Author’s response to reviews

Title: Alternative regression models to assess increase in childhood body mass index

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Author's response to reviews: see over
Dear Prof. Puebla,

Thank you for considering our paper for publication in *BMC Medical Research Methodology*. We appreciate the constructive comments of the reviewers and have changed the manuscript according to their suggestions. All changes in the amended version of the manuscript are highlighted. We have answered the comments of the reviewers (bold type) as follows:

**REVIEWER 1:**

Following the reviewer’s comments we corrected minor language errors in the amended version of the manuscript.

**Abstract**

The abstract would benefit from report 1-2 key findings - e.g., one example where the risk factor was robust to statistical model and one risk factor where the inference changed based on the statistical model selected.

Thank you. We added the following: “The variables TV watching, maternal BMI and weight gain in the first 2 years were directly, and meal frequency was inversely significantly associated with body composition in any model type examined. In contrast, smoking in pregnancy was not directly and breastfeeding and parental social class were not inversely significantly associated with body composition in GLM models, but in GAMLSS and partly in quantile regression models.” (l. 33-39)

**Intro**

I would remove the medline search - not sure if that makes the point without carefully reviewing the articles

Thank you. We removed the information on the search accordingly.

Third paragraph "comparisons between regression models were discussed but not quantified" -clarify what you mean here - do you mean based on AIC – for these references the point estimates from the different models were presented.

Thank you. We clarified this: “Comparisons between different regression models were discussed, but not quantified by model fit criteria such as AIC.” (l. 64-65)

**Methods**

There is more missing data on some of the covariates than others - it would be worthwhile to discuss this in methods and maybe in discussion section

Discuss whether any of the statistical models are better for using MI methods

Thank you. We added a paragraph to the discussion: “We confined our sample to cases with complete information in all variables. Since underreporting with respect to
pregnancy smoking and high values of maternal BMI is well-known, this might have led to underestimation of the effects of the corresponding covariates on childhood BMI. However, such an underestimation is likely to similarly affect all examined statistical approaches and therefore be of minor relevance for assessment of the appropriate approach. It might be of interest, however, to compare how sensitive the statistical models are to several methods of missing data imputation such as multiple imputation. However, this question leads deeply into other statistical methodology and is therefore beyond the scope of our study.” (l. 273-281)

Page 8, top reword "its lack in quantile regression"
Thank you. We replaced this by “The comparison of quantile regression and generalized linear models is a major challenge due to the inapplicability of the GAIC in quantile regression.” (l. 141-142)

Results

Paragraph - define 'peak'
Thank you. We tried to clarify this by an example: “When present, most risk factors seemed to increase BMI values of upper BMI regions: For example, there was a higher proportion of children with a BMI>18 in non-breastfed compared to breastfed children, although the distribution curves of both strata were of almost identical shape for BMI values of <18.” (l. 162-165)

Why categorize mother’s BMI?
Thank you. We had to dichotomize maternal BMI for the visual comparison of density plots between different levels of maternal BMI in figure 1. For all regression analyses, we considered maternal BMI as a continuous variable.

Paragraph 4 - Clarify which variables are confounders, exposures, and modifiers.
Thank you. Sex and age were considered as confounders, while all other covariates were considered as exposures. We have clarified this now in the data section: "Sex and age were considered as confounders, while explanatory variables with previously reported associations to childhood body composition were a priori considered as exposures (abbreviations in brackets). These exposure variables included maternal smoking in pregnancy (PS), amount of watching TV (TV), breast feeding (BF), daily meal frequency (MF), highest graduation of either parent (elementary / secondary / at least A-level) (PG), maternal BMI (MB) and child's weight gain from birth to 2 years of life (WG)” (l. 81-86)

In discussion would be worthwhile to discuss how some of the models being compared are multiplicative models and some are additive - this has implications for interpretation of interaction/cross product terms.
Thank you. We added the following to the discussion: “The same explanatory variables had significant associations to body composition across all GLM models, although models contained either additive (linear regression) or multiplicative components (loglinear regression, Box Cox regression and gamma regression).” (l. 233-236)
We abandoned to mention the interaction terms because they were not significant for any model used.

**Discussion**

Page 13, paragraph 3, last sentence, clarify what you mean - reference 7 and other references compare different approaches for BMI models
Thank you. We deleted this sentence because it was indeed misleading.

**Tables 1 and 2**

Might be clearer to use 0 to indicate no association - usually conotates an inverse association.
Thank you. We replaced “-“ by “0”.

Many of the risk factors are robust to statistical model in terms of whether or not an association is detected (e.g., mothers BMI, meal frequency, weight gain). This should be mentioned in the abstract and discussion but then clarified that the different models yield different magnitude of associations.
Thank you. We added the following paragraph to the discussion: “In our study, the variables TV watching, maternal BMI and weight gain in the first 2 years of life were directly and meal frequency was inversely significantly associated with body composition in every examined model type. However, the strength of the associations was of different magnitude across model types (table 4).” (l. 262-265)

To this end, may be worth adding the magnitude of effect to the tables and also consider modeling interaction terms since the different models have different implications with respect to interactions.
Thank you. We have added table 1 showing the regression coefficients from the GAMLSS model. We think giving all coefficients of all GLM models might inflate the paper and confuse the reader.

May be more helpful to show quantile plots rather than just the estimates for 0.9 and 0.97
Thank you for addressing this issue. However, we decided to show regression coefficients of the most interesting quantile regression models instead of quantile plots to limit the space need of the information given.
2 Specific comments

- p3 l 6 bottle feeding rather than breastfeeding as a risk factor.
- p5 l 3 give the distribution of $\varepsilon_d$
- p6 l 4 change from lognormal to log-linear
- p6 l 6 replace $\mu^\lambda - 1$ with $(\mu^\lambda - 1)$. Also effectively this link function includes the other three as special cases.
- p6 l 7 remove "which ... regression" and replace in the next line with something like "The above link function can be applied to exponential family distributions including the normal gamma and inverse Gaussian distributions."
- p6 l 10 replace $c \times p$ with $(c \times p)$
• p6 l 13 replace $\prod_{i=1}^{n} f(y_i; \theta)$ with $\sum_{i=1}^{n} \log f(y_i; \theta)$
• p6 l 19 remove "the mean" and "the variance"
• p6 l 20 replace "skewness $\nu$" with "skewness parameter $\nu$" and "kurtosis $\kappa$" with "kurtosis parameter $\kappa$"
• p7 l 1 Note that a multiplicative (rather than additive) model for $\mu$ is obtained setting $g_1(\mu) = \log \mu$.
• p7 l 14 replace "least squares (ls)" with "distribution based"
• p9 l 11 replace "density" with "non-parametric kernel density estimate of the"
• p9 l 18 replace "multivariate analysis" with "multivariate regression analysis"
• p9 l 22 replace "lognormal" with "log-linear"
• p9 l 22 was gamma regression used or just the inverse link function with normal errors?
• p10 l 8 "capacity"? Do you mean "high computational demand"?
• p10 l 8-11 "Instead ... procedure": not very clear.
• p11 l 7 is it "gamma" or "inverse gamma"
• p11 l 7 replace "lognormal" with "log-linear"
• p11 l 13 replace "E.g." with "For example"
• p12 l 8 and l 10 replace "variance" with "scale"
• p12 l 11 Add "The scale parameter $\sigma$ in the distribution used (BCT) in GAMLSS is a approximate centile based coefficient of variation measure [16]."
• p12 l 13 add "higher coefficient of variation"
• p13 l 4 replace "0.9" with "90"
• p13 p 6 add: mean MBI (although it was a significant predictor of $\sigma$)
• p13 l 22 replace "variance" with "scale"
• A table for fitted GAMLSS model parameters like the one in table 3 would be very helpful for comparison, for example something like:

<table>
<thead>
<tr>
<th>explanatory variables</th>
<th>$\mu$</th>
<th>$\log \sigma$</th>
<th>$\nu$</th>
<th>$\log \kappa$</th>
</tr>
</thead>
</table>
3 Comments on the comparison of methods

This suggestion is a more formal way of comparing the methods used in the paper. The GAMLSS and the logistic model both produce probabilities of being obese so some comparison can be made between them. The quantile regression and GAMLSS can be compared in terms of centiles. No sensible comparison between the logistic model and the quantile regression model can be made.

3.1 Comparison of probabilities of being obese from GAMLSS and logistic regression

The fitted values of the logistic model are the fitted probabilities \( \hat{p} = \hat{p}(\text{BMI} > c) \) for a given a critical cut off “obesity” point \( c \). In a GAMLSS model \( \hat{p} = \hat{p}(\text{BMI} > c) = \hat{p}(Z > z) \) where

\[
    z = \begin{cases} 
        \frac{1}{\hat{\sigma}} \left[ \frac{\hat{\xi}}{\hat{\mu}} \right]^{\hat{\nu}} - 1, & \text{if } \hat{\nu} \neq 0 \\
        \frac{1}{\hat{\sigma}} \log\left( \frac{\hat{\xi}}{\hat{\mu}} \right), & \text{if } \hat{\nu} = 0 
    \end{cases}
\]  

(1)

and \( Z \sim t_\xi \). Hence the GAMLSS \( \hat{p} = \hat{p}(\text{BMI} > c) \) increases if \( z \) decreases i.e. if \( \hat{\mu} \) increases, or \( \hat{\sigma} \) increases (provided \( c > \hat{\mu} \)). The effect of increasing \( \hat{\nu} \) or \( \hat{\xi} \) on \( \hat{p} \) is more complex but can be investigated as follows:

Suppose we are interested to investigate the effect on \( \hat{p} \) say of WG, we can plot the \( \hat{p} \) against WG for fixed values of the other explanatory variables (e.g. fixed at their means for continuous variables and modes for categorical variables). Note that \( \hat{p} \) for the BCT distribution is given in R by \( \text{pBCT}(c, \hat{\mu}, \hat{\sigma}, \hat{\nu}, \hat{\xi}) \) where the fitted parameters values (for new data) can be obtained by \( \text{predict}() \).

It would be interesting to compare the GAMLSS with the logistic regression results. Note that in GAMLSS the critical (cut off) point \( c \) can be changed in (1) above without the need to refit the model, while you need to reselect and refit the model in logistic regression. GAMLSS model fitting
Thank you very much for your detailed specific comments. We have considered all of them. Table 1 now contains all GAMLSS model parameters.

Thank you again for your suggestions regarding the comparison of models. We decided not to include the logistic regression model into our comparisons, because the focus of our study was on models based on a continuous response variable. However, we compared GAMLSS and quantile regression following the reviewer’s comment (figure 2, table 4). The following passages have been added:

Abstract: “Risk factor specific BMI percentile curves could be estimated from GAMLSS and quantile regression models.” (l. 38-39)

Methods: “To compare GAMLSS and quantile regression, we plotted estimated values of the 90th and 97th BMI percentiles for weight gain in the first two years, while the other covariates were considered at their mean values (if continuous) or their modes (if categorical). We similarly calculated the estimated percentiles for each category of meal frequency, holding the other variables fixed accordingly.” (l. 142-146)
Results: “In figure 2, estimated values of the 90th and 97th BMI percentiles from GAMLSS and quantile regression were compared for weight gain with fixed values of the other covariates. Similarly, table 4 shows percentile values estimated with both methods for different values of meal frequency. Both figure 2 and table 4 indicate that estimated values for the 90th percentile obtained by GAMLSS and quantile regression were similar, while the 97th percentile was slightly higher in quantile regression models. While percentile curves estimated by quantile regression were linear, those obtained by GAMLSS showed a shaped curve due to the combinations of the additional parameters $\sigma$, $\nu$ and $\zeta$.” (l. 223-230)

Discussion: “In our study, a comparison of GAMLSS and quantile regression by estimated values of the 90th and 97th percentiles with respect to certain covariates (weight gain and meal frequency) showed similar results for both methods at the 90th percentile, while the estimated 97th percentile was slightly higher in the quantile regression model. Since implementation of percentile curves is existent only for univariate models in the gamlss package, some computational effort was necessary to gain the respective GAMLSS curves with fixed effects of other covariates. Furthermore, it might be worthwhile to consider nonlinear quantile regression (20) in future studies.” (l. 292-299)

We hope that the revised version of our paper can be considered for publication in *BMC Medical Research Methodology*. Thank you for your kind consideration,

Yours sincerely,

Andreas Beyerlein (for all authors)