketing against smoking in public places.

49. Page 20, line 35 "physiological variables..", are these physiological variables or just anthropometric measures of adiposity?

Response: By physiology (we mean measures related to biology). In this case, this was not just limited to adiposity but included measures like height, sex and heart rate. We believe the use of “physiological” best conveys the message. We have also defined the use of physiology as it pertains to its use in this manuscript as (factors related to biology) see page 5, line 23.

In conclusion, a relevant study, but it needs at least a major revision

Good luck!

VERSION 2 – REVIEW

REVIEWER	Toby Candler MRC The Gambia at LSHTM
REVIEW RETURNED	21-Jan-2019

GENERAL COMMENTS	Points addressed adequately from my initial review.
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REVIEWER	Jeroen De Wilde Leiden University Medical Center
REVIEW RETURNED	01-Feb-2019

GENERAL COMMENTS	The authors have provided a thoroughly revised manuscript, including elaborate answers to the comments and questions. The quality has greatly improved, and the questions and comments made have been addressed sufficiently.
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