Review

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Childhood prediction models for hypertension later in life: a systematic review

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Background: Hypertension, even during childhood, increases the risk of developing atherosclerosis and cardiovascular disease. Therefore, starting prevention of hypertension early in the life course could be beneficial. Prediction models might be useful for identifying children at increased risk of developing hypertension, which may enable targeted primordial prevention of cardiovascular disease.

Objective: To provide an overview of childhood prediction models for future hypertension.

Methods: Embase and Medline were systematically searched. Studies were included that were performed in the general population, and that reported on development or validation of a multivariable model for children to predict future high blood pressure, prehypertension or hypertension. Data were extracted using the CHARMS checklist for prediction modelling studies.

Results: Out of 12 780 reviewed records, six studies were included in which 18 models were presented. Five studies predicted adulthood hypertension, and one predicted adolescent prehypertension/hypertension. BMI and current blood pressure were most commonly included as predictors in the final models. Considerable heterogeneity existed in timing of prediction (from early childhood to late adolescence) and outcome measurement. Important methodological information was often missing, and in four studies information to apply the model in new individuals was insufficient. Reported area under the ROC curves ranged from 0.51 to 0.74. As none of the models were validated, generalizability could not be confirmed.

Conclusion: Several childhood prediction models for future hypertension were identified, but their value for practice remains unclear because of suboptimal methods, limited information on performance, or the lack of external validation. Further validation studies are indicated.

Keywords: adolescents, blood pressure, children, hypertension, prediction, review, risk assessment

Abbreviations: AUC, area under the ROC curve; BP, blood pressure; CHAID, chi-square automatic interaction detection; CHARMS, Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies; CI, confidence interval; CRP, C-reactive protein; C-statistic, concordance statistic; CVD, cardiovascular disease; HDL, high-density lipoprotein; IDI, integrative discrimination index; IOTF, International Obesity Task Force; LDL, low-density lipoprotein; NA, not applicable; NPV, negative predictive value; NR, not reported; NRI, net reclassification improvement index; OR, odds ratio; PPV, positive predictive value; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; ROC, receiver operating characteristic; SD, standard deviation; TRIPOD, Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis

INTRODUCTION

Adulthood hypertension is a very common and established risk factor for cardiovascular disease (CVD) [1]. There is increasing evidence that adulthood hypertension and CVD originate in early life; risk factors such as overweight, lipid abnormalities, and high blood pressure are prevalent in children, and the process of atherosclerosis can already be observed in childhood [2]. For example, in autopsy studies, childhood high blood pressure has been associated with atherosclerosis in the coronary arteries and the aorta [2–4]. It has also been associated with unfavorable changes in markers of subclinical atherosclerosis in adulthood such as increased carotid intima-media thickness and coronary artery calcification, independently of adulthood blood pressure [5,6].

Considering the above, and given that average blood pressure levels in children have increased over recent decades (largely driven by the rising levels of childhood overweight and obesity) [2,7], primordial prevention of CVD by preventing the development of hypertension is

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becoming increasingly relevant. This is also reflected in guidelines by American and European medical organizations that underline the importance of starting primordial and primary prevention of CVD early in the life course [8–10].

Strategies for preventing hypertension, for example aimed at improving nutrition and increasing physical activity [2], might be especially effective if targeted to individual children at an increased risk of developing hypertension. As blood pressure tracks into adulthood [11], current blood pressure values might be useful to identify these high-risk children. Other characteristics, such as BMI or the presence of parental hypertension, may also be useful in the prediction of future hypertension. With this systematic review, we aimed to provide an overview of prediction models that aim to identify children at increased risk for future hypertension, which could enable targeted primordial prevention.

METHODS

This systematic review is reported in accordance with recommendations as presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [12]. The protocol for this systematic review has been published on PROSPERO, and is available at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015027446.

Search strategy

A systematic literature search was conducted in Embase and Medline in July 2015, with the support of an information specialist, and was updated in March 2018. The search included synonyms for the terms: high blood pressure or prehypertension or hypertension, prediction model, and children. The complete search syntaxes for the different databases can be found in Supplemental Table 1, http://links.lww.com/HJH/B32. Additionally, the references of the included studies were hand searched.

Study selection

We included original studies that were performed in the general population, and that reported on the development or validation of a multivariable prediction model, to estimate in childhood or adolescence, the risk of high blood pressure, prehypertension or hypertension later in life. We considered as multivariable prediction models those based on two or more variables, where we counted stratification by sex also as a variable. In case more than one multivariable prediction model was presented in a study, characteristics on all of the eligible prediction models were extracted for the purpose of this review. Studies not focused on the development or validation of a prediction model, for example studies aimed at predictor finding or tracking, were excluded for this review. Also, we excluded studies with the outcome defined as either high SBP or high DBP, as the internationally accepted definitions of high blood pressure, prehypertension, and hypertension combine both SBP and DBP [13,14]. Abstracts from conference proceedings, editorials and reviews were excluded as well, and language was restricted to English.

After removing the duplicates, one reviewer (M.H.) screened all titles and abstracts according to the predefined inclusion and exclusion criteria. A second and third reviewer (M.K. and Y.V.) each checked half of a 10% random sample of these titles and abstracts to see if results corresponded. Full texts of eligible articles were retrieved and assessed by two members of the review team (M.H. and M.K.). Any discrepancies between the two reviewers were managed by consensus discussion. In case of no consensus, the opinion of a third reviewer (Y.V.) was decisive.

Data extraction and evaluation

Data were extracted from the articles using a standardized data extraction form based on the Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (CHARMS) [15]. Extraction was done independently by two reviewers (M.H. and M.W.). Lack of clarity during the extraction process was resolved by consulting a third reviewer (M.K. or Y.V.). If questions remained, an attempt was made to contact the corresponding author, first author or last author by e-mail; in case of no response the e-mail was sent one more time.

On the basis of the completed CHARMS checklist, two reviewers (M.H. and M.W.) summarized and critically appraised the following elements for each study: study design, study population, measurement and definition of outcome and predictors, time interval between prediction and outcome, sample size, number of events, handling of missing data, modelling method, validation method, model performance (discrimination, calibration, explained variation), and model presentation. As there is not yet a formal risk of bias score for prediction modelling studies, we performed a risk of bias assessment using criteria that we adapted from a systematic review on asthma prediction models by Smit *et al.* [16], which were in turn derived from the CHARMS checklist [15]. Our criteria are described in Supplemental Table 2, http://links.lww.com/HJH/B32. Both reviewers (M.H. and M.W.) independently assessed the following aspects: selection bias (selection of participants and sample attrition), information bias (predictors and outcome) and bias related to the analysis. In case of disagreement, results were discussed until consensus was reached. For each item, the risk of bias was then classified as low, moderate, or high.

RESULTS

Study selection

With the systematic literature search, 12 780 unique references were found, which were screened on title and abstract. The agreement between the first and second or third reviewer (M.H. and M.K. or Y.V.) for the random 10% sample was higher than 99.5%. The first reviewer (M.H.) included four references that the second or third reviewer did not include; after consensus discussions these references were not considered relevant for this review. Next, 78 references were considered for the full text screening. From these references, six studies satisfied the inclusion criteria and were selected for this review (Fig. 1). Each study presented multiple prediction models that could be included in this review, ranging from two to four models per study, and a total of eighteen models that are discussed in this review.

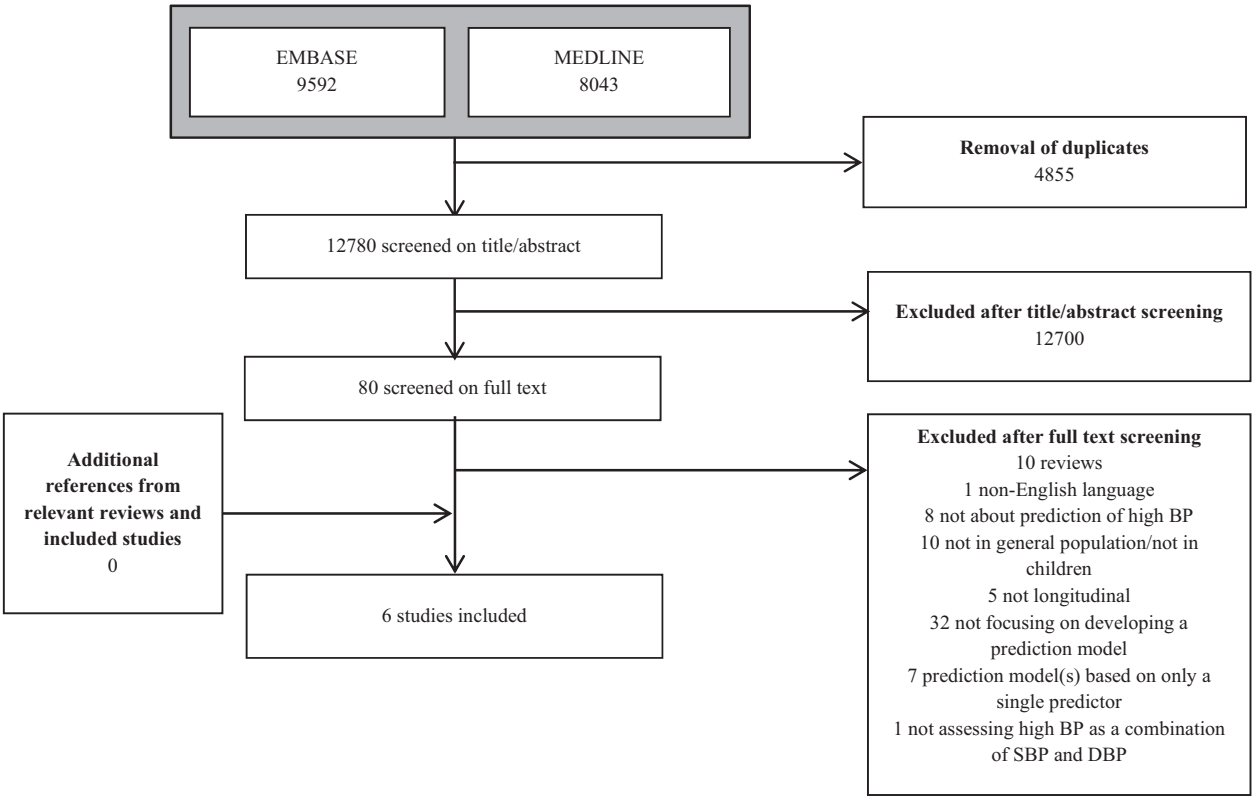

FIGURE 1 Flowchart of selection process. BP, blood pressure.

Study aims

Although in each study multivariable prediction models were developed, we noticed that in none of the studies it was part of the study aim(s) to show how the model could be translated into practice. Study aims were more generally formulated, for example as 'examining the predictive utility of certain predictors' or 'examining the best combinations of predictors.' The study aims of the included studies are presented in Table 1.

Study designs and populations

Table 1 shows key characteristics of the six included studies. The study results were published between 2003 and 2015, and the studies were conducted in five different countries (Cuba [17], Finland [18,19], Netherlands [20], United Kingdom [21], and United States [22]). All studies were based on cohorts with longitudinal data; five were prospective cohort studies [17–19,21], and one was a retrospective cohort study [20].

There was variation between studies with regard to study population characteristics such as age and ethnicity. For age at time of prediction, two studies specifically examined adolescents around the age of 13 years [17,20]. In the other studies, predictors were measured in both children and adolescents, with wider age ranges: 3–18 years [19], 5–17 years [22], 6–18 years [18], and 7–17 years [21]. With regard to ethnicity, two of the included studies were performed in the Cardiovascular Risk in Young Finns Study, in which only children from white European ethnicity were included [18,19]. One study included mostly non-Hispanic whites [22]. In three of the studies, ethnicity was not reported [17,20,21].

In one study, it was unclear how the cohort was recruited exactly [17]. In another study, it was not clear how the sample for analysis was selected from the original cohort [22]. In three studies, information on the distribution of predictors was lacking [17,18,22]. In the five prospective studies, there was loss to follow-up ranging from 8 to 45%; in two of these studies, there was no clear comparison of key characteristics between responders and nonresponders [17,22], and in three of these studies some significant differences in key characteristics between responders and nonresponders were found, for example in sex, age or socioeconomic status [18,19,21].

Definition of hypertension

The outcome definitions in each study are summarized in Table 1 (more details in Supplemental Table 3, http://links.lww.com/HJH/B32). Five studies predicted adulthood hypertension, which in three studies was defined as SBP at least 140 mmHg and/or DBP at least 90 mmHg, or the use of antihypertensive medication [18,20,21]. In one study, it was defined as SBP at least 130 mmHg and/or DBP at least 85 mmHg, or the use of antihypertensive medication [19]. In another study, the outcome was defined as the first appearance of hypertension (>130/85 mmHg) at or after the age of 30 years [22], however, it remained unclear how a first appearance of hypertension occurring before the age

TABLE 1. Characteristics of the included studies[a]

Author (year)	Study aims[b]	Study design Location Name of cohort/ study	Study population	Age at measurement of predictors (baseline)	Age at outcome measurement	Outcome definition	*n* events/*n* total
Ferrer *et al.* (2015) [17]	Describing the development of hypertension during adolescence, including factors influencing its persistence and progression. Developing forecasting models.	Prospective cohort study Plaza de la Revolución municipality, Havana, Cuba	Adolescents from the catchment area of the Héroes del Moncada Polyclinic, assessed at baseline in January-December 2004 and at follow-up in December 2008.	12–15 years. Mean 13.2 years.	Adolescence, 4 years later. Mean 17.1 years (range 16–19 years).	Prehypertension or hypertension: For age 16–18 years: SBP and/or DBP at least 90th percentile or at least 120/80 mmHg. For age 19 years: SBP and/or DPB at least 120/80 mmHg.	47/252
Juhola *et al.* (2012) [19]	Examining the best combination of childhood physical and environmental factors to predict adult hypertension. Examining whether newly identified genetic variants increase the prediction of adult hypertension.	Prospective cohort study Finland Cardiovascular Risk in Young Finns Study	Children from five population centers across Finland. Participants were randomly chosen from the national population register and included in this study if baseline BP and risk factors were measured in 1980 and if their adult BP was measured at follow-up in 2001 or 2007.	3, 6, 9, 12, 15 or 18 years. Mean 10.6 years (SD 5.0 years).	Adulthood. Range at follow-up in 2001: 24–39 years Range at follow-up in 2007: 30–45 years. Mean not reported.	Hypertension: SBP at least 130 mmHg and/or DBP at least 85 mmHg, or use of antihypertensive medication in 2001 and/or 2007.	893/2625
Juhola *et al.* (2011) [18]	Examining tracking and predictive usefulness of childhood risk factors for adulthood risk factor status. Determining the best age to measure childhood risk factor levels.	Prospective cohort study Finland Cardiovascular Risk in Young Finns Study	Children from five population centers across Finland. Participants were randomly chosen from the national population register. In this study, participants in the survey of 2007 were included.	6, 9, 12, 15 or 18 years. Mean not reported.	Adulthood. 30–45 years. Mean not reported.	Hypertension: SBP at least 140 mmHg and/or DBP at least 90 mmHg, or use of medication for hypertension.	?/1808
Li *et al.* (2011) [21]	Establishing how well the IOTF and population-specific cut-offs predict adult CVD risk factors.	Prospective cohort study England, Wales, Scotland 1958 British birth cohort	All births in 1 week in March 1958. 11 971 cohort members, still living in Britain and in contact with the survey were invited at age 45 years for a medical assessment. Information on hypertension was collected for 9297 of them.	7 years: mean 7.4 years (range 7.1–8.5 years) 11 years: mean 11.5 years (range 10.9–13.3 years) 16 years: mean 15.9 years (range 14.8–17.0 years)	Adulthood. 45 years.	Hypertension: SBP at least 140 mmHg and/or DBP at least 90 mmHg or use of antihypertensive medication.	Sizes for each model not clearly reported (minimum sample size $n = 4497$). Probability of event in overall study population ($n = 9297$): 34.6% in men, 16.3% in women.
Sun *et al.* (2007) [22]	Establishing criterion values for blood pressure that predict hypertension and metabolic syndrome in later life.	Prospective cohort study Yellow Springs and nearby towns in southwestern Ohio Fels Longitudinal Study	Participants drawn from the Fels Longitudinal Study population, aged 20 years or older at the time of analysis (born between 1930 and 1983), and who had been monitored since birth and had serial BP readings recorded from age 2 into adulthood.	5–18 years. Mean not reported.	Adulthood. Means presented for men and women with and without metabolic syndrome, mean in years (SD) Men without metabolic syndrome: 34.6 (5.9) Men with metabolic syndrome: 45.2 (10.30) Women without metabolic syndrome: 34.0 (4.8) Women with metabolic syndrome: 47.3 (11.1)	First appearance of hypertension at age of 30 years or older, defined as SBP greater than 130 mmHg and/or DBP greater than 85 mmHg.	204/493

TABLE 1 (*Continued*)

Author (year)	Study aims[b]	Study design Location Name of cohort/ study	Study population	Age at measurement of predictors (baseline)	Age at outcome measurement	Outcome definition	*n* events/*n* total
Vos *et al.* (2003) [20]	Assessing whether screening of BP in adolescence has additional predictive value to already routinely collected indicators of later hypertension and cardiovascular risk.	Retrospective cohort study Utrecht and The Hague, Netherlands Atherosclerosis Risk in Young Adults (ARYA) study	Utrecht: children born between 1970 and 1973, attending secondary school in Utrecht, with birth weight and blood pressure in adolescence available were invited in young adulthood. The Hague: first-year students starting in 1978 and 1979 at a secondary school, who had blood pressure measured during biennial measurements by the Municipal Health Service, and who were invited in young adulthood.	Adolescence. Mean in years (SD): Utrecht, boys: 13.5 (1.1) Utrecht, girls: 13.4 (1.1) The Hague, boys: 13.2 (0.7) The Hague, girls: 13.1 (0.7)	Young adulthood. Mean in years (SD): Utrecht, men: 28.4 (0.9) Utrecht, women: 28.4 (0.9) The Hague, men: 34.3 (0.8) The Hague, women: 34.3 (0.7)	Hypertension. SBP at least 140 mmHg and/or DBP at least 90 mmHg or use of antihypertensive medication.	167/998

BP, blood pressure; CVD, cardiovascular disease; IOTF, International Obesity Task Force; SD, standard deviation.
[a]Detailed information on measurements and exact definitions of candidate predictors and outcomes is presented in Supplemental Table 3, http://links.lww.com/HJH/B32.
[b]Extracted from the abstract (aims and/or methods).

of 30 years was handled (study participants were aged 20 years or older).

One study predicted adolescent prehypertension (including hypertension) at the age of 16–19 years. For children aged 16–18 years, this was defined as SBP and/or DBP at least 90th percentile (for sex, age and height), or SBP at least 120 mmHg and/or DBP at least 80 mmHg. For those aged 19 years, percentiles were not used and prehypertension was defined as SBP and/or DBP at least 120/80 mmHg [17].

In all studies, multiple measurements of blood pressure were performed, and in five studies it was clear that average SBP and DBP values were used to assess the presence of hypertension. In one study, an average based on the last two out of three measurements was used [22], in three studies, the average of all three measurements was used [18,19,21], and in one study the average of four measurements, spread over two visits, was used [20]. Ferrer *et al.*[17] reported to have performed repeated measurements at 5-min intervals, but did not report the number of measurements, and if averages were calculated or not. Use of antihypertensive medication was self-reported in all studies that included this in the outcome [18–21].

Predictors

In Table 2 the candidate predictors and final predictors of the models are shown (more detail on definition and measurement can be found in Supplemental Table 3, http://links.lww.com/HJH/B32).

In three studies, a fixed set of predictors was chosen a priori, meaning that there was no selection from a broader range of candidate predictors; this choice was related to the specific aim(s) of each study [18,21,22]. For example, one study investigated the usefulness of childhood levels of cardiovascular risk factors (i.e. definitions of childhood overweight, obesity, prehypertension/hypertension, dyslipidemia) for predicting the adulthood risk factor levels, separately for boys and girls [18]. Similarly, another study aimed to establish criterion values for childhood blood pressure to predict hypertension in later life, which were then combined in a model with BMI and age [22]. The third study aimed to establish how well different cut-offs for BMI and BMI gain in childhood predict hypertension in adulthood [21]. In three studies a selection from multiple candidate predictors was made to obtain the final models [17,19,20].

In most studies, continuous variables were categorized [17–19,21,22]. This was inherent to the aims in three of these studies, as described in the previous paragraph [18,21,22], but not in the other two studies [17,19].

Childhood overweight was considered as a predictor in three studies [17,19,21], and was a predictor in final models in two of these [19,21]. BMI was a predictor in three studies [17,20,22]. In two of these, BMI was not selected in all of the final models, for example not in the models stratified for girls and boys [20], and not in the model for girls [17].

Childhood high blood pressure or high SBP was considered as a predictor in four studies [17–20]. In two of those studies, it was the main predictor of interest [18,22]. In the other two, it was a candidate predictor before the selection procedure [17,19], and it ended up in the final model in one

TABLE 2. Characteristics of the included prediction models[a]

Author (year)	Modelling method and method for selection of predictors	Models	(Candidate) predictors							Presentation of final prediction model(s)
			Overweight/ obesity	BMI	High BP, high SBP or high DBP	SBP	DBP	Hypertension in parents	Other	
Ferrer *et al.* (2015) [17]	Classification trees using the chi-square automatic interaction detection method (CHAID) Selection: CHAID	Tree 1, based on categorical variables	□		■[d]			□	□ Waist circumference > 90th percentile □ Smoking	Classification trees
		Tree 2, based on continuous variables		■		■	□		□ Waist circumference	
		Tree 3, based on continuous variables, for males		■		■	□		□ Waist circumference	
		Tree 4, based on continuous variables, for females		□		□	■		■ Waist circumference	
Juhola *et al.* (2012) [19]	Logistic regression Preselection: Age-adjusted and sex-adjusted analysis per candidate predictor; significant variables were included in a multivariable model. Independent predictors in this multivariable analysis were included in the final models.	Model 1 Model 2 Model 3 Model 4	□ ■[b] ■[b] ■[b]		□ □ □ □	■ ■ ■ ■	□ □ □ □	□ ■ □ ■	■ Age (model 1–2–3-4) ■ Sex (model 1-2-3-4) □ Resting heart rate □ Parental smoking □ Parental educational level □ Family income ■ Parental occupational status (model 2-3-4) □ Fruit/vegetable consumption □ Milk consumption □ Physical activity index □ Smoking □ Age at menarche □ Birth weight □ Preterm birth □ Impaired fetal growth □ Total cholesterol □ Triglycerides □ HDL cholesterol □ LDL cholesterol □ Insulin □ CRP ■ Genetic risk score (model 3-4)	OR's for model comparable with model 4. In the supplemental information a risk score is provided derived from the full model, but this does not provide an intercept. No prediction of individual absolute risk possible.
Juhola *et al.* (2011) [18]	Not explicitly mentioned, could have been performed using two-by-two tables (stratified for sex). Selection: NA	Model 1, males Model 2, females			■[d] ■[d]					Tables with positive and negative predictive values per sex and age.

TABLE 2 (*Continued*)

Author (year)	Modelling method and method for selection of predictors	Models	(Candidate) predictors: Overweight/obesity	BMI	High BP, high SBP or high DBP	SBP	DBP	Hypertension in parents	Other	Presentation of final prediction model(s)
Li *et al.* (2011) [21]	ROC analysis Selection: NA	Model 1 Model 2 Model 3	■[b] ■[c]						■ Sex ■ Sex ■ Sex ■ BMI gain	No probabilities reported, no individual risk prediction possible.
Sun *et al.* (2007) [22]	Logistic regression Selection: NA	Model 1, males Model 2, females		■ ■	■[e] ■[e]				■ Age at first diagnosis of hypertension ■ Age at first diagnosis of hypertension	Regression equations (but one predictor not available for new individual).
Vos *et al.* (2003) [20]	Logistic regression Selection: backward selection, *P* value for removal 0.10	Model 1, both genders Model 2, males Model 3, females		■ □ □		■ ■ ■	□ □ □		■ Sex ■ Age □ Age □ Age	ORs only, no individual risk prediction possible.

BP, blood pressure; CHAID, chi-square automatic interaction detection; CRP, C-reactive protein; HDL, high-density lipoprotein; IOTF, International Obesity Task Force; LDL, low-density lipoprotein; NA, not applicable; OR, odds ratio; ROC, receiver operating characteristic.
□, included as candidate predictor but not selected as predictor in final model. ■, predictor in final model.
[a]Detailed information on measurements and exact definitions of candidate predictors and outcomes is presented in Supplemental Table 3, http://links.lww.com/HJH/B32.
[b]Overweight/obesity according to IOTF cut-offs.
[c]Overweight/obesity according to study-specific cut-offs.
[d]SBP or DBP at least 90th percentile or at least 120/80 mmHg (according to Fourth Report) [30].
[e]Elevated blood pressure, defined as a single mean elevated SBP that exceeded age-specific and sex-specific criterion values derived in first part of the study.

study [17]. Continuous SBP and DBP were candidate predictors in three studies, and SBP was in at least one of the final models in all three of these studies [17,19,20]. DBP was only selected in the final model for girls in one study [17].

Other variables that were in a final model were: sex [17–22], age [19,20], BMI gain [21], parental hypertension [19], parental occupational status [19], and a genetic risk score [19]. In one study, the predictor 'age when adulthood hypertension was first diagnosed' was included [22], which raised serious concerns about the quality and applicability of the prediction models developed in this study. Most importantly, the 'age when adulthood hypertension was first diagnosed' would not be available in childhood, the intended time point of use of the models, and implies an unrealistic predictor that is based on outcome information. This might explain why this predictor was so important, as well as the high discriminative performance of the models. Also, it remained unclear how this variable was dealt with for participants who were not diagnosed with hypertension during the follow-up.

Time interval between prediction and outcome

In three studies, the time interval between prediction and outcome was the same for all participants [17,18,21]. In one of these studies this interval was 4 years [17], in the other two studies, this interval was longer, namely 27 years [18] and 38 years [21]. In two other studies, there was some variation between participants in the time interval, ranging from 21 to 27 years in one study [19], and on average from 15 to 21 years in the other study [20]. In another study, participants were born between 1930 and 1983, but whether hypertension had occurred was assessed at the time of analysis, and therefore, follow-up durations differed between participants [22]. Hence, older participants were followed for a longer period of time, and would have been more likely to have developed hypertension at the time of analysis than younger participants. Therefore, the mean age of participants with hypertension was probably higher than the age of those who had not developed hypertension. This might also explain why 'age at diagnosis of hypertension' was such an important predictor in this study, although, as mentioned before, we could not determine how this variable was filled in for those participants who did not develop hypertension.

Sample size and number of events

Reported sample sizes for model development ranged from 252 [17] to 4497 [21] (Table 1). The number of events was reported clearly in four studies [17,19,20,22], and the number of events-per-variable (ideally at least 10–15 events per variable) [23] was adequate in three of them [19,20,22]. In one study, the number of events was 47, whereas five to six variables were considered [17], leading to less than 10 events per variable. In two studies, the number of events was not clearly reported for the exact sample in which the models were developed [18,21]. However, as these studies had large sample sizes and their models were developed based on two predictors, we consider it likely that the number of events per variable was adequate in these studies.

Handling of missing data

The handling of missing values was reported clearly in only one study; here missing values were imputed using multiple imputation [21]. In the other studies, information on the handling of missing data was lacking [17–20,22]; most likely complete case analyses were performed in these studies.

Modelling methods

Modelling methods are described in Table 2; they consisted of multivariable logistic regression analysis (three studies) [19,20,22], receiver operating characteristic (ROC) analysis (one study) [21], stratified cross-tabulations (one study) [18], and classification tree analysis (one study) [17]. In three of the studies, a selection procedure was applied to select the predictors for the final models from a broader range of candidate predictors [17,19,20]. In one study, classification trees were developed using the chi-square automatic interaction detection method [17]. One study selected predictors using logistic regression with backward selection [20]. In the other study, univariable preselection preceded the multivariable analysis [17].

Validation

None of the models had been validated, neither internally (e.g. using cross-validation or bootstrapping procedures) nor externally.

Model performance

Results on model performance are presented in Table 3. The area under ROC curve (AUCs) for the prediction models was reported in four studies [19–22]. In one study, in which models were developed by selecting from a broad range of candidate predictors, AUCs ranged from 0.718 (for the smallest model) to 0.742 (for the most extensive model). In this study, the four models were also compared using the net reclassification improvement and the integrative discrimination index, which showed that the more extensive the model, the better the discriminative performance [19]. AUCs of 0.74 were also reported in one other study, but only for the overall model and the model for women (AUCs of 0.74). The model stratified for men had a remarkably lower AUC of 0.59 [20]. In one study, with models based only on BMI and sex, the reported AUCs were low, ranging from 0.51 to 0.54 [21]. One study reported very high AUCs, ranging from 0.86 to 0.93 [22]. This may be explained by the inclusion of 'age at first diagnosis of hypertension' as a predictor, which, as mentioned previously, would not be available at the intended time point of prediction, and is not realistic for application in practice.

Sensitivity and specificity were reported in two studies [18,21], and could be calculated from the trees in one study [17]. There was wide variation in sensitivity (8.3–78.6%) and specificity (25.7–96.1%). Positive and negative predictive values (PPV and NPV) were only reported in one study, and ranged from 10.9 to 51.4% for PPV and from 71.3 to 95.7% for NPV [18]. In another study, PPV and NPV could be derived from the classification trees; PPV ranged from 36.7 to 68.0% and NPV from 84.2 to 96.9%) [17]. Calibration and explained variation were reported in only one study, and there was no indication that models were not adequately calibrated (i.e. the Hosmer-Lemeshow P value was >0.05). The explained variation for the most elaborate model was 22% [19].

Model presentation

In only two studies, models were presented in such a way that it was possible to calculate a predicted risk for a new individual child, either by following the steps in the classification trees [17], or by using the reported age-specific and sex-specific PPVs of the corresponding childhood risk factor [18]. One study presented a full regression equation [22], but as the predictor 'age at first diagnosis of hypertension' is naturally not available at the time point of prediction, this model cannot be applied in a new individual. Another study presented a regression equation in the supplementary material, but without providing the intercept, hampering the calculation of a predicted risk [19].

Risk of bias assessment

Table 4 shows the results of the risk assessment for selection bias, information bias, and bias related to the analysis in the included studies. Two studies [17,22] scored 'high' for risk of selection bias related to participant selection; for both studies this was because of limited or unclear information on recruitment and selection of the study population, and because of limited information on key characteristics and predictors for the study sample. For selection bias related to sample attrition, all five prospective studies [17–19,21,22] reported the amount of loss to follow-up, and four [17–19,21] of these scored 'moderate,' as loss to follow-up was higher than 20%. With regard to risk of information bias for predictors, two studies [20,22] scored 'high,' which was because of: unclear definitions/measurements of predictors [20,22], possibly less valid and reproducible measurements [20], lack of standardized measurements [20], different timing of predictor assessment within the study sample [22], and/or unavailability of predictors at the intended time point of use of the model [22]. For the risk of information bias related to the outcome, four studies [17–19,22] scored 'high,' because of lack of information on blinding for predictor information [17–19,22], unclear definitions of outcome and measurement of outcome [17,22], possibly less valid and reproducible measurements [17–19,22], and/or different assessment (including timing) within the study sample [18,19,22]. Lastly, for risk of bias related to the analysis, four studies [17–19,22] scored 'high' and the other two studies [20,21] 'moderate.' Continuous predictors were sometimes categorized without this being part of the research question [17,19], and missing values were often not clearly reported and only complete cases seem to have been included [18–20,22]. Furthermore, the number of events per variable was too low in one study [17], and unclear in another [18]. Most notably, as mentioned before, none of the studies accounted for overfitting and optimism, that is, no internal validation and/or external validation was performed [17–22].

TABLE 3. Performance of the included prediction models, including age-specific performance if available

Author (year) [ref.]	Model	Discrimination						Calibration	Explained variation
		AUC or C-statistic (95% CI)	Other	Sensitivity	Specificity	PPV	NPV		
Ferrer *et al.* (2015) [17]	Tree 1, based on categorical variables	NR	NR	34.0%[a]	96.1%[a]	66.7%	86.4%	NR	NR
	Tree 2, based on continuous variables	NR	NR	Node 4 vs. other nodes: 44.7%[a]	Node 4 vs. other nodes: 89.8%[a]	Node 4 vs. other nodes: 50.0%	Node 4 vs. other nodes: 87.6%[a]	NR	NR
	Tree 3, based on continuous variables, for males	NR	NR	Node 2 vs. other nodes: 51.5%[a]	Node 2 vs. other nodes: 91.4%[a]	Node 2 vs. other nodes: 68.0%	Node 2 vs. other nodes: 84.2%	NR	NR
	Tree 4, based on continuous variables, for females	NR	NR	Node 4 vs. other nodes: 78.6%[a]	Node 4 vs. other nodes: 83.0%[a]	Node 4 vs. other nodes: 36.7%	Node 4 vs. other nodes: 96.9%[a]	NR	NR
Juhola *et al.* (2012) [19]	Model 1	0.718 (0.695–0.741)	NA	NR	NR	NR	NR	Hosmer-Lemeshow, $\chi 2$ (*P* value) 11.3 (0.19)	NR
	Model 2	0.733 (0.711–0.756) *P* value model 2 vs. 1: 0.0007	NRI (*P* value) model 2 vs. 1: 5.8 (< 0.0001) IDI (*P* value): model 2 vs. 1: 2.0 (< 0.0001)	NR	NR	NR	NR	Hosmer-Lemeshow, $\chi 2$ (*P* value) 12.5 (0.13)	NR
	Model 3	0.734 (0.712–0.756) *P* value model 3 vs. 1: 0.0008 *P* value model 3 vs. 2: 0.91	NRI (*P* value) model 3 vs. 1: 9.5 (< 0.0001) model 3 vs. 2: 3.8 (0.007) IDI (*P* value): model 3 vs. 1: 2.2 (< 0.0001) model 3 vs. 2: 0.2 (0.48)	NR	NR	NR	NR	Hosmer-Lemeshow, $\chi 2$ (*P* value) 0.54 (0.99)	NR
	Model 4	0.742 (0.720–0.764) *P* value model 4 vs. 1: < 0.0001 *P* value model 4 vs. 2: 0.015 *P* value model 4 vs. 3: 0.008	NRI (*P* value) model 4 vs. 1: 10.4 (<0.0001) model 4 vs. 2: 4.8 (0.0002) model 4 vs. 3: 1.0 (0.28) IDI (*P* value) model 4 vs. 1: 3.1 (< 0.0001) model 4 vs. 2: 1.2 (< 0.0001) model 4 vs. 3: 0.92 (< 0.0001)	NR	NR	NR	NR	Hosmer-Lemeshow, $\chi 2$ (*P* value) 6.7 (0.57)	Nagelkerke pseudo-R^2 22%

TABLE 3 (*Continued*)

Author (year) [ref.]	Model	Discrimination						Calibration	Explained variation
		AUC or C-statistic (95% CI)	Other	Sensitivity	Specificity	PPV	NPV		
Juhola *et al.* (2011) [18]	Model 1 males								
	Age 6 years	NR	NR	55.6%	63.8%	26.3%	86.1%	NR	NR
	Age 9 years	NR	NR	76.5%	52.6%	29.2%	89.7%	NR	NR
	Age 12 years	NR	NR	47.1%	69.6%	41.4%	74.3%	NR	NR
	Age 15 years	NR	NR	53.7%	69.4%	51.4%	71.3%	NR	NR
	Age 18 years	NR	NR	87.5%	25.7%	39.5%	78.8%	NR	NR
	All ages	NR	NR	63.8%	56.7%	37.7%	79.3%	NR	NR
	Model 2 females								
	Age 6 years	NR	NR	75.0%	47.6%	10.9%	95.7%	NR	NR
	Age 9 years	NR	NR	71.4%	47.5%	15.2%	92.7%	NR	NR
	Age 12 years	NR	NR	53.7%	62.4%	24.7%	85.4%	NR	NR
	Age 15 years	NR	NR	46.0%	69.4%	24.6%	85.5%	NR	NR
	Age 18 years	NR	NR	74.5%	51.1%	33.3%	85.9%	NR	NR
	All ages	NR	NR	62.4%	55.7%	21.4%	88.5%	NR	NR
Li *et al.* (2011) [21]	Model 1 IOTF cut-offs								
	Age 7 years	NR	NR	8.3%	92.7%	NR	NR	NR	NR
	Age 11 years	NR	NR	10.6%	93.1%	NR	NR	NR	NR
	Age 16 years	NR	NR	12.5%	92.2%	NR	NR	NR	NR
	Model 2 Study-specific cut-offs								
	Age 7 years	0.53 (0.52–0.55)	NR	39.0%	69.7%	NR	NR	NR	NR
	Age 11 years	0.54 (0.52–0.55)	NR	55.7%	56.1%	NR	NR	NR	NR
	Age 16 years	0.54 (0.52–0.55)	NR	44.8%	73.9%	NR	NR	NR	NR
	Model 3 BMI gain								
	Age 11 years	0.53 (0.51–0.54)	NR	63.7%	48.8%	NR	NR	NR	NR
	Age 16 years	0.51 (0.49–0.53)	NR	53.5%	62.1%	NR	NR	NR	NR
Sun *et al.* (2007) [22]	Model 1, males								
	Age 5–7 years	0.86	NR	NR	NR	NR	NR	NR	NR
	Age 8–12 years	0.86	NR	NR	NR	NR	NR	NR	NR
	Age 13–18 years	0.86	NR	NR	NR	NR	NR	NR	NR
	Model 2, females								
	Age 5–7 years	0.93	NR	NR	NR	NR	NR	NR	NR
	Age 8–12 years	0.91	NR	NR	NR	NR	NR	NR	NR
	Age 13–18 years	0.93	NR	NR	NR	NR	NR	NR	NR
Vos *et al.* (2003) [20]	Model 1, both sexes	0.74 (0.70–0.77)	NR	NR	NR	NR	NR	NR	NR
	Model 2, males	0.59 (0.53–0.65)	NR	NR	NR	NR	NR	NR	NR
	Model 3, females	0.74 (0.67–0.82)	NR	NR	NR	NR	NR	NR	NR

[a]Calculated from reported numbers.
AUC, area under the receiver operating characteristic curve; BMI, body mass index; CI, confidence interval; C-statistic, concordance statistic; IDI, integrative discrimination index; IOTF, International Obesity Task Force; NA, not applicable; NPV, negative predictive value; NR, not reported; NRI, net reclassification improvement index; PPV, positive predictive value.

TABLE 4. Results of risk of bias assessment

	Risk of bias[a]				
	Selection bias		Information bias		Other
Author (year) [ref]	Selection of participants	Sample attrition	Predictors	Outcome	Analysis
Ferrer *et al.* (2015) [17]	H	M	M	H	H
Juhola *et al.* (2012) [19]	M	M	M	H	H
Juhola *et al.* (2011) [18]	M	M	L	H	H
Li *et al.* (2011) [21]	M	M	L	M	M
Sun *et al.* (2007) [22]	H	L	H	H	H
Vos *et al.* (2003) [20]	M	NA	H	L	M

H, high risk of bias; L, low risk of bias; M, moderate risk of bias; NA, not applicable (retrospective study).
[a]The criteria that were used to perform this risk of bias assessment are shown in Supplemental Table 2, http://links.lww.com/HJH/B32.

DISCUSSION

We identified six studies meeting the inclusion and exclusion criteria, in which a total of 18 eligible models were presented. These models predict, in childhood, the risk of hypertension in later life, mostly in adulthood. However, no studies were identified that aimed to translate the prediction model into practice, which is reflected in the results of our systematic review. First of all, in each study, multiple combinations of predictors were investigated (e.g. age-specific models and models comparing categorized and continuous predictors), without presenting one final prediction model as the one most optimal for use in clinical practice, in a format that could be applied by others. Related to this, in the majority of the included studies, the development of models was based on a few predictors chosen a priori, such as sex, BMI, overweight or earlier (high) blood pressure. In fact, only one study considered a large number of candidate predictors in order to find the best combination for the prediction model [19]. For clinical or public health practice, it will possibly be more useful to have one optimal prediction model incorporating information on all of the most relevant predictors. Secondly, we saw that only two out of six studies presented prediction models in a format that would allow for application in new individuals [17,18], and that in one study, a predictor was part of the models that would not be available at the intended time point of use [22]. Finally, the lack of attention for the application in practice might also explain the limited information on performance for most models, as well as the lack of validation. Our results, therefore, underline the need for further development and validation studies of childhood prediction models for future hypertension, in order to pave the way for early targeted primordial prevention.

The completeness of reporting varied across the included studies. Inadequate reporting makes it more difficult to assess the quality of the prediction models, and to draw conclusions about the reliability, validity and generalizability of the prediction models [24]. We identified the following important aspects related to reporting and to model development that deserve attention. First of all, sample selection procedures were not always described clearly, and most studies dealt with loss to follow-up whereas failing to report on differences in key characteristics between the sample for analysis and the participants that were lost to follow-up. Secondly, all studies had some limitations with regard to the outcome assessment, such as different follow-up durations for participants, and details on blinding the outcome assessment were often lacking. With regard to the quality of model development, in most studies some aspects could be improved, such as the use of continuous variables, the handling of missing values and the prevention of overfitting (e.g. having an adequate number of events per variable, and not performing univariable preselection). Categorization of continuous variables can lead to a loss of predictive information, and should ideally be avoided [25]. Performing a complete case analysis instead of imputing missing values, might lead to a loss of statistical power and to incorrect estimates of the predictive performance of the model and the predictors [25].

For most models, the information about the performance was very limited, making it difficult to evaluate and compare the capability of the models to predict high blood pressure in later life. A direct comparison was also difficult because the prediction models in the different studies were targeted at different age groups, and the age at outcome assessment also varied widely. Furthermore, as none of the models was internally or externally validated, and it cannot be determined how optimistic the presented performance is, that is, how well these models would perform in slightly different populations. The AUCs reported in two studies (AUC 0.71–0.74) showed that discrimination between children who did and who did not have hypertension in adulthood was reasonable [19,20]. These results support the idea that the development of a reasonably performing prediction model for high blood pressure might be possible.

A strength of this review is that we applied a comprehensive search strategy in both Medline and Embase, two databases that together cover the majority of the medical scientific literature. By hand searching the reference lists of relevant reviews and the included studies, no new studies were identified. We, therefore, consider it unlikely that we have missed a relevant prediction modelling study for this topic. Nevertheless, it should be noted that we restricted our search to English publications, and although we did not identify relevant non-English publications through hand searching, we cannot fully exclude that we might have missed studies on prediction models written in another language. Another strength is that we used the CHARMS checklist to systematically extract the data on key characteristics of the study population, the model development, and the final models. A limitation might be that, because of the large amount of references identified with the search

strategy, title and abstract screening was primarily performed by one reviewer (M.H.). Two other reviewers (M.K. and Y.V.) together checked a random 10% sample, and as the agreement was over 99%, and the first reviewer (M.H.) was being more inclusive of titles/abstracts, we consider the selection to be adequate. Another limitation could be that during data extraction, the two reviewers M.H. and M.W. were not blinded for journal and author details. However, both M.H. and M.W. do not have any affiliations with any of the authors or journals and, therefore, we do not believe it to have had any effect on the data extraction and evaluation.

On the basis of the results of this review, we would recommend to perform additional analyses (including validation and/or adaptation) on the existing models in order to move towards implementation in practice, or the development of a new model to identify children at high risk of hypertension. When developing such a new model, it is important to carefully choose the target age (or age range) for application of the prediction model, the age for outcome assessment, and the candidate predictors. For the latter, it can be recommended to consider a broad range of candidate predictors (e.g. based on literature) if the sample size and the number of events allow for it. On the basis of the results of this systematic review, the following predictors can be considered relevant: weight status, blood pressure, parental hypertension, parental occupational status, sex, and age. With regard to weight status, in the studies both continuous measures (BMI) and categorized measures (overweight/obesity) were used [17,19–22]. As dichotomization of continuous predictors can lead to a loss of valuable information [23,26], using BMI instead of overweight/obesity is to be preferred. Moreover, in children it might be better to use standardized measures of BMI, such as *z*-scores or standard deviation scores relative to age and sex, because of normal changes in BMI that occur as children age [27]. For blood pressure, similar considerations are important. For example, a continuous measure of blood pressure, especially SBP, was shown to be a more important predictor than childhood prehypertension, a dichotomized predictor [19]. SBP might be more predictive of future hypertension than DBP [17,19,20]. The use of blood pressure standard deviation scores or percentiles (based on sex-specific and age-specific reference values) as a continuous variable might also be considered [18,28]. Parental occupational status was identified as a predictor in one of the studies [19], but other socioeconomic indicators such as parental educational level or income might also be relevant [29]. Next, helpful methodological resources are available to further improve prediction model development [23,25]; these discuss appropriate model selection methods, dealing with missing values, and internal and external validation methods. Also, it can be recommended to report the methods and results with help of the 'Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis' (TRIPOD) statement and the TRIPOD explanation and elaboration document, in order to improve the quality and transparency of reporting [24]. Lastly, it is important that prediction models are presented in such a way that they can be applied in new individuals by other researchers or healthcare professionals interested in the model. This will also allow for external validation (by others), which is essential to evaluate the generalizability and applicability of a prediction model in other populations than the study population.

In conclusion, several prediction models were identified that predict, in childhood, the risk of hypertension in later life, mostly in adulthood. Important predictors were weight status (BMI or overweight/obesity), current high blood pressure, SBP, DBP, sex, age, parental hypertension, and socioeconomic status. In general, the quality of reporting and model development was suboptimal, and as none of the identified models were validated, it is not possible to assess their value for practice and to recommend the use of any of these models. Because of the lack of validation, the reported estimates of the performance are likely to be too optimistic. The results of this review indicate that there is some potential for a prediction model for future hypertension based on multiple characteristics in childhood.

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Conflicts of interest

There are no conflicts of interest.

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