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

Supplementary material

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**Supplemental Table 1.** Search strategy used for this review in EMBASE and MEDLINE

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Database** | **Search syntax** |  |  |  |  |  |  |
| EMBASE | ('elevated blood pressure'/exp OR (hypertensi\* OR prehypertensi\* OR ((high OR elevated OR increased) NEAR/6 ('blood pressure' OR 'blood pressures' OR bloodpressure))):ab,ti) AND ('prediction and forecasting'/exp OR 'algorithm'/exp OR 'validation study'/de OR 'risk assessment'/de OR (predict\* OR prognos\* OR validat\* OR 'ROC curve' OR 'Receiver Operating Characteristic' OR algorithm\* OR probabilit\* OR C-index OR C-indices OR ((risk\*) NEAR/6 (estimat\* OR model\* OR score\* OR profil\* OR index OR indices OR instrument\* OR tool OR stratif\* OR test\* OR classif\* OR assessment\* OR assessor\* OR chart\* OR equation\* OR appraisal OR calculator\* OR engine\* OR table\* OR treshold\* OR discrimination OR scor\* OR function\*)) OR ((scoring) NEAR/3 (system\*))):ab,ti) AND ('childhood'/exp OR 'adolescence'/exp OR child/exp OR adolescent/exp OR (child\* OR infant\* OR newborn\* OR neonat\* OR toddler\* OR baby OR babies OR kid OR kids OR adolescen\* OR teenage\* OR boy\* OR girl\* OR ((new\*) NEXT/1 (born\*)) OR ((earl\* OR young\*) NEXT/1 (age\*))):ab,ti) AND [english]/lim NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim OR review/exp OR 'case report'/de OR 'case study'/de OR (review\* OR case-report\* OR case-serie\* OR case-stud\*):ti) NOT ('pulmonary hypertension'/exp OR 'intracranial hypertension'/exp OR 'portal hypertension'/exp OR 'leukemia'/exp OR 'liver cell carcinoma'/exp OR (((pulmonar\* OR intracranial\* OR portal) NEAR/3 hypertensi\*) OR leukemi\* OR leukaemi\* OR encephalopath\* OR ((liver-cell\* OR Hepatocell\*) NEAR/3 carcinoma)):ab,ti) |
| MEDLINE | (exp "hypertension"/ OR exp "prehypertension"/ OR (hypertensi\* OR prehypertensi\* OR ((high OR elevated OR increased) ADJ6 ("blood pressure" OR "blood pressures" OR bloodpressure))).ab,ti,kf.) AND ("prediction and forecasting"/ OR exp "sensitivity and specificity"/ OR exp "algorithms"/ OR "validation studies"/ OR "risk assessment"/ OR (predict\* OR prognos\* OR validat\* OR "ROC curve" OR "Receiver Operating Characteristic" OR algorithm\* OR probabilit\* OR C-index OR C-indices OR ((risk\*) ADJ6 (estimat\* OR model\* OR score\* OR profil\* OR index OR indices OR instrument\* OR tool OR stratif\* OR test\* OR classif\* OR assessment\* OR assessor\* OR chart\* OR equation\* OR appraisal OR calculator\* OR engine\* OR table\* OR treshold\* OR discrimination OR scor\* OR function\*)) OR ((scoring) ADJ3 (system\*))).ab,ti,kf.) AND ("childhood"/ OR "adolescence"/ OR child/ OR adolescent/ OR (child\* OR infant\* OR newborn\* OR neonat\* OR toddler\* OR baby OR babies OR kid OR kids OR adolescen\* OR teenage\* OR boy\* OR girl\* OR ((new\*) ADJ (born\*)) OR ((earl\* OR young\*) ADJ (age\*))).ab,ti,kf.) AND english.la. NOT ((letter OR news OR comment OR editorial OR congresses OR abstracts).pt. OR review/ OR "case report"/ OR "case study"/ OR (review\* OR case-report\* OR case-serie\* OR case-stud\*).ti.) NOT (exp "Hypertension, Pulmonary"/ OR exp "Intracranial Hypertension"/ OR exp "Hypertension, Portal"/ OR exp "leukemia"/ OR "Carcinoma, Hepatocellular"/ OR (((pulmonar\* OR intracranial\* OR portal) ADJ3 hypertensi\*) OR leukemi\* OR leukaemi\* OR encephalopath\* OR ((liver-cell\* OR Hepatocell\*) ADJ3 carcinoma)).ab,ti,kf.) |

**Supplemental Table 2.** Criteria for scoring the risk of bias, adapted from Smit et al.[1] and based on items in the CHARMS checklist[2]

|  |  |  |  |
| --- | --- | --- | --- |
| **Type of bias** | **Item** | **Risk of bias**  | **Description of criteria for risk of bias categories** |
| Selection bias | Selection of participants | Low | Satisfying all of the criteria below:1. Adequate description of recruitment and selection of the study population, AND
2. Adequate description of in- and exclusion criteria AND
3. Participants enrolled with similar health status AND
4. Adequate description of the sample with regard to key characteristics and predictors, with no indications of selection bias
 |
| Moderate | Not satisfying one of the above criteria |
| High | Not satisfying two or more of the above criteria  |
| Sample attrition | Low | Satisfying all of the criteria below:1. Loss to follow up adequately reported AND
2. No loss to follow up OR loss to follow up < 20% with comparison on key characteristics and no important differences
 |
| Moderate | Not satisfying one of the above criteria |
| High | Not satisfying both of the above criteria |
| Information bias | Predictors | Low | Satisfying all of the criteria below:1. Clear definition of predictors and measurement of predictors
2. Valid and reproducible measurement of predictors
3. Measurement of predictors blinded for the outcome (if applicable)
4. Assessment (including timing) of predictors similar in all participants
5. All predictors available at intended time point of use of the model
 |
| Moderate | Not satisfying one of the above criteria |
| High | Not satisfying two or more of the above criteria |
| Outcome | Low | Satisfying all of the criteria below:1. Clear definition of outcome and measurement of outcome
2. Valid and reproducible measurement of outcome
3. Measurement of outcome blinded for predictors
4. Assessment (including timing) of outcome similar in all participants
 |
| Moderate | Not satisfying one of the above criteria |
| High | Not satisfying two or more of the above criteria |
| Other | Analysis | Low | Satisfying all, or all but one of the criteria below:1. Adequate description of analysis, enough to judge the quality of the other criteria
2. Adequate handling of continuous predictors
3. Adequate handling of missing values
4. Adequate selection method
5. Events-per-variable reasonable
6. Accounted for overfitting/optimism
7. Assessment of model performance: explained variation and/or calibration and/or discrimination (with a-priori defined cut-off)
 |
| Moderate | Not satisfying two of the above criteria |
| High | Not satisfying three or more of the above criteria |

**Supplemental Table 3.** Exact definitions of final predictors and outcomes in the included studies

| **Author (year)** | **Type** | **Variable** | **Timing** | **Definition** | **Measurement** |
| --- | --- | --- | --- | --- | --- |
| Ferrer et al. (2015) | Predictors | Initial BP classification categorical) | Age 12-15 years | Abnormal BP: prehypertensive or hypertensive: SBP and/or DBP ≥ 90th percentile or ≥ 120/80 mmHg as per the Fourth Report on Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents. | SBP and DBP were taken after subjects had rested for 5 minutes, sitting upright, with the right arm positioned at heart level, without having smoked or taken medication that day. An aneroid blood pressure cuff and calibrated stethoscope (SMIC, China) were used. Repeated measurements were taken at 5-minute intervals. It is not reported how many measurements were taken, and whether an average was calculated and used. It is not reported whether Korotkoff IV or V was used for measuring DBP. |
| BMI (categorical) | Age 12-15 years |  ≥ 90th percentile for Cuban children and adolescents | Anthropometric measures were taken three times on the same day, and included waist circumference, weight and height. The average was calculated. Equipment was calibrated and monitored. Research team members received training on study procedures. To calculate BMI, the Quetelet index was used (weight in kg/(height in m)2).  |
| Waist circumference (categorical) | Age 12-15 years | > 90th percentile according to CDC | Anthropometric measures were taken three times on the same day, and included waist circumference, weight and height. The average was calculated. Equipment was calibrated and monitored. Research team members received training on study procedures. |
| SBP (continuous) | Age 12-15 years | mmHg | SBP and DBP were taken after subjects had rested for 5 minutes, sitting upright, with the right arm positioned at heart level, without having smoked or taken medication that day. An aneroid blood pressure cuff and calibrated stethoscope (SMIC, China) were used. Repeated measurements were taken at 5-minute intervals. It is not reported how many measurements were taken, and whether an average was calculated and used. |
| DBP (continuous) | Age 12-15 years | mmHg | SBP and DBP were taken after subjects had rested for 5 minutes, sitting upright, with the right arm positioned at heart level, without having smoked or taken medication that day. An aneroid blood pressure cuff and calibrated stethoscope (SMIC, China) were used. Repeated measurements were taken at 5-minute intervals. It is not reported how many measurements were taken, and whether an average was calculated and used. It is not reported whether Korotkoff IV or V was used for measuring DBP. |
| BMI (continuous) | Age 12-15 years | kg/m2 | Anthropometric measures were taken three times on the same day, and included waist circumference, weight and height. The average was calculated. Equipment was calibrated and monitored. Research team members received training on study procedures. To calculate BMI, the Quetelet index was used (weight in kg/(height in m)2).  |
| Waist circumference (continuous) | Age 12-15 years | cm | Anthropometric measures were taken three times on the same day, and included waist circumference, weight and height. The average was calculated. Equipment was calibrated and monitored. Research team members received training on study procedures. |
| Gender (categorical, stratified analysis) | NA | male/female | NA |
| Outcome | Abnormal BP | Age 16-19 years | Abnormal BP: prehypertensive or hypertensive: ≤18 years: SBP and/or DBP ≥ 90th percentile or ≥ 120/80 mmHg as per the Fourth Report on Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents.> 18 years: SBP and/or DBP ≥ 120/80 mmHg | SBP and DBP were taken after subjects had rested for 5 minutes, sitting upright, with the right arm positioned at heart level, without having smoked or taken medication that day. An aneroid blood pressure cuff and calibrated stethoscope (SMIC, China) were used. Repeated measurements were taken at 5-minute intervals. It is not reported how many measurements, and whether an average was calculated and used. It is not reported whether Korotkoff IV or V was used for measuring DBP. |
| Juhola et al. (2012) | Predictors | SBP (continuous) | Age 3-18 years | mmHg, transformed into age- and sex-specific z scores | BP was measured from the right brachial artery with a standard mercury sphygmomanometer, except for 3-year-old participants where BP was measured with an ultrasound scanning device. BP was measured in sitting position, after a 5-minute rest. Korotkoff 1st phase was used for SBP. Readings were performed to the nearest integer mm of mercury, at least 3 times on each participant and the average of these 3 measurements was used in the analysis. |
| Overweight/obesity (categorical) | Age 3-18 years | Definition based on age- and sex-specific cut-offs for BMI recommended by the IOTF were used. | Height and weight were measured and BMI was calculated as weight in kg divided by height in m2. |
| Age (continuous) | At baseline  | years | NA |
| Sex (categorical) | NA | NA | NA |
| Parental hypertension (categorical) | Age 3-18 years | Self-reported diagnosis of hypertension in either parent | Questionnaire |
| Parental occupational status (categorical) | Age 3-18 years | Divided into 3 categories: manual, lower-grade non-manual, and higher-grade non-manual | Questionnaire |
| Genetic risk score(continuous) | Age 3-18 years | A genetic risk score was calculated as an arithmetic sum of risk alleles in 29 SNPs, transformed into age- and sex-specific z scores | The score included 29 SNPs associated with SBP and DBP recently identified in genome-wide association studies. Genotyping was successfully performed for 1939 individuals, using the Illumina Bead Chip (Human 670K). The individual SNPs are shown in Supplemental Table IV of the study. |
| Outcome | Hypertension | Age 24-45 years | SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHg, or use of antihypertensive medication in 2001 and/or 2007.  | BP was measured from the right brachial artery with a random-zero sphygmomanometer (Hawksley & Sons LtD, Lancin, UK). BP was measured in sitting position, after a 5-minute rest. Korotkoff 1st phase was used for SBP, and both 4th and 5th phases for DBP. Not clearly reported whether DBP Korotkoff 4th or 5th phase was used for the outcome assessment. Readings were performed to the nearest integer mm of mercury, at least 3 times on each participant and the average of these 3 measurements was used in the analysis.Use of antihypertensive medication was determined with self-administered questionnaires. |
| Juhola et al. (2011) | Predictors | Childhood prehypertension/hypertension  | At baseline age: 6, 9, 12, 15 or 18 years | According to height, sex, and age tables from the National High Blood Pressure Education Program (Fourth Report, 2004). | BP was measured from the right brachial artery with a standard mercury sphygmomanometer, in a sitting position, after a 5-minute rest. Korotkoff 1st phase was used for SBP, and the 5th phase for DBP. Readings were performed to the nearest even number of millimeters of mercury, at least 3 times on each participant and the average of these 3 measurements was used in the analysis. |
| Gender | NA | male/female | NA |
| Outcome | Hypertension | Age 30-45 years | Hypertension: SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg, or use of antihypertensive medication for hypertension.  | BP was measured from the right brachial artery with a standard mercury sphygmomanometer, in a sitting position, after a 5-minute rest. Korotkoff 1st phase was used for SBP, and the 5th phase for DBP. Readings were performed to the nearest even number of millimeters of mercury, at least 3 times on each participant and the average of these 3 measurements was used in the analysis.Use of antihypertensive medication was determined with self-administered questionnaires. |
| Li et al. (2011) | Predictors | Overweight/obesity according to IOTF cut-off (categorical) | Age 7, 11 or 16 years | Based on sex-specific IOTF cutoffs for BMI at centered ages: at 7.5 years for boys 18.2 kg/m2, girls 18.0 kg/m2, at age 11.5 years for boys 20.9 kg/m2, girls 21.2 kg/m2, at age 16 years for boys 23.9 kg/m2, girls 24.4 kg/m2. | Height and weight were measured by medical personnel using standard protocols at age 7, 11 and 16. For children measured outside the ranges 7.25-7.75, 11.25-11.75, 15.75-16.25, BMI was centered at 7.5, 11.5 and 16 years respectively, using regression models that assume a linear trend over these short growth periods. |
| Overweight/obesity according to study-specific cut-off (categorical) | Age 7, 11 or 16 years | Based on ROC analysis: at each age the optimal cut-off was chosen as the point on the ROC curve that was closest to the (0,1), to achieve the highest combination of sensitivity and specificity. At 7.5 years for boys 16.1 kg/m2, girls 16.6 kg/m2, at age 11.5 years for boys 16.5 kg/m2, girls 17.7 kg/m2, at age 16 years for boys 19.8 kg/m2, girls 24.3 kg/m2. | Height and weight were measured by medical personnel using standard protocols at age 7, 11 and 16. For children measured outside the ranges 7.25-7.75, 11.25-11.75, 15.75-16.25, BMI was centered at 7.5, 11.5 and 16 years respectively, using regression models that assume a linear trend over these short growth periods. |
| BMI gain above to study-specific cut-off (categorical) | Age 7-11 years or 11-16 years | Based on ROC analysis: at each age the optimal cut-off was chosen as the point on the ROC curve that was closest to the (0,1), to achieve the highest combination of sensitivity and specificity. At 7-11 years for boys 0.65 kg/m2, girls 1.69 kg/m2. At 11-16 years for boys 2.65 kg/m2, girls 4.65 kg/m2. | Height and weight were measured by medical personnel using standard protocols at age 7, 11 and 16. For children measured outside the ranges 7.25-7.75, 11.25-11.75, 15.75-16.25, BMI was centered at 7.5, 11.5 and 16 years respectively, using regression models that assume a linear trend over these short growth periods. |
| Gender | NA | male/female | NA |
| Outcome | Hypertension | Age 45 years | SBP ≥ 140 and/or DBP ≥ 90 mmHg or use of antihypertensive medication | Measured by nurses using standardized protocols. BP was measured 3 times using an Omron 705CP automated digital oscillometric sphygmomanometer, after the participant had been seated for 5 minutes. A normal cuff was used for a circumference (at the mid-point of the upper arm) < 32 cm, otherwise a large cuff was used. The means of 3 measurements (SBP and DBP) was calculated and used for analysis. Current use of antihypertensive medication was recorded by the nurse as well. |
| Sun et al. (2007) | Predictors | EBP (categorical) | 3 different age ranges:5-7 years8-12 years13-18 years | A single mean SBP (at any examination within the age interval) exceeding age- and gender-specific criterion values developed in part 1 of the study. Figure 2 of the original paper shows childhood SBP values at different childhood ages (2-18 years) of males and females with and without metabolic syndrome. The values for the participants with metabolic syndrome at a certain age were used as criterion values for childhood SBP. | SBP was measured with a standard mercury sphygmomanometer every 6 months (from age 2 through age 18 years), by trained technicians, with participants seated. Three BP measurements were taken at each examination, and the mean of the last two readings was used in the analysis. |
| BMI | 3 different age ranges:5-7 years8-12 years13-18 years | kg/m2 | Weight and height were measured during examinations every 6 months in childhood, no further details on exact measurement method are reported in the paper. Also it is not clear which BMI in a certain age range was used for the logistic regression model in case multiple BMI measurements were available in a certain age range. |
| Age at first diagnosis of hypertension | During follow up | years | NA |
| Outcome | Hypertension | At ≥ 30 years (in study population from ≥ 20 years) | SBP > 130 mmHg and/or DBP of > 85 mmHg | SBP and DBP were measured with a standard mercury sphygmomanometer every 2 years after the age of 18 years, by trained technicians, with participants seated. Three BP measurements were taken at each examination, and the mean of the last two readings was used in the analysis.It is not clearly reported whether hypertension had to be diagnosed during a measurement from the study, or whether a diagnosis of hypertension or treatment for hypertension (e.g. during the 2 year interval) were considered as well. Also, it is not clear what was done if hypertension was first diagnosed in participants between 20-30 years of age. The first author of the study was contacted, but did not respond. |
| Vos et al. (2003) | Candidate predictors | SBP | Adolescence | Single/first SBP value (continuous) | Utrecht: routinely measured single BP value, using a sphygmomanometer. No standardization concerning cuff size and rest before measurements.The Hague: BP was measured three times within 3 minutes in a sitting position at the right upper arm with an automated device (Physiometrics SR-2) with a cuff of 13 x 23.5 cm. First measurement used for analysis. |
| Gender | NA | male/female | NA |
| Age | Adolescence | years | NA |
| BMI | Adolescence | kg/m2 | Utrecht: routinely measured body height and weightThe Hague: body weight and height were measured without shoes |
| Outcome | Hypertension | Young adulthood | Average (of all measurements at two visits) SBP value ≥ 140 mmHg or DBP value ≥ 90 mmHg or use of antihypertensive medication | BP was measured using Dynamap, in sitting position, at the left upper arm. BP was measured during two visits, with two measurements at both visits. First measurement after a 5-minute rest, second measurement after another 5-15 minutes rest. Information on the use of antihypertensive medication was obtained with a written questionnaire. |

*Abbreviations:*

BMI: body mass index

BP: blood pressure

CDC: Centers for Disease Control and Prevention

DBP: diastolic blood pressure

EBP: elevated blood pressure

IOTF: International Obesity Task Force

NA: not applicable

ROC: receiver operating characteristic

SBP: systolic blood pressure

SNP: single nucleotide polymorphism

**References**

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2. Moons KG, de Groot JA, Bouwmeester W, Vergouwe Y, Mallett S, Altman DG, et al. Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the CHARMS checklist. PLoS Med. 2014; 11 (10):e1001744.