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ORIGINAL RESEARCH

Dynamic prediction model to identify young children at high risk of future overweight: Development and internal validation in a cohort study

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Summary

Background: Primary prevention of overweight is to be preferred above secondary prevention, which has shown moderate effectiveness.

Objective: To develop and internally validate a dynamic prediction model to identify young children in the general population, applicable at every age between birth and age 6, at high risk of future overweight (age 8).

Methods: Data were used from the Prevention and Incidence of Asthma and Mite Allergy birth cohort, born in 1996 to 1997, in the Netherlands. Participants for whom data on the outcome overweight at age 8 and at least three body mass index SD scores (BMI SDS) at the age of ≥ 3 months and ≤ 6 years were available, were included (N = 2265). The outcome of the prediction model is overweight (yes/no) at age 8 (range 7.4–10.5 years), defined according to the sex- and age-specific BMI cut-offs of the International Obesity Task Force.

Results: After backward selection in a Generalized Estimating Equations analysis, the prediction model included the baseline predictors maternal BMI, paternal BMI, paternal education, birthweight, sex, ethnicity and indoor smoke exposure; and the longitudinal predictors BMI SDS, and the linear and quadratic terms of the growth curve

Abbreviations: AUC, area under the curve; BMI, body mass index; CBS, Statistics Netherlands; EPODE, Ensemble Prévenons l'Obésité Des Enfants; EPV, events per variable; GEE, Generalized Estimating Equations; IOTF, International Obesity Task Force; LMS, lambda mu sigma; MICE, Multivariate Imputation by Chained Equations; NPV, negative predictive value; PCHC, Preventive Child Health Care; PIAMA, Prevention and Incidence of Asthma and Mite Allergy; PPV, positive predictive value; ProCOR, Prediction Of Child CardioMetabolic Risk; SDS, SD score; SES, socioeconomic status; WHO, World Health Organization.

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describing a child's BMI SDS development over time, as well as the longitudinal predictors' interactions with age. The area under the curve of the model after internal validation was 0.845 and Nagelkerke R^2 was 0.351.

Conclusions: A dynamic prediction model for overweight was developed with a good predictive ability using easily obtainable predictor information. External validation is needed to confirm that the model has potential for use in practice.

KEYWORDS

cohort study, dynamic prediction model, future overweight, general population, primordial prevention, young children

1 | BACKGROUND

Overweight and obesity are important global health problems. The World Health Organization estimated that the percentage of children aged 5 to 19 who were overweight had increased from 4% in 1975 to 18% in 2016 worldwide.¹ In the Netherlands, an increase in overweight was also seen: in 2009, 13% to 15% of all Dutch children were overweight, which is a two- or threefold increase of the 1980 prevalence rates.² Children with overweight or obesity are more likely to have cardiovascular risk factors (such as high blood pressure, dyslipidaemia and hyperinsulinemia) and psychological problems, and are more likely to be overweight as adults.³⁻⁵ In turn, overweight and obesity in adulthood have been associated with mental and physical diseases such as diabetes mellitus type 2, cardiovascular diseases, certain types of cancer and depression, and are estimated to be the cause of 4.8% of all deaths worldwide.^{6,7}

Due to the tracking of overweight from childhood into adulthood, the adverse effects of overweight and obesity on an individual's (future) health, and the difficulty of changing one's lifestyle, with people often reverting to their old habits causing weight fluctuations resulting in even poorer health,⁸ primary prevention is to be preferred. Primary prevention strategies using universal approaches, that is, community-based interventions, such as the Ensemble Prévenons l'Obésité Des Enfants approach have shown their merits.⁹

Primary prevention targeted at individual young children at high risk of future overweight could be a valuable addition to the universal prevention. Ideally, children would be monitored over time and being offered a primary preventive intervention whenever they appear to be at increased risk of future overweight. This would require a dynamic prediction model, enabling the identification of children at increased risk and updating a child's risk estimate each time new information becomes available.

Therefore, we aimed to develop, and internally validate, a dynamic prediction model that can identify young children at high risk of future overweight by using both time-independent (data available soon after birth) and time-dependent (growth data till age 6) information. The model will be able to provide risk estimations at every age between birth and age 6, as studies have shown that overweight adolescents had the most rapid gain in body mass index SD score (BMI

SDS) between ages 2 and 6,¹⁰ and that BMI SDS changes in this time period are the most predictive for cardiometabolic risk at young adulthood.¹¹ Also, a literature review by Stocks et al. showed that weight gain at age 0 to 2 was associated with body size at age 5 to 13.¹² The current study is part of the Prediction Of Child Cardiometabolic Risk (ProCOR) project.¹³

2 | METHODS

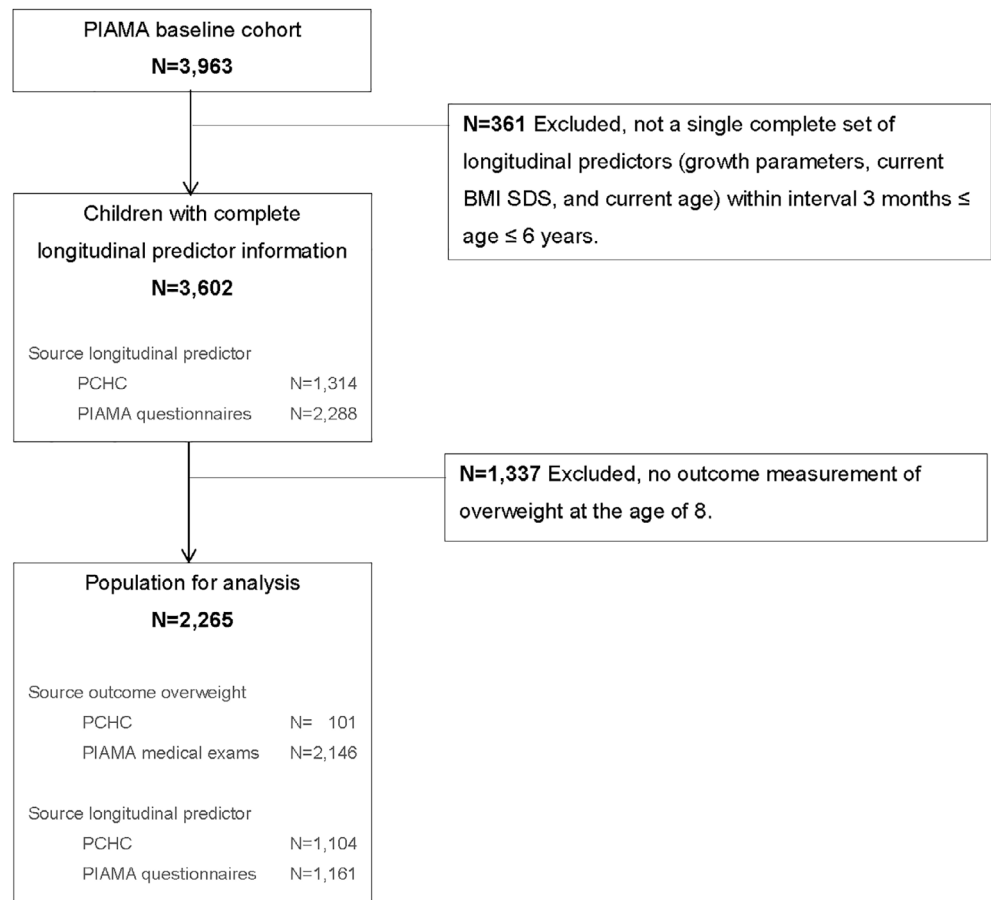
2.1 | Study design and population

For this study, we used data from the ongoing Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort. Pregnant women (N = 4146) were recruited from the general population through 52 antenatal clinics in three different regions (North: provinces Groningen, Friesland, Drenthe; Central: Utrecht, Gelderland; West: Rotterdam) of the Netherlands. Their children (N = 3963) were born in 1996 to 1997.¹⁴ Data were obtained through questionnaires and through growth assessments, recorded during the study's clinical examinations or by the Dutch Preventive Child Health Care (PCHC) organizations.

The questionnaires, completed by the parents during pregnancy, at child age 3 months, and then annually from the age of 1 up to 8 years, provided information on child and family characteristics, lifestyle, environment and health.¹⁴ Additional home visits and clinical examinations were conducted in subgroups at the child's ages of 1, 4 and 8 years.¹⁴ At the age of 18 years, 3047 children were still in the study and asked for permission to retrieve their growth data registered by the PCHC organizations. We received 1537 written informed consents and were able to retrieve PCHC growth data for 1444 of these children.

For the current study, we excluded 361 participants who did not have at least three BMI SDS measurements (minimum needed for estimating a quadratic growth curve, a longitudinal candidate predictor) available at the age of ≥ 3 months and ≤ 6 years. Of the remaining 3602 participants, another 1337 were excluded as information on the outcome (overweight at the age of 8) was missing, leaving a population for analysis of N = 2265. See Figure 1 for the flow chart.

FIGURE 1 Flow chart of the selection of population for analysis



The aimed setting for the implementation of the prediction model developed in this paper is the Well-Child Clinics. In the Netherlands, Well-Child Clinics are part of the Dutch PCHC. The Dutch PCHC is organized nationally, and monitors and promotes optimal growth and development of children. If needed, PCHC professionals refer directly to general practitioners or paediatricians. PCHC is offered free of charge to all children from birth until the age of 19 years and has a high reach (minimum of 90%-95% of all children¹⁵). The care for children is organized along a standard set of consultations: 15 check-ups between birth and age 4, 3 at school age 4 to 12, and another 2 in adolescence between age 12 and 18.¹⁵ The check-ups include routine measurements of a child's weight and height according to protocol. The timely identification of children with increased risk of future health problems is an important part of the care provided by PCHC to children.¹⁵ This, combined with the fact that PCHC records the results from visits in children's digital medical files, makes PCHC a very suitable setting for the implementation of a dynamic prediction model.

2.2 | Outcome

The outcome is overweight, including obesity, (yes vs no) at the average age of 8 years (range 7.4-10.5 years), defined according to the sex- and age- (monthly) specific BMI cut-offs of the International Obesity Task Force (IOTF) from 2012.¹⁶ We consider the outcome of

overweight at age 8 to be relevant, since there is already a considerable correlation between BMI at young adulthood and BMI at age 8.¹⁷

BMI in kg/m^2 was calculated from the weight and height of the child measured without shoes and clothes on (except for underwear) by trained research staff of the PIAMA study. Weight was measured to the nearest 0.1 kg on a calibrated scale and height was measured to the nearest 0.1 cm.¹⁸ In case no BMI measurement was available for the 8 year PIAMA medical examination, BMI (measured by a professional according to a similar protocol as for the PIAMA medical examination) was obtained from PCHC reports: selecting the BMI measurement reported by PCHC that fell within the age range of ≥ 7.4 and ≤ 10.5 years, where 7.4 is the minimum age as occurred in the PIAMA medical examination data and 10.5 is the maximum age (set by us to limit the possibility that some children had reached puberty). If multiple BMI measurements were reported by PCHC within this age range, the one measured closest to the mean PIAMA medical examination age of 8.2 years was selected.

2.3 | Candidate predictors

Based on previous research, availability of data within the study, and availability and feasibility in PCHC, the following baseline candidate predictors were selected: (a) maternal BMI¹⁸⁻²³ in kg/m^2 , calculated from the mother's weight before pregnancy and height as reported in

the 1-year PIAMA questionnaire; (b) paternal BMI,^{18,19,21-23} calculated from the father's weight and height as reported in the 8-year PIAMA questionnaire (first available BMI measurement) as a proxy for paternal BMI before pregnancy, which was not available; (c) maternal and (d) paternal highest attained educational level (as proxy for socioeconomic status [SES]),¹⁸⁻²² assessed in the 1-year PIAMA questionnaire and categorized into low (ie, primary school, lower vocational or lower secondary education), intermediate (ie, intermediate vocational education or intermediate/higher secondary education), and high (ie, higher vocational education or university); (e) maternal smoking during pregnancy,¹⁸⁻²³ assessed in the PIAMA pregnancy questionnaire and dichotomized into: the mother still smoked at 4 weeks after the start of the pregnancy vs the mother did not smoke or stopped smoking before being 4 weeks pregnant; (f) maternal weight gain during pregnancy²⁰⁻²² in kilograms, obtained from the reported weight gain during pregnancy in the 1-year PIAMA questionnaire and, if missing, from the 14-year PIAMA questionnaire (N = 39, 1.1% of valid values of the variable in PIAMA cohort); (g) whether the child was born by means of caesarean section^{18,20,22} (yes vs no), (h) gestational age at birth^{18,22} in weeks, calculated from the reported due date and birth date, (i) birthweight^{18-20,22,23} in kg, (j) and sex of the child^{18,23} (girl vs boy), all obtained from the 3-month PIAMA questionnaire; (k) ethnicity of the child^{18,19,21} was based on country of birth of the mother and the father, as reported in the 2-year PIAMA questionnaire, according to the definition of Statistics Netherlands and was categorized into three groups: Dutch, Western (Non-Dutch), and non-Western; (l) information on breastfeeding,¹⁸⁻²¹ obtained from the 3-month (and if missing the 1-year) PIAMA questionnaire and dichotomized into ever vs never been breastfed; (m) the number of older siblings,^{18,20,22} assessed in the 3-month PIAMA questionnaire and dichotomized into presence of older siblings in the household (yes vs no); (n) information on indoor smoking,¹⁸ obtained from the 3-month PIAMA questionnaire and dichotomized into smoking indoors occurred once a week or more vs never or less than once a week.

Regarding the longitudinal predictors, BMI of the child was calculated from the child's weight and length/height as obtained from the records of the PCHC organizations. Cole's LMS-method²⁴⁻²⁶ was used to convert BMI into BMI SDS.²⁷ The sex- and age-dependent BMI values from the Fifth Dutch Growth Study² were used as reference standard.²⁷ Age of the child in years at time of the BMI SDS measurement was calculated from the date of birth and the date of the BMI SDS measurement. If there was no date available, the recorded age was used. In case a child had no complete PCHC information on all the longitudinal candidate predictors (BMI SDS, age, and growth curve parameters) at any time point within the age range of ≥ 3 months and ≤ 6 years, we used weight and length/height data from the 3-month, 1-, 2-, 3-, 4-, 5- and 6-year PIAMA questionnaires and converted them into BMI SDS values (as described above for PCHC data).

The growth curve of a specific time point describes a child's BMI SDS development from the first measurement after birth up till his or her current age. Differences in growth between boys and girls were thus accounted for by the use of age and sex specific BMI SDS values. Growth curve parameters were calculated according to the growth

curve parameters method described in our previous study.²⁸ Based on the results of this study,²⁸ a quadratic function seemed to be the most appropriate and was chosen to describe the growth curves. In short, the growth curve parameters were derived by performing a linear regression analysis for each child separately in a long structured dataset with the child's BMI SDS measurements, from the first available measurement after birth up to and including the current BMI SDS measurement at time of risk prediction (with the latter not exceeding the age of 6.0 years), as dependent variable and the corresponding age and the quadratic function of age as independent variables. For each BMI SDS measurement between ages 3 months and 6 years, the corresponding growth curve parameters were calculated based on this and all previous BMI SDS measurements. Thus, the growth curve parameters were updated each time a new BMI SDS measurement was performed (and therefore the growth curve parameters can also be considered to be longitudinal predictors). The start of risk prediction was reset at age 3 months due to the need of multiple BMI SDS measurements for growth curve estimation, which could be available for children at this age.

Possible non-linearity of the relationship between the continuous candidate predictors and the outcome was assessed with univariable models, that is, by examining if the associations were better described by a cubic spline function than a linear function. Based on results of these analyses, the spline variables of maternal BMI and of the child's current BMI SDS measurement were also considered to be candidate predictors (see Supporting Information Text S1 for more information on spline variables). Interactions of the longitudinal candidate predictors current BMI SDS measurement (original and spline variable) and the two growth curve parameters with current age were also considered to be candidate predictors. By including these interactions, the regression coefficients of the BMI SDS and growth curve parameters are allowed to vary for different ages at risk assessment while the regression coefficients for the other predictors remain constant. This way, instead of having multiple models for different ages at risk assessment, only a single prediction model is needed to generate age-specific risk estimations.

Altogether, 14 (fixed) baseline variables measured after birth (plus three additional dummy variables, due to 3 variables with 3 categories), 4 longitudinal variables on the child's growth over time, 2 spline variables, and 4 interactions were selected as candidate predictors. With a total of 27 candidate predictors, the number of events per variable (EPV) in this study was 11.26 (304/27), which falls within the advised minimum of 10EPV.²⁹

2.4 | Missing Data

The percentage of missing values in the baseline predictors ranged from 0.0% for sex to 11.4% for paternal BMI (Table 1). All missing values were imputed using multiple imputation according to the Multi-variate Imputation by Chained Equations procedure³⁰ in Statistical Package for the Social Sciences (SPSS). We used a wide structured dataset, predictive mean matching, and 50 iterations to generate

TABLE 1 Baseline candidate predictors and information on growth parameters of the children (N = 2265) included in the analyses

	Original dataset (N = 2265)	Number of missing values
Baseline candidate predictors		
Maternal BMI (kg/m ²)	22.3 (18.4; 31.4)	157 (6.9%)
Paternal BMI (kg/m ²)	25.0 (20.2; 32.5)	259 (11.4%)
Maternal educational level		4 (0.2%)
Low	452 (20.0%)	
Intermediate	954 (42.2%)	
High	855 (37.8%)	
Paternal educational		23 (1.0%)
Low	517 (23.1%)	
Intermediate	793 (35.4%)	
High	932 (41.6%)	
Maternal smoking during pregnancy		18 (0.8%)
Mother did not smoke or stopped before being 4 weeks pregnant	1884 (83.8%)	
Mother still smoked ≥4 weeks after start of pregnancy	363 (16.2%)	
Maternal weight gain during pregnancy (kg)	13.6 (5.1)	81 (3.6%)
Caesarean section		23 (1.0%)
No caesarean section	2044 (91.2%)	
Caesarean section	198 (8.8%)	
Gestational age (weeks)	40.1 (35.7; 42.1)	6 (0.3%)
Birthweight (kg)	3.5 (0.5)	6 (0.3%)
Sex		0 (0.0%)
Boys	1130 (49.9%)	
Girls	1135 (50.1%)	
Ethnicity		55 (2.4%)
Dutch	2038 (92.2%)	
Western	102 (4.6%)	
Non-Western	70 (3.2%)	
Breastfeeding		14 (0.6%)
Never been breastfed	358 (15.9%)	
Ever been breastfed	1893 (84.1%)	
Presence of older siblings in household		2 (0.1%)
No	1131 (50.0%)	
Yes	1132 (50.0%)	
Indoor smoke exposure		2 (0.1%)
Never or less than once a week	1685 (74.5%)	
Once a week or more	578 (25.5%)	

(Continues)

TABLE 1 (Continued)

	Original dataset (N = 2265)	Number of missing values
Growth measurements (no missing values, due to inclusion criteria)		
At time of prediction (3 months ≤ age ≤ 6 years)		
Number of children	2265	
Specified per age range		
3 months ≤ age < 6 months	1002	
6 months ≤ age < 1.5 years	1085	
1.5 years ≤ age < 2.5 years	1740	
2.5 years ≤ age < 3.5 years	1808	
3.5 years ≤ age < 4.5 years	1815	
4.5 years ≤ age < 5.5 years	1022	
5.5 years ≤ age ≤ 6 years	748	
Source of growth measurements (individuals)		
PCHC organizations	1104 (48.7%)	
PIAMA questionnaires	1161 (51.3%)	
Number of measurements	15 274	
Specified per age range		
3 months ≤ age < 6 months	2351	
6 months ≤ age < 1.5 years	4985	
1.5 years ≤ age < 2.5 years	2192	
2.5 years ≤ age < 3.5 years	2126	
3.5 years ≤ age < 4.5 years	1839	
4.5 years ≤ age < 5.5 years	1031	
5.5 years ≤ age ≤ 6 years	750	
Source of growth measurements (measurements)		
PCHC organizations	11 789 (77.2%)	
PIAMA questionnaires	3485 (22.8%)	
BMI SDS measurement (SDS)	0.0 (1.0)	
Overweight (IOTF)		
No overweight	6281 (91.1%)	
Child was overweight	612 (8.9%)	
Missing values, due to age <2 years ^a	8381 (54.9%)	
Growth curve linear term (SDS/y)	0.4 (8.9)	
Growth curve quadratic term (SDS/y ²)	-0.9 (17.0)	
At time of outcome (7.39 ≤ age ≤ 10.5 years)		
Number of children	2265	
Number of measurements	2265	
Age (years)	8.1 (7.6; 9.7)	

(Continues)

TABLE 1 (Continued)

	Original dataset (N = 2265)	Number of missing values
BMI SDS measurement (SDS)	-0.1 (1.0)	
BMI (kg/m ²)	16.1 (13.5; 21.7)	
Overweight		
Not overweight	1961 (86.6%)	
Overweight	304 (13.4%)	
Source of BMI-outcome measurement		
PIAMA medical examination	2164 (95.5%)	
PCHC organizations	101 (4.5%)	

Note: The descriptive values are expressed as the mean (SD), median (95% range) or number N (valid %).

Abbreviations: BMI, body mass index; IOTF, International Obesity Task Force; PCHC, Preventive Child Health Care; PIAMA, Prevention and Incidence of Asthma and Mite Allergy; SDS, SD score.

^aIOTF overweight cut-offs are only defined for age 2 onwards. Missing value percentages of overweight were calculated as a percentage of the number of measurements.

22 imputed datasets. The number of imputed datasets was set equal to the percentage of incomplete cases for the baseline candidate predictors.

2.5 | Statistical analysis

A full model was fitted by performing a Generalized Estimating Equations analysis with an independent correlation structure in a long structured dataset. This procedure is also known as a 'pooled logistic regression model' and provides the same regression coefficients as a logistic regression analysis, but with increased standard errors. The latter is necessary to take into account that children contributed to the model multiple times. The full model included all 27 candidate predictors (baseline and longitudinal candidate predictors, spline variables and interactions) as independent variables and overweight at age 8 as outcome.

To obtain our final prediction model, we performed a manual backward selection on the full model using a *P*-value <.157 (Akaike information criterion)³¹ as criterion for variable selection. The backward selection procedure is the preferred automated predictor selection procedure³¹ and helped us to get a model with the best combination of predictive quality and number of variables. The Akaike information criterion, that is, a less strict *P*-value of .157, 'accounts for model fit while penalizing for the number of parameters being estimated'.³¹ Categorical variables were assessed for exclusion based on the dummy variable with the lowest pooled *P*-value. Similarly, interactions with multiple variables representing the same subject (ie, variable and matching spline variable; or variable and quadratic variable) were all simultaneously included or excluded from the model and

were assessed for exclusion based on the interaction term with the lowest pooled *P*-value.

The prediction model was internally validated in the imputed datasets with 250 bootstrap samples to adjust for overfitting and optimism as recommended by the Transparent Reporting of a multivariable model for Individual Prognosis or Diagnosis (TRIPOD) statement.³¹ See Supporting Information Text S1 'Elaboration on Methods; Internal Validation' for more detailed information on this procedure. After internal validation, the model was updated: the regression coefficients were multiplied by the shrinkage factor and subsequently the intercept of the prediction model was also adjusted for optimism.

Performance of the prediction model in terms of explained variance and discrimination before and after validation was reported as the pooled (median³²) Nagelkerke *R*²- and area under the curve (AUC)-value from the 22 imputed datasets. Additional to the AUC of the model for all ages at time of risk prediction combined, the AUC was also assessed for specific age ranges separately. The overall and age-specific AUC's were calculated in the 22 imputed datasets using the linear predictor of the updated prediction model, the pooled (median³²) AUC estimates were reported. Moreover, the overall and age-specific AUC's were also assessed separately for children with and without (current) overweight at time of risk prediction.

For each child (and age) the mean³² of the updated linear predictors of the 22 imputed datasets was calculated and transformed into the (pooled) predicted risk, which was then used to determine the model's sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and number and percentage of predictions by the model in which children were classified as being at risk according to different cut-off values for predicted risk.

See Supporting Information Text S1 'Elaboration on Methods' for more detailed information on methods (baseline candidate predictors: ethnicity of the child; spline variables; imputation model; statistical analysis; internal validation). All analyses were performed using the Statistical Package for the Social Sciences version 25.0 for Windows (SPSS Inc., Chicago, IL) and R for Windows version 3.4.1 (The R Foundation).

3 | RESULTS

3.1 | Population characteristics

Table 1 shows the descriptive values of the baseline predictors for the included children. Of the 2265 children, 49.9% were boys; and the majority was of Dutch ethnicity (92.2%), had a mother with an intermediate educational level (42.2%), and a father with a high educational level (41.6%).

Table 1 also shows the descriptive values for the growth measurements of the children at the age of risk prediction and at the age of outcome assessment. For the 2265 participants, a total of 15 274 growth measurements were available for each of the longitudinal

predictors (BMI SDS, age, and the growth curve parameters). The age range of 6 months to 1.5 years contained most of these measurements 4985 (32.6%). The median age at outcome assessment was 8.1 years (95% range of 7.6-9.7), at which a total of 304 (13.4%) participants was classified as being overweight. See Table S1 for the descriptive values of the growth measurements specified for separate age ranges at time of risk prediction.

3.2 | The overweight prediction model

The prediction model obtained after backward selection included the following baseline predictors: maternal BMI (including spline), paternal BMI, paternal educational level, birthweight, sex, ethnicity and indoor smoke exposure. The following longitudinal predictors were included in the prediction model: current BMI SDS (including spline), the linear and quadratic parameters of the growth curve, and the interactions of BMI SDS (including spline) and the linear and quadratic growth curve parameters with age. Table 2 shows the regression coefficients, 95% confidence intervals, and *P*-values of the predictors before internal validation; and the adjusted regression coefficients of the prediction model after internal validation (the shrinkage factor was 0.99).

Table 3 illustrates how a prediction tool based on this model would work. Four example cases are shown with the necessary input for risk estimation and the corresponding output of such a tool. The growth curves for these example cases are shown in Figure 2. The first child has a 6.3% predicted risk of overweight at the age of 8. In contrast, the estimated risk for the third child was 93.3% due to less favourable predictor characteristics.

3.3 | Performance of the prediction model

Discriminative ability and explained variance of the prediction model are shown in Table 4. Before internal validation the overall AUC was 0.847. For separate age ranges the AUC ranged from 0.822 for age range 1.5 to 2.5 years to 0.942 for age range 5.5 to 6 years. After internal validation, the overall AUC was 0.845. The explained variance, Nagelkerke R^2 , was 0.355 before and 0.351 after internal validation.

The model's performance in terms of numbers classified as at risk, sensitivity, specificity, PPV and NPV for different cut-offs of the predicted risk is shown in Table S2. For example: if a 15% cut-off for predicted risk is chosen to distinguish between children 'at risk' and 'not at risk' of being overweight at the age of 8, one would classify 25.2% ($N = 3842$) of all children as being 'at risk'; of these 'at risk' children 32.0% would have overweight at time of prediction. The sensitivity corresponding to the 15% cut-off indicates that of all children who will be overweight at the age of 8, 71.9% will be correctly classified by the model as 'at risk'. The specificity shows that of all children who will not be overweight, 81.5% will be correctly classified by the model as 'not at risk'. The PPV indicates that 35.8% of all children classified by the model as 'at risk' will indeed be overweight at age

8, and the NPV indicates that 95.3% of all children classified as 'not at risk' will indeed not be overweight at age 8. Based on the 15% cut-off, example cases 3 and 4 from Table 3 would be identified as being 'at risk'. Different cut-offs for children with and without current overweight might also be considered, see Table S3 for the performance of the model stratified for these two groups. The pooled predicted risk was also used to make a calibration plot of the prediction model after internal validation, shown in Supporting Information Figure S1.

4 | DISCUSSION

4.1 | Principal findings

In this paper, we described the development and internal validation of a dynamic prediction model that can identify young children of the general population (at every age from birth to 6 years) at high risk of future overweight to enable targeted primary prevention of overweight in children. The following predictors were included in the final model: maternal BMI, paternal BMI, paternal educational level, birthweight, sex, ethnicity, indoor smoke exposure, current BMI SDS, the linear and quadratic parameters of the growth curve as well as the interactions of current BMI SDS and the linear and quadratic growth curve parameters with age. The model had a good performance with an AUC of 0.845 after internal validation, similar to the AUC of 0.847 before validation. The AUC for age range 5.5 to 6 years was highest, which is to be expected since there is only a small period of time between time of risk prediction and outcome at age 8. However, the performance of the model for the younger age ranges was already good with AUC values ranging from 0.822 to 0.862.

4.2 | Strengths and limitations

The most important strength of the present study is that a dynamic prediction model was developed. The dynamic model provides risk estimations which can be updated each time new growth information becomes available in practice. This way the risk can be monitored over time and a reduction or increase in the risk estimates between PCHC visits can be taken into account by the PCHC professionals in advising the parents.

Another strength of our study was that the data collection was not influenced by knowledge of the aims of this study. The PIAMA and PCHC data were gathered prospectively without the aim to build a prediction model. Moreover, in the PIAMA study, the outcome data were measured by fieldworkers who had no access to the predictor data. Also, limitations should be mentioned. The most important limitation is that the non-Western population was under-represented in our study. However, ethnicity remained in the final model, thus likely contributing to the generalizability of this model for children of non-Western descent. Furthermore, 1698 PIAMA participants were excluded due to missing values for the outcome or predictor growth measurements. Differences in baseline

TABLE 2 Prediction model to predict overweight at age 8 in children aged 3 months to 6 years

	Before internal validation			After internal validation	
	Coefficient	95% CI	P-value	Coefficient	
Intercept	-18.001	-23.210	-12.793	.000	-17.867
Baseline predictors					
Maternal BMI (kg/m ²)	0.411	0.196	0.625	.000	0.407
Spline variable maternal BMI	-0.267	-0.502	-0.033	.026	-0.265
Paternal BMI (kg/m ²)	0.184	0.132	0.236	.000	0.183
Paternal educational level					
Low	Reference	Reference	Reference	Reference	Reference
Intermediate	-0.293	-0.698	0.113	.157	-0.290
High	-0.447	-0.875	-0.018	.041	-0.443
Birthweight (kg)	0.413	0.084	0.742	.014	0.410
Sex					
Boy	Reference	Reference	Reference	Reference	Reference
Girl	0.241	-0.088	0.571	.151	0.239
Ethnicity					
Dutch	Reference	Reference	Reference	Reference	Reference
Western	0.454	-0.362	1.270	.276	0.450
Non-Western	0.804	-0.106	1.713	.083	0.797
Indoor smoke exposure					
Occurred never or less than once a week	Reference	Reference	Reference	Reference	Reference
Occurred once a week or more	0.495	0.133	0.858	.007	0.491
Longitudinal predictors					
Age (years)	-0.044	-0.148	0.060	.407	-0.044
BMI SDS measurement (SDS)	0.173	-0.315	0.662	.487	0.172
Spline variable BMI SDS measurement (SDS)	0.330	-0.110	0.769	.141	0.327
Growth curve (linear) (SDS/y)	-0.096	-0.144	-0.049	.000	-0.096
Growth curve (quadratic) (SDS/y ²)	-0.010	-0.030	0.010	.319	-0.010
Interactions of longitudinal predictors with age					
Age (years)					
*BMI SDS measurement (SDS)	0.132	-0.021	0.286	.092	0.131
*Spline variable BMI SDS measurement (SDS)	0.052	-0.092	0.196	.481	0.051
*Growth curve (linear) (SDS/y)	0.009	-0.031	0.048	.671	0.009
*Growth curve (quadratic) (SDS/y ²)	-0.115	-0.210	-0.019	.018	-0.114

Note: Values are expressed as the pooled regression coefficient, 95% confidence interval (95% CI) and P-values of the intercept and predictors in the prediction model developed in a multiple (N = 22) imputed dataset. Analyses were based on 15 274 measurements of 2265 children, of whom 304 had overweight at age 8. Abbreviations: BMI, body mass index; SDS, SD score.

*Indicates the multiplication of the particular variable by Age (years), resulting in the interaction variable.

The model's predicted probability of being overweight at the age of 8 can be calculated as: $1/(1 + e^{-LP})$, where the linear predictor (LP) is calculated as: $-17.867 + 0.407 * \text{maternal BMI} - 0.265 * \text{spline variable maternal BMI} + 0.183 * \text{paternal BMI} - 0.290 * \text{intermediate paternal educational level} - 0.443 * \text{high paternal educational level} + 0.410 * \text{birthweight} + 0.239 * \text{girl sex} + 0.450 * \text{Western ethnicity} + 0.797 * \text{non-Western ethnicity} + 0.491 * \text{indoor smoke exposure occurred once a week or more} - 0.044 * \text{age} + 0.172 * \text{BMI SDS} + 0.327 * \text{spline BMI SDS} - 0.096 * \text{growth curve linear term} - 0.010 * \text{growth curve quadratic term} + 0.131 * \text{interaction age and BMI SDS} + 0.051 * \text{interaction age and spline BMI SDS} + 0.009 * \text{interaction age and growth curve linear term} - 0.114 * \text{interaction age and growth curve quadratic term}$.

predictors between the in- and excluded population, seem to mainly reflect lower parental educational level in the excluded population, where 28.6% and 30.0% of the participants had a low maternal and paternal educational level compared to 20.0% and 23.1% in the included group (see Supporting Information Table S4).

However, we do not expect that the associations between the predictors and outcome would have been very different if we could have included all participants and therefore the generalizability of the model is still expected to be good (See Supporting Information Text S1 'Sensitivity analysis').

TABLE 3 Example cases of risk prediction, as calculated with the developed prediction model

Input	Case 1	Case 2	Case 3	Case 4
Baseline predictors				
Maternal BMI (kg/m ²)	23	20	23	31
Paternal BMI (kg/m ²)	21	23	25	38
Paternal educational level	High	Intermediate	Intermediate	Low
Birthweight (kg)	3.6	3.9	4.0	3.6
Sex	Boy	Boy	Girl	Girl
Ethnicity	Dutch	Dutch	Dutch	Dutch
Indoor smoke exposure	Occurred never or less than once a week	Occurred never or less than once a week	Occurred never or less than once a week	Occurred once a week or more
Longitudinal predictors				
Age (years)	3.9	2.0	2.0	4.0
BMI SDS measurement (SDS)	0.3	1.6	2.5	0.2
Growth curve (linear) (SDS/y)	-0.2	0.0	1.3	0.3
Growth curve (quadratic) (SDS/y ²)	0.1	0.1	-0.3	0.0
Output				
Predicted risk	2.9%	7.2%	52.1%	85.8%

Abbreviations: BMI, body mass index; SDS, SD score.

An excel tool to predict the risk of overweight for an individual according to this study's prediction model is available upon reasonable request to the corresponding author.

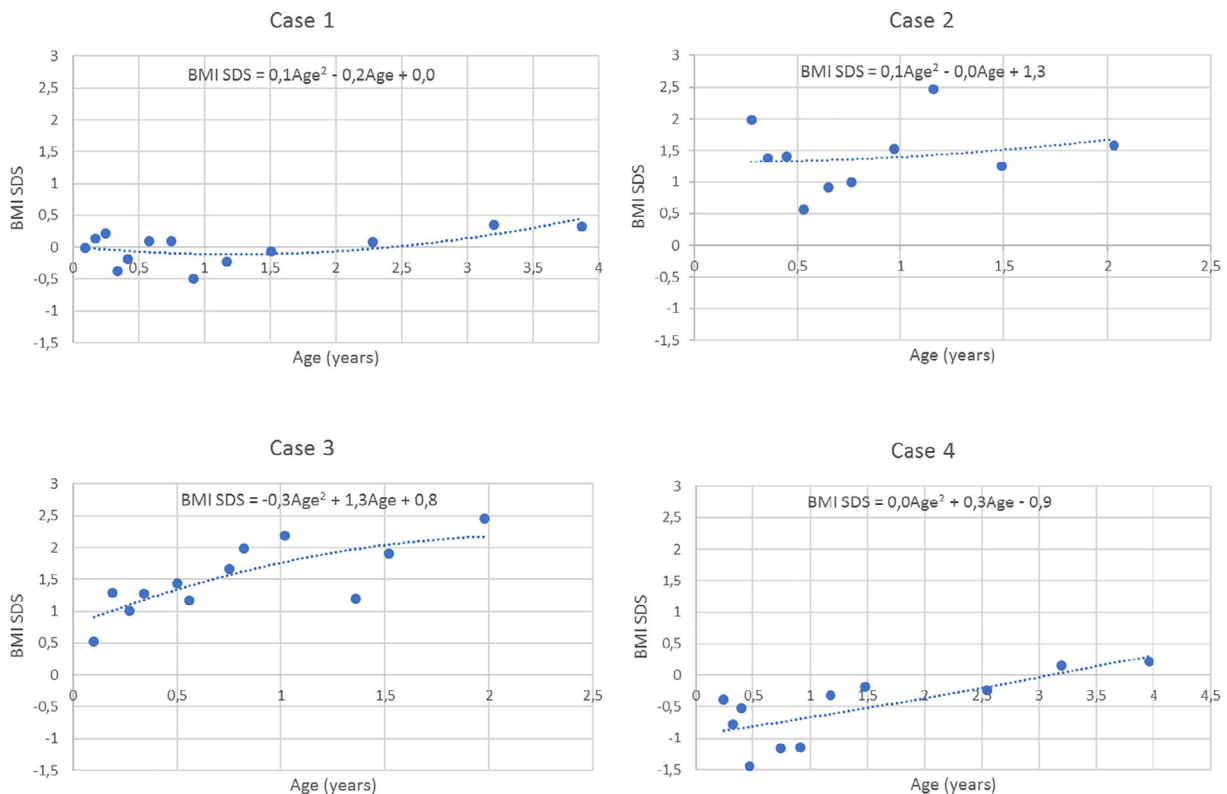


FIGURE 2 Growth curves, showing the development in body mass index SD score over time for four example cases

TABLE 4 Discriminative ability and explained variance of the prediction model

Discriminative ability (age specific)	Whole study population	Currently no overweight	Currently overweight
Age at time of prediction	AUC	AUC	AUC
3 months ≤ age < 6 months	0.850	– ^a	– ^a
6 months ≤ age < 1.5 years	0.835	– ^a	– ^a
1.5 years ≤ age < 2.5 years	0.822	0.792	0.878
2.5 years ≤ age < 3.5 years	0.841	0.805	0.772
3.5 years ≤ age < 4.5 years	0.862	0.816	0.777
4.5 years ≤ age < 5.5 years	0.855	0.791	0.783
5.5 years ≤ age ≤ 6 years	0.942	0.910	0.770
Overall (3 months ≤ age ≤ 6 years)	0.847	0.814	0.802
Results internal validation (overall)	Whole study population	Whole study population	
	AUC	R ²	
Validity before validation	0.847	0.355	
Validity after validation	0.845	0.351	

Note: Values are expressed as the pooled (median) area under the curve (AUC) and Nagelkerke R^2 of the prediction model in the multiple ($N = 22$) imputed dataset. The number of measurements that the overall results are based on: whole study population 15 274 (2265 children); currently no overweight 6281 (2165 children); currently overweight 612 (354 children). The range of measurements that the age range specific results are based on: whole study population 750 to 4985 (748–1815 children); currently no overweight population 668 to 1960 (667–1673 children); currently overweight 82 to 166 (82–155 children).

^aNo data as International Obesity Task Force overweight cut-offs are only defined for age 2 onwards.

Paternal BMI at age 8 was used as a proxy for paternal BMI at birth. However, paternal BMI at age 8 is probably a better indicator of the lifestyle behaviour a child will have been exposed to over the first 8 years of his/her life within the household compared to paternal BMI at child birth. Therefore, it could be that the predictor paternal BMI came out stronger than the actual baseline measurement would have. However, a previous study by Steur et al., using the PIAMA-cohort for the development of a prediction model for overweight at age 8 using only baseline predictors around birth, also used paternal BMI at age 8 as a proxy for paternal BMI at birth.¹⁸ They concluded from a sensitivity analysis with simulations for paternal BMI at birth that the model would hardly have differed if paternal BMI at birth was used instead of paternal BMI at age 8.¹⁸

For the outcome 'overweight at age 8', the medical examination data was complemented with PCHC data when missing. We do not expect a systematic difference in BMI between the two sources as measurements from both sources were taken by professionals according to similar protocols. For predictor growth information, PCHC data was used to develop the model and complemented with PIAMA questionnaire data (22.8%) if missing. We expect the differences between BMI (SDS) from PCHC and PIAMA questionnaires to be similar to the observed differences between the PIAMA medical examination and questionnaire data, that is, a tendency to underreport BMI by parents of children with a high BMI and to over report BMI by parents of children with a low BMI.³³ The mean difference in measured and reported BMI was 0.7 kg/m² (SD 1.1) for children in the fourth measured BMI quartile; and 0.3 kg/m² (SD 0.8), –0.1 kg/m² (SD 0.8) and –0.4 kg/m² (SD 0.9) for children in the third, second and first measured BMI quartile.³³ Therefore, it cannot be excluded that overall the prediction model might overestimate the predicted risk of children slightly.

Finally, we cannot exclude the possibility that some children might have reached puberty at timing of outcome, as there is no data available on this. We set an age limit for the outcome at 10.5 years to prevent that children had reached puberty as much as possible, while also being able to include as many participants as possible by not setting the maximum age too low. According to the Dutch Center for Child and Youth Health Care (NCJ), puberty in girls starts on an average age of 10.5 years (range 9–12 years) and in boys on an average age of 11 years (range 9–13 years).³⁴ In our study 91% of the participants were younger than age 9 at the time of outcome measurement, implying that only a very small number of children in our study might have reached puberty. It is very unlikely that the data of this small number of children would have impacted our results significantly.

4.3 | Findings in relation to other studies

A systematic review by Ziauddeen et al.²³ on prediction models for childhood overweight and obesity identified eight prediction models. Seven predictors were included in two or more models: gender, weight gain between 0 and 1 year categorized and continuous, birthweight, maternal BMI, maternal smoking during pregnancy and paternal BMI.²³ Congruent with this review our model also includes the predictors sex, birthweight, maternal BMI, and paternal BMI. Similar information as in the predictor weight gain 0 to 1 year, that is, growth information, is included in our model through the inclusion of longitudinal growth curve predictors. Although the candidate predictor maternal smoking during pregnancy did not remain in our final prediction model, the model does include information on indoor smoke exposure in the child's home. None of the studies included in the review considered any other smoking variable than maternal (pre-)

pregnancy smoking for model development, except for the study by Steur et al. which is also based on PIAMA data and whose model included the predictor indoor smoke exposure. Additional predictors that are included in our model were current weight status (BMI SDS), ethnicity of the child and paternal educational level.

The review by Ziauddeen reported that the AUC's of the included prediction models ranged from 0.64 to 0.91 for the derivation AUC's and from 0.64 to 0.93 for the validation AUCs.²³ Compared to these results, the performance of the prediction model in the present study seems to be quite good: the only models with higher AUC's were in the study by Santorelli et al, who predicted obesity at age 1 (derivation AUC 0.91 and validation AUC 0.89)²³ and in the study by Redsell et al, who predicted obesity at age 5 (recalibrated model, validation AUC 0.93).²³

None of the prediction models included in the review were developed to make repeated risk assessments at a wide age range, whereas our model was developed to do so for age 0 to 6 years. Most models included in the review were developed to make a risk assessment at a certain age. If a model or tool could assess risk at a range of ages, the range was usually small, for example, 60 to 64 months (Pei et al.³⁵), 6 to 12 months (Weng et al.³⁶) or 4.5 to 13.5 months (Santorelli et al.³⁷), with the latter being a tool using 3 separate equations (for subintervals 4.5-7.5, 7.5-10.5, and 10.5-13.5) to cover the whole age range.

4.4 | Meaning of the study

Internal validation showed that our developed prediction model had a good performance with an AUC of 0.845. External validation and implementation research should further confirm the usefulness of the model in practice. The prediction model enables PCHC professionals to distinguish between children at low and at high risk of future overweight. This gives them the possibility to spend more time on personalized advice for the high-risk children and skip some of the 'one size fits all' overweight prevention advice when talking to parents of low risk children. PCHC professionals can decide at which predicted risk estimation(s) they want to take action. To determine a cut-off for a certain action, for example, offering an extra consult or intervention, one needs to find a cut-off with the optimal balance in its consequences. First, it is important to be aware that the number of children/families that will have to be offered an intervention, based on the cut-off, should be feasible with respect to finances, manpower, time availability, etc. Secondly, one should consider the number of children identified as 'at risk', who will not actually be overweight in the future. These children will unnecessarily be offered an advice, extra consultation or intervention. Although this is unlikely to be harmful, it will increase costs and pose a burden on these families. At last, there is the number of children being misclassified as 'not at risk' who will be overweight in the future to consider. These are the children who should have been offered an intervention, but were not. These missed children may require health care (and bring related costs) later in life through the development of overweight and subsequent morbidity, such as cardiometabolic diseases. Part of these problems may be solved by repeating risk assessments in the children with a slightly increased risk, and only offer

interventions if the risk is increasing over time. Finally, we should be aware that training in risk communication with parents and children is essential for professionals who use the results of the model, where the risk of stigmatization should be taken into account.

4.5 | Unanswered questions and future research

As previously described, children from a non-Western ethnicity were underrepresented in this cohort and it might therefore be interesting for future research to determine the model's validity in non-Western populations and to update it accordingly if necessary. Future research might also look into the added value of including maternal educational level (or other SES proxy) in addition to or instead of paternal educational level for younger populations, which probably include more highly educated and working mothers. Therefore, the education of mothers is likely to be a better proxy for family SES now compared to educational level of women in 1996 to 1997. External validation studies by independent researchers assessing the performance of the updated model in other cohorts would provide more insight into its clinical relevance and an implementation study of the model (with decisions on cut-off values and risk communication) could be carried out in order to assess its added value for preventive public health professionals and any aspects for improvement of the (usability) of the model. Based on external validation and implementation evaluation, the tool could be optimized further. In addition, multiple versions of the model with fewer variables could be developed or models allowing for handling of missing values in practice in individual cases, to enable risk prediction in cases with incomplete predictor data. Finally, studies researching the effectiveness of the use of the model in PCHC on the prevention of overweight would be desired, which would also require (the use of) effective interventions for overweight prevention in children.

In conclusion, a dynamic prediction model for overweight to be used in childhood was developed using easily obtainable predictor information. The predictive quality of the model is good with an AUC of 0.845 after internal validation. External validation is needed to confirm that the model has potential for use in practice.

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CONFLICT OF INTEREST

No conflict of interest was declared.

AUTHOR CONTRIBUTIONS

M.L.A.d.K. initiated the study and is the Principal Investigator; M.L.A.d.K. and A.H.W. conceived the study design. M.L.A.d.K. obtained funds for the ProCOR project. M.W. performed the analyses, supervised by J.W.R.T. and M.W.H. M.W. drafted the first version of the manuscript, with help from A.H.W., M.H., J.W.R.T., H.R., M.W.H. and M.L.A.d.K. A.H.W., U.G. and G.H.K. are principal investigators of the PIAMA birth cohort. The final manuscript was critically revised and approved by all authors.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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