Identifying Young Children without Overweight at High Risk for Adult Overweight

The Terneuzen Birth Cohort

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ABSTRACT

Objective
To develop a tool to identify children with high risk of adult overweight (AO), especially before developing overweight, based on BMI standard deviation score(s) (SDS) changes between 2-6 years (y).

Methods
We fitted a linear spline model to BMI SDS of 762 young Caucasian adults from the Terneuzen Birth Cohort at fixed ages between birth and 18y. By linear regression analysis, we assessed the increase in explained variance of the adult BMI SDS by adding the BMI SDS at 2y to the models including the BMI SDS at 4y, 6y and both 4y and 6y. AO risk was modelled by logistic regression. The internal validity was estimated using bootstrap techniques. Risk models were represented as risk score diagrams by gender for the age intervals 2-4y and 2-6y.

Results
In addition to the BMI SDS at a certain age, the previous BMI SDS during childhood is positively related to adult weight. ROC analysis provides insight into sensible cutoffs (AUC varied from 0.76 to 0.83). The sensitivity and specificity for 2-6y at the cutoff of 0.25 and 0.5 are respectively 0.76 and 0.74, and 0.36 and 0.93, whereas the PPV is respectively 0.52 and 0.67.

Conclusions
The risk score diagrams can serve as a tool for young children for primary prevention of adult overweight. To avoid wrongly designating children at risk for AO, we propose a cutoff with a high specificity at the risk of approximately 0.5. After external validation, wider adoption of this tool might enhance primary AO prevention.
INTRODUCTION

Overweight and obesity cause serious health hazards,\textsuperscript{1,2} especially if obesity develops during childhood and is sustained into adulthood.\textsuperscript{3-6} In young adulthood, not only obesity (Body Mass Index (BMI) $\geq 30$), but also overweight (BMI $\geq 25$) is associated with a considerable increase in cardiovascular risk.\textsuperscript{1} The increasing prevalences of overweight and the significantly increased risk for adult overweight in overweight children\textsuperscript{7} underline the need for effective prevention programs. Therefore much attention has been paid to identifying and treating children with overweight. However, the results of treatment for overweight and obesity are disappointing, especially in the long term. Consequently, today's challenge for Youth Health Care (YHC) is not only to reduce overweight and obesity in childhood, but especially to identify non-overweight children at high risk for developing adult overweight (AO), including obesity, and to offer them primary prevention. It makes sense to consider not only the actual Body Mass Index (BMI) status, but also the change in BMI level, especially in non-overweight children, as this change is an additional risk factor for later overweight.\textsuperscript{8-10}

To enable YHC workers to offer targeted primary prevention to normal-weight children with a high AO risk, a tool to assess this risk is needed. However, no such tool has been developed. Others have shown that from the age of 2 years (y) onwards abnormally high weight gain is associated with the risk of later obesity, also in normal weight children.\textsuperscript{11-16} Because overweight at the age of 6y often translates into overweight in adulthood,\textsuperscript{17} primary prevention especially before this age seems worthwhile. Moreover, at a young age lifestyle and risk factors of overweight and obesity are easier to modify.\textsuperscript{18} In a previous study we have shown that the age interval 2-6y is very sensitive in predicting overweight.\textsuperscript{19} The aim of our current study is to develop a tool enabling to identify young children at high risk of adult overweight, based on the BMI changes between 2 and 6 years of age.

RESEARCH DESIGN AND METHODS

Population and setting

We analyzed the data of weight and length of 762 Caucasians from the Terneuzen Birth Cohort from birth until young adulthood. The original cohort consists of all 2,604 Caucasian children born between 1977 and 1986 in the city of Terneuzen. Data for
weight and length as routinely registered by the Municipal Health Services were available from birth for 1,701 subjects. Of these subjects, 762 persons (45%) were willing to participate in a follow-up study in 2004-2005, when they were between 18 and 28 years of age. This follow-up study included measurements of weight and height and a questionnaire to collect socio-demographic characteristics, which is described in more detail elsewhere. The participants in the follow-up study did not differ from the original cohort regarding baseline characteristics, i.e. age, birth weight, BMI SDS at birth, and parity and age of the mother, except for gender (41% males vs. 51% in the original cohort, \(p<0.05\)). We used BMI values (kg/m\(^2\)) as the measure for (over)weight, converted to age-specific standard deviation scores (BMI SDS) based on Dutch reference data, because these are most comparable to our study population. The criterion for being overweight in young adulthood is defined as BMI \(\geq 25\).

The study protocol was approved by the Medical Ethics Committee of the VU University Medical Centre Amsterdam, and written informed consent was obtained from all participants.

**Statistical analyses**

We fitted the so-called 'broken stick' model\(^{21}\) to BMI SDS at fixed ages between birth and 18y (n=762), which approximates the observed BMI SDS trajectory of each individual by a series of straight lines that connect to each other at fixed ages. Multiple linear regression analysis was applied to assess the proportion of explained variance of the BMI SDS at young adulthood by adding the BMI SDS at 2y to the models that include the BMI SDS at 6y, the BMI SDS at 4y and the BMI SDS at both ages 6y and 4y respectively. Gender and age were analyzed as possible explanatory variables. Gender was analyzed as a potential confounder. Risk of AO was modeled by logistic regression. To test for internal validity, model optimism on the proportion of explained variance, \(R^2\), was estimated by the bootstrap procedure as given by Steyerberg,\(^{22}\) using 1000 bootstrap samples. In Addendum 1 the statistical methods are explained further. Risk models for AO were graphically represented as risk score diagrams with contour lines, given BMI SDS at the start and the end of the age intervals. For convenience, in the risk score diagrams intended for clinical practice, the axes are labeled by BMI values instead of BMI SDS values. Using ROC analysis we calculated the sensitivity
and specificity at various cut-off values for the probability of AO. We used S Plus 8.0 to fit the 'broken stick model' and to perform the statistical analyses.

RESULTS

The mean age of the participants was 23.1 years (SD 2.9), 23.2 years for males (SD 2.9) and 23.0 years (SD 2.9) for females. The prevalence of overweight (BMI ≥25) in young adults was 25.1% for males and 28.4% for females (p>0.05). Pearson correlations of BMI SDS at the ages of 2y, 4y and 6y, with BMI SDS at adulthood are respectively 0.36, 0.52, and 0.62 (p<0.001).

Linear regression analyses

Because gender appeared to be a confounder, but not an effect-modifier, males and females could be analyzed as one group in the multiple regression analyses. (Table 1). The proportion of explained variance in the multiple linear regression model of BMI SDS at adulthood as a function of BMI SDS at 4y increased from 0.28 to 0.34 after extending the model with BMI SDS at 2y (p<0.001).

Likewise, this proportion increased from 0.39 to 0.47 and from 0.39 to 0.48 by extending the model as a function of BMI SDS at 6y with the BMI SDS at 4y and the BMI SDS at 2y respectively (p<0.001). Finally the proportion increased from 0.47 to 0.48 by extending the model as a function of BMI SDS at 6y and 4y with the BMI SDS at 2y (p<0.001), and this remained almost constant, i.e. 0.48, by extending the model as a function of BMI SDS at 6y and 2y with the BMI SDS at 4y (p<0.001). Therefore, augmenting the model by a second observation obviously improved the prediction of BMI SDS at adult age, whereas the third observation had very little additional value. The positive value of the regression coefficient of the BMI SDS in the models including one BMI SDS increased by adding the BMI SDS at an earlier age, whereas the regression coefficient of the added BMI SDS became negative. This implies, as we showed previously, that an increase of BMI SDS in the age intervals is correlated with a higher BMI SDS at adulthood, and a decrease with a lower BMI SDS at adulthood.
Table 1. Prediction of BMI SDS at young adulthood by BMI SDS at one, two and three ages at childhood and BMI SDS at adulthood, adjusted for gender in models by multiple regression analysis: regression coefficients and adjusted $R^2$ (N=761).

<table>
<thead>
<tr>
<th>Prediction model</th>
<th>Independent variables in the model</th>
<th>$\beta$ (SE)</th>
<th>Adj $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BMI SDS at 2y</td>
<td>0.54 (0.05) *</td>
<td>0.14</td>
</tr>
<tr>
<td>2</td>
<td>BMI SDS at 4y</td>
<td>0.91 (0.06) *</td>
<td>0.28</td>
</tr>
<tr>
<td>3</td>
<td>BMI SDS at 6y</td>
<td>1.07 (0.05) *</td>
<td>0.39</td>
</tr>
<tr>
<td>4</td>
<td>BMI SDS at 2y</td>
<td>-0.85 (0.10) *</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td>BMI SDS at 4y</td>
<td>1.79 (0.12) *</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>BMI SDS at 4y</td>
<td>-1.75 (0.17) *</td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td>BMI SDS at 6y</td>
<td>2.72 (0.17) *</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>BMI SDS at 2y</td>
<td>-0.46 (0.08) *</td>
<td>0.48</td>
</tr>
<tr>
<td></td>
<td>BMI SDS at 6y</td>
<td>1.47 (0.07) *</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>BMI SDS at 2y</td>
<td>0.57 (0.14) *</td>
<td>0.48</td>
</tr>
<tr>
<td></td>
<td>BMI SDS at 4y</td>
<td>-3.05 (0.34) *</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BMI SDS at 6y</td>
<td>3.45 (0.24) *</td>
<td></td>
</tr>
</tbody>
</table>

All models are adjusted for gender and age  
* $p<0.001$

**Logistic regression analyses**

Four logistic regression models were fitted. The models incorporate respectively the BMI SDS at 4y and 2y, 6y and 4y, 6y and 2y and, finally, 6y, 4y and 2y. All models except the last one predict significantly better by adding the last mentioned BMI SDS to the model ($p<0.05$). Because the last model was of no surplus value in predicting AO in comparison to the second and third model, this model was not elaborated further. Based on the prediction models, it is possible to calculate the AO risk by hand, using the equations of Cole et al.\textsuperscript{23} the LMS parameters of the Dutch reference standard of BMI\textsuperscript{20} (Table 2) and the results of the logistic regression models (Table 3). An example of such a calculation is elaborated in Addendum 2. As shown in this example, it appears that, despite the fact that this boy has a normal BMI at age 6y, his AO risk is substantial considering the prevalence of overweight of young adult males in this cohort. Similar calculations apply to other pairs of BMI values observed at ages 2y, 4y and 6y. Model optimism of the logistic regression models, as calculated by the
procedure of Steyerberg,\textsuperscript{22} was small: the estimates were all lower than 0.01, so the expected \( R^2 \) in a similar - but new - sample will achieve almost the same value as the reported \( R^2 \).

Table 2. The Dutch reference for BMI at the ages of 2, 4 and 6 years.\textsuperscript{20}

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Boys ( \mu )</th>
<th>( \Sigma )</th>
<th>( \lambda )</th>
<th>Girls ( \mu )</th>
<th>( \sigma )</th>
<th>( \lambda )</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>16.42</td>
<td>0.0790</td>
<td>-0.007</td>
<td>16.07</td>
<td>0.0785</td>
<td>-0.815</td>
</tr>
<tr>
<td>4</td>
<td>15.61</td>
<td>0.0882</td>
<td>-0.375</td>
<td>15.51</td>
<td>0.0865</td>
<td>-1.416</td>
</tr>
<tr>
<td>6</td>
<td>15.52</td>
<td>0.0967</td>
<td>-1.324</td>
<td>15.47</td>
<td>0.1024</td>
<td>-1.663</td>
</tr>
</tbody>
</table>

The risk score diagram and the BMI for age diagram

How are these models related to the conventional BMI diagram? Figure 1a plots the trajectories of five hypothetical children A-E on the Dutch BMI for age diagram. Child A is at low risk and child E at high risk. However, it is not clear how we should distinguish between children B, C and D, who have exactly the same BMI at the age of 6 years. Figure 1b graphs the trajectories for the same children on our risk score diagram. Because the mean age of the cohort is 23.1 years the risk score diagrams have been developed for 23 years of age. The risk score diagram in this example contains five contour lines, which correspond to 10\%, 25\%, 50\%, 75\% and 90\% risk values for AO at various combinations of BMI SDS at 2 years and BMI SDS at 6 years. The line through the origin (angle of 45 degrees) consists of all combinations for which the change between the BMI SDS at these two ages equals zero. Children A, C and E are located on this line since their BMI SDS at 2y is identical to the BMI SDS at 6y. As expected, child A has the lowest risk of adult overweight and child E the highest. Children located above the main diagonal move upwards through the centiles. Child B has a much higher risk of AO than children C or D, although the BMI (SDS) at the age of 6 years are exactly the same for children B, C and D. According to their risks, the children should be ordered as A, D, C, B, E.
Table 3. Parameters of three risk models \( \text{logit}(P_\text{O}) = \alpha + \beta_{\text{age}}A + \beta_{Z_a}Z_a + \beta_{Z_b}Z_b \), where \( P_\text{O} \) stands for probability of adult overweight, \( \beta_{\text{age}} \) is the regression coefficient of the variable A, A equals the variable age minus 23, \( \beta_2 \) and \( \beta_4 \) are the regression coefficients and \( Z_a \) and \( Z_b \) stand for BMI SDS at ages 2y and 4y, 2y and 6y, and 4y and 6y, respectively.

<table>
<thead>
<tr>
<th>Period</th>
<th>Boys</th>
<th></th>
<th></th>
<th></th>
<th>Girls</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \alpha )</td>
<td>( \beta_{\text{age}} )</td>
<td>( \beta_2 )</td>
<td>( \beta_4 )</td>
<td>( \beta_6 )</td>
<td>( \alpha )</td>
<td>( \beta_{\text{age}} )</td>
<td>( \beta_2 )</td>
</tr>
<tr>
<td>2-4y</td>
<td>-1.26</td>
<td>0.33</td>
<td>-1.89</td>
<td>3.93</td>
<td>--</td>
<td>-0.85</td>
<td>0.07</td>
<td>-1.34</td>
</tr>
<tr>
<td>2-6y</td>
<td>-1.08</td>
<td>0.34</td>
<td>-1.03</td>
<td>--</td>
<td>3.40</td>
<td>-0.67</td>
<td>0.08</td>
<td>-3.02</td>
</tr>
<tr>
<td>4-6y</td>
<td>-0.97</td>
<td>0.33</td>
<td>--</td>
<td>-3.71</td>
<td>6.02</td>
<td>-0.75</td>
<td>0.08</td>
<td>--</td>
</tr>
</tbody>
</table>

At the age of 23 years, \( A = 0 \), so \( \text{logit}(P_\text{O}) = \alpha + \beta_{Z_a}Z_a + \beta_{Z_b}Z_b \).
Figure 1. Five BMI trajectories (A-E) plotted on the conventional diagram (left) and the risk score diagram (right)

**ROC analysis, PPV, sensitivity and specificity**

Figure 2a graphs the histogram of AO risk under the girls’ model 2y6y. About half of the girls have a negligible AO risk ($P_0 < 0.1$). In YHC practice, it is useful to set a cut-off value $\pi$ on AO risk such that all children with $P_0 \geq \pi$ are eligible for intervention. A nice property of such a rule is that the positive predictive value (PPV) of the group of children $P_0 = \pi$ is equal to $\pi$. Thus if we set $\pi = 0.5$ and refer those with $P_0 \geq \pi$, we expect that at least half of this group will be overweight as an adult. Figure 2b shows how the actual AO prevalence in the eligible group depends on the cut off $\pi$. At $\pi = 0$ the AO prevalence in the eligible group is equal to the prevalence of overweight at young adulthood. Increasing $\pi$ leads to a progressively higher AO proportion in this group, until the remaining group becomes so extreme (at $\pi = 0.82$) that all members fall into the AO group.
Figure 2.  
a. Histogram of frequency of girls (Y-axis) as a function of the risk of adult overweight under the model 2y6y (X-axis), and b. the prevalence of adult overweight (Y-axis) as a function of the cut-off value (X-axis).

Figure 3.  
ROC plots of models 2y6y and 2y4y, including the risk of AO at several points. The AUC was respectively 0.83 (95%CI 0.78-0.88) and 0.79 (95%CI 0.73-0.85) for boys, and respectively 0.80 (95%CI 0.75-0.84) and 0.76 (95%CI 0.71-0.81) for girls.
Occasional drops in AO prevalence occur at \( \pi \) values where many subjects with AO are placed. Changing \( \pi \) also affects the sensitivity and specificity of the rule. Figure 3 plots Receiver Operating Curves (ROC) under models 2y6y and 2y4y. Model 2y6y is more informative than model 2y4y, i.e. at the same specificity, model 2y4y has a lower sensitivity than model 2y6y. The AUC for the models 2y4y and 2y6y was respectively 0.79 (95%CI 0.73-0.85) and 0.83 (95%CI 0.78-0.88) for boys, and respectively 0.76 (95%CI 0.71-0.81) for girls 0.79 (95%CI 0.75-0.84). On the basis of the ROC analyses, the cut-off values for AO risk should be chosen around 0.25. In clinical practice this means that we single out those children with a risk of AO of 0.25 and higher and subsequently offer them targeted preventive interventions. In Table 4 the positive predictive value (PPV), the sensitivity and specificity of the models are given for different cutoffs on AO risk. At a rising cutoff the PPV rises, the sensitivity decreases and the specificity rises. The % of false-positive children can be derived from this table by calculating ‘1-specificity’, e.g. at a cutoff of 0.25 the % false positive children varies from 26 to 29%, whereas at a cutoff of 0.50 these values vary from 7 to 8%.

Table 4. The positive predictive value (PPV), sensitivity and specificity of the 3 risk models 2y6y, 2y4y and 4y6y at 23y of age at 3 different cutoffs.

<table>
<thead>
<tr>
<th>Cutoffs</th>
<th>PPV of model</th>
<th>Sensitivity of model</th>
<th>Specificity of model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25%</td>
<td>50%</td>
<td>75%</td>
</tr>
<tr>
<td>2y4y</td>
<td>0.49</td>
<td>0.75</td>
<td>0.71</td>
</tr>
<tr>
<td>4y6y</td>
<td>0.54</td>
<td>0.76</td>
<td>0.76</td>
</tr>
<tr>
<td>2y6y</td>
<td>0.52</td>
<td>0.76</td>
<td>0.74</td>
</tr>
</tbody>
</table>

The risk score diagrams and general practice

Figures 4 and 5 contain the risk score diagrams for respectively males and females for the age intervals 2-6y and 2-4y, which make it easy to identify children at high risk of adult overweight (AO). The risk score diagrams for the age interval 4-6y is not given.
as its practical value seems less obvious. For practical purposes the four risk score diagrams that can be used to estimate AO risk are expressed as a function of BMI instead of BMI SDS. The risk of AO can be read from the contour lines of these diagrams, and is based on the BMI at two ages, of which the BMI at the start of the interval is given by the value on the X-axis, and the end of the interval by the value on the Y-axis. If the child has the BMI at the age that is given on the X-axis, an indication of AO risk can be given for the combination of the BMI on the X-axis and various values of BMI at the age which will be reached as given on the Y-axis.

**DISCUSSION AND CONCLUSION**

We developed a tool to identify children with a high risk of AO and in particular those who are not yet overweight. The tools consist of several risk score diagrams, which are all based on two measurements of the BMI, because including a third did not improve the performance of the tools. The explained variance of adult BMI by the BMI development between 2 and 6 years of more than 40% is considerable, especially taking into account that this age interval concerns a very early growth period in human life and the age interval 2-6y only covers 22% of the age range between 0-18 years. The BMI changes in the age intervals 2-4y and 4-6y contribute equally to AO risk. We have developed risk score diagrams and illustrated the use of these diagrams.

*Cut-off values*

An indication of a normal growth of a child from 2 years onwards can be extracted from the risk score diagrams. The diagrams show how the BMI should develop to respectively 4 and 6 years of age to secure a low AO risk. In addition, the diagram for 2-4y offers a mid-term estimate of AO risk that could be used to evaluate weight change at the age of 4y. After an evaluation with the help of the diagram for 2-4y, the diagram for 2-6y should be applied to determine if the BMI development of the child is normal or whether it should be adjusted.

The ROC plots of the risk score diagrams suggest cut-off values for the risk at approximately 0.25. At this cut-off about 30% of the children that did not develop AO are wrongly designated as 'high risk'. Therefore the choice of a cut-off at 50% seems more sensible because this is associated with only 8% of false positive results. At the
Figure 4. Risk score diagram for boys measured at ages 2y and 4y (a) and ages 2y and 6y (b).

Figure 5. Risk score diagram for girls measured at ages 2y and 4y (a) and ages 2y and 6y (b)
cut-off around 0.5 we find that the PPV is 67% of the 2-6y old children with an estimated overweight risk of >0.5. Another important consideration in deciding to offer preventive intervention is its cost-effectiveness.

**Context of the study results**
The prevalence of adult overweight (BMI ≥25) in the Netherlands is still rising: in 2004 it was 51% and 42% for adult males and females respectively. In addition the prevalences are higher in later birth cohorts and tend to evolve into obesity at older ages.24 Therefore primary prevention of AO is very important in lowering these figures. In addition to interventions targeting the total population of children (universal prevention) it will be particularly efficient to identify children at high risk for developing overweight. Therefore tools are needed that can be easily incorporated within preventive health care. We developed this tool which is aimed at the age interval 2-6y, just before the AR, which is known to be crucial for developing overweight.12,25

Several studies have assessed the relationship between a relative fast BMI increase (or upwards centile crossing) between 2 to 5 or 6 years and adult overweight or obesity.12,14,25,26 One of these studies also constructed risk charts based on serial BMI SDS in a non-Caucasian cohort.26 Moreover, these charts are meant to identify children at risk of metabolic syndrome and diabetes.

**Strengths and limitations**
A methodological difficulty of our study is that we had to deal with missing values, which can cause the individual broken stick models to shrink further towards the overall mean. Therefore, any tests of differences will be conservative, and possibly underestimate the effects of BMI changes in age intervals in which fewer measurements are recorded. Another limitation was that as in most cohort studies there was a substantial loss to follow-up.9 Therefore sampling bias might be possible. However, there is no reason to assume that the loss to follow-up is related to the strength of the relationship between BMI changes in childhood and adult BMI. Moreover, no significant differences were found for the baseline characteristics for males and females between those that participated in the follow-up study and the original cohort.
We should be aware that no data on the representativeness of well-known risk factors for overweight such as socio-economic status, parental weight status and parenting were available. It is not clear if and how these risk factors influence the performance of the tool. The study population of Terneuzen differs slightly from the total Dutch population regarding e.g. the prevalence of overweight, which was higher in the Terneuzen cohort than in 15-25 year olds in the general Dutch population in 2006 (27.0 vs. 20.4%), although this difference might be largely due to the age distribution. Therefore cohort effects cannot be excluded.

Because of the above mentioned limitations, the tool should be validated in younger cohorts, before implementing the tool in YHC. This will improve its generalisibility. Beyond validation, adaptations of the tool to other ethnicities or other possible risk factors might be necessary. It is to be expected that the PPV of the tool will increase in younger birth cohorts as the higher prevalences of AO in younger cohorts will be in favor of the PPV of the tools. Also, we should realize that BMI at young adulthood possibly underestimates ultimate adult obesity. However, by developing a tool aimed at the risk estimation of overweight (including obesity) at young adulthood, this tool will probably also predict the more severe cases of overweight at later adulthood.

A limitation of the risk score diagram as presented is that it will only work if the children have been measured at ages 2y, 4y and 6y. As long as the age of the measurement does not differ substantially from the target by no more than 2-3 months, the risk score diagrams will remain valid, especially if the length of the age intervals remain close to two or four years.

Finally, because BMI SDS reflects total body mass and not body fatness, it might be possible that a relatively high BMI increase during the age interval 2-6 years is also due to increase in muscular and bone tissue. Therefore future research should take into account the predictive value of waist circumference or - less known - neck circumference at childhood, both strongly related to the risk of cardiometabolic diseases. However, the BMI is still the most common measurement used to estimate body fat. Moreover, several studies have shown that an early AR which is the result of upwards centile crossing of the BMI just before the age of 6 years is caused by a rapid elevation in the deposition of body fat rather than lean tissue mass.
The strength of our study is that we have developed a tool suitable for primary prevention for children who are not yet overweight. Two-dimensional easy-to-use risk score diagrams could be developed, because adding a third BMI SDS to the model did not significantly improve the performance of the model. The accepted definition of overweight in children is based on the cut-off values of the International Obesity Task Force (IOTF), centile curves with variable cut-off values for different ages. However, the risk of AO at the IOTF cut-offs increases with age. Therefore preventive interventions that are offered to children with a BMI above the IOTF cut-off point for overweight may have, depending on age, quite different implications for future weight. The advantage of the methodology proposed in this paper is that it provides an alternative that is directly based on risk of AO. Because the tools take both the actual BMI SDS and BMI SDS change into account, the new approach could lead to different interventions for children of the same age and same BMI.

Relevance and usefulness within the setting of the Youth Health Care (YHC)
In the Netherlands, the tool might be used within YHC that reaches more than 90% of all Dutch infants from birth onwards by a nationwide program at set ages. During the YHC check-ups the length and weight of each child are measured. Based on the information in the risk score diagrams (figures 4 and 5), parents can be given information and an indication about the risk of AO, and thereby be advised about the preferred growth and nutrition of their child until the ages of 4y and 6y. This also applies to parents of children who are already overweight at 2y or 4y, so they can be motivated to modify the family’s and children’s lifestyle to prevent AO. Within YHC it might also be considered to use the tool selectively for those children with a high risk of overweight which can already be assessed before the age of 2 years, e.g. by assessing risk factors, such as the BMI of the parents, ethnicity, or SES. Tailored primary prevention programs might be offered to these high-risk children, aimed at e.g. stimulating breastfeeding, daily physical activity, eating breakfast, and preventing the watching of television and consumption of sweetened beverages.

Conclusion
Our tool can support preventive healthcare professionals in the early detection of young children at high AO risk with the aim of deciding as whether or not tailored preventive interventions should be offered. Moreover, the tool can be used as an instrument for
primary prevention by informing parents about the risks of upward centile crossing during the age interval 2-6y. The feasibility and effectiveness of the tool in combination with offering tailored preventive interventions should be studied, e.g. in ongoing trials. After external validation and a positive evaluation of related interventions, a wider adoption of this tool might enhance primary prevention of overweight during a very sensitive period in human growth.

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Addendum 1  Modelling AO by logistic regression

BMI at age $t$ years is denoted by the random vector $Y_t$, e.g. $Y_2$ is the BMI at age 2y. BMI is expressed as age-specific standard deviation scores $Z_t$ (BMI SDS) by means of the LMS method relative to the Dutch reference data. Change in BMI and BMI SDS between ages $t$ and $u$ ($t<u$) is written as $\Delta Y_{t,u} = Y_u - Y_t$ and $\Delta Z_{t,u} = Z_u - Z_t$. The criterion used for AO is $Y_t \geq 25$ kg/m$^2$, where $t \geq 18$y. $Z_{18+}$ is the BMI SDS in young adulthood. Each individual BMI SDS trajectory was fitted by a piecewise linear spline model, known as the broken stick-model, with the knots set equal to the break ages. This model approximates the observed BMI SDS trajectory by a series of straight lines connecting to each other at the break ages. Individual trajectories are characterized by nine parameters, which is described in detail elsewhere (see also figure 1 of reference 19). Three of these parameters, $Z_2$, $Z_4$, and $Z_6$ can be interpreted as the BMI SDS at the ages of exactly 2y, 4y and 6y. We used the S Plus 8.0 function `bs()` to code the data into the appropriate form, and used the function `lme()` to estimate the parameters as random intercepts. The probability of AO, denoted as $P_O$, given $Z_2$, $Z_4$, and $Z_6$ was calculated by additive logistic regression using cubic splines by the R package gamlss, version 1.9.4. We chose the degrees of freedom for the smoothers by the profile likelihood using a penalty of 3. In nearly all cases, the optimal degree of freedom was close to zero. This corresponds to the model where $\log(P/(1-P))$ is linear in $Z_2$, $Z_4$, and $Z_6$. Therefore for simplicity the conventional logistic regression model was used throughout. Multiplicative interaction effects were entered, but none contributed significantly with a type I error rate of 0.10, so only main effects were used. The fitted models are graphed as a set of contour lines where $P_O$ is the dependent and where $Z_2$, $Z_4$, and $Z_6$ define the plotting surface.

Addendum 2  An example of calculating AO risk

Suppose a boy aged 2y has a height of 90cm and a weight of 12.3 kg. BMI is equal to $Y_2 = 12.3/0.9^2 = 15.18$ kg/m$^2$. Using equation (2) of Cole et al., $Z_2 = \ln(15.18/16.42)/0.079 = -0.99$. At age 6y, the boy has grown to a height of 120 cm and a weight of 22.4 kg, so $Y_6 = 15.55$. Using equation (1) of Cole et al., $Z_6 = ((15.55/15.52)^{1.324} - 1) / (-1.324 * 0.0967) = 0.02$. The AO risk at the age of 23 years is calculated in two steps, using the results presented in tables 2a and 2b. The logit $\varphi = -1.08 -1.03 * -0.99 + 3.4 * 0.02 = 0.0077$, so $P_O = e^{0.0077}/(1+e^{0.0077}) = 0.50$. 

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