PEER REVIEW HISTORY

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This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

(This paper received three reviews from its previous journal but only two reviewers agreed to published their review.)

ARTICLE DETAILS

TITLE (PROVISIONAL)	Dynamic prediction of childhood high blood pressure in a population-based birth cohort: a model development study
AUTHORS	Hamoen, Marleen; Vergouwe, Yvonne; Wijga, Alet H; Heymans, Martijn W; Jaddoe, Vincent; Twisk, Jos; Raat, Hein; de Kroon, M

VERSION 1 – REVIEW

REVIEWER	Cynthia Bell McGovern Medical School at UTHealth, Houston, TX, USA
REVIEW RETURNED	23-May-2018

GENERAL COMMENTS	The authors have used data from the Generation R cohort study to developed a "prediction model" to determine risk for high BP at 9-10yo based on familial measurements and early childhood measures (<6yo). To this end, their statistical methods are adequate but more details are needed to assess all statistical methods (see specific comments below). However, the main objective of prediction model does not seem very clinically useful. First, many of the variables needed as input into the prediction model are often lacking in a child's chart, particularly those on maternal factors pre- and during pregnancy. This point is supported by the fact that even in this prospective cohort study missingness was high for parental smoking status (61%), parental hypertension (48%), and CVD in family (48%). Thus, it is very unlikely EMRs will have enough information to use this prediction model in practice. Second, even if they are to implement this model effectively in clinical practice, it is not clear what effective interventions would be targeted on this population. However, the study does have utility in determining important longitudinal tracking factors associated with high BP at 9-10y and perhaps should be presented as such. Please see additional specific comments below: - Authors accurately reflect that the main outcome of "high BP" is not actually confirmed hypertension which must be measured multiple times. And estimate of how many of these children at 9-10y with high BP would be expected to have confirmed hypertension would be useful to add in the discussion. - Why was the age 9-10y chosen? The prevalence of high BP increases with age. Looking at 13+ would increase the prevalence of your outcome and perhaps have more clinically useful value. - Please check references, they are incorrect or in the wrong order. For example, 19 should be validation of automated BP device and

	20 should be German reference norms but they are not. - Why the use of the German threshold values? I cannot see the citation but would like to know if they are automated measures or manual? Also, how many children are represented? Is the decent mixed such as your population with some from Turkish background? - Page 12, line 3 states backward stepwise models used for individual logistic models with criteria for inclusion based on AIC "corresponding to a p-value of around 0.15". So did you use minimization of AIC as the criteria or p-value as the criteria for inclusion. Please be more clear about this. - Why are BP measurements included in the model? Wouldn't that be measured at visits>3y and be helpful in predicting future BP? - An "independent" correlation structure was used in the GEE model but I suggest that "exchangeable" correlation structure is more appropriate. You can test which is the best correlation structure by use of QIC to ensure best model fit for repeated measures. - Another issue with the development of this prediction model is that it has not been externally validated in another set of data to see if AUC is similar. Instead internal validation "using bootstrapping" was used. I am assuming this is a form of cross-validation but no citations are given and there are not enough details for me to discern exactly what was done. Please provide more information on this technique. - Instead of imputation I would suggest using a "missing" category for the variables with substantial missingness to see how that effects the fit of the model. Often it is found that the missing category itself is informative about the outcome in ways we would not expect. - Lastly, Figure 3 is quite nice and clearly shows the risk factors in varying patient profiles across age. Only one suggestion, please make lines more distinguishable (perhaps thicker vs thinner in addition to current formatting), particularly Child 1 and 4 are difficult to tell apart.

REVIEWER	Simonetta Genovesi Department of Medicine and Surgery of University of Milano-Bicocca, Italy
REVIEW RETURNED	24-May-2018

GENERAL COMMENTS	The idea of developing a dynamic prediction model for high blood pressure detection at the age of 9-10is good. However, in my opinion, the study has some weaknesses. • The sample of children is large, but the number of missing data for some predictors that do not perform in the final model is very high (not “relatively high” as the Authors write). As a result, even the number of data imputed is high and this may have weakened the model. • As also recognized by the authors, the model is not predictive of the presence of arterial hypertension, but only of the possibility of having “elevated”blood pressure values (a single measurement with values greater than the 95th percentile) at 9-10 years. This fact greatly reduces the clinical usefulness of the model. • The reference nomograms used to define "elevated blood pressure" are those of German nomograms derived from a population of normal-weight children (ref 20). Even if on the one hand it is correct to think that, given the epidemic of pediatric obesity, it is right to try to create blood pressure nomograms that exclude children in excess weight (see ref.21), on the other there is the problem that is not demonstrated that the reference nomograms that the authors used are associated with hypertension in adults and / or early organ damage in children. On the contrary, this is amply

	demonstrated for the Forth Report (Pediatrics 2004) nomograms, currently used by the guidelines of the European Hypertension Society. Moreover, given that ethnicity is one of the significant predictive factors of the model, we should know how many were non-Caucasian children in the population of the ref 20, and, in particular, how many were Turkish. • In this study blood pressure was measured in the supine position, but the guidelines suggest to measure it in a sitting position. • It should be explained in more detail how the predictors included in the model were decided. For example "expected predictive strengh": why expected? "Correlation between variables": which predictors were related to each other? • Predictors reported in Table1: -Smoking: when was this variable evaluated? A parent who smoked at the time of pregnancy may have stopped at the birth of the child. -Hypertension in at least one biological parent: parents of young children are often too young to present hypertension, but may become hypertensive later. It would have been better to evaluate the presence of family history for hypertension in the four grand parents. This also applies to "CVD in family", as the parents of a 10-year-old child are often far from age 65. Moreover, these variables were re-evaluated when the children were 9-10 years old? - When considering birth weight, you should distinguish between "small for gestational age" (SGA) children and premature children, with adequate weight for gestational age (AGA). The two conditions, in fact, have a different role in conditioning blood pressure values in the child's next life. The AGA / SGA variable should then be inserted into the model. - Given that this is a dynamic model, the BMI z-score delta at different ages should be evaluated, rather than the BMI z-score at different ages. It is evident that a child who has a high BMI z-score at 3-4-5-6 years will easily have a high BMI z-score even at 9-10 years. And the association of high BMI z-scores and high pressure values is known. Evaluating the BMI delta z-score would also allow to identify children with Early Adiposity Rebound, a factor associated with high blood pressure values in the child. - The AUC of the ROC curves is quite low. So the model does not seem to be very performing. Furthermore, the model should be validated in another population to be considered solid.

REVIEWER	Bernard Rosner Harvard Medical School, United States of America
REVIEW RETURNED	30-May-2018

GENERAL COMMENTS	Comments for the Author 1. p. 10, lines 45-54 What if ethnicity varies between parents? How are children categorized? 2. p. 11, lines 45-49 What about child BP at ages 5-6? It is likely the best predictor of elevated BP at ages 9-10. 3. p. 13, lines 5-8 I don't understand how bootstrapping can be considered validation. Almost the same subjects, albeit with different sampling weights, are used for model derivation and validation. I recommend cross-validation as an alternative if no external validation sample is available. 4. p. 13, lines 22-23 Can the authors define calibration slope and perhaps give a reference for this procedure? What is calibration in the large?

	5. p. 14, lines 40-41 Maybe a table with observed and expected values of children with high BP could be provided by risk decile? 6. p. 15, lines 33-34 It is surprising that hypertension in the parents was not a significant predictor. 7. p. 12, line 34 I don't see how GEE can be used here. The same outcome status is present for prediction based on BMI SDS at different ages. GEE is usually used with replicate outcome measures, e.g., different outcomes at different ages for the same child and possibly different predictors (the latter is the case here).

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

1. The authors have used data from the Generation R cohort study to developed a "prediction model" to determine risk for high BP at 9-10yo based on familial measurements and early childhood measures (<6yo). To this end, their statistical methods are adequate but more details are needed to assess all statistical methods (see specific comments below). However, the main objective of prediction model does not seem very clinically useful. First, many of the variables needed as input into the prediction model are often lacking in a child's chart, particularly those on maternal factors pre- and during pregnancy. This point is supported by the fact that even in this prospective cohort study missingness was high for parental smoking status (61%), parental hypertension (48%), and CVD in family (48%). Thus, it is very unlikely EMRs will have enough information to use this prediction model in practice. Second, even if they are to implement this model effectively in clinical practice, it is not clear what effective interventions would be targeted on this population. However, the study does have utility in determining important longitudinal tracking factors associated with high BP at 9-10y and perhaps should be presented as such.

In this comment, the reviewer discusses two important issues related to the usefulness of the model: 1) unavailability of information in electronic medical records (EMRs) and 2) the question what effective interventions would exist that could be targeted to this population.

Relating to issue 1, we agree with the reviewer that not every community-based child health care setting might have all the information needed for the prediction model readily available in their EMR. This is because we not only included predictors that are likely to be routinely recorded, but also predictors that otherwise would be (relatively) easy to obtain in such settings. Information on maternal health (BMI, hypertensive disease in pregnancy) and socio-economic indicators could for example be obtained by consulting obstetric records or through self-report by the mother or parents. In order to make this more clear to the reader, we adjusted the related paragraph as follows.

Based on previous studies and expert consultations, variables were identified that have been associated with childhood blood pressure, and that are usually recorded or would otherwise be relatively easy to obtain (e.g. through self-reports or extracted from medical reports) in community-based child health care settings.

Considering the importance of these predictors, which might well extend to other outcomes such as childhood overweight, it might be a point of discussion whether this information should be routinely recorded in the future.

In order to make sure we did not include predictors that would be difficult or unacceptable to measure, we discussed the selection of candidate predictors with our stakeholder group,

including community-based child health care professionals from different organizations in the Netherlands, as well as a parent representative (as mentioned in the manuscript, see below).

Outcome definition and selection of candidate predictors were presented and discussed in a meeting with a group of stakeholders involved with our research project, including child health care professionals and a parent representative from for a Dutch parent organization.

Relating to issue 2, we agree with the reviewer that there is a lack of evidence for effectiveness of interventions that could be targeted at this population after applying our prediction model. Therefore, invasive, intensive or possible harmful interventions should not be offered based on this prediction model. On the other hand, it could be valuable to identify higher risk groups that should receive more attention from community-based child health care professionals, e.g. by offering targeted lifestyle and nutritional advice, in order to improve prevention of cardiovascular disease across the life course. It might lead to a better distribution of efforts spent on prevention in community-based child health care. We modified the discussion section accordingly:

Considering that the performance of the prediction model is only moderate, that it predicts *high blood pressure* and not *hypertension*, and that it has not yet been studied whether targeted interventions in this population would be effective, we propose that strategies offered to high-risk children based on this prediction model should be minimally intensive, and not invasive or harmful. The prediction model could be helpful to guide the community-based child health care professional in better distributing their time and efforts, by identifying children (and their families) that need relatively more attention to prevention of CVD, for example in the form of tailored lifestyle and nutritional advice,(1, 2) and measurement of the child's current blood pressure. In overweight or obese children, a higher predicted risk could help to underline the importance of improving weight status. Depending on available and preferred preventive strategies, a setting might prefer to use a higher or lower cut-off to define the high-risk group, and the use of multiple cut-offs and differentiated strategies might also be considered.

Also, we mention in the discussion that a randomized or cluster randomized trial is necessary to investigate the effects of applying the model in combination with targeted prevention on the occurrence of high blood pressure:

Lastly, to investigate the effects of applying the model in combination with targeted prevention on the occurrence of high blood pressure, a randomized or cluster randomized trial is necessary.

2. Authors accurately reflect that the main outcome of "high BP" is not actually confirmed hypertension which must be measured multiple times. And estimate of how many of these children at 9-10y with high BP would be expected to have confirmed hypertension would be useful to add in the discussion.

We agree this is useful and added an estimate of how many children would be expected to have confirmed hypertension in the discussion, based on available literature, as shown below.

Based on previous studies, we estimate that about 1 in 4 to 5 children with high blood pressure in our study would be diagnosed as hypertensive (3, 4).

3. Why was the age 9-10y chosen? The prevalence of high BP increases with age. Looking at 13+ would increase the prevalence of your outcome and perhaps have more clinically useful value.

We agree it would be interesting to also assess if we can predict high blood pressure at those ages, but unfortunately we do not have these data yet. At the moment of performing this study, the research stage for children aged 9-10 years just finished. Currently, children aged 13-14 years are visiting the research center.

4. Please check references, they are incorrect or in the wrong order. For example, 19 should be validation of automated BP device and 20 should be German reference norms but they are not.

We checked and where needed adjusted the references to ensure that they are correct.

5. Why the use of the German threshold values? I cannot see the citation but would like to know if they are automated measures or manual? Also, how many children are represented? Is the decent mixed such as your population with some from Turkish background?

We chose this reference values because of the comparable height distribution with the Dutch population, and because blood pressure was measured with the same automated device as that was used in the Generation R study. We further clarified our choice of these reference values, and included details on the measurements in that study, as well as the number of children included in the reference study and information on their background, as shown below.

These percentiles are based on the distribution of blood pressure in a non-overweight population of 12,199 children, that was considered representative of the German population, and also included children with a migrant background (17.1% had a two-sided migrant background, most commonly Turkish or Russian). Height percentiles were comparable to the Dutch population, and blood pressure was measured with the same automated device as in Generation R (5).

6. Page 12, line 3 states backward stepwise models used for individual logistic models with criteria for inclusion based on AIC "corresponding to a p-value of around 0.15". So did you use minimization of AIC as the criteria or p-value as the criteria for inclusion. Please be more clear about this.

To answer the reviewer's question: we used the AIC for predictor selection, which for variables with one parameter (i.e. not more than two categories) equates to selecting at a P value of 0.157. We adjusted the methods to further clarify this and added a supporting reference, as shown below.

For each age, a backward stepwise selection procedure was performed, using the Akaike Information Criterion for predictor selection. For a variable with one parameter this corresponds to selection at a p-value of 0.157 (6).

7. Why are BP measurements included in the model? Wouldn't that be measured at visits>3y and be helpful in predicting future BP?

We assume that the reviewer means 'why BP measurements were **not** included in the model'. We agree with the reviewer that earlier BP measures could be very helpful in predicting future BP, but we explain in the discussion why we decided not to include these for this prediction modelling study. This section is displayed below.

As blood pressure was measured in Generation R participants at the age of 5-6 years, we have considered adding SBP and/or DBP at this age to the model to improve its discriminative ability, but decided not to, because in most countries routine measurement of blood pressure has not been incorporated into communitybased child health care (7, 8). Even though American and European medical societies recommend routine measurement of blood pressure for children from the age of 3 years (9, 10), the debate on its usefulness is still ongoing (9, 11). If blood pressure measurement would become a standard procedure in community-based child health care, updating the prediction model with information on current blood pressure should be considered.

We have to note that this study is part of a project that aims to develop prediction tools for use in community-based child health care, initially in Dutch Preventive Child Health Care. This is an example of a setting in which blood pressure is not measured routinely, partly because of lack of evidence on the benefits of screening for high blood pressure, but also due to time and material constraints. Similar reasons for not routinely measuring blood pressure likely also play a role in community-based child health care in other countries where blood pressure is not measured.

8. An "independent" correlation structure was used in the GEE model but I suggest that "exchangeable" correlation structure is more appropriate. You can test which is the best correlation structure by use of QIC to ensure best model fit for repeated measures.

When using GEE for a repeatedly measured outcome, different correlation structures might be appropriate in specific situations, which can indeed be investigated using the QIC. However, it has been shown that GEE can also be used with repeatedly measured predictors and a single outcome, in order to calculate robust standard errors that take into account that participants contribute to a model multiple times.(12, 13) In order words, GEE can be used to perform an 'ordinary' regression analysis with a robust estimation of standard errors for repeatedly measured predictors. For that purpose, it is necessary to specify an independent working correlation matrix, as shown by Hernán et al.(12) Because this should be more clear from our text, we adjusted the relevant paragraph in the method section as shown here.

As these conditions were satisfied, we developed a dynamic prediction model by including the selected baseline predictors and an interaction between BMI SDS and age. By doing so, the predictive value of BMI SDS was allowed to vary with the child's age at measurement, while associations of the other predictors were kept constant. This approach is referred to in the literature as *dynamic logistic regression* or *pooled logistic regression* (13), and reduces the needed for age-specific models. To take into account that each child contributes to the model with multiple measurements of BMI SDS (ranging from 0 to 14 measurements), robust standard errors were calculated by fitting the model using generalized estimating equations (GEE) with the *independence* correlation structure. GEE is usually used to deal with repeatedly measured outcomes, but can also be used to adjust standard errors for repeatedly measured predictors or exposures (such as BMI SDS and age in our study).(12, 13) For this purpose, an independent working correlation matrix must be specified.(12)

9. Another issue with the development of this prediction model is that it has not been externally validated in another set of data to see if AUC is similar. Instead internal validation "using bootstrapping" was used. I am assuming this is a form of cross-validation but no citations are given and there are not enough details for me to discern exactly what was done. Please provide more information on this technique.

We agree with the reviewer's comment that external validation of this prediction model is still needed, which we also stress in our discussion. However, in order to give an idea of the optimism of developing the model in this specific dataset, bootstrapping was performed as internal

validation. It is a recommended method to perform internal validation. The difference with crossvalidation is that with bootstrapping random sets of data are drawn (resampling with replacement) from the observed data, that have the same size as the observed dataset, while with cross-validation the observed data is split into (k-fold) training and validation sets. A problem with cross-validation is that it may not reflect all sources of model uncertainty. For example, uncertainty caused by variable selection methods such as backward selection is not captured.(14) Bootstrapping on the other hand is able capture this uncertainty,(14) and because we performed a selection procedure in our study, bootstrapping is the preferred method. In order to clarify the method and our choice for this method, we adjusted the relevant paragraph and included the supporting reference.

… we performed internal validation procedures on the logistic regression models at each age using bootstrapping. 250 random sets of data were generated, with the same size as the original dataset, drawn with replacement from the original data. These datasets were used to estimate, for each age, the optimism in the quality of the prediction model. Compared to other internal validation techniques such as cross-validation, bootstrapping is better able to capture model uncertainty caused by variable selection methods such as backward selection.(14)

10. Instead of imputation I would suggest using a "missing" category for the variables with substantial missingness to see how that effects the fit of the model. Often it is found that the missing category itself is informative about the outcome in ways we would not expect.

The reviewer is referring to using the missing-indicator method to deal with missing data, instead of using multiple imputation. We considered using this technique, but it has been shown that the missing-indicator method typically results in biased estimates in non-randomized studies, and that therefore multiple imputation is a better alternative in this situation.(15) Therefore, we decided to use multiple imputation and not the missing-indicator method.

11. Lastly, Figure 3 is quite nice and clearly shows the risk factors in varying patient profiles across age. Only one suggestion, please make lines more distinguishable (perhaps thicker vs thinner in addition to current formatting), particularly Child 1 and 4 are difficult to tell apart.

We kindly thank the reviewer for the feedback on the figure. We adjusted the lines so that they can be better distinguished.

Reviewer 2

1. The idea of developing a dynamic prediction model for high blood pressure detection at the age of 9-10is good. However, in my opinion, the study has some weaknesses. The sample of children is large, but the number of missing data for some predictors that do not perform in the final model is very high (not "relatively high" as the Authors write). As a result, even the number of data imputed is high and this may have weakened the model.

We agree with the reviewer that the number of missing data for some predictors was very (and not only relatively) high, and we therefore adjusted the wording. We also agree that this might be one of the explanations for these predictors not being selected for the final model. This is also something we discuss in our manuscript, which we fine-tuned in the revision, as shown below:

Further, the high proportions of missing values for parental smoking, parental hypertension and family history of CVD could have decreased the power to detect associations between these candidate predictors and childhood high blood pressure.

An important limitation of our study is that for some candidate predictors based on information from both parents, the proportions of missing values were very high. Even though we included all available information from each individual parent in the imputation model, the missing values may have reduced the power to detect these variables as predictors for high blood pressure in our model, and therefore we cannot exclude that information about these predictors in reality might be useful.

2. As also recognized by the authors, the model is not predictive of the presence of arterial hypertension, but only of the possibility of having "elevated"blood pressure values (a single measurement with values greater than the 95th percentile) at 9-10 years. This fact greatly reduces the clinical usefulness of the model.

We agree that this is an important limitation, which is also mentioned by reviewer #1. Unfortunately, we did not have the opportunity to develop a model that predicts hypertension instead of elevated blood pressure, because children were not followed-up for more than one occasion at this age. In order to provide some insight, we added an estimate of how many children would have hypertension, according to the suggestion from reviewer #1. Considering this limitation, we also think it is important to note that the 'interventions' we would suggest to target to these children should be not too intensive, and not invasive or harmful. We adjusted our discussion accordingly (similarly to the reply to reviewer #1).

Based on previous studies, we estimate that only about 1 in 4 to 5 children with high blood pressure in our study would be diagnosed as hypertensive (3, 4).

Considering that the performance of the prediction model is only moderate, that it predicts *high blood pressure* and not *hypertension*, and that it has not yet been studied whether targeted interventions in this population would be effective, we propose that strategies offered to high-risk children based on this prediction model should be minimally intensive, and not invasive or harmful. The prediction model could be helpful to guide the community-based child health care professional in better distributing their time and efforts, by identifying children (and their families) that need relatively more attention to prevention of CVD, for example in the form of tailored lifestyle and nutritional advice,(1, 2) and measurement of the child's current blood pressure. In overweight or obese children, a higher predicted risk could help to underline the importance of improving weight status. Depending on available and preferred preventive strategies, a setting might prefer to use a higher or lower cut-off to define the high-risk group, and the use of multiple cut-offs and differentiated strategies might also be considered

3. The reference nomograms used to define "elevated blood pressure" are those of German nomograms derived from a population of normal-weight children (ref 20). Even if on the one hand it is correct to think that, given the epidemic of pediatric obesity, it is right to try to create blood pressure nomograms that exclude children in excess weight (see ref.21), on the other there is the problem that is not demonstrated that the reference nomograms that the authors used are associated with hypertension in adults and / or early organ damage in children. On the contrary, this is amply demonstrated for the Forth Report (Pediatrics 2004) nomograms, currently used by the guidelines of the European Hypertension Society. Moreover, given that ethnicity is one of the significant predictive factors of the model, we should know how many were non-Caucasian children in the population of the ref 20, and, in particular, how many were Turkish.

With regard to the first comment, the reviewer is right that the Fourth Report reference values from 2004 have been used more often to investigate associations with adulthood hypertension

and early organ damage in children, and that this is not (yet) the case for the newer reference values based on non-overweight children only. Therefore, we added a sentence to the paragraph in the discussion to recognize this:

On the other hand, several studies have shown that high blood pressure in childhood measured on only one occasion is associated with an increased risk of hypertension in later life (16, 17). Therefore, extra attention to these children could still be warranted, although we must be aware that this has not yet been studied for the more recent reference values for high blood pressure based on non-overweight populations.

Although for the newer reference values this has not yet been studied, this does not preclude us to think carefully about what reference values for blood pressure represent, and how they are influenced by increasing levels overweight and obesity. Reference values based on a population where overweight and obesity are highly prevalent can lead to an underestimation of the real prevalence of high blood pressure. This is reflected in the development of other reference values based on non-overweight children, e.g. in the Pediatric Task Force database (which was also used for the Fourth report references),(18) and on an international level.(19) Therefore, after careful consideration, we decided to use the outcome based on reference values of non-overweight children.

With regard to the second comment, we adjusted the method section by including information on the number of children with a migrant background in this study (including Turkish background), as also requested by reviewer #1, as follows:

These percentiles are based on the distribution of blood pressure in a non-overweight population of 12,199 children, representative of the German population, and also included children with a migrant background (17.1% had a two-sided migrant background, most commonly Turkish or Russian). Height percentiles were comparable to the Dutch population, and blood pressure was measured with the same automated device as in Generation R (5).

4. In this study blood pressure was measured in the supine position, but the guidelines suggest to measure it in a sitting position.

It is true that guidelines suggest measuring blood pressure in a sitting position, while in Generation R this was measured in a supine position (because ultrasound measures were performed as well), and we added a comment about this limitation to the discussion, as shown below.

On the other hand, the high blood pressure prevalence in our study might be slightly underestimated, because blood pressure was measured in a supine position, which tends to give lower blood pressure values than measurement in a sitting position, as in the study for the reference values (5).

5. It should be explained in more detail how the predictors included in the model were decided. For example "expected predictive strengh": why expected? "Correlation between variables": which predictors were related to each other?

Expected predictive strength was based on the identified studies that are presented in the Supplementary Material. We investigated various correlations, and e.g. correlations between maternal and paternal educational level (r_s 0.48) and between maternal smoking during pregnancy and parental smoking (r_s 0.51) were relatively high, so that we decided to select only one of them for the analysis. We adjusted the method section as shown below to further clarify this.

Based on previous studies and expert consultations, variables were identified that have been associated with childhood blood pressure, and that are usually recorded or would otherwise be relatively easy to obtain (e.g. through self-reports or extracted from medical reports) in community-based child health care settings. These are presented in Supplemental Table S1 (Online Supplementary Material), with supporting literature. To prevent overfitting of the prediction model, a selection from these potential candidate predictors was made based on 1) expected predictive strength based on the literature, 2) correlations between variables (e.g.
between maternal and paternal educational level, and maternal smoking during and after pregnancy), and 3) feasibility in community-based child health care.

6. *Predictors reported in Table1:*

- *Smoking: when was this variable evaluated? A parent who smoked at the time of pregnancy may have stopped at the birth of the child.*

We agree with the reviewer that smoking behavior can change before, during and after pregnancy. Smoking by the partner was asked retrospectively about the two months before pregnancy. Smoking by the mother was assessed at 6 months after birth. We added this information to the method section, as shown below. However, because the variable was not selected in the final model, this does not constitute an issue for applying the prediction model.

Parental smoking was assessed through questionnaires during pregnancy (asking the partner whether he smoked in the two months before pregnancy), and the first six months (asking the mother whether she smoked at that time point). Next, parental smoking was categorized as none of the parents smoke or at least one parent smokes.

- *Hypertension in at least one biological parent: parents of young children are often too young to present hypertension, but may become hypertensive later. It would have been better to evaluate the presence of family history for hypertension in the four grandparents. This also applies to "CVD in family", as the parents of a 10-year-old child are often far from age 65. Moreover, these variables were re-evaluated when the children were 9-10 years old?*

We agree with the reviewer that the prevalence of hypertension in parents of young children, assessed at baseline, is (still) low. We also explain in the discussion that this might be a reason why it was not a predictor in this study. Unfortunately we did not have information on parental hypertension at a later time point within the prediction timeframe (0-6 years). Hypertension in the grandparents was included in the variable ‘CVD in the family of biological parents).
Parental hypertension was re-evaluated at the age of 9-10 years, but since this is outside of the prediction timeframe this could not be included as a predictor.

- *When considering birth weight, you should distinguish between "small for gestational age" (SGA) children and premature children, with adequate weight for gestational age (AGA). The two conditions, in fact, have a different role in conditioning blood pressure values in the child's next life. The AGA / SGA variable should then be inserted into the model.*

We agree with the reviewer that it is important to take into account whether birth weight is high, adequate or low for gestational age. Therefore, we did not use birth weight in grams or kilograms, but birth weight standard deviation scores (SDS) which were adjusted for gender and gestational age according to the commonly used reference values by Niklasson.(20) Compared to using SGA/AGA/LGA as categories, this has the benefit of being a continuous variable with a higher power for birth weight relative to gestational age.

Furthermore, we also separately included gestational age as a candidate predictor, but this was not part of the final model after backward selection.

- *Given that this is a dynamic model, the BMI z-score delta at different ages should be evaluated, rather than the BMI z-score at different ages. It is evident that a child who has a high BMI z-score at 3-4-5-6 years will easily have a high BMI z-score even at 9-10 years. And the association of high BMI z-scores and high pressure values is known. Evaluating the BMI delta z-score would also allow to identify children with Early Adiposity Rebound, a factor associated with high blood pressure values in the child.*

In preliminary analyses we studied whether the BMI SDS (= BMI z score) trajectory of a child would predict high blood pressure better than the most recent BMI SDS only. We applied a two-step model to investigate the use of BMI SDS trajectories. In the first step each child's BMI SDS trajectory was modelled using a random effects model, and in the second step the individual coefficients of each child's trajectory were used as a predictor in a logistic regression model with high blood pressure as the outcome. We saw that in our study, the trajectory, which would also capture Early Adiposity Rebound, was not of added predictive value when the most recent BMI SDS and birth weight SDS were already included. Therefore, in the subsequent analysis we used only the most recent BMI SDS and not the BMI SDS trajectory. We added this explanation to the method section, as follows:

First, we studied whether the BMI SDS trajectory of a child would predict high blood pressure better than the most recent BMI SDS only. We applied a two-step model to investigate the use of BMI SDS trajectories. In the first step each child's BMI SDS trajectory was modelled using a random effects model with restricted cubic splines, and in the second step the individual coefficients of each child's trajectory were used as a predictor in a logistic regression model with high blood pressure as the outcome. We saw that, in our study, the trajectory was not of added predictive value when the most recent BMI SDS and birth weight SDS were already included. Therefore, in the subsequent analysis we used only the most recent BMI SDS and not the BMI SDS trajectory.

- *The AUC of the ROC curves is quite low. So the model does not seem to be very performing. Furthermore, the model should be validated in another population to be considered solid.*

We agree that the AUC is only moderate, especially below the age of 5 years, and that external validation is needed and preferably should be performed independently by another research group.(14) Additionally, we think that in order to evaluate the performance/usefulness of the model, another important aspect to consider is the prevalence of high blood pressure across risk categories, which is therefore presented in Table 5 (previously Table 4).

Reviewer 3

1. *p. 10, lines 45-54. What if ethnicity varies between parents? How are children categorized?*

According to Statistics Netherlands, if both parents were not born in the Netherlands, the child's ethnicity is based on the country of birth of the mother. We further clarified this in the methods, as shown here.

Child ethnicity was based on questionnaires and determined in accordance with Statistics Netherlands according to country of birth of the child's parents: if one parent was born outside the Netherlands, that country was used to determine the child's ethnicity, and if both parents were born outside the Netherlands, the country of birth of the mother was used to determine the child's ethnicity (21).

2. p. 11, lines 45-49. What about child BP at ages 5-6? It is likely the best predictor of elevated BP at ages 9-10.

We agree with the reviewer that this is likely a very important predictor, as was also noted by reviewer #1, but we did not include it as a candidate predictor in our study because of the rationale that is presented in our discussion, as shown below.

As blood pressure was measured in Generation R participants at the age of 5-6 years, we have considered adding SBP and/or DBP at this age to the model to improve its discriminative ability, but decided not to, because in most countries routine measurement of blood pressure has not been incorporated into communitybased child health care (7, 8). Even though American and European medical societies recommend routine measurement of blood pressure for children from the age of 3 years (9, 10), the debate on its usefulness is still ongoing (9, 11). If blood pressure measurement would become a standard procedure in community-based child health care, updating the prediction model with information on current blood pressure should be considered.

3. p. 13, lines 5-8. I don't understand how bootstrapping can be considered validation. Almost the same subjects, albeit with different sampling weights, are used for model derivation and validation. I recommend cross-validation as an alternative if no external validation sample is available.

Bootstrapping is a recommended method to perform internal validation. The difference with cross-validation is that with bootstrapping random sets of data are drawn (resampling with replacement) from the observed data, that have the same size as the observed dataset, while with cross-validation the observed data is split into (k-fold) training and validation sets. A problem with cross-validation is that it may not reflect all sources of model uncertainty. For example, uncertainty caused by variable selection methods such as backward selection is not captured. Bootstrapping on the other hand is able capture this uncertainty,(14) and because we performed a selection procedure in our study, bootstrapping is the preferred method. In order to clarify the method and our choice for this method, we adjusted the relevant paragraph and included the supporting reference.

… we performed internal validation procedures on the logistic regression models at each age using bootstrapping. 250 random sets of data were generated, with the same size as the original dataset, drawn with replacement from the original data. These datasets were used to estimate, for each age, the optimism in the quality of the prediction model. Compared to other internal validation techniques such as cross-validation, bootstrapping is better able to capture model uncertainty caused by variable selection methods such as backward selection.(14)

4. p. 13, lines 22-23. Can the authors define calibration slope and perhaps give a reference for this procedure? What is calibration in the large?

We added brief explanations about the calibration slope and calibration-in-the-large, and added supporting references, as shown below.

Next, we assessed the calibration slopes calculated in the bootstrap procedure, which represent, at different ages, the ability of the model to estimate the level of risk accurately. It can range from 0 to 1, where 1 means that the model is perfectly calibrated (22).

As a final step, the intercept was adjusted to re-establish the calibration-in-the-large, so that the mean of the predicted risks was again in line with the mean of the observed risks (22).

5. p. 14, lines 40-41. Maybe a table with observed and expected values of children with high BP could be provided by risk decile?

In Table 5 (previously Table 4) we display the observed probabilities of high blood pressure in children in different risk categories (not for deciles, but for 0-5%, 5-10%, 10-15% and 15% or more). After consideration, we decided that as there were very few children in the very high risk categories, we would not display all risk deciles, but rather these more specific risk categories in the lower risk range.

6. p. 15, lines 33-34. It is surprising that hypertension in the parents was not a significant predictor.

We agree. This might be related to the low prevalence of self-reported hypertension in these relatively young parents (3.7%), and/or the degree of missing values and/or correlation with other predictors. We adjusted the discussion to further elaborate on this, as shown here.

One reason these predictors proved unimportant in our study could be that they were correlated with other predictors we included, for example, parental hypertension with maternal BMI. For parental hypertension, another explanation might be that parents were still relatively young and therefore the prevalence was low. Further, the high proportions of missing values for parental smoking, parental hypertension and family history of CVD could have decreased the power to detect associations between these candidate predictors and childhood high blood pressure.

7. p. 12, line 34. I don't see how GEE can be used here. The same outcome status is present for prediction based on BMI SDS at different ages. GEE is usually used with replicate outcome measures, e.g., different outcomes at different ages for the same child and possibly different predictors (the latter is the case here).

The reviewer is right that GEE is commonly used for repeatedly measured outcomes. However, it has been shown that GEE can also be used with repeatedly measured predictors and a single outcome, to allow for calculation of robust standard errors that take into account that participants contribute to a model multiple times.(12, 13) In order words, GEE can be used to perform an 'ordinary' regression analysis with a robust estimation of standard errors for repeatedly measured predictors. Because this should be more clear from our text, we adjusted the relevant paragraph in the method section as shown here.

As these conditions were satisfied, we developed a dynamic prediction model by including the selected baseline predictors and an interaction between BMI SDS and age. By doing so, the predictive value of BMI SDS was allowed to vary with the child's age at measurement, while associations of the other predictors were kept constant. This approach is referred to in the literature as *dynamic logistic regression* or *pooled logistic regression* (13), and reduces the need for age-specific models. To take into account that each child contributes to the model with multiple measurements of BMI SDS (ranging from 0 to 14 measurements), robust standard errors were calculated by fitting the model using generalized estimating equations (GEE) with the *independence* correlation structure. GEE is usually used to deal with repeatedly measured outcomes, but can also be used to adjust standard errors for repeatedly measured predictors or exposures (such as BMI SDS and age in our study).(12, 13) For this purpose, an independent working correlation matrix must be specified.(12)

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VERSION 2 – REVIEW

REVIEWER	Cynthia Bell McGovern Medical School at UTHealth, Houston
REVIEW RETURNED	08-Jul-2018

GENERAL COMMENTS	The authors have completely addressed all of my issues with very well written explanations and edits to the paper. I support publication of this manuscript.

REVIEWER	Simonetta Genovesi Università di Milano-Bicocca, Milano, Italy
REVIEW RETURNED	The authors responded promptly and honestly to all the objections raised by the reviewers. However, in my opinion, some important limitations of the study, admitted by the authors themselves, remain. • The impossibility of correctly assessing the role of parental smoking status, parental hypertension, and CVD in family due to the high number of missing data, is an important limitation for the score validity. • The fact that the most recent BMI assessment has a greater weight than the BMI trajectory weakens the strength of a dynamic score. • The predictive value of the ROC curves is quite low. • My main concern remains about the real clinical usefulness of this score. Instead, I share with authors the idea that finding a way to identify children with a high cardiovascular risk early to devote more resources to changing their lifestyles is a point of great clinical importance. I am not sure that this study reaches the goal, however.

VERSION 2 – AUTHOR RESPONSE

Reviewer 1

1. *The authors have completely addressed all of my issues with very well written explanations and edits to the paper. I support publication of this manuscript.*

   We would like to thank the reviewer for these positive comments, and for supporting publication of the manuscript.

Reviewer 2

1. The authors responded promptly and honestly to all the objections raised by the reviewers. However, in my opinion, some important limitations of the study, admitted by the authors themselves, remain.

We would like to thank the reviewer for her thorough assessment of our manuscript and for pointing out limitations of our study that should be addressed more. We adjusted the manuscript in line with the reviewer's comments.

2. The impossibility of correctly assessing the role of parental smoking status, parental hypertension, and CVD in family due to the high number of missing data, is an important limitation for the score validity.

We agree with the reviewer that the high proportions of missing data for these variables are an important limitation of our study. Even though we performed multiple imputation, the high levels of missing data could be an explanation for these variables not ending up in the final prediction model after backward selection. We adjusted the discussion to further stress this limitation. Furthermore, we added that in external validation studies with more complete data on these variables it should be studied whether these variables would be of added predictive value to the current model. The adjusted paragraph is shown below.

An important limitation of our study is that for some candidate predictors based on information from both parents (parental smoking, parental hypertension, and CVD in the family), the proportions of missing values were very high. Even though we included all available information from each individual parent in the imputation model, the missing values could have reduced the power to detect these variables as predictors for high blood pressure in our model. Therefore, we cannot exclude that information about these variables in reality might be of added predictive value (and hence increase the performance of the model). This should be investigated in external validation studies with more complete data on these variables.

While the missing data can be one explanation for these variables not being selected for the final prediction model, there might also be other explanations, which we already mentioned in the discussion, i.e. correlations with other predictors (for example with maternal BMI), or low prevalence of hypertension and CVD in the parents and family of children assessed at birth.

3. The fact that the most recent BMI assessment has a greater weight than the BMI trajectory weakens the strength of a dynamic score.

As mentioned in the methods of the first revision, in our study the BMI SDS trajectories of individual children were not adding information when already including the most recent BMI SDS and birth weight SDS, and therefore we did not use the trajectories as a candidate predictor. This has the advantage that for applying the prediction model it is not a problem if earlier BMI SDS measurements are lacking, as long as the current BMI SDS and the birth weight SDS are available. Responding to the reviewer's comment, this does not impair the dynamic nature of the prediction model, because based on this model, the risk estimation can be updated repeatedly by incorporating the most recent information on the age and BMI SDS of the child.

To be more clear about the concept 'dynamic prediction', we adjusted the first paragraph of the discussion as follows.

We developed a dynamic model to predict, for children from birth until the age of 6 years in the general population, their risk of high blood pressure at the age of 9-10 years, based on information that is relatively easy to obtain. The dynamic nature of the prediction model allows for incorporating new information on BMI SDS that becomes available as a child gets older, so that the predicted risk can be updated.

4. The predictive value of the ROC curves is quite low.

We agree with the reviewer that the AUCs after internal validation are relatively low and therefore we adjusted the wording in the first paragraph of the discussion to say that the discriminative performance – after internal validation – is moderate (instead of reasonable). On the other hand, we think that the model did allow for identification of a group of children at a considerably higher risk than the overall study population, as indicated by the prevalence of high blood pressure in the risk categories as presented in Table 5. Therefore, the prediction model – of course if external validity would be confirmed and after possible preventive strategies and possible benefits and harms have been discussed – might be helpful to child health care professionals in objectively identifying children that might benefit from extra prevention efforts.

Reflecting this, we adjusted the discussion on the discriminative performance as follows.

After internal validation, the discriminative ability of the prediction model was moderate, and highest at the age of 5-6 years (AUC 0.73), which can be explained by the higher predictive value of BMI SDS at an age closer to the age at outcome assessment. Although the overall discrimination as measured by the AUC was not excellent or good, the prediction model did allow for identification of a group of children at a considerably higher risk than the overall study population to have high blood pressure at the age of 9-10 years. The prediction model might therefore prove helpful to community-based child health care professionals, because it would allow them to objectively select children for targeted prevention.

5. My main concern remains about the real clinical usefulness of this score. Instead, I share with authors the idea that finding a way to identify children with a high cardiovascular risk early to devote more resources to changing their lifestyles is a point of great clinical importance. I am not sure that this study reaches the goal, however.

We are happy that the reviewer underlines the relevance of the idea of targeted prevention, but we also understand the reviewer's concern about the real clinical usefulness of the prediction model. We think there are several important considerations related to the clinical usefulness, and that we should be careful and make clear that implementation is not yet indicated. Therefore, in line with the reviewer's comments, we further addressed the following aspects as thoroughly as possible in the final manuscript, as outlined below (pointby-point).

- Performance

  The AUCs after internal validation are moderate at most. Although we believe this is not a limitation of our study itself – we tried to obtain the best model based on easily obtainable characteristics – it is a relatively disappointing result. On the other hand, it is important to also share such results with the scientific, public health and clinical community. Furthermore, even if the AUC is not good or high, this does not necessarily mean that the model is not clinically useful. We showed that with the model and certain cut-offs, it is possible to identify a group of children with a considerably higher risk for high blood pressure than the average risk, and that could

still be relevant for targeted primary prevention. As mentioned in our response to the previous comment, we adjusted the first paragraph of the discussion as follows.

After internal validation, the discriminative ability of the prediction model was moderate, and highest at the age of 5-6 years (AUC 0.73), which can be explained by the higher predictive value of BMI SDS at an age closer to the age at outcome assessment. Although the overall discrimination as measured by the AUC was not excellent or good, the prediction model did allow for identification of a group of children at a considerably higher risk than the overall study population to have high blood pressure at the age of 9-10 years. The prediction model might therefore prove helpful to community-based child health care professionals, because it would allow them to objectively select children for targeted prevention.

- Validation

  Before considering implementing the model in practice, it is very important that the external validity of the model is confirmed in other populations. If the model is performing worse in other populations this will probably mean that the model is indeed not clinically useful. External validation studies could also address some of the limitations of our study, such as the candidate predictors with high numbers of missing values that were not selected for the final model. We adjusted the discussion at several points to be more clear about the necessity of external validation, as shown below (underlining the most relevant parts of sentences).

Moved to second paragraph from the second to last paragraph in the previous version:

On the other hand, before considering implementation of this prediction model, first external validation studies are needed, in order to study the generalizability of the prediction model and to see what adaptations to specific populations might be necessary to improve the performance of the model.

Even though we included all available information from each individual parent in the imputation model, the missing values could have reduced the power to detect these variables as predictors for high blood pressure in our model. Therefore, we cannot exclude that information about these variables in reality might be of added predictive value, and this should be investigated in external validation studies with more complete data on these variables. Another point that should be noted is that we performed the internal validation of the GEE model indirectly, i.e. through bootstrapping the logistic regression models at each age, as there is not yet a software package available that is able to perform this directly on the GEE model. The results were stable over the different ages and standard errors are correct in the analyses for one time point. Therefore, the estimated optimism may be considered as realistic, although external validation is again recommended.

- Possible implementation

  First, external validation studies are needed, but we also wanted to think ahead and discuss steps that will have to be taken if external validity would be confirmed. We have made some adjustments in the discussion, as shown below (underlining the most relevant parts of sentences), in order to clarify that implementation could be a possible step in the future, that is not yet indicated.

  We also added that in very young children it might be a possible strategy to wait for the result of the next risk assessment before starting with targeted prevention (considering the relatively limited discriminative ability at earlier ages).

On the other hand, before considering implementation of this prediction model, first external validation studies are needed, in order to study the generalizability of the prediction model and to see what adaptations to specific populations might be necessary to improve the performance of the model.

If external validity can be confirmed, we would propose that, based on this prediction model, only minimally intensive (and not invasive or harmful) strategies should be offered to high-risk children, considering that 1) the discriminative performance is only moderate, 2) it concerns prediction of *high blood pressure* and not *hypertension*, and 3) it has not yet been studied whether targeted interventions in this population would be effective. As mentioned previously, the prediction model might be helpful to guide community-based child health care professionals in better distributing their time and efforts, by identifying children that need relatively more attention to prevention of CVD, for example in the form of tailored lifestyle and nutritional advice(1, 2), measurement of the child's current blood pressure, and monitoring of blood pressure during follow-up. In overweight or obese children, a higher predicted risk could help to underline the importance of improving weight status. Depending on the strategies to be offered, higher or lower cut-offs to define the high risk group might be used, and the use of multiple cut-offs and differentiated strategies might also be considered. In very young children (e.g. < 4 years of age) with a high predicted risk, it might be a strategy to wait for the result of next risk assessment before starting with targeted prevention. Before implementation, the possible benefits and harms of the preferred strategies should be discussed. It would also be important to investigate how parents and health professionals could experience the use of such a prediction model, including the acceptability and effectiveness of risk communication. Lastly, if the model would be implemented in the future, the effects of applying the model in combination with targeted prevention on the occurrence of high blood pressure should be investigated in a randomized or cluster randomized trial.

In summary, we developed a dynamic prediction model to predict the development of childhood high blood pressure based on information that is usually recorded or is easy to obtain in community-based child health care practice. This can be seen as a first step towards applying childhood prediction models for future high blood pressure in order to offer targeted primordial prevention of CVD.

References

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