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Development of a prediction model to target screening for high blood pressure in children

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ABSTRACT

Targeted screening for childhood high blood pressure may be more feasible than routine blood pressure measurement in all children to avoid unnecessary harms, overdiagnosis or costs. Targeting maybe based e.g. on being overweight, but information on other predictors may also be useful. Therefore, we aimed to develop a multi-variable diagnostic prediction model to select children aged 9–10 years for blood pressure measurement. Data from 5359 children in a population-based prospective cohort study were used. High blood pressure was defined as systolic or diastolic blood pressure $\geq$ 95th percentile for gender, age, and height. Logistic regression with backward selection was used to identify the strongest predictors related to pregnancy, child, and parent characteristics. Internal validation was performed using bootstrapping. 227 children (4.2%) had high blood pressure. The diagnostic model included maternal hypertensive disease during pregnancy, maternal BMI, maternal educational level, parental hypertension, parental smoking, child birth weight standard deviation score (SDS), child BMI SDS, and child ethnicity. The area under the ROC curve was 0.73, compared to 0.65 when using only child overweight. Using the model and a cut-off of 5% for predicted risk, sensitivity and specificity were 59% and 76%; using child overweight only, sensitivity and specificity were 47% and 84%. In conclusion, our diagnostic prediction model uses easily obtainable information to identify children at increased risk of high blood pressure, offering an opportunity for targeted screening. This model enables to detect a higher proportion of children with high blood pressure than a strategy based on child overweight only.

1. Introduction

In recent decades, blood pressure levels in children have increased, which is likely to be related to the increase in the prevalence of childhood overweight and obesity, as high blood pressure tends to be higher in overweight children (Chiolero and Cechat, 2007) and adiposity trajectories are related to (pre-)hypertension at age 17–18 (Huang et al., 2015; Munthali et al., 2016), which could also be considered as proxies of high blood pressure at younger ages as blood pressure, specifically systolic blood pressure, tends to track from childhood until adulthood (Urbina et al., 2019; Theodore et al., 2015; Chen and Wang, 2008; Oikonen et al., 2016; Juhola et al., 2011). In addition, some biological pathways support the idea that elevated BMI is one of the strongest risk factor for developing primary hypertension in children

aged 4.6 and 11.2 years, respectively (Fujita et al., 2019; Correia-Costa et al., 2015). This suggests an important public health problem (Pediatrics, 2011; Rosner et al., 2013), as high blood pressure in childhood may have negative consequences for cardiovascular health in later life, partly through unfavorable cardiovascular changes (Herouvi et al., 2013; Day et al., 2017), and partly through tracking of high blood pressure into adulthood (Chen and Wang, 2008), specifically when the systolic blood pressure (SBP) is increased (Urbina et al., 2019; Theodore et al., 2015), or when the high blood pressure is assessed twice or more often in childhood (Oikonen et al., 2016). Childhood high blood pressure has been associated with increased intima-media thickness, as a non-invasive marker of atherosclerosis (Day et al., 2017).

Even though childhood blood pressure does not seem to track as strongly into adulthood as other cardiovascular risk factors such as

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cholesterol and body fat (Twisk et al., 1997), it is moderately predictive of hypertension in adulthood (Lai et al., 2014), an established risk factor for cardiovascular disease (CVD) (GBD Risk Factors Collaborators, 2016; Piepoli et al., 2016).

Because high blood pressure tends to track from childhood into adulthood, and high blood pressure in early life has a possibly negative effect on health in later life (Urbina et al., 2019; Theodore et al., 2015; Chen and Wang, 2008; Oikonen et al., 2016; Juhola et al., 2011; Herouvi et al., 2013; Day et al., 2017; Twisk et al., 1997), experts are increasingly convinced that prevention of CVD could benefit from a life-course approach, by aiming to detect and treat high blood pressure as early as possible (Piepoli et al., 2016; Weintraub et al., 2011). Unfortunately, childhood high blood pressure is usually asymptomatic and, without measurement of blood pressure, it often escapes detection. When high blood pressure remains undetected, necessary diagnostics and adequate management (including lifestyle changes and/or pharmacologic therapy) cannot be offered (Lurbe et al., 2016; Flynn et al., 2017).

American and European medical societies recommend routine measurement of blood pressure in children attending health services (Lurbe et al., 2016; Flynn et al., 2017). However, this recommendation is still being debated, as it is not yet clear whether the benefits would outweigh the possible harms, such as inconvenience from the measurement, anxiety or stress resulting from being labeled hypertensive, and overdiagnosis (Chiolerio et al., 2013a; Bloetzer et al., 2015a; Moyer and Force USPST, 2013; Thompson et al., 2013a). Questions on the cost-effectiveness remain as well (Chiolerio et al., 2013a; Bloetzer et al., 2015a; Moyer and Force USPST, 2013; Thompson et al., 2013a; Wolfe and McKee, 2013; Baltag et al., 2015). Therefore, in many countries, routine measurement of blood pressure is currently not implemented in community-based child health care settings, such as school-based or preventive child health care (Wolfe and McKee, 2013; Baltag et al., 2015).

Another proposed strategy is targeted screening in high risk children, where blood pressure is only measured in children that are at an increased risk for high blood pressure, for example because of overweight or a family history of hypertension (Bloetzer et al., 2015a; Bloetzer et al., 2017; Bloetzer et al., 2015b; Ide and Thompson, 2018). This strategy may (partly) eliminate some of the disadvantages of routine screening for elevated blood pressure in childhood, such as unnecessary burden for children (e.g. stress in those children that are being labeled hypertensive) (Chiolerio et al., 2013), and enhance a more favorable cost-effectiveness ratio (Wang et al., 2011).

An example of targeted screening is the preventive child health care guideline in the Netherlands, which recommends to measure blood pressure in overweight children aged five years or older (Kist-van Holthe et al., 2012). However, a study performed in this setting showed that this strategy identified only 21% of the 5- to 6-year-old children with high blood pressure (Vermeulen and de Kroon, 2016). A study in Switzerland reported the performance of targeted screening based on both child overweight and parental hypertension in 10–14 year old children. This strategy identified a higher proportion of children with high blood pressure than a strategy based on child overweight only (65% compared to 43%) (Bloetzer et al., 2015a).

Several other risk factors for childhood high blood pressure, such as maternal hypertensive disease in pregnancy and child ethnicity (Fraser et al., 2013; de Hoog et al., 2012), have been described. Thus, targeted screening may be further improved by considering such other risk factors. We therefore set out to develop a diagnostic prediction model for identifying children at increased risk of high blood pressure by considering a range of possible predictors, that might be used to select children aged 9–10 years for measurement of blood pressure. We took into account that these predictors should be usually recorded or relatively easy to obtain in community-based child health care settings. We also aimed to compare the performance of this prediction model to the performance of targeted screening strategies based on 1) child

overweight, and 2) child overweight and/or parental hypertension. This study is part of the Prediction Of Child Cardiometabolic Risk (ProCOR) project (de Kroon et al., 2016).

2. Methods

2.1. Participants

We used data from the Generation R study, a population-based prospective birth cohort study in Rotterdam, the Netherlands. Full details of the study design are provided elsewhere (Kooijman et al., 2016a). Pregnant women with an expected delivery date between April 2002 and January 2006, living in the study area at the time of birth, were eligible for participation in the study. The majority of women were enrolled in pregnancy, but enrollment was allowed until birth.

The original cohort consisted of 9749 live born children, of whom 8458 children were invited for the follow-up visit around the age of 9 years. 5862 of the invited children attended the research center, and 5488 of them had complete blood pressure measurements at the age of 9–10 years. For the current analysis, children who were aged 8 or 11 years at this visit ($n = 129$) were excluded. As the aim was to develop a prediction model suitable for all children from the general population, no other exclusion criteria were applied. Therefore, a total of 5359 children are included in this analysis (Fig. 1). The Medical Ethics Committee of the Erasmus University Medical Center approved the study and written informed consent was obtained from the parents of all participating children.

2.2. Outcome measure

Blood pressure was measured in the Generation R research center, by well-trained staff, at a median age of 9.7 years (range 9 to 11 years). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in supine position, at the right brachial artery, with the validated automatic sphygmomanometer Datascope Accutorr Plus (Wong et al., 2006). For each child, an appropriately sized cuff was used, with a bladder width of 40% of the arm circumference, and a bladder length of $> 80\%$ of the arm circumference. Blood pressure was measured four times with one-minute intervals. Mean SBP and DBP values based on the last three measurements were calculated and used for this analysis. To define the outcome high blood pressure, we used gender-, age- and height-specific blood pressure percentiles that were derived from German reference values (Neuhauser et al., 2011). These reference values represent the blood pressure distribution in a non-overweight population of children with height percentiles comparable to the Dutch population, in which blood pressure was measured with the same device as in Generation R (Neuhauser et al., 2011). The choice for percentiles, derived from a non-overweight population, was made because increasing levels of overweight shift the blood pressure distribution of populations upwards, while this is not a healthy situation (Flynn et al., 2017). In this study, high blood pressure was defined as a mean SBP and/or mean DBP at or above the 95th percentile for gender, age and height.

2.3. Candidate predictors

The following candidate predictors were considered: maternal hypertensive disease in pregnancy, maternal educational level, educational level of the partner, maternal body mass index (BMI), hypertension in the biological parents, CVD in the biological mother, CVD in the family of the biological parents, parental smoking, child ethnicity, gender, birth weight standard deviation score (SDS), current BMI SDS, physical activity, and screen time.

The presence of maternal hypertensive disease during the pregnancy of the child – including pregnancy-induced hypertension, pre-eclampsia and hemolysis elevated liver enzymes and low platelets

Fig. 1. Flowchart of study participants. BP, blood pressure.

syndrome (HELLP syndrome) – was based on delivery reports, which were cross-checked with hospital charts at admission and the Netherlands Perinatal Registry. Pre-existing hypertension was not considered as maternal hypertensive disease in pregnancy, unless there was superimposed pre-eclampsia or HELLP syndrome. Maternal educational level and educational level of the partner (highest level completed) were based on questionnaires at the age of 6 years, and categorized as none or primary education; secondary education; and higher education. Maternal BMI (kg/m^2) was based on weight and height measured at the research center during the child's visit at the age of 9–10 years. If the mother was pregnant during this visit, we used maternal BMI measured during the child's visit at the age of 5–6 years (if

the mother was not pregnant then). Hypertension in the biological parents was self-reported in questionnaires at the age of 9–10 years, and categorized as no parental hypertension or at least one parent with hypertension. CVD in the biological mother was self-reported at the same time point, and considered positive if the mother reported to have ever been diagnosed by a doctor with at least one of the following conditions: atherosclerosis of the coronary arteries/angina pectoris, myocardial infarction, heart failure, stroke, transient ischemic attack or (peripheral) vascular disease/intermittent claudication. CVD in the family of the biological parents was self-reported at inclusion (prenatal or at birth), and considered positive if at least one parent had at least one relative (mother, father, sister, brother or child) with hypertension,

myocardial infarction before the age of 65 years, or stroke. Parental smoking was assessed through questionnaires at the age of 9–10 years, and categorized as ‘none of the parents smoke’ versus ‘at least one parent smokes’. Child ethnicity was questionnaire-based, and determined in accordance with Statistics Netherlands based on the country of birth of the child's parents (Statistics Netherlands, 2014). Categories were created by considering studies on the relation between childhood high blood pressure and ethnicity in the Netherlands, and the larger ethnic groups in the Netherlands (de Hoog et al., 2012; Statistics Netherlands, 2014; Gishti et al., 2015), resulting in the following five categories: Western (including Dutch, other European, western American, western Asian, Oceanian), Turkish, Moroccan, Surinamese, and other non-western (including Cape Verdean, Dutch Antilles, African, non-western Asian, Indonesian, non-western American). Birth weight was derived from delivery reports, and birth weight SDS, adjusted for gestational age, was determined according to Niklasson (Niklasson et al., 1991). BMI SDS values, adjusted for age and gender, were based on measurements of weight and height at the research center at the age of 9–10 years. SDS values were constructed using Dutch reference growth curves from 2010 (Schönbeck et al., 2011). The average duration in hours per day of the child's physical activity and screen time (computer and television) were based on parental questionnaires at the age of 9–10 years. For physical activity duration, parents reported: 1) number of days and duration walking/cycling to and from school, 2) time spent weekly on doing sports, 3) number of days and duration of playing outside. These numbers were combined to calculate the total hours of physical activity per week, which was divided by seven to obtain the average hours per day. For screen time, parents reported the number of weekdays and weekend days, and the duration on these days, that the child watched TV (television, video, DVD) and used a computer or game computer. These numbers were combined to calculate the total hours of screen time per week, which was again divided by seven to obtain the average hours per day.

2.4. Statistical analyses

The percentage of missing values ranged from 0 to 41% per candidate predictor (Table 1). To avoid a decrease of statistical power and confounding by selection as much as possible, we imputed missing values. We assumed that missing values were missing at random and imputed missing values in candidate predictors 30 times using multiple imputation with chained equations (MICE), which leads to valid results also in data with high percentages of missing values (up to 50%) (White et al., 2011; Steyerberg, 2019). To investigate the robustness of our results to the missing at random assumption we performed sensitivity analyses for variables with over 40% of missing values.

To remove outliers, the variables screen time and duration of physical activity were truncated at the 99th percentile. To investigate the robustness of our results to the missing at random assumption we performed sensitivity analyses for variables with over 40% of missing values, by investigating whether results of the regression analyses would differ if all missing values would belong to one category.

Univariable and multivariable associations of the candidate predictors with high blood pressure at the age of 9–10 years were assessed with logistic regression models. We combined the predictors that were part of a previously developed prognostic prediction model for high blood pressure into one linear predictor score, using the regression coefficients from this earlier prognostic study (Hamoen et al., 2018). Hereby, we used less degrees of freedom for these known predictors, which allowed us to consider more of the other candidate predictors without the risk of overfitting. The other candidate variables (educational level of the partner, hypertension in the biological parents, CVD in the biological mother, CVD in the family of the biological parents, parental smoking, gender, physical activity, and screen time) were separately included in the full model. Possible non-linearity in the associations between physical activity duration and high blood pressure,

Table 1

Description of candidate predictors for the population for analysis (n = 5359).

Candidate predictor	Descriptive	Available data, n (%)
Pregnancy characteristics		
Maternal hypertensive disease in pregnancy, n (%)	306 (6.4)	4745 (88.5)
Parental characteristics		
Maternal BMI (kg/m ²), median (range)	24.7 (15.3–56.0)	5188 (96.8)
Maternal educational level		4603 (85.9)
No education/primary education, n (%)	153 (3.3)	
Secondary education, n (%)	1706 (37.1)	
Higher education, n (%)	2744 (59.6)	
Educational level partner		4215 (78.7)
No education/primary education, n (%)	202 (4.8)	
Secondary education, n (%)	1506 (35.7)	
Higher education, n (%)	2507 (59.5)	
Smoking by at least one parent, n (%) ^a	1140 (31.0)	3679 (68.7)
Hypertension in at least one biological parent, n (%) ^b	353 (11.2)	3153 (58.8)
CVD in biological mother, n (%)	53 (1.3)	4089 (76.3)
CVD in family of at least one biological parent, n (%)	2611 (74.6)	3498 (65.3)
Child characteristics		
Male gender, n (%)	2627 (49.0)	5359 (100.0)
Ethnicity		5240 (97.8)
Western, n (%)	3636 (69.4)	
Turkish, n (%)	328 (6.3)	
Moroccan, n (%)	258 (4.9)	
Surinamese, n (%)	366 (7.0)	
Other non-western, n (%)	652 (12.4)	
Birth weight SDS, mean (SD)	−0.07 (1.02)	5311 (99.1)
BMI SDS, mean (SD)	0.55 (1.16)	5359 (100.0)
Screen time (hours per day), median (range)	2.1 (0–15.7)	4027 (75.1)
Physical activity (hours per day), median (range)	1.3 (0–5.9)	4387 (81.9)

BMI, body mass index; CVD, cardiovascular disease; SD, standard deviation, SDS, standard deviation score.

^a Smoking in the father, mother and both was present in 14.5, 19.2 and 5.6% of the children.

^b Hypertension in the father, mother and both parents was present in 5.1, 4.4 and 0.2% of the children.

and between screen time and high blood pressure, was examined using restricted cubic splines, but was not found. The strongest predictors were identified with backward selection using the Akaike Information Criterion as stopping rule, which corresponds to a *p*-value of around 0.157.

The resulting model and the predictive measures were internally validated using bootstrapping with 250 bootstrap samples (Moons et al., 2015; Austin and Steyerberg, 2017). Hereby we considered all imputed datasets, yielding estimates for the optimism in the performance for both discrimination and calibration. We assessed the area under the ROC curve (AUC) as a measure of discrimination. AUC reflects the ability of the model to correctly assign higher risks to individuals who have the outcome compared to individuals who do not. The calibration slope from the bootstrapping procedure was used to shrink the regression coefficients, and the intercept adjusted to re-establish calibration-in-the-large. The final model was implemented in an Excel risk calculator. Next, we calculated sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for different cut-offs of predicted probabilities ($\geq 5\%$, $\geq 7.5\%$, $\geq 10\%$ and $\geq 15\%$).

We determined the AUCs, sensitivity, specificity, PPV, and NPV of the following alternative targeted screening strategies: 1) presence of child overweight based on cut-offs from the International Obesity Task Force (IOTF) (Cole and Lobstein, 2012), and 2) presence of child

overweight and/or parental hypertension (in at least one parent). Additionally, we compared our diagnostic model with a strategy based on child overweight by creating reclassification tables. We also assessed the AUC of using BMI SDS as a single predictor. All analyses were performed in R, version 3.3.2.

3. Results

3.1. Model development

In Table 1 the characteristics of the 5359 included children are shown; 150 were twins (2.8%) and 323 (6.1%) were born preterm. 227 children (4.2%) had high blood pressure at the age of 9–10 years. For one candidate predictor ‘Hypertension in at least one parent’ the percentage of missing values was > 40%.

In addition to the prognostic variables for high blood pressure from our previous study (maternal hypertensive disease in pregnancy, maternal BMI, maternal educational level, child ethnicity, birth weight SDS, and BMI SDS), hypertension in one of the biological parents and smoking by at least one of the parents were selected in the final model. Table 2 shows the odds ratios of the univariable and multivariable predictors. For the variables that were combined in the linear predictor score in the multivariable analysis, the individual regression coefficients were estimated by multiplying the original coefficient (from the previous study) with the regression coefficient for the linear predictor score. The confidence intervals for these variables are relatively narrow as there is uncertainty only for the estimated regression coefficient of the linear predictor score. Sensitivity analysis for changing the imputed values for hypertensive disease in at least one parent did not lead to the inclusion of other predictors in the final model, and showed similar results in terms of estimated regression coefficients (see Supplemental Fig. 1).

The apparent AUC for the model was 0.74 (Fig. 2). With overweight as the only predictor, the AUC was 0.65, and with the presence of either overweight or parental hypertension as a predictor the AUC was 0.67. When using BMI SDS as the only predictor, the AUC was 0.69 (Fig. 2). After correcting for optimism, the AUC for the model was 0.73. The calibration slope was 0.96, which was applied as a shrinkage factor to the coefficients of the model, and the intercept had to be adjusted with −0.11. Fig. 3 shows the Excel risk calculator to calculate the predicted probability of high blood pressure.

3.2. Clinical usefulness of the model

Using this diagnostic model, the predicted probabilities in the population for analysis ranged from 0.3% to 47.3% (median 2.7%). The effect of using different cut-offs for the predicted probabilities to label children as ‘at risk (screening required)’ is shown in Table 3. The higher the cut-off value, the lower the sensitivity and NPV, and the higher the specificity and PPV.

Comparing the use of the presence of overweight to select children for screening, our diagnostic prediction model, with a cut-off of $\geq 5\%$, correctly classified net 28 more children from the total of 227 children with high blood pressure, compared to the ‘overweight strategy’. However, from the 5132 children without high blood pressure, the model would net incorrectly classify 333 more children as having high blood pressure, compared to the ‘overweight strategy’. Comparing the use of the presence of either overweight or parental hypertension as a targeted screening strategy, the cut-off had to be lowered to about 4.5%, to obtain a similar level of sensitivity with our model. From the ROC curves in Fig. 2, it can be inferred that, at equal sensitivity, the specificity of our prediction model was higher than the specificity of the ‘overweight strategy’ and slightly higher than that of the ‘overweight & parental hypertension strategy’, and vice versa at equal specificity, the sensitivity of our model is higher. When a high specificity is preferable, using BMS SDS would perform just as well as our model, but when a

Table 2

Associations between candidate predictors and childhood high blood pressure.

Candidate predictors	Univariable OR (95% CI)	Multivariable OR from final model (95% CI)
Pregnancy characteristics		
Maternal hypertensive disease in pregnancy	2.68 (1.77–4.05)	2.31 (1.99–2.68)
Parental characteristics		
Maternal BMI ^a , 28 kg/m ² vs. 22 kg/m ²	1.54 (1.36–1.76)	1.05 (1.04–1.06)
Maternal educational level		
No education/primary education	Reference category	Reference category
Secondary education	0.79 (0.46–1.35)	0.95 (0.94–0.96)
Higher education	0.39 (0.22–0.69)	0.59 (0.54–0.65)
Educational level partner		
No education/primary education	Reference category	–
Secondary education	1.12 (0.64–1.98)	–
Higher education	0.58 (0.32–1.04)	–
Smoking by at least one parent	1.94 (1.43–2.63)	1.27 (0.92–1.76)
Hypertension in at least one biological parent	2.77 (1.84–4.17)	1.70 (1.11–2.58)
CVD in biological mother	1.11 (0.29–4.30)	–
CVD in family of at least one biological parent	1.36 (0.87–2.13)	–
Child characteristics		
Female gender	0.87 (0.66–1.13)	–
Ethnicity		
Western	Reference category	Reference category
Turkish	3.57 (2.42–5.25)	1.79 (1.62–1.99)
Moroccan	1.07 (0.54–2.11)	0.70 (0.65–0.74)
Surinamese	1.07 (0.60–1.92)	0.74 (0.71–0.78)
Other non-western	1.86 (1.29–2.69)	1.31 (1.25–1.37)
Birth weight, +1 SDS vs −1 SDS	0.65 (0.50–0.84)	0.64 (0.60–0.70)
BMI SDS, +1 SDS vs −1 SDS	3.80 (3.04–4.76)	2.58 (2.18–3.04)
Screen time, hours per day	1.15 (1.06–1.25)	–
Physical activity, hours per day	0.92 (0.76–1.11)	–

BMI, body mass index; CVD, cardiovascular disease; OR, odds ratio; SDS, standard deviation score.

^a OR is presented for a comparison between the outer values of the inter-quartile range.

high sensitivity is preferable, the model we developed may perform slightly better.

4. Discussion

We developed a diagnostic prediction model for children aged 9–10 years, that, based on easily obtainable information, can predict a child's risk of having high blood pressure. With this diagnostic prediction model, a group of children at considerably higher risk of high blood pressure than the overall study population could be identified: PPV ranged from 10 to 26% for the presented cut-offs, while the overall prevalence of high blood pressure was 4.2%. The model might therefore be considered to select children for measurement of blood pressure in community-based child health care, i.e. for targeted screening.

4.1. Predictors

A subset of the predictors in the final model (maternal hypertensive disease in pregnancy, maternal BMI, maternal educational level, child ethnicity, birthweight SDS and BMI SDS) were selected based on a previously developed prognostic prediction model for high blood pressure (Hamoen et al., 2018), and are known to be associated with childhood blood pressure or high blood pressure (de Hoog et al., 2012; Gishti et al., 2015; Alsnes et al., 2017; Shi et al., 2012; Lawlor et al., 2004; Zhang et al., 2013; Uiterwaal et al., 1997; Juhola et al., 2012).

Fig. 2. ROC curves from the prediction model (blue solid line, with cut-offs displayed) and other predictive strategies for comparison. AUC, area under the ROC curve; BMI, body mass index; SDS, standard deviation score. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

For parental hypertension and parental smoking, the two additional predictors, associations with higher blood pressure in children have also been reported (Shi et al., 2012; Juhola et al., 2012; Simonetti et al., 2011). These two predictors were not selected in our previously developed prognostic prediction model, which might be explained by the use of earlier measurements (namely around birth instead of at 9–10 years) of parental smoking and parental hypertension in that prognostic prediction modelling study (Austin and Steyerberg, 2017). These earlier measurements might not display the same associations with high blood pressure at the age of 9–10 years as later measurements.

4.2. Diagnosis of hypertension

For children that are labeled as ‘at risk’ for high blood pressure, the most logical next step would be to measure their blood pressure. At the very least, blood pressure would have to be measured multiple times during one visit, after a period of rest, with an appropriately sized cuff. In community-based child health care settings it might not be feasible (because of time constraints) to perform four measurements of blood pressure as was done in this cohort study. A good alternative might be to perform two measurements, and only a third measurement if blood pressure is elevated the first two measurements (Wirix et al., 2016). If the lowest SBP or DBP is $\geq$ the 95th percentile for gender, age, and height, a follow-up visit is indicated to measure blood pressure again (Wirix et al., 2016). If blood pressure is then still high, a child can be referred to a general practitioner or pediatrician for a third measurement. A diagnosis of hypertension can only be made if blood pressure is ‘high’ at three different occasions (Flynn et al., 2017). In the Generation R cohort the diagnosis (pre-)hypertension has not been formally made in children with a high blood pressure, which preferably should be based on a 24 hour measurement.

Prediction model for childhood high blood pressure

Predictors		Values	Values
Maternal hypertensive disease in pregnancy	yes = 1/no = 0	0	1
Maternal BMI	kg/m ²	22.0	25.0
Maternal educational level			
	No/primary education yes = 1/no = 0	1	1
	Secondary education yes = 1/no = 0	0	0
	Higher education yes = 1/no = 0	0	0
Parental smoking	yes = 1/no = 0	0	0
Parental hypertension	yes = 1/no = 0	0	0
Child ethnicity			
	Western yes = 1/no = 0	1	0
	Turkish yes = 1/no = 0	0	1
	Moroccan yes = 1/no = 0	0	0
	Surinamese yes = 1/no = 0	0	0
	Other non-western yes = 1/no = 0	0	0
Birth weight SDS	SDS	0.0	-0.5
BMI SDS	SDS	1.0	1.5
Predicted probability of high blood pressure		4%	18%

Fig. 3. Screenshot of spreadsheet with examples of risk calculations based on the prediction model. BMI, body mass index; BP, blood pressure; SDS, standard deviation score. Linear predictor (LP) for high BP at age 9–10 years = $-3.866 + 0.808 * \text{maternal hypertensive disease in pregnancy} + 0.008 * \text{maternal BMI} - 0.049 * \text{maternal educational level: secondary education} - 0.506 * \text{maternal educational level: higher education} + 0.221 * \text{parental smoking} + 0.507 * \text{parental hypertension} + 0.563 * \text{Turkish ethnicity} - 0.351 * \text{Moroccan ethnicity} - 0.286 * \text{Surinamese ethnicity} + 0.261 * \text{other non-western ethnicity} - 0.212 * \text{birth weight SDS} + 0.457 * \text{BMI SDS}$. Probability of high BP at age 9–10 years = $1 / (1 + e^{-LP})$. The Excel risk calculator is available upon request to the corresponding author.

Table 3

Performance at different cut-offs of predicted risk of high blood pressure (BP) according to the prediction model (a), according to the 'overweight' strategy (b) and according to (overweight and parental hypertension strategy (columns 2–6), and the number of children that need to be screened in order to find one child with high BP (column 7).

Screening strategy	N at risk (%)	Sensitivity in %	Specificity in %	PPV in %	NPV in %	Number of children needed to test their BP in order to find one child with increased BP
Prediction model: cut-offs for predicted risk:						
≥ 5%	1344 (25.1)	59	76	10	98	10
≥ 7.5%	722 (13.5)	44	88	14	97	7.1
≥ 10%	421 (7.9)	32	93	17	97	5.9
≥ 15%	167 (3.1)	19	98	26	96	3.8
Presence of overweight	18%	47	83	11	97	9.1
Presence of overweight or high BP in parents	29%	62	69	9	98	11.1

PPV Positive predictive value, NPV Negative predicted value.

4.3. Clinical and public health relevance

Hypertension in adulthood is highly prevalent in Europe (30 to 45%) and one of the most important risk factors for almost all CVDs acquired during life (Kjeldsen, 2018), leading to more deaths from CVD than any other risk factor (Tzoulaki et al., 2016). However, still a lot of debate is ongoing whether or not screening in general is a good idea, as some long-term studies on cardiometabolic health outcomes do not really show an effect (Lozano et al., 2016; Selph et al., 2015). With respect to screening for primary hypertension in children, still more evidence is needed on the long-term cardiovascular effects of hypertension in childhood, although there is increasing evidence that childhood blood pressure predicts adult blood pressure (Chen and Wang, 2008; Oikonen et al., 2016), an important predictor of CVDs (Sun et al., 2007; Chen et al., 2008). However, the long-term effects of hypertension treatment in childhood are largely unknown. There is some evidence that medication combined with lifestyle components result in a significant decrease in blood pressure. With respect to lifestyle interventions alone, the results are mixed (Thompson et al., 2013b). Given the link between overweight and hypertension, it could be argued that specifically lifestyle intervention aimed at decreasing the blood pressure, have high potential benefit in aiming at the prevention of highly frequent, serious CVDs. In order to offer lifestyle interventions for children with increased blood pressure, screening is needed.

The advantage of our prediction model is that the risk of high blood pressure is calculated without actually measuring it. This implies that blood pressure measurements will only be offered to children with an increased risk according to the defined cut-offs of our model. The use of a prediction tool to identify a large group where blood pressure measurement can be dispensed would offer opportunities to measure blood pressure in a smaller high-risk group.

After the risk assessment and the assessment of a high blood pressure, the blood pressure will have to be verified in subsequent measurements over time, before a diagnosis of (pre-)hypertension can be established and treatment is justified. If the child indeed has (pre-)hypertension, confirmed in follow-up measurements, this also increases the likelihood that the hypertension assessed in childhood is predictive of adult hypertension and should be treated (Oikonen et al., 2016). Future studies with a long follow-up (preferably until adulthood) should assess if screening of high blood pressure outweighs the harms, and if so, which form of (general versus targeted) screening is preferable.

If our model will be used in practice, cut-offs of the models should be chosen, depending on the wishes, requirements, possibilities, and limitations of a specific setting, there might be a preference for either a high sensitivity or a high specificity. With a higher sensitivity more children with high blood pressure will be identified, but more children

that are labeled as 'at risk' while not having high blood pressure (e.g. when the cut-off is chosen at a sensitivity of 59%, the percentage of children to whom a targeted blood pressure screening is offered is 23%, whereas only 10% of these screened children will have a high blood pressure). With a higher specificity there will be less 'unnecessary' measurements of blood pressure, but more children with high blood pressure will be missed. It might be argued that a higher sensitivity should be preferred because it still is relevant to offer children with a high blood pressure a (preventive) intervention, especially if this has been assessed repeatedly (Oikonen et al., 2016). Moreover, children and their parents can be reassured if the repeatedly assessed blood pressure is normal, and the physical burden of these follow-up measurements are likely to be acceptable.

If indeed a high sensitivity is preferred, our prediction model, using a relatively low cut-off performs better than a strategy based on the presence of overweight, with a 12% higher sensitivity, while labeling 7% more children as 'at risk'. Compared to a strategy based on child overweight and parental hypertension, at equal sensitivity, our model is somewhat more specific, meaning that slightly fewer children would have to undergo unnecessary blood pressure measurements. For some settings, the question might remain whether this would outweigh the additional efforts that might be needed to obtain information on the other predictors in the model if these are not routinely recorded.

Finally, there might be several reasons for preferring high specificity over high sensitivity, for example time constraints that limit the possibility to measure blood pressure in too many children. In this case, our model, with a relatively high cut-off (e.g. ≥15%) has a higher specificity than the strategies based on overweight and based on overweight and parental hypertension. However, for settings in which the information needed on the predictors is not readily available, using only BMI SDS as a predictive model would then be an acceptable alternative.

5. Strengths and limitations

A strength of our study is that we used data from a large prospective cohort study, with data on many relevant candidate predictors. Secondly, we took into account that the model should be applicable in community-based child health care, by including candidate predictors that are likely already recorded or otherwise easy to obtain in such settings. A possible weakness is the loss to follow-up in the cohort: about 40% of the children in the original cohort did not attend the visit at age 9–10 years. The children that remained in the study more often had a Western ethnic background, and their mothers were older and better educated (Kooijman et al., 2016b). However, we consider it unlikely that this loss to follow-up had considerable influence on the associations found, since all educational levels and ethnicities were still well-represented.

Another limitation is that for some candidate predictors, the proportions of missing values were high and the validity of some variables uncertain. 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. This is also the case for the variables that have been assessed in a less accurate way, although it may have advantages in practice to use easily obtainable data. Although we internally validated the prediction model and the selected predictive measures by using bootstrapping with 250 bootstrap samples (Moons et al., 2015), this does not exclude that more accurate information about these variables might be of added predictive value (and hence increase the performance of the model). Especially the validity of the variables physical activity and screen time would likely have been better if an accelerometer (Robinson et al., 2003) and a validated questionnaire for screen time (Westerterp, 2014) would have been used. However, in general practice, using these measures in the general population may not be feasible as they take a lot of time from both the children and the preventive child care professionals.

Moreover, missing data are not completely at random, which might have influenced the selection of the final predictors. However, a sensitivity analysis showed this it is unlikely that this had any influence on the selection of final predictors in the model. To verify the robustness of our prediction model, external validation and adaptation studies are needed in cohorts with more complete and precise data on these variables. Another limitation is that the number of children that were finally diagnosed with hypertension is not known, as this has not been assessed in the GenerationR cohort.

Finally, we used bootstrapping to internally validate the prediction model. However, we recommend independent external validation to evaluate how well the model generalizes to other populations (e.g. in other cities, countries and cultures), and what adaptations might be needed for specific populations. Moreover, it is important that the final diagnosis, preferably to be based on Ambulatory Blood Pressure Monitoring (Patel and Daniels, 2019), will be predicted as well.

6. Future implementation

With regard to possible future implementation, it is necessary that, the pros and cons of targeted screening, screening all children or no screening at all for high blood pressure are carefully weighted, and that preferences are discussed with regard to sensitivity, specificity, and the number of children in which measurement of blood pressure is feasible. This might lead to different conclusions, e.g. deciding to apply no screening at all or to apply targeted screening using our prediction (or improved prediction) model because a high sensitivity is desirable, or using BMI SDS as a predictor because a high specificity is preferred and this is less complex to use than a prediction model including several variables. Further, it is important that when a specific targeted screening strategy is chosen, its possible benefits and harms are considered and weighed.

Future implementation studies should be carried out to compare different strategies. Additionally, a pilot study which is currently prepared can provide insight into feasibility and acceptability of using our prediction model before it might be implemented on a larger scale.

Additionally, a pilot study which is currently prepared can provide insight into feasibility and acceptability of using our prediction model before it might be implemented on a larger scale. During the pilot the experience of health professionals, parents and children and the feasibility to obtain data which are not obtained on a routine basis (such as parental BMI) or are missing will be taken into account. In future studies, models accounting for missing values (e.g. based on imputation techniques) (Van Buuren, 2012), might be developed as well.

In summary, we developed a diagnostic prediction model that uses easily obtainable information to identify children at increased risk of high blood pressure. After external validation, and eventually

adaptation, this model may be considered for performing targeted screening in community-based child health care.

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References

- Alsnes, I.V., Vatten, L.J., Fraser, A., Bjørngaard, J.H., Rich-Edwards, J., Romundstad, P.R., et al., 2017. Hypertension in pregnancy and offspring cardiovascular risk in young adulthood: prospective and sibling studies in the HUNT study (Nord-Trøndelag Health Study) in Norway. *Hypertension* 69 (4), 591–598.
- Austin, P.C., Steyerberg, E.W., 2017. Events per variable (EPV) and the relative performance of different strategies for estimating the out-of-sample validity of logistic regression models. *Stat. Methods Med. Res.* 26 (2), 796–808.
- Baltag, V., Pachyna, A., Hall, J., 2015. Global overview of school health services: data from 102 countries. *Health Behavior and Policy Review* 2 (4), 268–283.
- Bloetzer, C., Bovet, P., Suris, J.-C., Simeoni, U., Paradis, G., Chioloro, A., 2015a. Screening for cardiovascular disease risk factors beginning in childhood. *Public Health Rev.* 36 (1), 9.
- Bloetzer, C., Paccaud, F., Burnier, M., Bovet, P., Chioloro, A., 2015b. Performance of parental history for the targeted screening of hypertension in children. *J. Hypertens.* 33 (6), 1167–73.30.
- Bloetzer, C., Bovet, P., Paccaud, F., Burnier, M., Chioloro, A., 2017. Performance of targeted screening for the identification of hypertension in children. *Blood Press.* 26 (2), 87–93.
- Chen, X., Wang, Y., 2008. Tracking of blood pressure from childhood to adulthood: a systematic review and meta-regression analysis. *Circulation* 117 (25), 3171–3180.
- Chen, X., Wang, Y., Appel, L.J., Mi, J., 2008. Impacts of measurement protocols on blood pressure tracking from childhood into adulthood: a metaregression analysis. *Hypertension* 51 (3), 642–649. <https://doi.org/10.1161/HYPERTENSIONAHA.107.102145>.
- Chioloro, A., Cechat, F., 2007. Prevalence of hypertension in schoolchildren based on repeated measurements and association with overweight. *J. Hypertension* 25 (11), 2209–2217.
- Chioloro, A., Bovet, P., Paradis, G., 2013a. Screening for elevated blood pressure in children and adolescents: a critical appraisal. *JAMA Pediatr.* 167 (3), 266–273.
- Cole, T.J., Lobstein, T., 2012. Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. *Pediatr. Obes.* 7 (4), 284–294.
- Correia-Costa, L., Santos, A.C., Severo, M., Guerra, A., Schaefer, F., Caldas Afonso, A., et al., 2015. Sex-specific mediating role of insulin resistance and inflammation in the effect of adiposity on blood pressure of prepubertal children. *PLoS One* 10 (6), e0132097. <https://doi.org/10.1371/journal.pone.0132097>. (eCollection 2015).
- Day, T.G., Park, M., Kinra, S., 2017. The association between blood pressure and carotid intima-media thickness in children: a systematic review. *Cardiol. Young* 27 (7), 1295–1305. <https://doi.org/10.1017/S1047951117000105>. Sep.
- de Hoog, M.L., van Eijsden, M., Stronks, K., Gemke, R.J., Vrijkotte, T.G., 2012. Ethnic differences in cardiometabolic risk profile at age 5–6 years: the ABCD study. *PLoS One* 7 (8), e43667.
- de Kroon, M.L., Wijga, A., Vergouwe, Y., Heijmans, M.W., Jaddoe, V.W., Twisk, J.W., et al., 2016. Prediction of preadolescent overweight and poor cardiometabolic outcome in children up to 6 years of age: research protocol. *JMIR Res Protoc* 5 (2), e85.
- Flynn, J.T., Kaelber, D.C., Baker-Smith, C.M., Blowey, D., Carroll, A.E., Daniels, S.R., et al., 2017. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics* 140 (3).
- Fraser, A., Nelson, S.M., Macdonald-Wallis, C., Sattar, N., Lawlor, D.A., 2013.

- Hypertensive disorders of pregnancy and cardiometabolic health in adolescent offspring. *Hypertension* 62 (3), 614–620.
- Fujita, Y., Kouda, K., Ohara, K., Nakamura, H., Iki, M., 2019. Leptin mediates the relationship between fat mass and blood pressure: the Hamamatsu School-based health study. *Medicine (Baltimore)* 98 (12), e14934. <https://doi.org/10.1097/MD.00000000000014934>.
- GBD Risk Factors Collaborators, 2016. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 388 (10053), 1659–1724.
- Gishti, O., Gaillard, R., Felix, J.F., Bouthoorn, S., Steegers, E., Raat, H., et al., 2015. Early origins of ethnic disparities in cardiovascular risk factors. *Prev. Med.* 76, 84–91.
- Hamoen, M., Vergouwe, Y., Wijga, A.H., Heymans, M.W., Jaddoe, V.W.V., Twisk, J.W.R., et al., 2018. Dynamic prediction of childhood high blood pressure in a population-based birth cohort: a model development study. *BMJ Open* 8 (11), e023912.
- Herouvi, D., Karanasios, E., Karayianni, C., Karavanaki, K., 2013. Cardiovascular disease in childhood: the role of obesity. *Eur. J. Pediatr.* 172 (6), 721–732. <https://doi.org/10.1007/s00431-013-1932-8>.
- Huang, R.C., Burrows, S., Mori, T.A., Oddy, W.H., Beilin, L.J., 2015. Lifecourse adiposity and blood pressure between birth and 17 years old. *Am. J. Hypertens.* 28 (8), 1056–1063. <https://doi.org/10.1093/ajh/hpu266>.
- Ide, N., Thompson, M., 2018. Screening children for hypertension: the case against 2018. *Pediatr Nephrol* 33, 93–100. <https://doi.org/10.1007/s00467-017-3807-0>.
- Juhola, J., Magnussen, C.G., Viikari, J.S., Kahonen, M., Hutri-Kahonen, N., Jula, A., et al., 2011. Tracking of serum lipid levels, blood pressure, and body mass index from childhood to adulthood: the Cardiovascular Risk in Young Finns Study. *J. Pediatr.* 159 (4), 584–590.
- Juhola, J., Oikonen, M., Magnussen, C.G., Mikkilä, V., Siitonen, N., Jokinen, E., et al., 2012. Childhood physical, environmental, and genetic predictors of adult hypertension: the cardiovascular risk in young Finns study. *Circulation* 126 (4), 402–409.
- Kist-van Holthe, J.E., Bulk-Bunschoten, A.M.W., Renders, C.M., L'Hoir, M., Kuijpers, T., HiraSing, R.A., 2012. Richtlijn 'Overgewicht' voor de jeugdgezondheidszorg [Guideline 'Overweight' for child health care].
- Kjeldsen, S.E., 2018. Hypertension and cardiovascular risk: general aspects. *Pharmacol. Res.* 129, 95–99. <https://doi.org/10.1016/j.phrs.2017.11.003>.
- Kooijman, M.N., Kruithof, C.J., van Duijn, C.M., Duijts, L., Franco, O.H., van, I.M.H., et al., 2016a. The generation R study: design and cohort update 2017. *Eur. J. Epidemiol.* 31 (12), 1243–1264.
- Kooijman, M.N., Kruithof, C.J., van Duijn, C.M., Duijts, L., Franco, O.H., van Zendoorn, I., et al., 2016b. The generation R study: design and cohort update 2017. *Eur. J. Epidemiol.* 31 (12), 1243–1264. <https://doi.org/10.1007/s10654-016-0224-9>.
- Lai, C.C., Sun, D., Cen, R., Wang, J., Li, S., Fernandez Alonso, C., et al., 2014. Impact of long-term burden of excessive adiposity and elevated blood pressure from childhood on adulthood left ventricular remodeling patterns: the Bogalusa Heart Study. Impact of long-term burden of excessive adiposity and elevated blood pressure from childhood on adulthood left ventricular remodeling patterns. *J. Am. Coll. Cardiol.* 64, 1580–1587.
- Lawlor, D.A., Najman, J.M., Sterne, J., Williams, G.M., Ebrahim, S., Davey Smith, G., 2004. Associations of parental, birth, and early life characteristics with systolic blood pressure at 5 years of age: findings from the Mater-University study of pregnancy and its outcomes. *Circulation* 110 (16), 2417–2423.
- Lozano, P., Henrikson, N.B., Morrison, A.C., Dunn, J., Nguyen, M., Blasi, P.R., et al., 2016. Lipid screening in childhood and adolescence for detection of multifactorial dyslipidemia: evidence report and systematic review for the US preventive services task force. *JAMA* 316 (6), 634–644.
- Lurbe, E., Agabiti-Rosei, E., Cruickshank, J.K., Dominiczak, A., Erdine, S., Hirth, A., et al., 2016. European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. *J. Hypertens.* 34 (10), 1887–1920 (2016).
- Moons, K.G., Altman, D.G., Reitsma, J.B., Ioannidis, J.P., Macaskill, P., Steyerberg, E.W., Vickers, A.J., Ransohoff, D.F., Collins, G.S., 2015. Transparent reporting of a multi-variable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. *Ann. Intern. Med.* 162, W1–73.
- Moyer, V.A., Force USPST, 2013. Screening for primary hypertension in children and adolescents: U.S. Preventive Services Task Force recommendation statement. *Pediatrics* 132 (5), 907–914.
- Munthali, R.J., Kagura, J., Lombard, Z., Norris, S.A., 2016. Childhood adiposity trajectories are associated with late adolescent blood pressure: birth to twenty cohort. *BMC Public Health* 16, 665. <https://doi.org/10.1186/s12889-016-3337-x>.
- Neuhauser, H.K., Thamm, M., Ellert, U., Hense, H.W., Rosario, A.S., 2011. Blood pressure percentiles by age and height from nonoverweight children and adolescents in Germany. *Pediatrics* 127 (4), e978–e988.
- Niklasson, A., Ericson, A., Fryer, J.G., Karlberg, J., Lawrence, C., Karlberg, P., 1991. An update of the Swedish reference standards for weight, length and head circumference at birth for given gestational age (1977–1981). *Acta Paediatr. Scand.* 80 (8–9), 756–762.
- Oikonen, M., Nuotio, J., Magnussen, C.G., Viikari, J.S., Taittonen, L., Laitinen, T., et al., 2016. Repeated blood pressure measurements in childhood in prediction of hypertension in adulthood. *Hypertension* 67 (1), 41–47. <https://doi.org/10.1161/HYPERTENSIONAHA.115.06395>. Jan.
- Patel, S.S., Daniels, S.R., 2019. Ambulatory blood pressure monitoring in pediatrics. *Curr. Hypertens. Rep.* 21 (9), 71. <https://doi.org/10.1007/s11906-019-0976-1>. 2019.
- Expert panel on integrated guideline for cardiovascular health and risk reduction in children and adolescents. Expert panel on integrated guideline for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics* 128 (Suppl. 5), S213–S256.
- Piepoli, M.F., Hoes, A.W., Agewall, S., Albus, C., Brotons, C., Catapano, A.L., et al., 2016. European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Atherosclerosis* 252, 207–274 (2016).
- Robinson, T.N., Killen, J.D., Kraemer, H.C., et al., 2003. Dance and reducing television viewing to prevent weight gain in African-American girls: the Stanford GEMS pilot study. *Ethn Dis* 13 (S1), s65–s77 (PubMed: 12713212).
- Rosner, B., Cook, N.R., Daniels, S., Falkner, B., 2013. Childhood blood pressure trends and risk factors for high blood pressure: the NHANES experience 1988–2008. *Hypertension* 62 (2), 247–254.
- Schönbeck, Y., Talma, H., van Dommelen, P., Bakker, B., Buitendijk, S.E., Hirasing, R.A., et al., 2011. Increase in prevalence of overweight in Dutch children and adolescents: a comparison of nationwide growth studies in 1980, 1997 and 2009. *PLoS One* 6 (11), e27608.
- Selph, S., Dana, T., Blazina, I., Bougatsos, C., Patel, H., Chou, R., 2015. Screening for type 2 diabetes mellitus: a systematic review for the U.S. Preventive Services Task Force. *Ann. Intern. Med.* 162 (11), 765–776.
- Shi, Y., de Groh, M., Morrison, H., 2012. Increasing blood pressure and its associated factors in Canadian children and adolescents from the Canadian Health Measures Survey. *BMC Public Health* 12, 388.
- Simonetti, G.D., Schwartz, R., Klett, M., Hoffmann, G.F., Schaefer, F., Wuhl, E., 2011. Determinants of blood pressure in preschool children the role of parental smoking. *Circulation* 123 (3), 292–298.
- Statistics Netherlands, 2014. Jaarrapport Integratie 2014 [Annual Report Integration 2014]. Den Haag/Heerlen.
- Steyerberg, E.W., 2019. Clinical Prediction Models. A Practical Approach to Development, Validation, and Updating, 2nd edition.
- Sun, S.S., Grave, G.D., Siervogel, R.M., et al., 2007. Systolic blood pressure in childhood predicts hypertension and metabolic syndrome later in life. *Pediatrics* 119, 237.
- Theodore, R.F., Broadbent, J., Nagin, D., Ambler, A., Hogan, S., Ramrakha, S., et al., 2015. Childhood to early-midlife systolic blood pressure trajectories: early-life predictors, effect modifiers, and adult cardiovascular outcomes. *Hypertension* 66 (6), 1108–1115. <https://doi.org/10.1161/HYPERTENSIONAHA.115.05831>.
- Thompson, M., Dana, T., Bougatsos, C., Blazina, I., Norris, S.L., 2013a. Screening for hypertension in children and adolescents to prevent cardiovascular disease. *Pediatrics* 131 (3), 490–525.
- Thompson, M., Dana, T., Bougatsos, C., Blazina, I., Norris, S., 2013b. Screening for hypertension in children and adolescents to prevent cardiovascular disease: Systematic review for the U.S. In: Preventive Services Task Force. Evidence Synthesis No. 99. AHRQ Publication No. 13–05181-EF-1. Rockville, MD, Agency for Healthcare Research and Quality.
- Twisk, J.W., Kemper, H.C., van Mechelen, W., Post, G.B., 1997. Tracking of risk factors for coronary heart disease over a 14-year period: a comparison between lifestyle and biologic risk factors with data from the Amsterdam Growth and Health Study. *Am. J. Epidemiol.* 145 (10), 888–898.
- Tzoulaki, I., Elliott, P., Kontis, V., Ezzati, M., 2016. Worldwide exposures to cardiovascular risk factors and associated health effects: current knowledge and data gaps. *Circulation* 133 (23), 2314–2333. <https://doi.org/10.1161/CIRCULATIONAHA.115.05831>.
- Uiterwaal, C.S.P.M., Anthony, S., Launer, L.J., Witteman, J.C.M., Trouwborst, A.M.W., Hofman, A., et al., 1997. Birth weight, growth, and blood pressure - an annual follow-up study of children aged 5 through 21 years. *Hypertension* 30 (2), 267–271.
- Urbina, E.M., Khoury, R.R., Bazzano, L., Burns, T.L., Daniels, S., Dwyer, T., et al., 2019. Relation of blood pressure in childhood to self-reported hypertension in adulthood. *Hypertension* 73 (6), 1224–1230.
- Van Buuren, S., 2012. Flexible Imputation of Missing Data, 1st edition. Taylor & Francis Ltd EAN 9781439868249.
- Vermeulen, G., de Kroon, M.L.A., 2016. De prevalentie van hoge bloeddruk bij kleuters met en zonder overgewicht [The prevalence of high blood pressure in preschool children with and without overweight]. *JGZ Tijdschrift voor jeugdgezondheidszorg* 48 (1), 8–13.
- Wang, Y.C., Cheung, A.M., Bibbins-Domingo, K., et al., 2011. Effectiveness and cost effectiveness of blood pressure screening in adolescents in the United States. *J. Pediatr.* 158 (2), 257.e7–264.e7.
- Weintraub, W.S., Daniels, S.R., Burke, L.E., Franklin, B.A., Goff Jr., D.C., Hayman, L.L., et al., 2011. Value of primordial and primary prevention for cardiovascular disease: a policy statement from the American Heart Association. *Circulation* 124 (8), 967–990.
- Westerterp, F., 2014. Reliable assessment of physical activity in disease: an update on activity monitors. *Curr Opin Clin Nutr Metab Care* 17 (5), 401–406. <https://doi.org/10.1097/MCO.0000000000000080>.
- White, I.R., Royston, P., Wood, A.M., 2011. Multiple imputation using chained equations: issues and guidance for practice. *Stat. Med.* 30 (4), 377–399.
- Wirix, A.J., Nauta, J., Groothoff, J.W., Rabelink, T.J., HiraSing, R.A., Chinapaw, M.J., et al., 2016. Is the prevalence of hypertension in overweight children overestimated? *Arch. Dis. Child.* 101 (11), 998–1003.
- Wolfe, I., McKee, M., 2013. European Child Health Services and Systems. Lessons Without Borders. Open University Press.
- Wong, S.N., Tz Sung, R.Y., Leung, L.C., 2006. Validation of three oscillometric blood pressure devices against auscultatory mercury sphygmomanometer in children. *Blood Press Monit* 11 (5), 281–291.
- Zhang, Y., Li, H., Liu, S.J., Fu, G.J., Zhao, Y., Xie, Y.J., et al., 2013. The associations of high birth weight with blood pressure and hypertension in later life: a systematic review and meta-analysis. *Hypertens. Res.* 36 (8), 725–735.