Author’s response to reviews

Title: Overweight at age two years in a multi-ethnic cohort (ABCD study): the role of prenatal factors, birth outcome and postnatal factors

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Author’s response to reviews: see over
To the editors,

First of all, we would like to thank you for the opportunity to re-submit a revised version of our manuscript and to thank both reviewers for the valuable comments to improve our paper. Below we present our point-by-point response to each of the Editor's/Reviewers’ comments. We hope that we have adequately revised the manuscript, and look forward to your response in due course.

For any further inquiries or concerns please contact us via the email address below.

Yours sincerely,

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Reviewer's report
Reviewer 1: Grete Helen Bratberg

Major Compulsory revisions:

1) The title of this paper may mislead the reader to think that the findings could be generalized to ethnic differences in general. All children included in this study were born in Amsterdam, with its own urban characteristics and with its own ethnic minorities/cultures. The title should therefore make it clear that this study is derived from the ABCD study.

Response 1: As requested, we have changed the title to:
Overweight at age two years in a multi-ethnic cohort (ABCD study): the role of prenatal factors, birth outcome and postnatal factors

2) It was concluded that the ethnic differences largely were attributed to their mothers BMI before pregnancy and 6 months weight gain, but how much these factors exactly contributed remains inconclusive. In the discussion part the statements were more discreet (p 11, paragraph 2) “…and the results suggest at least a role for the maternal prepregnancy BMI and infant weight gain in the first 6 months to explain the ethnic differences…” . There is some discrepancy between these statements that should be clarified.

Response 2: We agree that more information on the magnitude of the contribution should be given. On average, 17% of the ethnic differences in overweight was attributed to pre-pregnancy BMI, and 33% to weight gain during the first 6 months.

- We have added this information to the Results section (see also comment 21e).
- Also, we have changed the sentence in the Discussion to read: …. the explanatory role of maternal pre-pregnancy BMI and infant weight gain appeared to be large.

3) The authors’ state in the abstract (and elsewhere) that little is known about ethnic differences and explanatory factors related to overweight in infancy. According to PubMed there is a large body of literature, also from the Netherlands with focus on ethnic differences especially between Dutch, Turkish and Moroccan children. For some reason, only a few of them have been mentioned. E.g. a recent study of de Wilde et al. (2009) showed that the prevalence of overweight among Dutch girls 3-16 years had decreased between 1999 and 2007 while Turkish children had become more obese during the same period. Since the outcome data in this study
was obtained during 2005-2006, these changes in prevalence trends should be of relevance for
the findings of this study.

Response 3: We agree that it is well known that the percentage of overweight among ethnic
minorities living in the Netherlands (and elsewhere) is higher compared to the natives. However,
most of these studies included older children; moreover, they did not address the explanatory
role of several factors for these ethnic differences in overweight.

- We have added the reference of Wilde et al. and some others, and we are now more
discrete about the statement in the Background section regarding the increasing
prevalence of overweight in the Netherlands.

4) The follow-up study of Mesman et al. (2009) based on the same study cohort (ABCD),
showed that ethnic differences in BMI were present when these children were 14 months and
that weight and BMI levels largely were explained by mothers pre-pregnancy BMI. Although the
study of Mesman et al. was cited in the discussion part (p 12, paragraph 2), a more detailed
account of this previous study could have been given in the introduction. On basis of the body of
knowledge within this research area, the authors could make it more ready what this study
adds.

Response 4: Indeed, the follow-up study of Mesman et al. is an important and paper. However,
their study did not focus specifically on ethnic differences and underlying explanatory factors,
and did not take into account early postnatal growth.

- We have now mentioned Mesman et al. [22] in the Introduction section (page 5).

5) Measuring weight gain
Despite of many disparities between the ethnic groups, the weight gain the first 6 months
appeared to be the predictor that remained most important. Since Turkish and Moroccan
children on average were born smaller than Dutch children, the phenomenon of “catch up
growth” may have been more present. Previous studies have shown that the tempo of weight
gain seem to be of more importance than the actual increase in weight, but this distinction is to
my knowledge not made or discussed in this article. The authors could make it more clear for
the reader whether “weight gain during the first 6 months (per 100 gram) (p.7 paragraph 2)
refers to absolute or relative weight gain.

Response 5: We agree that the definition of weight gain during the first 6 months was not clear.
It is an absolute weight gain; we did not calculate differences in standard deviation scores.

- In the Methods section we have added a clear definition (page 7):
‘... and weight gain during the first six months of life (g/mo). This was calculated as the difference between weight at age 6 months and birth weight divided by the exact age at the 6-month examination’.

- This definition is also reflected in the tables: ‘Infant weight gain (100 g/mo)’.

Furthermore, the reviewer commented on the phenomenon ‘catch up growth’. It is known that low birth weight is more common in Turkish and Moroccan children, but this is mainly due to shorter maternal height (Goedhart et al., 2008). In model 3, the explanatory role of weight gain during the first 6 months was tested, with maternal height and birth weight (amongst others) already in the model. This means that possible ethnic differences in ‘catch up’ growth were already accounted for.

Biological interactions and analytic approach

6) Ethnicity was the main exposure (predictor) and overweight was the main (and only) outcome variable. A range of other potential predictors were included, but it is not clear whether these predictors could act as confounders, mediators or also effect modifiers in multivariate models. In the above mentioned study of Mesman et al. (2009), it was suggested that at least one third of the effect between pre-pregnancy BMI and infant BMI was due to intrauterine influences reflected through birth weight, but such premises have not been taken into account.

Response 6: The goal of our study was to explore which potential predictors (based on literature) could explain the ethnic differences in overweight.

7) It has also been suggested that there may be an additive interaction between maternal pre-pregnancy BMI (overweight) and breast-feeding on the risk of overweight among children 2 to 14 years of age. Li C, et al (2005) found that children of mothers who were obese and who were never breast-fed had the greatest risk of becoming overweight. If, e.g. this combination was more common among Turkish and Moroccan mothers, the conclusions of this study could be far more complex. Perhaps the authors could stratify the study cohort and conduct analyses within the different ethnic groups to explore the impact of each of the explanatory factors.

Response 7: We thank the reviewer for this suggestion and agree that it would be interesting. Unfortunately, we are not able to stratify, because large numbers for each ethnic group (due to dichotomous outcome) would be needed. We tested all first-order interactions with ethnicity and
none was significant. This means that we did not have indications for ethnic differences in the relationships.

8) Dutch mothers as reference group were on average taller with lower BMI (before pregnancy) and with higher education than mothers in other ethnic groups. At least theoretically, one could suggest that a statistical interaction between maternal education and ethnicity may explain some of the observed differences in overweight at age 2 years. Tests of interaction terms between ethnicity and some of the potential determinants (i.e. maternal BMI, gender and weight gain) were performed (p.11 first paragraph), but it is not clear for the reader why these variables in particular and not others, were tested.

Response 8: We agree that there may be more interesting interactions with ethnicity, and we tested all potential determinants with ethnicity in the univariable analyses. None of the interactions were significant (see also response 7).

9) Since many of the included predictors may be related, e.g. mothers height and BMI, actions to avoid colinearity in multivariate models should have been described.

Response 9: We tested the correlations between all explanatory factors to test for collinearity. Correlations between the factors were all below 0.39, indicating no collinearity.

• We have described this procedure in the data analyses paragraph of the Method section (page 8):

Correlations between the explanatory factors were all below 0.39, indicating no collinearity.

Minor Essential Revisions:

10) The reference list is only partly carried out according to the reference style used in BMC Public Health.

Response 10: We apologize for the inconvenience. We have now ensured that all references are presented according to the reference style used in BMC Public Health.

11) This is a prospective study including 3156 infants followed from before birth until 2 years of age. Information was collected from different data sources and different time periods dealing with both cases (infants) and their maternal origins, i.e. before pregnancy (mothers’ recall), different medical records (pregnancy, delivery and child health care) combined with self report
questionnaires. A flow-chart may have made it easier for the reader to get a better overview and thus improving this paper.

**Response 11:** The Method section is a brief description of the entire course of events of the ABCD study. We refer to our cohort profile by Manon van Eijsden et al. for an extensive description of the study (with flow chart). In addition, we have changed the Subject section of the Methods according to the reviewer’s suggestion.

12) It is not enough clarified why this study is based on data from only about the half (N=3432) of the 7050 women included in the ABCD study (p. 6, first paragraph). In the result section mothers of included cases were compared with those excluded but criterions are not outlined in the method section.

**Response 12:** Following on from response 11, we have revised the Subject section of the Methods.

13) Weight and length data at age 2 years, were collected (phase 2) from the Youth Health Care (p 6). I assume this refers to the public child health centers in Amsterdam? Preferably this could be better explained for the reader. Moreover, the standard procedures (last paragraph p. 6) used at the YHC centers could be described in more detail. It is not clear from the paper whether postnatal information i.e. duration of breast feeding and weight gain during first 6 months were obtain from the YHC centers or elsewhere.

**Response 13:** We agree that it was not clear which information was collected by the YHC centers. The information about breast feeding and growth in weight/length was collected during the routine follow-up measurements at the YHC centers.

- We have clarified this in the Method section (page 6).

14) In this study the authors state (p.7 last paragraph) that analyses have followed a rational hierarchical format with no reference. Despite that the authors thoroughly explained the analytic steps that were followed and that tables were very informative, it is not quite clear what this particular approach aim at.

**Response 14:** By a ‘rational hierarchical format’ we mean that the structure of the model was built following a logical sequence from prenatal factors to postnatal factors.
15) There are some slips of the pen (especially inconsistent wordings) throughout the article and in the method section in particular. These could easily be adjusted and thus improve the article.

**Response 15:** This entire revised paper has been corrected by a native English speaker who has experience in checking scientific manuscripts.

16) In the discussion part the authors ask whether mothers recalls of their weight before pregnancy could be biased (self-reports of BMI), but suggest this problem to be similar for all groups of women. According to literature however, ideal body sizes, are relative and not necessarily similar for the included ethnic groups.

**Response 16:** We agree that ideal body weight can differ between ethnicities. However, we asked the women during their pregnancy to fill in their weight before pregnancy and not their opinion about their weight status.

17) Due to the limitations discussed (p 13, paragraph 2), the other ethnic groups included in this study, i.e. “African descents” and “others” should perhaps have been excluded from this study cohort.

**Response 17:** We are aware of the limitations of these groups; however, we would like to keep these groups in our analysis.

- We have added some information about these groups in the Abstract (page 2) Results (page 9) and Discussion (page 11, 12, and 14) sections.
Reviewer 2: Magnus Fasting

Major compulsory revisions:

18) The language and flow of the paper is not so good. I also noticed several typographical errors, and I probably missed several more. It would be nice if someone proficient in English looked over it. Also, it is smart to start every paragraph with a sentence summarizing what the paragraph is about. It makes the text much easier to read.

Response 18: As requested, we have rewritten some parts of the Introduction (see point 22), Methods (see points 11 and 12) and Discussion (see point 21) sections.

- In addition, the entire revised paper has been corrected by a native English speaker who has experience in checking scientific manuscripts.

19) The authors state in their introduction that overweight is a large problem, that some ethnic groups are hit harder than others and they introduce the developmental origins hypothesis. I miss a clear hypothesis.

Response 19: The goal of this study is to explore which factors explain ethnic differences in overweight at early age.

- We have added our hypothesis at the end of the Introduction section (page 5).

20) You have created “African descent” and “others” as separate groups, but fail to comment them in the results section and in the discussion. You should either remove them both from the study, or comment and discuss them as well.

Response 20: For the discussion about excluding the groups from the study please see our response to point 17 from Reviewer 1. We agree that these groups need more attention in the Results and Discussion.

- We have added some extra information in the Abstract (page 2), Results (page 9) and in the Discussion (page 11, 12, 14).

21) The discussion needs to be reviewed. It is unstructured and does not read well. Some points:

21a) The authors start the discussion with the sentence “to our knowledge this is the first study to examine in detail ethnic differences in overweight in children of preschool age,”. A quick
PubMed search reveals several other papers (and reviews) on this subject. You also cite other works on this subject, ref 12 and ref17.

Response 21a: By this statement we wanted to make clear that there are previous studies concerning childhood overweight in ethnic minorities (ref 12) and we know that some ‘risk factors’ for childhood overweight are more prone in some US ethnic groups (ref 17). However, no study has yet investigated to what extent these factors explain the ethnic differences in overweight.

- We agree that the statement sounds too strong and have deleted that sentence, and have rewritten the first paragraph (see response 21b).

21b) The first paragraph of the discussion does not do a good job in presenting your paper’s main findings. It should be rewritten.

Response 21b: We have rewritten the first paragraph and also mentioned the non-significant findings in the ‘African descent’ and ‘other’ group.

21c) In the second paragraph of the discussion, you state: “Most studies however, presented overweight prevalence in older children” without a citation.

Response 21c: As requested, we have added some references [5,14,29,31] to support this statement.

21d) In the third paragraph I miss discussion about the role of shared genetics and social environment as the mediator of the pre-pregnancy# offspring overweight association.

Response 21d: Thank you for this suggestion. Indeed we did not take the influence of shared genetics and social environment into account.

- We have added extra text about this in the Discussion (page 12-13).

21e) In the fourth paragraph you state that weight gain was the most important factor explaining the ethnic differences in overweight. Where did you show that? Furthermore, that paragraph should be rewritten, and possibly merged with paragraph six.

Response 21e: Table 3 shows the decrease in odds ratios after including each model into the regression analyses. The largest differences are seen from model 2 to model 3, where rate of infant weight gain was added.
• We agree this was not clearly stated in the Results section so have now clarified this (page 11):

‘Finally, after adding the postnatal factor ‘average infant weight gain during the first 6 months’ in model 3, the largest decrease in ORs was seen (Table 3). On average, in the Turkish and Moroccan groups, 33% of the ethnic differences in overweight were attributed to early weight gain.’

• We also calculated the contribution of maternal BMI in model 1 (17%), which is also described in the Result section (page 10) in the ‘Prenatal’ section.

• Furthermore, we have rewritten the fourth paragraph and merged it with paragraph 5.

21f) I don’t understand what you mean with the last sentence on p 13.

**Response 21f:** We agree that the sentence was confusing and have deleted it.

**Minor compulsory revisions:**

22) I wonder why the fifth paragraph in the introduction was added. Surely, there are several studies on multiethnic pre-school children and determinants for overweight and obesity. Many of these are also prospective as well. I would suggest deleting the entire paragraph, it does not add anything.

**Response 22:** We have deleted the fifth paragraph and have rewritten the fourth paragraph.

23) In the third last sentence in the first paragraph on p7, the “[31]” should be in front the period.

**Response 23:** This has been corrected.

24) The fourth last sentence on page 8 is in the active form, while the rest of the paragraph is in the passive form. You should be consistent.

**Response 24:** We have changed this sentence to be consistent with the rest of the paragraph.

25) You don’t state that you wish to study differences in covariates among the different ethnicities. These differences are also not discussed in the discussion. Why do you then present comparisons between the groups for variables such as mean age, parity, maternal education etc. ? I suggest that you at least remove the last column of table 1 and only comment the noteworthy differences in the text.
Response 25: We presented the last column of table 1 to give extra insight into the differences between the groups.

- However, we agree that this is not necessary and we have deleted the last column.

26a) In general, if you in an epidemiological paper state that “something is different from something else”, it is implicit that you have done a statistical test giving a p-value or something equivalent to find that. So you can remove the word “significant” almost everywhere. Also, that 0.05 is used as a cut off is almost self evident. So it is okay to remove the last sentence from p 8.

Response 26a: In line with your comment we have deleted the word “significant” where appropriate.

26b) Additionally, presenting only the fact that p<0.05 in the text does not tell the reader anything (the difference could be large or the sample size could be large). I prefer that you write “something is different from something else (15 units v 10 units, p = 0.03)” or something like that.

Response 26b: Based on this comment we have clarified the non-response analysis - which was first stated in the Methods section, as suggested in comment 27, has been moved to the Method section.

27) The second paragraph of p 9 belong in the methods section.

Response 27: As suggested, we have moved the non-response analysis from the Result section to the Method section - in a separate section called ‘Non-response’.

28) In the last paragraph of p9, you say that “the risk of overweight was increased”. Risk is not the same as odds ratio, especially when the outcome is so prevalent such as overweight.

Response 28: We agree that ‘the risk’ is not the same as odds ratio. Therefore, we have changed ‘the risk’ to read ‘odds’.

29) On p 15 you have written “Haque” not “Hague” (which I suppose you mean?).

Response 29: We apologize for the typographic error and have corrected it.

30) In reference 11, you have written “Ref Type: Report”. Should that be there?

Response 30: We have deleted the text “Ref Type: Report”.
31) It doesn’t say where ref 12,16,22,24,29,30,33 and 39 can be found.

Response 31: We apologize for the inconvenience. We used an automatic numbering system and did not fully format the bibliography before submission.

32. In both Table 2 and Table 3, you present p-values. That is unnecessary as the point estimate and the confidence interval give the estimate and the precision of the estimate. It is evident from these numbers which values have high and low p-values.

Response 32: We have removed the p-values in Tables 2 and 3.

33) In the title of table 2, “an” is misspelled “and”.

Response 33: We apologize for the typographic error and have corrected it.

34) Discretionary revisions:
1. I am not so happy with the use of mechanistic methods in epidemiology such as the method you have used, in the way that you blindly include or exclude covariates depending on a p-value without thinking. A better way to create this model would in my opinion to be to use what you know from the literature, and include those factors. Why would for example more alcohol during pregnancy lead to less overweight?

Response 34: The covariates used in this study are based on previous literature, for example:


We understand the confusion regarding more alcohol and the decrease in risk for overweight. The Dutch mothers (the largest group in our study) drank more alcohol during pregnancy and had the lowest prevalence of childhood overweight. It is probably more a socio-economic factor than a factor with a physiological meaning.

- We have now deleted this factor from the study.
A factor can only explain ethnic differences in overweight if that factor is related to overweight status. Therefore we decided to only include those factors with an association (p-value <0.10) in the univariable analyses.

Editorial Request:

35) Regarding ethical approval in your manuscript you state, "the study was approved by the review boards of all Amsterdam hospitals and the Registration Committee of Amsterdam". Please can you confirm that this was ethical approval and can you provide the specific names of the committees?

Response 35: ‘Ethical approval of the study was obtained from the Central Committee on Research involving Human Subjects in the Netherlands, the Medical Ethical Committees of participating hospitals, and from the Registration Committee of the Municipality of Amsterdam’.

- We have clarified this in the Methods section of the revised manuscript (page 6).