The Terneuzen Birth Cohort

Detection and Prevention of Overweight and Cardiometabolic Risk from Infancy Onward

Marlou de Kroon
The study project presented in this thesis was conducted within the EMGO+ Institute for Health and Care Research, Department of Public and Occupational Health of the VU Medical Center in Amsterdam. The EMGO+ Institute participates in the Netherlands Academy of Arts and Sciences. In 2010 the EMGO+ Institute received an excellent review by the external evaluation committee of all Dutch university research, as organized by the universities in the Netherlands.

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VRIJE UNIVERSITEIT

The Terneuzen Birth Cohort
Detection and Prevention of Overweight and Cardiometabolic Risk from Infancy Onward

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dr. J.P. van Wouwe
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Introduction
Worldwide, many initiatives have been undertaken to fight human overweight and obesity, a rapidly growing public health problem which has type 2 diabetes and cardiovascular diseases as serious health consequences.\(^1,2\) It is anticipated that in the near future more people will die from the complications of overnutrition than from starvation.\(^3,4\)

Overweight and obesity are a continuing problem over generations. Parental overweight and related cardiometabolic risk are related to higher prevalences of overweight and cardiovascular diseases in their offspring,\(^5\) leading to an intergenerational cycle of obesity.\(^6\) In addition, overweight often persists throughout life, referred to as tracking.\(^7\) Therefore, the primary prevention of overweight and its related cardiometabolic risk is important.

The Child Health Care (CHC) in the Netherlands offers preventive care to all infants, children and adolescents. The CHC routinely invites them from birth onwards for regular health evaluations at set ages: 10 times between birth and 1 year of age, 3 times between 1 and 2 years, and 7 times between 2 years and 14 years of age. During these check-ups development and growth are monitored. Within the Dutch CHC centers, a lot of effort is taken to prevent overweight in children and adolescents. The CHC professionals advise the parents of all infants on the duration of exclusive breastfeeding and on other aspects of lifestyle, related to the prevention of overweight. Furthermore, if the CHC professional assesses overweight in children between 2 and 19 years of age, secondary preventive interventions are offered. Currently, the “Transitional Plan” is used as such an intervention, until an evidence-based program applicable within CHC practice becomes available.\(^8\)

Primary prevention of overweight and its comorbidity is to be preferred above secondary prevention. At present there is insufficient knowledge and evidence about the optimal timing of primary prevention of overweight. Neither is there sufficient knowledge to detect those children and young adults with increased risk of later overweight and/or cardiometabolic diseases.

The aim of this thesis is to contribute to early identification and prevention of (adult) overweight and related cardiometabolic risk in the earliest possible phase of life, and to
offer primary preventive interventions at the right time to those who need it most. The data for the underlying analyses come from the Terneuzen Birth Cohort.

OVERWEIGHT, OBESITY AND RELATED CARDIOMETABOLIC RISK

Overweight and obesity

Definitions of overweight and obesity
Overweight and obesity are the result of an imbalance between energy intake and energy expenditure. Overweight refers to the condition of a person having more body fat than is healthy. Obesity is a degree of overweight to such an extent that it has an adverse effect on health.\(^9\) Generally, the degree of overweight is approximated by the body mass index (BMI), which is given by the formula weight (mass) in kilograms divided by the square of height in meters. For adults, the WHO classifies a BMI $\geq 25$ and $<30$ kg/m\(^2\) as overweight, and a BMI $\geq 30$ kg/m\(^2\) as obesity.\(^10\) For international comparisons, overweight and obesity in children are defined according to the age and sex-specific international IOTF criteria.\(^11\) These are based on BMI centile curves that pass through the adult cut-offs of a BMI of 25 kg/m\(^2\) for overweight and 30 kg/m\(^2\) for obesity at the age of 18 years, comparable to Dutch BMI standard deviations (SDS) of 1.1 and 2.3, respectively.\(^12\)

Prevalences of overweight and obesity
Although much attention is being paid to keeping a healthy weight, prevalences of overweight and obesity are rising, both in developed and in developing countries.\(^13\) The worldwide increasing prevalence of overweight and obesity among preschool children is worrisome. In 2010, worldwide 43 million preschool children were estimated to be overweight or obese according to the World Health Organization standards.\(^14\) From 1995 to 2010 the prevalence of childhood overweight increased from 4.0% to 6.1% in developing countries, and from 8.8% to 11.7% in developed countries.\(^13\) This corresponds to an increase with a factor of 1.5 and 1.3, respectively. The comparison of the Dutch Fourth (1997) and Fifth National Growth Study (2009) shows that in the Netherlands prevalences of overweight and obesity in 2 to 21 year olds were higher in 2009 than in 1997. For overweight (including obesity) the frequencies in 1997 and 2009 were 9.4% and 13.3% in boys, and 11.9% and 14.9% in girls. This corresponds to a multiplication of the prevalences by a factor 1.4 in boys, and 1.3 in girls. For obesity
the prevalences in 1997 and 2009 were 0.9% and 1.8% in boys, and 1.6% and 2.2% in girls. This corresponds to even higher multiplication factors of 2.0 in boys and 1.4 in girls.\textsuperscript{16}

\textit{Interventions aimed at overweight}

Many risk factors for overweight and obesity have been identified, such as parental overweight\textsuperscript{5} and other factors related to dietary behaviour\textsuperscript{17,18-21} as well as physical activity and sedentary behavior.\textsuperscript{22-25} For children with overweight many, especially secondary, preventive interventions have been developed focusing on these risk factors. Although several interventions are promising, none of these interventions have yet been proven effective in the long term. In addition, most interventions are time consuming, expensive and have a small reach. In addition, it is not known if aiming at certain critical growth periods may contribute to the effectiveness of these interventions.

\textbf{Cardiometabolic risk and metabolic syndrome}

\textit{Definition of cardiometabolic risk and metabolic syndrome}

Cardiometabolic risk refers to the existence of one or more of the following risk factors: obesity, hyperglycemia, hypertension, insulin resistance, dyslipoproteinemia, and lifestyle factors like physically inactivity and smoking. The risk increases when these factors occur simultaneously.\textsuperscript{26} Often metabolic syndrome, a constellation of risk factors for type 2 diabetes and cardiovascular diseases,\textsuperscript{27} is used to identify subjects with increased cardiometabolic risk.\textsuperscript{28} Metabolic syndrome is associated with perturbations of the lipoprotein-lipid profile and of the plasma glucose-insulin homeostasis.\textsuperscript{29} Frequently applied definitions of metabolic syndrome in adults are those assessed by the European Group for the Study of Insulin Resistance (EGIR), National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII), International Diabetes Federation (IDF) and the WHO.\textsuperscript{27,30}

Today, the most widely accepted definition for metabolic syndrome in adults is the one according to the NCEP ATP III,\textsuperscript{31} which applies if at least 3 out of the following 5 components are met: an increased waist circumference (>102 and >88 cm for males and females respectively), elevated triglycerides (≥1.7 mmol/l), reduced HDL
cholesterol (<1.0 mmol/l and <1.3 mmol/l for males and females respectively), increased blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg) and elevated fasting plasma glucose (≥5.6 mmol/l). Metabolic syndrome according to this definition gives a twofold increase in the risk of cardiovascular disease and a threefold increase in the risk of diabetes.32

Prevalences of metabolic syndrome
Worldwide, different prevalences of metabolic syndrome in adults according to the NCEP ATPIII definition have been reported from 7% to over 50% in populations with different physique, genetic susceptibility, age and lifestyle.33 Since metabolic syndrome has not been unambiguously defined in children, prevalence rates in children cannot properly be compared. At least 40 different definitions have been used for children, of which most were adaptations of the National Cholesterol Education Program (NCEP ATPIII).34

Interventions aimed at metabolic syndrome
The effects of overweight on later cardiometabolic risk amplify with age,35 leading to irreversible precursors of diabetes and cardiovascular disease already detectable in young persons.36 For adults with increased cardiometabolic risk, it is evident that lifestyle modification consisting of regular, moderate-intensity physical activity and/or caloric restriction to prevent the development of overt type 2 diabetes, is useful.37 Lifestyle modification lowers cardiometabolic risk, even if weight loss has not been achieved. This is relevant since weight loss, still the ideal outcome of the intervention, is seldom achieved.37

PRIMARY PREVENTION
As a consequence of the increased prevalences of overweight and obesity in children, and the tracking of overweight,7 the risk of young female adults to develop glucose intolerance and gestational diabetes is increasing. This generation of young mothers will give birth to heavier babies who are themselves prone to become obese in childhood and develop type 2 diabetes. This creates a vicious intergenerational amplification of higher birth weight, childhood obesity, and early type 2 diabetes. Despite the enormous efforts involved with secondary preventive interventions of
overweight, it is extremely difficult to reverse the obesity pandemic. So it seems important to strive for primary prevention of overweight, obesity and related cardiometabolic risk starting from a very early age.

**Primary prevention of overweight**

Primary prevention of adult overweight and related cardiometabolic risk should be aimed at the most critical and earliest possible growth periods. As far as we know, no efforts have been undertaken to optimize the timing for primary preventive interventions. Neither is there any evidence-based protocol to select children without overweight that are at highest risk of adult overweight and its comorbidity. Current cut-offs of overweight and obesity in children have been developed with the goal of making international comparisons of prevalences of overweight and obesity.\(^{11,12}\) In addition, these cut-offs are used as the only practical tool available, for selecting children with overweight or obesity with the aim of offering them preventive interventions. However, the utility of these cut-offs for offering prevention programs has not been studied in a systematic way. Current application of the cut-offs implies that preventive interventions are offered to individuals with different levels in fat mass and related cardiometabolic risk. Indeed, it has been shown that the correlation of BMI SDS and body fat percentage rises from 0.62 to 0.78 (between the ages of 3.5 and 7 years),\(^{38}\) and that it varies substantially according to the degree of body fatness.\(^{39}\) On the basis of serial measurements of BMI SDS recognizing growth trajectories, deviating from the individual’s expected trajectory, seems possible. This offers the opportunity to identify children with increased risk to develop overweight and its related cardiometabolic risk. In a non-Caucasian population a BMI SDS increase in late childhood and adolescence has been associated with adult overweight and impaired glucose tolerance,\(^{40}\) although these children did not necessarily have a high BMI in absolute terms. Gaining more insight into this topic might contribute to an evidence-based selection of children with increased overweight and cardiometabolic risk. This may be particularly interesting within the existing infrastructure of the CHC in the Netherlands and in other countries where children's height and weight are measured regularly.\(^{41}\) This might lead to cost-effective primary prevention programs by offering interventions to children at highest risk in a period they are most susceptible to developing overweight.
Primary prevention of cardiometabolic diseases
Overweight in childhood often tracks into adulthood,\textsuperscript{42} and is a strong predictor of coronary heart disease in young adulthood.\textsuperscript{43} Therefore the obesity pandemic in children will result in an increasing number of young adults with cardiometabolic risk. If these young adults can be identified and offered lifestyle interventions, primary prevention of overt type 2 diabetes and cardiovascular disease is within reach. Especially young persons with metabolic syndrome who still are at the start of their reproductive life phase will benefit from early detection and lifestyle advice. By adapting a healthy lifestyle, cardiometabolic risk will decrease over a full lifespan. Moreover, this will also diminish the risk of birth defects in future offspring, due to type 2 diabetes and/or hypertension of the mother.\textsuperscript{44,45} However, until now, little effort has been made to detect young adults with overweight-related cardiometabolic risk in a general population with the aim of offering them preventive interventions.

Breastfeeding
The promotion of exclusive breastfeeding for at least 6 months has been recommended as one of the promising population-based approaches in the prevention of overweight. Several studies showed an inverse dose-response relationship between duration of breastfeeding and overweight at later ages,\textsuperscript{7,46,47} of which a few assessed this relationship up until adulthood.\textsuperscript{46,47} In these studies overweight has been defined on the basis of BMI or weight by height. It is not yet clear how the duration of breastfeeding is related to waist circumference and waist-hip ratio, both proxies of visceral fat. Studies of the relationship of the duration of exclusive breastfeeding with cardiometabolic risk are sparse. Moreover, the few study results existing on the relationships with blood pressure, blood cholesterol and glucose metabolism are contradictory.\textsuperscript{48-50} The evidence to date suggests that the protective effects of breastfeeding against overweight are small. On the other hand, even a small effect might be beneficial at the population level if large numbers of children are involved. The pathways evolving to its protective effects are not well understood and possibly very complex.\textsuperscript{51} Dietary factors likely play a mediating role in this relationship.\textsuperscript{52}
THE TERNEUZEN BIRTH COHORT

Statistical analyses in this thesis are based on data from the Terneuzen Birth Cohort. This cohort consists of all children born between 1977 and 1986 in the city of Terneuzen, the Netherlands (n= 2,604). The mothers of these children participated in an observational study at the CHC center in Terneuzen with the aim of evaluating and monitoring the initiation and duration of breastfeeding. Data on breastfeeding duration were prospectively collected from birth until the age of 6 months during the regular visits of mothers and their babies to the CHC in Terneuzen. For each child the duration of exclusive breastfeeding, the date of the introduction of formula and the last day that breastfeeding was given, was recorded. In 2004-2005, a total of 2,022 persons from the original cohort could be traced, and they were invited to participate in a follow-up study. Detailed data on growth (weight and height) as routinely collected by the CHC and the Municipal Health Services were yielded for 1,701 subjects in the Terneuzen Birth Cohort. Of these subjects, 822 persons participated in the follow-up study at young adulthood that included questionnaires (n=822) for the young adults themselves and for their mothers to obtain information on lifestyle factors, health and sociodemographic characteristics, and measurements (n=762) of weight, height, waist circumference, blood pressure and skinfold thickness. From 642 participants venous blood samples were drawn after a fast of at least 12 hours. Glucose, HDL cholesterol, triglycerides and high-sensitivity C-reactive protein (hsCRP) were measured.

OUTLINE OF THE THESIS

The aim of this thesis is to contribute to early identification and prevention of (adult) overweight and related cardiometabolic risk in the earliest possible phases of life. In order to achieve this goal, we will
1. study during which age intervals children are most susceptible to developing overweight and its related cardiometabolic risk,
2. investigate how young adults with increased cardiometabolic risk can be detected in a general population, and
3. assess the relationship of exclusive breastfeeding duration with BMI, waist circumference and waist-hip ratio at young adulthood.
Questions to be answered in this thesis are the following.

1. During which age intervals are children most susceptible to adult overweight and related cardiometabolic risk?

For primary prevention of adult overweight and cardiometabolic risk, identification of sensitive or 'critical' growth periods is useful. On the basis of data from the Terneuzen Birth Cohort the following objectives are pursued in the first part of the thesis:
- Assessment of the relative contribution of BMI SDS changes between 0-18 y of age to adult overweight, and identification of the earliest relevant, critical growth period for adult overweight (Chapter 2),
- Assessment which age interval is most predictive of cardiometabolic risk at young adulthood (Chapter 3),
- Development of a tool enabling the identification of children at high risk of adult overweight, based on the earliest relevant growth period for developing overweight (Chapter 4).

2. How can we detect young adults with metabolic syndrome in a general population?

The assessment of metabolic syndrome is expensive, because it requires physical examination and blood tests. Therefore, it may be useful to develop a quick and user-friendly population-based method to detect metabolic syndrome in young adults. In the second part of the thesis the following two objectives are pursued:
- Assessment of the prevalence of metabolic syndrome in young adults, and the development of a simple stepwise strategy to identify metabolic syndrome in young adults (Chapter 5),
- Development of a risk score using easily obtainable data to detect young adults with metabolic syndrome in a general population. The question is if a simple and short questionnaire can be used as the first step to identify young adults with metabolic syndrome (Chapter 6).
3. What is the relationship between exclusive breastfeeding duration and BMI, waist circumference and waist-hip ratio at young adulthood?

The decision of the mother to breast or formula feed is one of the first and irreversible steps in a child's life, occurring during the very first growth period. Bearing this in mind, it is relevant to study if a relationship between longer exclusive breastfeeding duration and overweight exists at young adulthood, whether exclusive breastfeeding duration is related to cardiometabolic risk in young adults, and whether pathways of its effect can be shown. In the last part of this thesis, we determine the relationship of the duration of exclusive breastfeeding with BMI, WC and WHR at young adulthood. The extent to which dietary behaviour explains these relationships is also investigated (Chapter 7).

Finally, the results and implications are discussed (Chapter 8).
REFERENCES


The Terneuzen Birth Cohort

BMI Changes between 2 and 6 Years Correlate Strongest with Adult Overweight

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ABSTRACT

Background
Complications of overweight amplify with age, and irreversible damage already exists in young persons. Identifying the most sensitive age interval(s) for adult overweight is relevant for primary prevention. The aim of the study was to assess the relative contribution of body mass index (BMI) changes between 0 and 18 years to adult overweight, and to identify the earliest critical growth period.

Methods and findings
Data from 762 subjects in the Terneuzen Birth Cohort with an average of 21 growth measurements per subject from birth until 18 years were used. The main outcome measure was the BMI standard deviation score (SDS) at young adulthood. For each subject BMI SDS was fitted by a piecewise linear model at eight different ages and correlated to adult BMI SDS. The age intervals in between are considered critical according to three criteria, tested by respectively Students’ t-tests, multiple linear regression analyses and Pearson’s correlation tests. In the age intervals 4 months(m) -1 year(y), 2-6y, 6-10y and 10-18y the BMI SDS change differs between adults with and without overweight (p≤0.001). The age intervals 2-6y and 10-18y also meet the second criterion, implying that the BMI change during this period has a predictive value for adult BMI SDS in addition to BMI SDS at the end of the period. The largest rise in correlation between estimated BMI SDS and measured adult BMI SDS occurs during the period 2-6y (from 0.36 to 0.63), which results in a high sensitivity (0.6) and specificity (0.8) by the age of 6y.

Conclusions
The age interval from 2y to 6y is the earliest and most critical growth period for adult overweight. Therefore, primary prevention of adult overweight seems most likely to be successful if targeted at this specific age interval. By identifying those with an upwards centile crossing between 2 and 6 years, the development towards adult overweight might be reversed.
INTRODUCTION

The effect of overweight on later cardiovascular health problems amplifies with age,\(^1\) and irreversible precursors of diabetes and cardiovascular disease already exist in young persons.\(^2\) Not only is weight in itself a risk factor, but so is also a fast BMI increase during childhood.\(^1,3-7\) For the prevention of adult overweight, research has focused on the identification of sensitive or so-called 'critical' growth periods. A growth period is critical for adult overweight if changes within this period increase the risk of adult overweight.\(^8\) Several investigators have distinguished growth periods with increased risk.\(^7,9-17\)

Figure 1 illustrates how the BMI standard deviation score (BMI SDS) in five hypothetical growth patterns evolves into adult overweight. The first pattern is a simple trajectory with a constant increase in BMI SDS over a prolonged time interval, e.g. 0-20y. Every period seems to be critical here (a ‘long critical’ period). Another simple trajectory occurs if children are already overweight at birth and remain overweight until adulthood, so in essence no critical period exists (‘no critical’ period). By contrast, the ‘short early’ and ‘short late’ trajectories have large increases in BMI SDS during short time periods. The rise in BMI SDS could also be broken into a smaller number of critical periods, e.g. ‘two critical’ periods. The last three patterns (‘short early’, ‘short late’ and ‘two critical’ periods) suggest that prevention opportunities are to be found before or within the periods of BMI SDS increase, rather than after. In all situations statistical evidence is required to confirm that changes in BMI SDS effectively influence the risk of adult overweight.

Few studies have followed the BMI changes in children from birth to adulthood; most studies limit themselves to a time interval during childhood\(^11,12,14,15,17-21\) or have a follow-up that does not exceed puberty.\(^9,12,16,18,21\) Also, their results are sometimes contradictory.\(^5,10,18,21\) Two recent studies without these shortcomings included respectively males only\(^10\) and no Caucasians.\(^13\)

We aim to assess the relative contribution of BMI SDS changes between 0-18 y of age to adult overweight, and to identify the earliest relevant, critical growth period for adult overweight.
METHODS

Ethics Statement
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.

Population and study design
The original cohort consists of all 2,604 children born between 1977 and 1986 in the city of Terneuzen. Of the 1,701 subjects data for weight and length as routinely registered by the Municipal Health Services were available from birth. Of these subjects, 762 persons (45%) were willing to participate in a follow-up study at young adulthood that included measurements of weight, height and waist circumference and a questionnaire to collect sociodemographic characteristics. This is described in more detail elsewhere. The participants in the follow-up study did not differ from the original cohort regarding baseline characteristics collected at birth, e.g. date of birth, birth weight, BMI SDS at birth, age of the mother, and parity, except for gender (41% were 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 SDS \( \geq 1.3 \) (roughly a BMI \( \geq 25 \)).

In contrast to most studies that are limited to a specific period (infancy, childhood or adolescence) and lack of follow-up to adulthood, our cohort covers the complete growth from birth to adulthood. For comparison purposes with other studies, we divided the growth period of our cohort into the following age intervals: 0-8 days (0-8d), 8 days-4 months (8d-4m), 4 months-1 year (4m-1y), 1-2 years (1-2y), 2-6 years (2-6y), 6-10 years (6-10y), and 10-18 years (10-18y). The upper limit in the age interval 6-10y was set since Dutch children go into puberty after 10 years of age; the upper limit of 18 years marks the start of adulthood. The limits of all periods (0d, 8d, 4m, 1y, 2y, 6y, 10y and 18y) are called break ages.
BMI Changes between 2 and 6 Years Correlate Strongest with Adult Overweight

Figure 1. Five hypothetical trajectories towards overweight

Statistical analysis
The major analytic problem was that the number and the timing of the measurements vary between individuals. We solved this by fitting each individual BMI SDS trajectory by a piecewise linear model, otherwise known as a broken stick-model, with the knots set equal to the break ages. We also dealt with missing data in this way. This model approximates each person’s observed BMI SDS trajectory by a series of straight lines that connect to each other at the break ages. In order to stabilize the parameter estimates, we fitted these parameters as randomly varying slopes in a linear multilevel model. 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 effects. The procedure resulted in eight parameters per person that together describe the persons’ BMI SDS trajectory. Each parameter corresponds to the predicted value for each individual, using both random and fixed estimates. We call these status scores. They are represented as $Z_{0d}$, $Z_{8d}$, and so on. The change in BMI SDS per period is equivalent to the difference between two successive status scores, i.e. $Z_{8d} - Z_{0d}$, $Z_{4m} - Z_{8d}$, and so on. We call these change scores.
We define a growth period, bounded by ages T1 and T2, as critical if:

a. the mean change score $Z_{T2} - Z_{T1}$ is significantly different between those with and without adult overweight,

b. the change score $Z_{T2} - Z_{T1}$ and $Z_{T2}$ are both significantly related to adult BMI SDS in a multiple regression analysis, which is, as has been suggested by Lucas, equivalent to the significance of $Z_{T1}$ as predictor in addition to the significance of $Z_{T2}$ as predictor (see Addendum 1 for further explanation), and

c. the score $Z_{T2}$ is relatively close to BMI SDS at adult age.

Criterion a will filter out periods during which the two mean curves of the BMI SDS trajectory diverge, so significant differences in growth of those who do and those who do not become overweight emerge. Criterion b indicates if the preceding change score has additional value to the status score at the end of the period, in predicting the BMI SDS at adulthood. Criterion c will select periods for which it is easier (i.e. with higher sensitivity and specificity) to identify children at risk for adult overweight.

We tested for these criteria in SPSS 14.0 by applying Student's t-tests (2-sided), Pearson's correlation coefficients and multiple regression analysis (with alpha=0.05 for statistical significance). In the multiple regression analyses multiplicative interaction effects were entered to explore whether early weight is modifying the effect of later weight size on adult overweight with a type I error rate of 0.10. Age, gender, parity, exclusive breastfeeding (<90 vs ≥90 days) were included to study potential confounding or effect modification.

**RESULTS**

The mean age of the 762 subjects is 23.1 (SD 2.9). No difference in baseline characteristics between males (n=307) and females (n=455) were found ($p>0.05$). An average number of 21 growth measurements per participant between 0y and 18y were performed. Table 1 provides baseline characteristics at birth and adulthood and the average number of growth measurements per age interval.

Figure 2A shows the fitted broken sticks trajectories for each subject. Figure 2B demonstrates the means of the broken sticks trajectories for young adults with normal
Table 1. General characteristics at birth and at adulthood, number of subjects (N), and their mean (SD) number of height and weight measurements per age interval.

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<td>709</td>
<td>1.8 (0.7)</td>
<td>710</td>
<td>1.8 (0.8)</td>
</tr>
<tr>
<td>2-6y</td>
<td>802</td>
<td>2.7 (0.9)</td>
<td>804</td>
<td>2.7 (1.0)</td>
</tr>
<tr>
<td>6-10y</td>
<td>734</td>
<td>1.6 (0.6)</td>
<td>735</td>
<td>1.6 (0.6)</td>
</tr>
<tr>
<td>10-18y</td>
<td>723</td>
<td>1.7 (0.8)</td>
<td>724</td>
<td>1.7 (0.8)</td>
</tr>
</tbody>
</table>
weight and overweight. It is noteworthy that those with overweight track differently: the change scores differ, i.e. the lines are not parallel with those of normal weight.

We tested criterion \( a \) by Student's \( t \)-tests applied to the change scores at successive age intervals. Based on the recommendations of Jones and Spiegelhalter,\(^2^9\) we applied the analyses to unconditional change scores, because the correlations between subsequent values of the BMI SDS at the break-ages were substantially higher than 0.5, except for a slightly lower correlation between the BMI SDS at 8 days and 4 months (\( \rho = 0.48 \)). Significant differences were found for four age intervals: 4m-1y, 2-6y, 6-10y and 10-18y. No differences in the change scores were found for the age interval 1-2y (Table 2).

Table 2. Mean change score (SE) per age interval for subjects with adult normal weight (BMI SDS <1.3, \( n=608 \)) and with overweight (BMI SDS \( \geq 1.3, n=154 \)).

<table>
<thead>
<tr>
<th>Age interval</th>
<th>Mean change score (SE) for adults with normal weight</th>
<th>Mean change score (SE) for adults with overweight</th>
<th>( P ) (( t )-test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-8d</td>
<td>-0.87 (0.024)</td>
<td>-0.79 (0.055)</td>
<td>0.145</td>
</tr>
<tr>
<td>8d-4m</td>
<td>-0.31 (0.030)</td>
<td>-0.34 (0.065)</td>
<td>0.703</td>
</tr>
<tr>
<td>4m-1y</td>
<td>0.42 (0.025)</td>
<td>0.62 (0.056)</td>
<td>0.001</td>
</tr>
<tr>
<td>1-2y</td>
<td>0.22 (0.020)</td>
<td>0.28 (0.044)</td>
<td>0.183</td>
</tr>
<tr>
<td>2-6y</td>
<td>-0.36 (0.018)</td>
<td>-0.10 (0.041)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6-10y</td>
<td>0.05 (0.014)</td>
<td>0.35 (0.029)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>10-18y</td>
<td>0.09 (0.027)</td>
<td>0.42 (0.043)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Similar results were found for males and females, although for the age interval 4m-1y the difference became non-significant in males (\( p=0.078 \)). In addition \( t \)-tests were applied to test differences in BMI SDS changes for those with or without increased waist circumference at young adulthood as defined by IDF criteria. These analyses showed significant results for exactly the same intervals (\( p<0.001 \)).

The results of the multiple regression analyses to test criterion \( b \) are shown in Table 3, in which adult BMI SDS is the outcome, and the status score(s) the predictor(s).
Figure 2. A. Broken sticks trajectories for subjects with normal weight (green lines) versus subjects with overweight (red lines) at young adulthood, B. Broken-stick model of mean increments for subjects with normal weight (green line) and with overweight (red line) at young adulthood.
Because no effect-modification was found for gender \((p>0.3)\), in applying multiple regression analyses and correlation coefficients males and females could be analyzed as one group, increasing statistical power. As parity and breastfeeding duration did not influence the results \((p>0.05)\), these variables were not included in the final models. Not surprisingly, in the simple linear regression analyses BMI SDS is significantly related to adult weight at all ages. After including the previous status score as a second (linear) predictor, only two age intervals, 2–6y and 10–18y, met both criterion \(a\) and criterion \(b\). Moreover, these periods are both characterized by significant predictors with opposite regression signs, which means that especially the BMI SDS changes in these age intervals are relevant.\(^{28}\) We extended the smaller time intervals between birth and the age of 2 years to one age interval, in order to assess if the length of the age intervals influenced the results of the analyses. However, no significant effect has been shown by adding the status score at birth to the status score at 2 y: the increase in explained variance is zero; \(\beta\) in the multiple regression model at 2 y and at 0 d are respectively 0.548 (SE 0.06, \(p<0.001\)) and 0.039 (SE 0.046, \(p=0.394\)).

The increase of explained variance caused by including BMI-SDS at T0 into the model containing BMI-SDS at T1 was largest for the period 2-6 years. This implicates that the influence of the change scores on adult overweight is largest for the age interval 2-6y.

Because the relative changes in regression signs after extending the models is highest in the age interval 2-6y, especially in this age interval upwards centile crossing is an additional risk to the status score at the end of these age intervals (see addendum 1). For comparisons reasons with a recent study,\(^{10}\) we added an additional breakpoint at 4y, and found that the proportion of increased variance as a function of the status score at the end of the period for the age intervals 2-4y and 4-6y are respectively 0.05 and 0.04 by adding the status score at the start of the period to the model. In modelling the Z-score of the waist circumference at young adulthood as the outcome measure (number of missing outcomes is 5), we obtained similar results for the age interval 2-6y. In the multiple regression the coefficients of the status scores at 6y and at 2y coefficients are respectively 0.31 (SE 0.09, \(p<0.001\)) and -0.14 (SE 0.08, \(p=0.048\)), with an increased explained variance of 3% by augmenting the model with the preceding BMI SDS. Finally, because extreme high BMI at adulthood is more closely related to fat mass than lower values of BMI, we performed additional analyses by using adult obesity (BMI \(\geq 30\)) as the outcome. These analyses identified only the
Table 3. Linear relation between BMI SDS at young adulthood and BMI SDS at earlier age: Model A includes one status score as independent variable(a), model B is model A extended with the preceding BMI SDS# (b) as independent variable.

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Models A</th>
<th></th>
<th></th>
<th></th>
<th>Models B</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta$</td>
<td>SE</td>
<td>$P$</td>
<td>Adj $R^2$</td>
<td>$\beta_1$</td>
<td>SE</td>
<td>$P$</td>
<td>Adj $R^2$</td>
<td></td>
</tr>
<tr>
<td>(a) BMI sds at birth</td>
<td>0.158</td>
<td>0.047</td>
<td>0.001</td>
<td>0.035</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>(a) BMI sds at 8d</td>
<td>0.320</td>
<td>0.057</td>
<td>&lt;0.001</td>
<td>0.060</td>
<td>0.390</td>
<td>0.084</td>
<td>&lt;0.001</td>
<td>0.061</td>
<td></td>
</tr>
<tr>
<td>(b) BMI sds at birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.077</td>
<td>0.069</td>
<td>0.260</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) BMI sds at 4m</td>
<td>0.307</td>
<td>0.060</td>
<td>&lt;0.001</td>
<td>0.054</td>
<td>0.210</td>
<td>0.066</td>
<td>0.002</td>
<td>0.071**</td>
<td></td>
</tr>
<tr>
<td>(b) BMI sds at 8d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.239</td>
<td>0.063</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) BMI sds at 1y</td>
<td>0.562</td>
<td>0.057</td>
<td>&lt;0.001</td>
<td>0.138</td>
<td>0.591</td>
<td>0.068</td>
<td>&lt;0.001</td>
<td>0.138</td>
<td></td>
</tr>
<tr>
<td>(b) BMI sds at 4m</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.052</td>
<td>0.071</td>
<td>0.464</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) BMI sds at 2y</td>
<td>0.559</td>
<td>0.053</td>
<td>&lt;0.001</td>
<td>0.146</td>
<td>0.346</td>
<td>0.081</td>
<td>&lt;0.001</td>
<td>0.158**</td>
<td></td>
</tr>
<tr>
<td>(b) BMI sds at 1y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.291</td>
<td>0.083</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) BMI sds at 6y</td>
<td>1.095</td>
<td>0.049</td>
<td>&lt;0.001</td>
<td>0.407</td>
<td>1.583</td>
<td>0.077</td>
<td>&lt;0.001</td>
<td>0.454**</td>
<td></td>
</tr>
<tr>
<td>(b) BMI sds at 2y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.557</td>
<td>0.069</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) BMI sds at 10y</td>
<td>1.014</td>
<td>0.035</td>
<td>&lt;0.001</td>
<td>0.530</td>
<td>1.126</td>
<td>0.080</td>
<td>&lt;0.001</td>
<td>0.530</td>
<td></td>
</tr>
<tr>
<td>(b) BMI sds at 6y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.155</td>
<td>0.099</td>
<td>0.177</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) BMI sds at 18y</td>
<td>1.065</td>
<td>0.020</td>
<td>&lt;0.001</td>
<td>0.790</td>
<td>1.292</td>
<td>0.041</td>
<td>&lt;0.001</td>
<td>0.790**</td>
<td></td>
</tr>
<tr>
<td>(b) BMI sds at 10y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.305</td>
<td>0.047</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Intercepts not reported. **Interaction effects between BMI SDS at the end and at the start of the periods were not included in models B, because they were all non-significant. **$F$-test for comparing the multiple regression model with the simple regression model is significant ($P<0.001$), \*values of $\beta$, $\beta_1$ and $\beta_2$ are adjusted for gender and the age at the measurement of BMI SDS at young adulthood, -- Not applicable, Adj $R^2$ adjusted variance.
period 2-6y as critical (OR of BMI SDS at respectively 6y and 2y were 41.27, 95%CI 15.8-107.7 and 0.24, 95%CI 0.12-0.50), whereas none of the other periods were found to comply with the conditions of a critical period.

Criterion $c$ was assessed by Pearson's correlation between status scores and adult BMI SDS (Figure 3). From the age of 6 years onwards the correlation between the status score and adult BMI SDS is greater than 0.6, which implies that prevention of a (relatively) high BMI SDS at the age of 6y is relevant in terms of health outcome at adulthood.

![Figure 3. The correlation (Y-axis) of BMI SDS at several ages (X-axis) with the BMI SDS at young adulthood](image)

Table 4 summarizes previous results by age interval. It appears that the age intervals 2-6y and 10-18y fulfill all criteria for the definition of a critical growth period for adult overweight. The age interval 2-6y is the earliest growth period fulfilling these criteria.
Table 4. Summary of the results of the analyses and the interpretation per age interval based on criteria a, b and c.

<table>
<thead>
<tr>
<th>Age interval</th>
<th>Criterion a.</th>
<th>Criterion b.</th>
<th>Criterion c.</th>
<th>Critical age interval based on results of analyses concerning criteria a, b and c.</th>
<th>Confirmation of other study results reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-8d</td>
<td>NS</td>
<td>NS</td>
<td>no</td>
<td>no</td>
<td>no&lt;sup&gt;15&lt;/sup&gt;</td>
</tr>
<tr>
<td>8d-4m</td>
<td>NS</td>
<td>yes**</td>
<td>no</td>
<td>no</td>
<td>no&lt;sup&gt;9,14,15&lt;/sup&gt;</td>
</tr>
<tr>
<td>4m-1y</td>
<td>yes*</td>
<td>NS</td>
<td>no</td>
<td>no</td>
<td>partly, concerning results of t-tests&lt;sup&gt;14&lt;/sup&gt;</td>
</tr>
<tr>
<td>1-2y</td>
<td>NS</td>
<td>yes*</td>
<td>no</td>
<td>no</td>
<td>yes&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td>2-6y</td>
<td>yes**</td>
<td>yes**</td>
<td>yes**</td>
<td>yes</td>
<td>yes&lt;sup&gt;6,13,18&lt;/sup&gt;</td>
</tr>
<tr>
<td>6-10y</td>
<td>yes**</td>
<td>NS</td>
<td>yes**</td>
<td>no</td>
<td>possibly, not validated yet&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
<tr>
<td>10-18y</td>
<td>yes**</td>
<td>yes**</td>
<td>yes**</td>
<td>yes</td>
<td>yes&lt;sup&gt;25&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

NS not statistically significant (p>0.05), *P=0.001, **P<0.001
DISCUSSION

This paper addresses the issue whether sensitive or so-called critical periods in human growth exist during which BMI SDS changes have a significant impact on adult overweight. Our study results show that the change score during the age interval between 2 and 6 years is the earliest period with an effect on adult overweight. Moreover, the effect of this period is more substantial than the effects we found for other periods. This result indicates that the age interval 2-6 years is especially important to develop strategies for primary prevention of overweight. Our study shows that two children with identical BMI SDS at age 6y have different risks for becoming overweight depending on their BMI SDS at 2y. Also the correlation with adult overweight rises most during this age period (from 0.36 to 0.63), indicating that the rise in sensitivity and specificity for predicting adult overweight based on childhood BMI SDS in this period is high. Ideally, primary prevention should be realized before the point of high sensitivity and specificity has been reached. For the age interval 10-18y a similar relation between change score and adult overweight is found, although weaker. In contrast during the age interval 6-10y and up to the age of 2 years, change scores are not very predictive for adult overweight.

At first sight, our results deviate from the GOOD study in young male adults. In this study both early and late childhood (defined as 1-4y and 4-10y) were found to be predictors of adult BMI. Their breakpoint was chosen at 4y which is exactly in the middle of the age interval 2-6y. By additional analyses, we found that the age intervals 2-4y and 4-6y are quite similar in terms of their predictive ability. Therefore it might be possible that the predictive value of the early child period in the GOOD study might be mainly explained by the predictive value of the period 2-4 years and the predictive value of the late childhood period mainly by the period 4-6 years.

We found that changes in BMI SDS up to the age of 2 years have hardly any predictive value for adult overweight. The change score in the period 4m-1y differs significantly between adults with and without overweight, but this effect disappears once BMI SDS at 1y is included in the statistical model. Thus, a change score in the age interval from 4 months to 1 year of age seems not to correlate with a higher adult overweight risk at the age of 1 year.
Our study confirms the results from other studies that growth during certain age intervals in childhood are more sensitive in predicting overweight. However the explanation for these ‘critical’ growth periods is still unclear.\textsuperscript{7,11,12,15,24,25} It is possible that changing relations between BMI SDS and fat, lean and bone mass at different ages\textsuperscript{30} and other biological explanations concerning the changing growth velocity of fat tissue play a role.\textsuperscript{16,9,10,13,31} The results of this study did not show that rapid growth during the first years of life is a predictor for adult overweight, which is in contrast to the results from similar studies.\textsuperscript{9,13,15} Possible explanations are a shorter follow-up,\textsuperscript{9} the selection of the study population,\textsuperscript{13,15} or higher statistical power due to a larger study population.\textsuperscript{13} Our conclusion that the age period between 2 and 6 years emerges to be critical for adult (over-)weight confirms other study results, that show a rapid elevation in the deposition of body fat rather than lean tissue mass just before the age of 6 years in children with a related early adiposity rebound (AR).\textsuperscript{32,33} Other studies have also pointed to this crucial age period, with an early AR as a risk for adult overweight.\textsuperscript{3,7,15,18,21} The importance of adolescence for developing adult overweight was also reported in another study,\textsuperscript{10} which showed that changes in BMI SDS during adolescence reflect changes in visceral fat mass, more than in other periods.

The strengths of our study are that it was carried out in a general population, and weight and height were frequently measured between 0 and 14 years according to the protocol used within Youth Health Care. The addition of protocolised measurements of weight and height at adulthood offered the opportunity to study the importance of all subsequent growth periods from birth to adulthood in the prediction of overweight at young adulthood. We also had to deal with limitations. As in most birth cohort studies, there was a substantial loss in the follow-up. Therefore sampling bias might be possible. However, there is no reason to assume that loss to follow up is related to the strength of the relation between BMI changes in childhood and adult BMI. Moreover, no significant differences were found for the baseline characteristics between the participants of the measurements and the other subjects of the original cohort except for gender. Another limitation of our study is that we had to deal with missing data. This problem was solved by applying the broken stick method. The broken stick method results in estimates that are closer to the mean. This implies that any tests of differences will be conservative, and possibly underestimates the effects of BMI changes in periods in which fewer measurements are recorded. Also using BMI SDS
(changes) as a predictor and as an outcome has limitations, although the correlation between BMI SDS and body fat% is reasonable and increases from 0.62 to 0.78 (between the ages of 3.5 and 7 years). Post hoc analyses with waist circumference, a proxy of central fat tissue considered most harmful to health, and with adult obesity as the outcome measure, showed similar results for the period 2-6y. This, strengthens our impression that BMI SDS change, especially in the period 2-6y, has a strong relationship with bodyfat% over the years. More fundamental research is needed to study the age dependency of the relation between BMI and several body components.

Our study indicates that the BMI change between 2 and 6 years of age (and, to a lesser degree, the age interval 10-18y) has relatively the largest contribution to adult overweight. It would be interesting to study if in younger cohorts, living in an increasingly obesogenic society, the age interval between 2 and 6 years is also more predictive for adult overweight than other age intervals. If replicated in other studies, primary prevention of overweight should be more directed towards upwards centile crossing in the age interval 2-6 years. Especially in children with a normal weight, this may have a large payoff in terms of overweight reduction at adulthood, and the development towards adult overweight might be reversed.

**ACKNOWLEDGEMENTS**

We gratefully thank all participants for their time, the assistants for their contribution in the field work, the laboratory of the Community Hospital in the city of Terneuzen, especially Ruud Muusze, PhD, the Municipal Health Services of Terneuzen (GGD Zeeland) for support and cooperation, and Guus A. de Jonge, PhD, professor emeritus, for laying the foundations of this study in 1977-1986.
REFERENCES


The Terneuzen Birth Cohort

BMI Change between 2 and 6 Years is Most Predictive of Adult Cardiometabolic Risk

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**Chapter 3**

**ABSTRACT**

**Background**
We recently reported the age interval 2-6y being the earliest and most critical for adult overweight. We now aim to determine which age intervals are predictive of cardiometabolic risk at young adulthood.

**Methods and findings**
We analyzed data from 642 18-28 years olds from the Terneuzen Birth Cohort. Individual BMI SDS trajectories were fitted by a piecewise linear model. By multiple regression analyses relationships were assessed between subsequent conditional BMI SDS changes and components of the metabolic syndrome (MetS), skinfold thickness and hsCRP at young adulthood. Results were adjusted for gender and age, and other confounders. Gender was studied as an effect modifier. All BMI SDS changes throughout childhood were related to waist circumference and skinfold thickness. No other significant relationship was found before the age of 2 years, except between the BMI SDS change 0-1y and hsCRP. Fasting blood glucose was not predicted by any BMI SDS change. BMI SDS change 2-6y was strongly related to most outcome variables, especially to waist circumference (ß 0.47, SE 0.02), systolic and diastolic blood pressure (ß 0.20 SE 0.04 and ß 0.19 SE 0.03), and hsCRP (ß 0.16 SE 0.04). The BMI SDS change 10-18y was most strongly related to HDL cholesterol (ß -0.10, SE 0.03), and triglycerides (ß 0.21, SE 0.03). To a lesser degree, the BMI SDS change 6-10y was related to most outcome variables. BMI SDS changes 2-6y and 10-18y were significantly related to MetS: the OR was respectively 3.39 (95%CI 2.33-4.94) and 2.84 (95%CI 1.94-4.15).

**Conclusion**
BMI SDS changes from 2y onwards were related to cardiometabolic risk at young adulthood, the age interval 2-6y being the most predictive. Monitoring and stabilizing the BMI SDS of children as young as 2-6y may not only reverse the progression towards adult overweight, but it may also safeguard cardiometabolic status.
INTRODUCTION

The high prevalence of overweight and obesity in children is worrisome as among others it is related to cardiometabolic risk even at young ages. In childhood, not only the BMI status itself, but particularly the BMI increase, is strongly related to cardiometabolic risk at adulthood. As an increase in BMI SDS implies a more than normal increase in the BMI with age as such, an increase in BMI SDS during childhood might explain the high cardiometabolic risk even in adults with a normal BMI. In the Terneuzen Birth Cohort, we found the age interval from 2 to 6 years to be the earliest and most critical growth period for adult overweight. As overweight reflects total body mass and not only body fat mass, we question whether this age interval is also most predictive of cardiometabolic risk.

Several studies have addressed the relation between BMI increase in childhood and cardiometabolic risk at adulthood. Longitudinal data from birth into adulthood are needed to estimate the relative contribution of subsequent changes in BMI SDS to cardiometabolic risk. Only a few studies have valid longitudinal data to study these relationships. Study results differ with respect to which age interval is most predictive. One study has assessed adolescence to be the only sensitive period for developing visceral fat at adulthood. Others have shown that the BMI increase from 2 years onwards is associated with cardiometabolic risk. Yet another study did not find a critical age interval: the weight increase from birth onwards had an evenly spread influence on adult fat patterns. Height and weight data collected from birth up until young adulthood are at our disposal. We aim to find whether there is a most critical age interval predictive of cardiometabolic risk at young adulthood.

METHODS

Ethics statement
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 the participants.
Population
The Terneuzen Birth Cohort consists of all 2,604 children born between 1977-1986 in the city of Terneuzen, the Netherlands. Data for height and weight from 1,701 subjects as registered according to a standard protocol by the Municipal Health Services were available from birth until adolescence. These subjects were invited to participate in a follow-up study that included a physical examination, blood tests and a questionnaire to collect sociodemographic characteristics and data about cigarette smoking and their mothers’ actual BMI. Of these 1,701 subjects, 577 could not be traced, 362 completely refused to participate, and 120 refused to participate in blood drawing. Therefore the analyses were restricted to the remaining 642 subjects. The males and females in this follow-up study do not differ from the original cohort regarding baseline characteristics, i.e. age, birth weight, BMI SDS at birth, age of the mother, parity, and breastfeeding. The only difference was the difference for gender itself (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\(^{10}\) most comparable to our study population.

Physical examination and blood tests
Physical examinations were performed by two assistants who received standardized training at the Municipal Health Services in Terneuzen (GGD Zeeland). Waist circumference was measured mid-way between the lower side of the lowest rib and the upper side of the pelvis, on bare skin, after a normal expiration, and with muscles relaxed. Blood pressure (BP) was measured twice (with a 5-minute rest interval) on the left upper arm with the Omron 5-1, which is a fully automatic blood pressure monitor. The mean values of systolic blood pressure (SBP) and diastolic blood pressure (DBP) were used as outcomes. Triceps, biceps, subscapular and suprailiacal skinfolds were measured three times to the nearest 0.1 mm with a Holtain skinfold caliper (Holtain Ltd, Crosswell, United Kingdom) on the left side of the body. Skinfold thickness was defined as the sum of the mean values of the three measurements of every skinfold.

Fasting venous blood samples were drawn in the clinical chemistry laboratory of the Community Hospital at Terneuzen. After centrifugation (10 minutes 1500xG), plasma was analyzed with a routine clinical chemical analyzer, Synchron LX20PRO (Beckman Coulter Inc., USA). Glucose, HDL cholesterol, triglycerides and high-sensitivity
C-reactive protein (hsCRP) were measured. Detailed information about the anthropometric measurements and the blood tests is described elsewhere. An external quality control was performed. Metabolic syndrome, a progressive disorder and a useful tool for the long-term risk assessment of cardiometabolic diseases, was defined using the NCEP ATPIII definition.

Based on reported associations between rising BMI SDS and cardiometabolic risk and characteristics of human growth, we divided the age scale a priori into the following intervals: birth-1 year, 1-2 years, 2-6 years, 6-10 years, and 10-18 years. We used narrow age intervals between birth and 2 years because of the rapid changes in the BMI during infancy: during the first year of life the BMI mostly increases and during the second year it decreases. In addition, the BMI at 1 year of age is strongly associated with the BMI at 7 years at age. The age limit at two years was chosen because it has been shown that a rapid weight gain in the first two years of life is associated with adolescent overweight, and that adults with impaired glucose tolerance or diabetes have an accelerated BMI increase from two years onward. The age of 6 years tallies with the approximate age of adiposity rebound and the onset of adrenarche in children. The upper limit in the interval 6-10 years (y) was chosen since most children go into puberty after 10 years of age. The upper limit of 18 years was chosen because it marks the start of adulthood and the cessation of height growth.

Statistical analyses
The average number of BMI data points per subject between 0-18 years is 21. The means (and SD) of the numbers of BMI measurements in the age intervals birth-1y, 1-2y, 2-6y, 6-10y and 10-18y are respectively 12.8 (2.1), 1.8 (0.7), 2.7 (0.9), 1.8 (0.9) and 1.9 (0.7). Individual BMI SDS trajectories were fitted by a piecewise linear model otherwise known as the broken-stick model, which has been described in more detail in a previous manuscript. For each subject, this model approximates the observed BMI SDS trajectory by a series of straight lines that connect to each other at the break ages. The expected value of BMI SDS at a break age is called the status score. The change between the status score at the start and the end of the various age intervals is called the change score. The S Plus 8.0 function bs() was used to perform these analyses. For further analyses we have used the status scores from the multilevel analysis instead of the raw data.
To assess the relative contribution of the respective age intervals, change scores in the age intervals were regressed on the BMI SDS at birth and all previous change scores. When relationships between change scores are nonlinear, quadratic terms of the independent variables were included in these regression calculations. By expressing residuals as BMI SDS changes, uncorrelated independent variables describing BMI SDS changes, *conditional change scores*, were obtained, and regression to the mean was taken into account. Associations between BMI SDS changes in early life and adult outcomes were examined using linear and logistic regression analysis, in which the BMI SDS at birth and subsequent conditional change scores were all included in one model. This implies that if a conditional change score turned out to be a significant predictor of the outcome variable at adulthood, the change score is a significant predictor of the outcome variable, irrespective of the BMI SDS at birth and preceding change scores. Age, gender, exclusive breastfeeding (<90 vs. ≥90 days), cigarette smoking (none vs. ≥1 cigarette a day) of the subject, and parity and BMI of the mother were studied as possible confounders. Effect modification for gender was tested by including the interaction between gender and change scores (at a type 1 error rate of 0.05). Non-linearity was tested by adding quadratic terms of subsequent conditional BMI SDS scores to the models (at a type 1 error rate of 0.05). Standardized regression coefficients were calculated to estimate the impact of a unit standard deviation in the predictor.

The outcome variables were the components of the metabolic syndrome, skinfold thickness and hsCRP value. The age of the subjects varied between 18 and 28 years. The residuals of the blood concentrations and SBP and DBP showed a skewed distribution. These variables were log-transformed so that the distribution is closer to normal. The regression coefficients and outcome variables were standardized so that the effects on different outcomes can be compared quantitatively. Results were adjusted for gender and age. As far as indications existed for confounding by parity, exclusive breastfeeding, smoking behavior, and BMI of the mother (p<0.10), the outcomes were also adjusted for these variables.

For the models with the highest (adjusted) explained variance (i.e. ≥0.25), the effects of the change scores on the levels of the outcome variables at young adulthood were quantified. The change in the levels of these outcomes was calculated for a
BMI Change between 2 and 6 Years is Most Predictive of Adult Cardiometabolic Risk

hypothetical increase in the conditional change score from 0 to 1 SDS for each age interval.

RESULTS

Characteristics of the study population (n=642) and the results of the anthropometric measurements and blood tests are shown in Table 1. Significant differences between adult males and females are found for the levels of waist circumference, skinfold thickness, HDL cholesterol, hsCRP, fasting glucose and systolic blood pressure.

Table 1. Characteristics of the study population (n=642) and the outcomes of the anthropometric measurements and blood tests by gender

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>mean</td>
</tr>
<tr>
<td>age at young adulthood (y)</td>
<td>265</td>
<td>23.10</td>
</tr>
<tr>
<td>BMI at young adulthood (kg/m²)</td>
<td>265</td>
<td>23.06</td>
</tr>
<tr>
<td>BMI mother (kg/m²)</td>
<td>218</td>
<td>24.90</td>
</tr>
<tr>
<td>BMI father (kg/m²)</td>
<td>210</td>
<td>26.05</td>
</tr>
<tr>
<td>waist circumference (cm)*</td>
<td>265</td>
<td>84.31</td>
</tr>
<tr>
<td>skinfold thickness (mm)*</td>
<td>264</td>
<td>44.85</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)*</td>
<td>265</td>
<td>1.25</td>
</tr>
<tr>
<td>triglycerides (mmol/L)</td>
<td>265</td>
<td>0.95</td>
</tr>
<tr>
<td>hsCRP (mg/L)*</td>
<td>264</td>
<td>2.42</td>
</tr>
<tr>
<td>fasting glucose (mmol/L)*</td>
<td>265</td>
<td>5.23</td>
</tr>
<tr>
<td>systolic blood pressure (mmHg)*</td>
<td>265</td>
<td>135.01</td>
</tr>
<tr>
<td>diastolic blood pressure (mmHg)</td>
<td>265</td>
<td>76.05</td>
</tr>
<tr>
<td>parity (% firstborn)</td>
<td>265</td>
<td>58.1</td>
</tr>
<tr>
<td>breastfeeding (≥90 days)</td>
<td>265</td>
<td>24.9</td>
</tr>
<tr>
<td>smoking behaviour</td>
<td>265</td>
<td>24.2</td>
</tr>
<tr>
<td>metabolic syndrome</td>
<td>265</td>
<td>6.4</td>
</tr>
</tbody>
</table>

* statistically significant difference between males and females (p<0.05)
birth and the conditional change scores were modeled as independent variables. No evidence was found for confounding by exclusive breastfeeding and smoking behavior of the subject, or parity and BMI of the mother, so these variables were not included in the final models. The quadratic term of the conditional change score did not appear to be significantly related to the outcome variables ($p>0.05$) for any of the age intervals.

The explained variance is highest for the outcomes of the two anthropometric measurements, waist circumference and skinfold thickness, followed by systolic blood pressure and the hsCRP level. All conditional change scores from birth onwards show a significant relationship with waist circumference and skinfold thickness at young adulthood. The conditional change score 2-6y is the only significant predictor for all outcome variables, with the exception for fasting glucose for which no significant relation was found for any age interval. Moreover, the conditional change score 2-6y is most predictive of the outcome variables, with the exception for triglycerides and HDL cholesterol. It is noteworthy that the regression coefficient of 6-10y was positive for HDL cholesterol, whereas for other age intervals, the regression coefficient was negative. Apart from the anthropometric outcomes the only other outcome that was predicted by a BMI increase before the age of 2 years was hsCRP, i.e. by change score 0-1y. The odds ratios of MetS at young adulthood are also shown. Significant odds ratios were found for the conditional change scores 2-6y and 10-18y. The age interval 2-6y and after that 10-18y are most strongly related to the prevalence of MetS (OR was 3.39 and 2.84 respectively).

Figure 1 shows associations between the conditional change score from 0 to +1 SDS for the respective age intervals for the models with the highest adjusted explained variance (>0.25) and the actual changes in the values of the outcome variables. The change in these outcome variables is highest for the age interval 2-6y. This figure also shows differences between males and females.
Table 2. Health outcomes at young adulthood by multiple and logistic regression analyses in models including BMI SDS at birth and the conditional change scores.

<table>
<thead>
<tr>
<th>Outcome variables (in SDS)</th>
<th>Standardized regression coefficients and 95% CI</th>
<th>Odds ratios and 95%CI</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>BMI SDS at birth</td>
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<tr>
<td></td>
<td>change score birth - 1y B</td>
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<tr>
<td></td>
<td>change score 1-2y B</td>
<td></td>
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<tr>
<td></td>
<td>change score 2-6y B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>change score 6-10y B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>change score 10-18y B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adj R²</td>
<td></td>
</tr>
<tr>
<td>waist circumference</td>
<td>0.10 0.04- 0.16**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.24 0.18- 0.30**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.12 0.08- 0.16**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.47 0.43- 0.51**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.23 0.17- 0.29**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.36 0.32- 0.40**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>skinfold thickness</td>
<td>0.07 0.01- 0.13**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.20 0.14- 0.26**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.09 0.03- 0.15**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.38 0.32- 0.44**</td>
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</tr>
<tr>
<td></td>
<td>0.24 0.18- 0.30**</td>
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<tr>
<td></td>
<td>0.33 0.29- 0.37**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.56</td>
<td></td>
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<tr>
<td>systolic blood pressure^A</td>
<td>0.02 -0.04- 0.08</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.01 -0.05- 0.07</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.00 -0.06- 0.06</td>
<td></td>
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<tr>
<td></td>
<td>0.19 0.13- 0.25**</td>
<td></td>
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<tr>
<td></td>
<td>0.11 0.05- 0.17**</td>
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<tr>
<td></td>
<td>0.11 0.05- 0.17**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.11 0.05- 0.17**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>diastolic blood pressure^A</td>
<td>0.02 -0.06- 0.10</td>
<td></td>
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<tr>
<td></td>
<td>0.04 -0.04- 0.12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.01 -0.07- 0.09</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.20 0.12- 0.28**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.10 0.02- 0.18*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.04 -0.02- 0.10</td>
<td></td>
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<tr>
<td></td>
<td>0.06</td>
<td></td>
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<tr>
<td>HDL cholesterol^A</td>
<td>-0.01 -0.09- 0.07</td>
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<td></td>
<td>-0.07 -0.15- 0.01</td>
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<td></td>
<td>-0.05 -0.13- 0.03</td>
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<tr>
<td></td>
<td>-0.08 -0.16- 0.00*</td>
<td></td>
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<tr>
<td></td>
<td>0.09 0.01- 0.17*</td>
<td></td>
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<tr>
<td></td>
<td>-0.10 -0.16- -0.04**</td>
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<tr>
<td></td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.10- 0.16- 0.00*</td>
<td></td>
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<tr>
<td></td>
<td>0.11 0.05- 0.17**</td>
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</tr>
<tr>
<td></td>
<td>0.11 0.05- 0.17**</td>
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<tr>
<td></td>
<td>0.11 0.05- 0.17**</td>
<td></td>
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<tr>
<td></td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>triglycerides^A</td>
<td>0.00 -0.08- 0.08</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.00 -0.08- 0.08</td>
<td></td>
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<tr>
<td></td>
<td>-0.06 -0.14- 0.02</td>
<td></td>
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<tr>
<td></td>
<td>0.18 0.10- 0.26**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.08 0.00- 0.16*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.21 0.15- 0.27**</td>
<td></td>
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<tr>
<td></td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>fasting glucose^A</td>
<td>-0.03 -0.11- 0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.02 -0.06- 0.10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-0.06 -0.14- 0.02</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.06 -0.02- 0.14</td>
<td></td>
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<tr>
<td></td>
<td>0.00 -0.08- 0.08</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.05 -0.01- 0.11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>hsCRP^A</td>
<td>-0.04 -0.12- 0.04</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.10 0.02- 0.18*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.02 -0.06- 0.10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.16 0.08- 0.24**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.09 0.01- 0.17*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.15 0.09- 0.21**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.27</td>
<td></td>
</tr>
</tbody>
</table>

All analyses are adjusted for age and gender. *p<0.05, **p<0.01 (statistically significant relations are printed in bold; p<0.05). ^ Log transformed variables ^ The independent variables between birth and 18y are conditional measures. i.e., they are regressed on the BMI SDS at birth and previous change scores, so the BMI SDS changes are uncorrelated. The formula to obtain the conditional change scores is X_res_n = Y - α - β Z_0 - γ(n-(n-1)) X_res (n-(n-1)) - γ(n-(n-2)) X_res (n-(n-2)) - … - γ(n-1) X_res (n-1), where Z_0 equals BMI SDS at birth, X_res n conditional change scores, and Y the outcome variable. If statistically significant the quadratic term of X_res n was added to the formula.
Figure 1. Association between the conditional change score from 0 to +1 SDS for the respective age intervals and the actual change (+/- 1 SE) of outcome variables at adulthood of a) waist circumference (cm), b) skinfold thickness (mm), c) systolic blood pressure (mm Hg) and d) hsCRP (mG/L) at 23y (males: black squares, females: white circles)

DISCUSSION

Our aim was to assess the relationship of change scores during childhood (BMI SDS changes) with cardiometabolic risk at young adulthood. All BMI changes, including those before the age of 2 years, were significantly related with waist circumference and skinfold thickness at adult age. However, the association between BMI changes and other cardiometabolic risk factors at adulthood, except for hsCRP, only became
apparent from the age of 2y onwards. The change scores 2-6y and 10-18y were most predictive of the outcome variables (Table 2). An unexpected finding was that the relationship between the change score 6-10y and HDL cholesterol at young adulthood was positive ($p=0.004$). The change scores 2-6y and 10-18y were associated with high risk for metabolic syndrome, with the change score 2-6y having the highest odds-ratio (3.39, 95%CI 2.33-4.94).

Our results are highly similar to the findings of the New Delhi Birth Cohort, even though the studied populations differ to a great extent with respect to ethnicity and welfare. In both cohorts the BMI changes from 2 years onwards are associated with cardiometabolic risk. Due to the chosen study design, we were able to distinguish the impact of relatively small age intervals.

For the first two years of life, the available evidence to date points in different directions. We found, in line with the New Delhi Birth Cohort, the BMI SDS increase between birth and the age of 2 years to be related only to waist circumference and skinfold thickness at young adulthood, whereas for all other identical outcomes in both cohort studies no significant relationships were found. In addition, we found that the BMI SDS increase between birth and 1y is also related to hsCRP, a strong predictor of cardiometabolic risk, which was not included in the Delhi Birth Cohort study. This would suggest that the hsCRP is more sensitive to BMI SDS increase between 0-1y than other studied outcomes. Generally, the age interval 1-2y showed even weaker associations than the age interval 0-1y. What happens during the age interval 1-2y seems to have very little effect on later cardiometabolic risk. We have no clear explanation for this finding. The way the fat mass expands at different ages during childhood, either by increasing the number of adipocytes or by increasing fat cell volume, and/or the development of motor skills, may play a role.

Another study found that the age interval 1 to 5 years predicts systolic blood pressure whereas before 1 year of age no relationship was found. This finding also seems in line with our results as the age intervals 1-5y and 2-6y largely overlap. In contrast, some other studies have found a significant relationship of growth before the age of one or two years with blood pressure, HDL cholesterol or triglycerides. These different findings might be due to specific characteristics of the populations studied, such as small for gestational age at birth or short stature at adulthood.
research, addressing the relationships between population characteristics, such as prematurity and dysmaturity, and growth parameters during the first two years of life, might clarify the differences between some of these study results.

The positive regression weight between the change score 6-10y and HDL level at young adulthood ($p=0.004$) is not in accordance with the expected negative regression weights of all other age intervals. An explanation for this finding might be the supposedly protective effect of subcutaneous fat against cardiometabolic risk, which during late childhood contributes more to the BMI increase than visceral fat. Further research is needed to investigate this hypothesis. The protective effect of subcutaneous fat might also partly explain that the association between the BMI SDS change in this age interval and the outcome variables is generally weaker than in the age intervals 2-6y and 10-18y.

As shown in Figure 1, an increase in the conditional change scores from 0 to +1 BMI SDS is associated with substantial increases in waist circumference, skinfold thickness, systolic blood pressure and hsCRP at young adulthood. Consistent with other studies, the levels of waist circumference, skinfold thickness, systolic blood pressure and hsCRP for males and females differ (Table 1). As no significant interaction between change scores and gender has been found, the different increases for males and females are due to the different levels for waist circumference, skinfold thickness, systolic blood pressure and hsCRP for males and females. In relative terms, the found increases in these outcome variables are approximately the same for both sexes.

Our study has some limitations. The age intervals were chosen on substantive grounds. However, it is noteworthy that this choice might have influenced the study results. By combining subsequent age intervals, the relationship with the outcome variable will be an average of the relationships of these age intervals. Also, increasing the width of an age interval generally increases the chance that a significant relationship will be found and vice versa. As in most birth cohorts, there was a loss to follow-up. However, selection bias is very unlikely. First, the males and females who participated were representative with regard to the baseline characteristics of the original cohort, and second, for this within-sample analysis, there is no reason to assume that a difference
exists between those included and not included in the study with regard to the relationships of the changes in BMI status at childhood with the studied outcomes at adulthood. The strength of our study is that it is population-based, with an average of 21 measurements between birth and young adulthood. Also, all height and weight measurements throughout childhood were recorded prospectively and the measurements in adulthood have been performed according to a protocol by specially trained personnel.

Notwithstanding the fact that several findings in our study are reason for further research or give rise to new hypotheses, our study shows that BMI SDS changes from 2 to 18 years are related to increased cardiometabolic risk at young adulthood, the age interval 2-6y being the most predictive. Along with the highest odds ratio on MetS for this age interval, our findings suggest that preventing BMI SDS increase during this age interval has the potential to prevent cardiometabolic disease at adulthood. Monitoring and stabilizing the BMI SDS of children as young as 2-6y may not only reverse the development towards adult overweight, it may also safeguard cardiometabolic status.

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Identifying Young Children without Overweight at High Risk for Adult Overweight
The Terneuzen Birth Cohort

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Jacobus P. Van Wouwe ³
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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, especially if obesity develops during childhood and is sustained into adulthood. 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. The increasing prevalences of overweight and the significantly increased risk for adult overweight in overweight children 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.

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. Because overweight at the age of 6y often translates into overweight in adulthood, 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. In a previous study we have shown that the age interval 2-6y is very sensitive in predicting overweight. 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. ¹ 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,²⁰ because these are most comparable to our study population. The criterion for being overweight in young adulthood is defined as BMI ≥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' model²¹ 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., the LMS parameters of the Dutch reference standard of BMI (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</th>
<th></th>
<th></th>
<th>Girls</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\mu$</td>
<td>$\Sigma$</td>
<td>$\lambda$</td>
<td>$\mu$</td>
<td>$\sigma$</td>
<td>$\lambda$</td>
</tr>
<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 $\text{logit}(P_O) = \alpha + \beta_{\text{age}}A + \beta_aZ_a + \beta_yZ_y$, where $P_O$ stands for probability of adult overweight, $\beta_{\text{age}}$ is the regression coefficient of the variable A, A equals the variable age minus 23, $\beta_a$ and $\beta_y$ are the regression coefficients and $Z_a$ and $Z_y$ 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></th>
<th>Girls</th>
<th></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>
<td>$\beta_4$</td>
<td>$\beta_6$</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>
<td>2.90</td>
<td>--</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>
<td>--</td>
<td>4.78</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>
<td>-0.73</td>
<td>2.52</td>
</tr>
</tbody>
</table>

At the age of 23 years, A=0, so $\text{logit}(P_O) = \alpha + \beta_aZ_a + \beta_yZ_y$. 

Table 3. Parameters of three risk models $\text{logit}(P_O) = \alpha + \beta_{\text{age}}A + \beta_aZ_a + \beta_yZ_y$, where $P_O$ stands for probability of adult overweight, $\beta_{\text{age}}$ is the regression coefficient of the variable A, A equals the variable age minus 23, $\beta_a$ and $\beta_y$ are the regression coefficients and $Z_a$ and $Z_y$ stand for BMI SDS at ages 2y and 4y, 2y and 6y, and 4y and 6y, respectively.
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 ($P_O < 0.1$). In YHC practice, it is useful to set a cut-off value $\pi$ on AO risk such that all children with $P_O \geq \pi$ are eligible for intervention. A nice property of such a rule is that the positive predictive value (PPV) of the group of children $P_O = \pi$ is equal to $\pi$. Thus if we set $\pi = 0.5$ and refer those with $P_O \geq \pi$, 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>25%</th>
<th>50%</th>
<th>75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPV of model</td>
<td>2y4y</td>
<td>0.49</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td>4y6y</td>
<td>0.54</td>
<td>0.66</td>
</tr>
<tr>
<td></td>
<td>2y6y</td>
<td>0.52</td>
<td>0.67</td>
</tr>
<tr>
<td>Sensitivity of model</td>
<td>2y4y</td>
<td>0.75</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>4y6y</td>
<td>0.76</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>2y6y</td>
<td>0.76</td>
<td>0.36</td>
</tr>
<tr>
<td>Specificity of model</td>
<td>2y4y</td>
<td>0.71</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>4y6y</td>
<td>0.76</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>2y6y</td>
<td>0.74</td>
<td>0.93</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.

*Cutt-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 $\geq 25$) 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.

ACKNOWLEDGEMENTS

This study received a grant from the Health Research and Development Council of the Netherlands (ZONMw Grants no. 2100.0092). The researchers are not dependent on the funder. We gratefully thank all participants for their time and efforts, the assistants for their contribution to the research, the Municipal Health Services of Terneuzen (GGD Zeeland) for their support and cooperation, and Guus A. de Jonge, PhD, professor emeritus, for laying the foundations of this study in 1977-1986.
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 \( Y_t \geq 25 \text{ kg/m}^2 \), where \( t \geq 18 \text{ y} \). \( Z_{18+} \) 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 \( \text{bs()} \) to code the data into the appropriate form, and used the function \( \text{lme()} \) 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 \( Y_2 = 12.3/0.9^2 = 15.18 \text{ kg/m}^2 \). 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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Identifying Metabolic Syndrome without Blood Tests in Young Adults
The Terneuzen Birth Cohort

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ABSTRACT

Background
Within the context of the obesity epidemic identifying young adults at risk for type 2 diabetes and cardiovascular disease is important. A practical approach is based on the identification of metabolic syndrome (MetS). Our objective was to develop a simple and efficient stepwise strategy to identify MetS in young adults.

Methods
Subjects were part of a birth cohort (n=2,599) in Terneuzen, the Netherlands, born in 1977-1986. In 2004-2005: 642 of these young adults participated in a physical examination and blood tests. Tree regression was used to determine the optimal decision strategy to identify MetS.

Results
Overall prevalence of MetS, defined according to the NCEP ATPIII, was 7.5%. The tree regression yielded an optimal stepwise strategy that eliminated the need for blood tests for the diagnosis of MetS in 50-90% of the cases, depending on the accepted level of error. A large group (52% of the total) with BMI <35 had a normal waist circumference (WC) and normal blood pressure (BP). None of them had MetS. Subjects with BMI ≥35 all had MetS. If BMI <30, 38% had an increased WC or increased BP with a risk of MetS of only 6%. So for them the omission of blood tests could also be considered.

Conclusion
In most young adults MetS can be identified or excluded without blood tests by a simple and stepwise strategy, based on the measurement of BMI, WC and BP. This makes it possible to develop simple prevention strategies for young adults at risk for type 2 diabetes and cardiovascular disease.
INTRODUCTION

The dramatic increase in the prevalence of obesity\(^1\text{--}^4\) results in an increase in adverse levels of insulin and lipids, high blood pressure and type 2 diabetes, also in young adults.\(^5\) Consequently, vascular damage will also occur in younger age-groups.\(^6\text{--}^7\) It is even anticipated that in the future more people will die from the complications of overnutrition than from starvation.\(^5\text{--}^7\) For the development of prevention strategies early detection of persons who are at high risk for these complications of overweight and obesity is a prerequisite. MetS, is a cluster of risk factors for type 2 diabetes and cardiovascular disease.\(^8\text{--}^12\) It is not sure that MetS as a cluster is better than its components in the prediction of cardiovascular disease. Besides, every component of MetS, in itself, merits specific attention and should be dealt with. However, it is also clear that the combined occurrence of these risk factors is associated with a high risk of the development of diabetes and cardiovascular disease, and - moreover - happens more often than could be expected on the basis of chance.\(^13\text{--}^14\) This makes identification of MetS a practical approach and a useful tool to identify people who are at high risk. According to most definitions, MetS is based on concentrations of triglycerides, cholesterol, HDL-cholesterol and glucose. The blood tests that are necessary for the identification of MetS are an invasive and costly procedure. The objective of this study was to develop an efficient and simple stepwise strategy to identify MetS in young adults, based on data from the population-based Terneuzen Prevention Study. (Table 1).

METHODS

Design and study population

The Terneuzen Birth Cohort consists of all 2,599 children who were born between 1977 and 1986 in the city of Terneuzen. In 2004-2005, a total of 2,022 persons from the original cohort could be traced, and were invited to participate in a follow-up study. The follow-up study included measurements of weight, height, blood pressure (BP), and waist circumference (WC). Data on baseline characteristics were obtained from questionnaires. Information about cigarette smoking was also gathered because smoking is an important short and long term risk factor, that might cause dislipidemie, high triglycerides and low HDL cholesterol. The participants were also asked to
undergo a vena puncture, following a fast of at least 12 hours. 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. Of the 2,022 subjects who were invited, 920 (45%) responded, 158 of whom did not participate for logistic reasons. Of the remaining 762 participants, 642 had a vena puncture, and the analyses presented here apply to these cases. No differences from the original cohort were found with regard to mean age, the age of the mother at birth, birth weight or parity. However, there was a significant gender difference: the percentage men in the original cohort was higher than in our study population.

Table 1. Adult Treatment Panel III definition of metabolic syndrome: at least three out of five criteria.  

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Cut-off points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Central obesity</td>
<td>Waist circumference</td>
</tr>
<tr>
<td></td>
<td>Men: &gt;102 cm</td>
</tr>
<tr>
<td></td>
<td>Women: &gt;88 cm</td>
</tr>
<tr>
<td>2. Elevated triglycerides</td>
<td>Triglycerides</td>
</tr>
<tr>
<td></td>
<td>≥1.7 mmol/l</td>
</tr>
<tr>
<td>3. Reduced HDL-cholesterol</td>
<td>HDL-cholesterol</td>
</tr>
<tr>
<td></td>
<td>Men: &lt;1.0 mmol/l</td>
</tr>
<tr>
<td></td>
<td>Women: &lt;1.3 mmol/l</td>
</tr>
<tr>
<td>4. Raised blood pressure</td>
<td>Systolic</td>
</tr>
<tr>
<td></td>
<td>≥130 mmHg</td>
</tr>
<tr>
<td>5. Elevated fasting plasma glucose</td>
<td>Fasting plasma glucose</td>
</tr>
<tr>
<td></td>
<td>≥5.6 mmol/l</td>
</tr>
</tbody>
</table>

Physical examination and blood tests
The physical examinations were performed by two assistants who received standardized training at the Municipal Health Service in Terneuzen (GGD Zeeland). Weight was measured, with the subject in underwear, to the nearest 0.1 kg on an electronic self-zeroing scale. Standing height was measured to the nearest 0.1 cm with the aid of a stadiometer. WC was measured mid-way between the lower side of the lowest rib and the upper side of the pelvis, on bare skin, after a normal expiration, and
with muscles relaxed. BP was measured twice (with a 5 minute rest interval) on the left upper arm with the Omron 5-1, which is a fully automatic blood pressure monitor. The mean values were used as outcomes. Fasting venous blood samples were drawn in the clinical chemistry laboratory of the Community Hospital in Terneuzen. After centrifugation (10 minutes 1500xG), plasma was analyzed with a routine clinical chemical analyser, Synchron LX20PRO (Beckman Coulter Inc, USA). The parameters that were measured were glucose, cholesterol, HDL cholesterol, and triglycerides. External quality control was performed.\textsuperscript{15-17}

\textit{Statistical analysis}

The characteristics of the participants were summarized by means, standard deviations and percentages, sub-divided into three Body Mass Index (BMI=weight/height\(^2\)) categories. Age and gender-specific international BMI criteria for overweight and obesity were applied for the 17 years-olds, and adult cut-off points for all older participants.\textsuperscript{18} Differences in baseline characteristics and the prevalence of (components of) MetS between weight groups were assessed with \emph{t}-tests, ANOVA and \(\chi^2\) tests. Linear regression analysis was performed to study the relationships between variables, and the correlation between smoking and the components of MetS were tested with \(\chi^2\) tests, ANOVA and logistic regression analyses. Analyes were performed with SPSS statistical software, version 14.0 for Windows (SPSS Inc. Chicago ILL).

Tree regression analyses were performed with the S-PLUS 7 tree( ) function. Given a set of predictors, this method searches for the cut-off point on any of the predictor that will optimally discriminate MetS from non-MetS. Subsequently, the sample is split into two parts, and the process is repeated for each part. The process is repeated again until no further useful splits can be made. The result is a binary tree.\textsuperscript{19-20} BMI, WC, BP and the biochemical measurements were used as predictors. The binary tree was pruned and adapted in such a way that easily measured variables (BMI, WC, BP) were located at the top of the tree.
RESULTS

The mean age of the 642 participants was 23.1 years (23.2 for men and 23.0 for women), 68.5% were of normal weight, 21.2% were overweight (not obese), and 5.6% were obese. No differences in baseline characteristics were found between these three groups. The percentages of MetS components were substantially higher in overweight and obese subjects (Table 2). Significant linear associations were found between BMI and all MetS components ($p<0.001$). The overall prevalence of MetS in this group of young adults was 7.5%. In those with normal weight, overweight (not obese) and obesity, the percentage was respectively 1.7%, 16.2% and 50.0%. The percentage of smokers was respectively 29.7, 30.5, and 44.8% (Table 2).

When comparing the baseline characteristics of the total study population with those of subjects with MetS, it appeared that MetS more often occurred between 23 and 28 years of age than between 18 and 22 years of age (OR 1.27, 95%CI 1.09-1.45). The prevalence of MetS appeared to be higher in smokers than in non-smokers (9.2 vs 5.6%), but this difference was not statistically significant. Logistic regression showed a significant relation between smoking and triglycerides and HDL cholesterol, independent of BMI and gender. The frequencies of all components of MetS were higher in subjects with MetS than in subjects with no MetS, especially reduced HDL-cholesterol (70.8%) central obesity (77.1%) and elevated BP (87.5%) (Table 3).

Several binary regression trees were calculated. Figure 1 presents the final model, in which several branches have been combined into one branch to reduce complexity. The tree analysis showed that the most efficient categorization of BMI was very close to the usual discretization of BMI in obesity versus no obesity, but differed from the usual categories of BMI in normal weight, overweight and obesity (Table 2). If BMI <30, refining the BMI-categories was of no additional value in estimating the risk of MetS. However if the BMI $\geq30$ estimates improved by dividing this category in two categories.
Table 2. Subject characteristics, and (components of) metabolic syndrome related to BMI groups (n=642)

<table>
<thead>
<tr>
<th></th>
<th>Normal weight BMI &lt; 25</th>
<th>Overweight 25 ≤ BMI &lt; 30</th>
<th>Obesity BMI ≥ 30</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Count (%)</td>
<td>470 (68.5)</td>
<td>136 (21.2)</td>
<td>36 (5.6)</td>
<td>642 (100)</td>
</tr>
</tbody>
</table>

**Subject Characteristics**

- Age (years) mean (SD) † 22.8 (2.9) 23.7 (2.7) 24.4 (2.9) 23.1 (2.9)
- Gender, men in % (n) † 42.6 (200) 40.4 (55) 30.6 (11) 41.4 (266)
- BMI: mean (SD) ‡ 21.6 (2.0) 26.9 (1.3) 33.2 (3.0) 23.4 (3.7)
- Smoking cigarettes, in %**,† 29.7 30.5% 44.8% 30.6%
- Level of education % (n) † 441 129 34 604 *
  - low, in % (n) † 18.1 (80) 24.8 (32) 23.5 (8) 19.9 (120)
  - medium, in % (n) † 60.1 (265) 54.3 (70) 58.8 (20) 58.8 (355)
  - high, in % (n) † 21.8 (96) 20.9 (27) 17.6 (6) 21.4 (129)

**(Components of) MetS in %**

- Central obesity ‡ 1.1 30.9 86.1 12.1
- High blood pressure § 39.4 48.5 63.9 42.7
- Low HDL-cholesterol ‡ 24.9 36.0 58.3 29.1
- High triglycerides ‡ 5.1 14.0 19.4 7.8
- High fasting plasma glucose §§ 9.8 14.7 25.0 11.7
- Metabolic syndrome ‡ 1.7 16.2 50.0 7.5

* Persons with underweight (BMI < 18.50; n=30) are included in the normal weight category: no statistical differences concerning subject characteristics and MetS (components) were found between underweight and normal weight persons, † no statistical significance, ‡ p<0.001, § p=0.005, §§ p=0.011, * missing data for n=38, ** missing data for n=57

Figure 1 shows the following:

- In participants with BMI ≥35, the risk of MetS is 100%.
- In participants with BMI ≥30 and BMI <35, the overall risk is 35.7%. The risk greatly depends on WC and BP. When both are elevated the risk is 64.3%,
when only one is elevated the risk is 8.3%, but when neither are elevated the risk is zero.

- With a BMI <30, the overall risk is 5.0%. If both WC and BP were elevated the risk is 66.7%, if only one of these is elevated it is 5.6%, but if neither are elevated the risk is zero.

Note that: 1) 48 out of 642 participants were definitely classified as having MetS, 2) 334 out of 642 participants were definitely classified as not having MetS, and 3) 250 out of 642 participants could be classified as not having MetS with an error rate of 5.6%. If we are prepared to accept this error, then 583 out of 642 (90%) can be classified with a tiny error without the need for a blood sample.

Table 3. Subject characteristics and components of metabolic syndrome in subjects with MetS compared to subjects with no MetS (in %).

<table>
<thead>
<tr>
<th>Subject Characteristics</th>
<th>MetS (n=48)</th>
<th>No MetS (n=594)</th>
<th>All participants* (n=642)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs) mean (SD)†</td>
<td>24.0 (2.8)</td>
<td>23.0 (2.9)</td>
<td>23.1 (2.9)</td>
</tr>
<tr>
<td>Gender (men %)*</td>
<td>35.4</td>
<td>41.9</td>
<td>41.4</td>
</tr>
<tr>
<td>BMI category (%)‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal weight (in %)</td>
<td>16.7</td>
<td>77.8</td>
<td>73.2</td>
</tr>
<tr>
<td>Overweight (in %)</td>
<td>45.8</td>
<td>19.2</td>
<td>21.2</td>
</tr>
<tr>
<td>Obesity (in %)</td>
<td>37.5</td>
<td>3.0</td>
<td>5.6</td>
</tr>
<tr>
<td>Smoking, (%)†</td>
<td>39.6</td>
<td>26.9</td>
<td>27.9</td>
</tr>
<tr>
<td>Level of education (%)†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>34.1</td>
<td>18.8</td>
<td>19.9</td>
</tr>
<tr>
<td>Medium</td>
<td>47.7</td>
<td>59.6</td>
<td>58.3</td>
</tr>
<tr>
<td>High</td>
<td>18.2</td>
<td>21.6</td>
<td>21.4</td>
</tr>
<tr>
<td>Central obesity‡</td>
<td>77.1</td>
<td>6.9</td>
<td>12.1</td>
</tr>
<tr>
<td>High triglycerides‡</td>
<td>45.8</td>
<td>4.7</td>
<td>7.8</td>
</tr>
<tr>
<td>Low HDL-cholesterol‡</td>
<td>70.8</td>
<td>25.8</td>
<td>29.1</td>
</tr>
<tr>
<td>High blood pressure‡</td>
<td>87.5</td>
<td>39.1</td>
<td>42.7</td>
</tr>
<tr>
<td>High fasting plasma glucose‡</td>
<td>43.8</td>
<td>9.1</td>
<td>11.7</td>
</tr>
</tbody>
</table>

† p < 0.05, ‡ p < 0.001, * not statistically significant
Figure 1. Tree model for the risk on MetS in percent (n = number of subjects) and decision to perform lab tests.
DISCUSSION

The results of this observational study shows that with this simple stepwise strategy most young adults with MetS can be identified or excluded by use of BMI, waist circumference and blood pressure without any need for blood tests.

Tree regression analysis showed that MetS is present in all young adults with a BMI \( \geq 35 \). For these young adults no additional blood tests or measurements are needed to identify those who are at high risk of developing type 2 diabetes and/or cardiovascular disease. If BMI <35, BP and WC should be measured. If both are normal, there is no risk of MetS, and blood tests are of no additional value in assessing MetS. If BMI <35, and both WC and BP are elevated, the risk of MetS is high, and additional blood tests should be performed. If only WC or only BP is elevated, the risk of MetS is comparable to the risk in the general population of young adults. In such cases the decision to perform additional diagnostic blood tests might depend on other factors, such as the absolute WC or BP, and smoking habits.

The overall prevalence of MetS in our study sample was 7.5%, which is comparable with the prevalence (5.2-10.3%) of MetS among young adults in Finland.\(^{21}\) However, it was lower than that found in two other Dutch studies among young adults\(^ {1,3} \), in which the age of the subjects was higher than in our study. This is consistent with the finding that the prevalence of the MetS depends on age.\(^ {1} \) The frequencies of (components of) MetS were significantly higher in overweight or obese subjects. The components of MetS that were most frequently found were a high WC, high BP and a low HDL-cholesterol. However, the stepwise method does not require the assessment of HDL-cholesterol in the majority of cases. The frequencies of obesity and a high WC in our study correspond with the frequencies reported in young adults in the Netherlands.\(^ {22,23} \) However, the percentage of young adults with an elevated BP in our study was higher than in other studies.\(^ {23,24} \) This could be the consequence of increased childhood obesity carrying over into adulthood. The prevalences of low HDL-cholesterol and raised triglycerides are similar to those reported in other studies.\(^ {1,21,25} \)

Of the 2,022 subjects who were invited to participate, 642 provided all data. Our sample might therefore be selective. However, we found no statistically significant
differences in any of the known variables of the original cohort, with the exception of gender. We do not expect that this gender difference will influence the findings, because we found no gender differences in the main analysis.

The cut-off points for the different components of MetS according to the NCEP ATP III 2005 definition, are based on samples that are older than our study population. Since the levels of cardiovascular risk factors are associated with age, these cut-off points might under-estimate the number of young adults who are at risk of developing type 2 diabetes and cardiovascular disease.

MetS increases the risk of cardiovascular morbidity and mortality 1.3 to 3 times and triples the risk of diabetes. The prognosis of type 2 diabetes with onset at an earlier age is even worse, causing a decline in quality of life and a shorter life-expectancy. Since MetS was found in over 7% of our sample, there is an urgent need to identify young adults with MetS and to develop prevention and treatment programs for this specific age-group. This is especially important because these youngsters seldom consult medical professionals.

Note that the tree model was based on just one single data set, and is restricted to people under 30 years of age. Because of the risk of data-fitting, we recommend that our results should be validated in other samples. As the prevalence of MetS increases with age, optimal trees for samples of other ages may be potentially quite different. However, the same methodology can be applied to suitable data from other age groups.

Despite the limitations in the study design, our results show great potential for the development of prevention strategies for young adults who are at high risk for type 2 diabetes and cardiovascular disease in the primary health care setting. Also in less frequent combinations, such as a BMI between 30 and 35 and a normal WC and BP (5.6% of the persons with this BMI), the omission of blood tests may have an important impact at population level. A blood test is not a very high risk test, and has a relatively limited burden at individual level. But, from a public health point of view, the burden is of much more concern. With regard to the rapid increase in the prevalence of overweight and obesity, the medical burden, the costs and time investments are enormous. Additional information on WC and BP, especially in those
with a BMI <30 will result in the need for fewer blood tests. The public health focus is on the management of excess weight, and not primarily on blood tests for lipid profiling. Lifestyle modification may be sufficient to prevent disease progression. Serological tests for lipid profiling are often not needed to assess or exclude MetS. However, for high risk groups the decision to request blood tests will also depend on therapeutic considerations, certainly if lifestyle modification does not succeed or does not produce the required result (Figure 1).

By following simple, stepwise methods in the diagnosis of MetS tremendous savings could be made in terms of laboratory and consultancy costs. Depending on the accepted level of error, between 50% and 90% of blood tests are superfluous for the diagnosis of MetS. Because there is a need for identifying young adults who are at risk for type 2 diabetes and cardiovascular disease, cost-effective prevention and effective treatment programs must be developed. Because of the prevalence and the risk of smoking, this is a very important lifestyle factor that should be dealt with in young people, especially in those with even more risk factors related to overweight. Youngsters who smoke and are diagnosed with MetS, should be offered an even more rigorous prevention program that focuses on several lifestyle factors, directed at both smoking and weight reduction. Our results can contribute to the development of more efficient, cheaper, and less invasive ways to assess the presence of MetS in young adults.

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REFERENCES


The Terneuzen Birth Cohort

Metabolic Risk Score (MRS) to Detect Metabolic Syndrome in Young Adults

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Carry M. Renders 3
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The Terneuzen Birth Cohort. Metabolic Risk Score (MRS) to detect metabolic syndrome in young adults. Submitted.

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ABSTRACT

Objective
To develop a Metabolic Risk Score (MRS), based on simple questions, to detect young adults with metabolic syndrome (MetS) from the general population.

Design and Methods
This cross-sectional study is based on the data of 642 young adults from the Terneuzen Birth Cohort, born between 1977-1986. At young adulthood data were obtained by postal questionnaires, anthropometric measurements and blood tests. Candidate predictors of MetS (NCEP ATPIII) were age, mother's age at delivery, participant's and parents' BMI, being first-born, smoking, having breakfast, drinking of sweet beverages, consumption of snacks, watching television, and participation in physical sports. We determined the final risk model by backward multiple logistic regression. Its performance was studied by discrimination, the explained variance and the area under the curve. Internal validation was performed by bootstrapping procedures. The regression coefficients were transformed into risk scores.

Results
The final diagnostic model to detect MetS in young adults includes BMI, having breakfast, smoking behaviour, participation in physical sports, and being firstborn. This model has high performance. After internal validation the AUC was 0.89, with Nagelkerke R2 0.40. The sum of the risk scores, the Metabolic Risk Score (MRS), can be used as a risk estimation instrument in general practice. At the cut-off MRS=25 the sensitivity, specificity, PPV and NPV were 0.88, 0.73, 0.21 and 0.99, respectively, implying that those without MetS who are invited for medical evaluation are a quarter of the total population.

Conclusions
The MRS is highly discriminatory in detecting young adults with MetS in a general population, even those with a normal BMI. At the cut-off MRS=25 in 1 out of the 5 persons who were invited for further diagnostics, MetS is assessed. This seems reasonable for the use of the risk score as a first detection instrument in the general population of young adults.
INTRODUCTION

In recent decades a tremendous rise in the prevalence of type 2 diabetes and cardiovascular diseases has been observed also in young people.\textsuperscript{1-3} The prevalence of metabolic syndrome (MetS) in 20-35 year olds varies from 5 to 10\% even in populations with a relative low prevalence of overweight and obesity.\textsuperscript{4-6} MetS is a progressive disorder often culminating in the development of type 2 diabetes, which further increases the risk of cardiovascular disease.\textsuperscript{7} MetS itself is associated with subclinical atherosclerosis independent of insulin resistance and arterial stiffness,\textsuperscript{8} and triples the risk of cardiovascular disease and all-cause mortality even in the absence of diabetes.\textsuperscript{9}

By lifestyle modification consisting of exercise and/or caloric restriction by persons with MetS, the development of overt type 2 diabetes can be prevented and the lifelong risk of cardiovascular disease will decrease.\textsuperscript{10} Therefore, identifying individuals with MetS and offering them preventive interventions can prevent the more severe sequelae of MetS. A first step in identifying individuals from a general population could be to use a simple and short questionnaire, and aggregate the responses into a risk score. Further medical examination into the presence of MetS is only needed for persons with a high risk score. In this way, it may be possible to achieve a lowered cardiovascular risk profile of the population in a cost-effective way.

The aim of the present study is to develop a risk score using easily obtainable anamnestic data to detect MetS in young adults from the general population, which can be easily applied in settings where many young adults spend their time.
METHODS

Ethics Statement
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.

Design and study population
This design of this study is cross-sectional and is performed within the Terneuzen Birth Cohort, consisting of all 2,604 Caucasian children, born between 1977 and 1986 in the city of Terneuzen, the Netherlands. In 2004-2005, 2,022 persons from the original cohort could be traced and were invited to participate in a follow-up study. Of the participating 762 participants, 642 had a vena puncture, following a fast of at least 12 hours. This has been described in more detail, previously. The analyses presented here apply to these 642 cases. Several data were obtained by postal questionnaires on baseline characteristics, including age, gender, mother's parity, and about known risk factors for overweight and/or cardiometabolic risk. These included smoking behaviour, alcohol consumption, physical activity, dietary habits such as the frequency of having breakfast, the consumption of snacks and sweetened beverages, sedentary behaviour, and height and weight of the young adult and his parents. No differences between the study population and the original cohort were found with regard to mean age, the age of the mother at birth, birth weight or parity. However, there were fewer males in the present study population compared to the original cohort (41% versus 51%).

Physical examination and blood tests
The measurements were performed by two assistants who received standardized training at the Municipal Health Services in Terneuzen (GGD Zeeland). Waist circumference was measured mid-way between the lower side of the lowest rib and the upper side of the pelvis, on bare skin, after a normal expiration, and with muscles relaxed. Blood pressure was measured twice (with a 5-minute rest interval) on the left upper arm with the Omron 5-1, which is a fully automatic blood pressure monitor. The mean values were used as outcomes. Fasting venous blood samples were drawn in the
clinical chemistry laboratory of the Community Hospital in Terneuzen, following a fast of at least 12 hours. After centrifugation (10 minutes 1500xG), plasma was analysed with a routine clinical chemical analyser, Synchron LX20PRO (Beckman Coulter Inc., USA). The parameters that were measured were glucose, cholesterol, HDL cholesterol, and triglycerides. External quality control was performed.26-28

Outcome measure

Metabolic syndrome was defined according to the NCEP ATPIII definition,29 being the most widely-accepted definition,30 which is fulfilled if at least 3 of the following criteria are met: central obesity (waist circumference >102 cm in men and >88 cm in women), high blood pressure (≥130/85 mmHg or documented use of antihypertensive therapy), hypertriglyceridemia (≥1.7 mmol/l), low HDL cholesterol (<1.0 mmol/l in men, and <1.3 mmol/l in women), high fasting glucose (≥5.6 mmol/l).

Candidate predictors

Table 1 displays our list of candidate predictors for MetS. The selection of predictors in this list was based on the following criteria. First, the predictors should be known risk factors for cardiometabolic-related health problems based on the literature.11-25 Second, the predictors should be easy to obtain by simple questions, do not appeal to the memory of the young adult (to avoid recall bias) or knowledge about family history of diabetes or cardiovascular diseases, do not require any new measurements or self-measurements, and are not a strong predictor of any of the other candidate predictors. Based on these criteria the following variables were initially included: age,4 mother’s age at delivery,25 participant’s BMI,4 mother’s BMI,14 father’s BMI,14 parity,25 eating breakfast,16,21 drinking sweet beverages,11 the consumption of snacks,18,22 watching television34 and participation in physical sports.15,17,21 For two possible predictors of overweight and/or cardiometabolic risk, i.e. sedentary behaviour and physical activity, we decided to choose a proxy of these variables. We decided to include ‘television watching’ as candidate predictor, which is one aspect of sedentary behaviour, because information about this variable can be obtained by a simple question. The cut-off at 3 hours of television watching is related to much higher prevalences of overweight in young adults.24 The variable ‘physical activity’ was simplified by the variable ‘physical sports participation’. Also about this variable information can be required by one
simple question. We choose the cut-off value at sporting twice a week, because of the described dose-response relationship between exercise training and blood lipid changes. Although alcohol is also a known cardiometabolic risk factor, we decided not to include this variable as a candidate predictor. Alcohol consumption seems hard to quantify on the basis of one simple question, as the consumption of alcohol varies over time and its severity should not only be based on the mean consumption per time interval but also on the frequency and severity of binge drinking. The risk factor socioeconomic background was not included because the relationship with metabolic syndrome is probably mediated by other, more easily obtainable risk factors, such as BMI and smoking behaviour.

Waist circumference, an important cardiometabolic risk factor, was not included as candidate predictor because this would require the self-measurement of waist circumference. Height and weight, and consequently BMI, was also obtained by measurements from the physical examination. Because our goal was to develop a risk score for the general population based on a simple questionnaire, we initially used BMI as determined by self-report. In addition we have studied the performance of the risk score where we replaced self-reported BMI by measured BMI.

Statistical analyses

Missing data
Most predictors were complete, but some had missing data (up to 31%). We used imputation to fill in variables with missing values by introducing information relating to other complete variables using the Multiple Imputation by Chained Equation procedure. By this method we generated 10 multiply-imputed data sets.

Model building
We applied univariable logistic regression analysis to estimate the effect of each candidate predictor on the probability of having MetS. We introduced interaction terms with gender in the univariable models, but as no such terms had a significant effect, we did not include these interactions in the model. We examined potential nonlinear behaviour of continuous factors with metabolic syndrome by using restricted cubic spline functions and spline plots. Multivariable logistic regression with backward
elimination determined the final model. The variable selection was done by taking into account the multiply-imputed datasets. All variables with a p-value <0.15 were retained in the final model, as a too strict p-value negatively affects the performance of the model. Regression coefficients and standard errors were converted to odds ratios (OR) and their 95% confidence intervals.

Performance of the risk model
We studied the performance of the risk model in terms of discrimination, explained variance and calibration. Discrimination expresses how well the prognostic model is able to distinguish between young adults with and without metabolic syndrome, and was calculated as the area under the Receiver Operating Characteristic (ROC) curve. The explained variance, calculated as Nagelkerke’s $R^2$ gives an indication of how much of the variance in the outcome can be explained by the predictors. We calculated the slope between the predicted and observed probabilities. This calibration slope was used as a shrinkage factor for the regression coefficients in order to account for model optimism in prognostic modelling. We estimated optimism in regression coefficients and performance by bootstrapping. This involved calculating the AUC, the explained variation and the slope on each imputed data set, and then averaged over the 10 imputed data sets.

Derivation of the clinical risk estimation rule
We derived a risk model for MetS in young adults by multiplying the regression estimates by the shrinkage factor. These new coefficients were transformed in easy-to-use risk scores by dividing all regression coefficients by the coefficient related to BMI, so that the BMI coefficient is equal to 1. We evaluated the performance of the resulting risk score in terms of sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV).

Software
Analyses were carried out in SPSS 15.0 and R 2.11.1 software. We used modified versions of the MICE and Design libraries.
RESULTS

Characteristics of the population

Table 1 describes characteristics of the candidate predictors. The mean age of this population is 23.1 years (SD 2.3). The prevalence of MetS is 7.5%. Data were missing for several variables, i.e. the mother's BMI, the father's BMI, the frequency of eating breakfast, consumption of snacks, drinking sweetened beverages and watching television (respectively 16, 22, 6, 5, 6 and 31%).

Univariable analysis

The results of the univariable logistic regression analyses are given in Table 2. The age of the young adult, the BMI of the young adult as well as of the mother and the father, parity, frequency of eating breakfast, and cigarette smoking are significantly related to the presence of MetS at young adulthood ($p<0.05$).

Development of the risk estimation rule

Backward selection with a p-value <0.15 retained the following predictors: the young adult's BMI, frequency of eating breakfast, smoking behaviour, participation in physical sports and being firstborn. The regression coefficient and odds ratios (95% CI) of the final model are given in Table 3. The risk scores, which were assigned in accordance with the shrunken and rescaled regression coefficients, are presented in the last column. The MetS risk score (MRS) of 18-28 year olds is defined as the sum of the risk scores, as outlined in Table 4. The BMI is the basis of the value of the MRS. For example, for a person with a BMI of 25, the MRS can vary between 23 and 29, depending on the other scores.

Performance of the risk estimation rule

The apparent AUC of the risk estimation rule is 0.90 and the explained variation 43%. After internal validation by bootstrapping, the AUC and explained variation remain high with values of 0.89 and 40% respectively. We determined optimism in the regression coefficients by estimating the slope index, i.e. the shrinkage factor, i.e. 0.94.
Table 1. Description of the independent variables and the outcome variable, continuous or categorical, entered into the initial logistic regression model as candidate predictors, n, medium (SD) or frequency (%)

<table>
<thead>
<tr>
<th>independent variables</th>
<th>continuous variables</th>
<th>N</th>
<th>% missings</th>
<th>mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (in years)</td>
<td>642</td>
<td>0</td>
<td>23.11 (2.92)</td>
<td></td>
</tr>
<tr>
<td>age of the mother at delivery (in years)</td>
<td>642</td>
<td>0</td>
<td>26.99 (4.21)</td>
<td></td>
</tr>
<tr>
<td>BMI of the participant (based on height and weight reported by questionnaire)</td>
<td>642</td>
<td>0</td>
<td>23.37 (3.73)</td>
<td></td>
</tr>
<tr>
<td>BMI of the mother (based on height and weight reported by questionnaire)</td>
<td>542</td>
<td>16</td>
<td>25.39 (4.23)</td>
<td></td>
</tr>
<tr>
<td>BMI of the father (based on height and weight reported by questionnaire)</td>
<td>506</td>
<td>22</td>
<td>26.19 (3.03)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>categorical variables</th>
<th>% missings</th>
<th>frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>gender (% males)</td>
<td>642</td>
<td>41.3</td>
</tr>
<tr>
<td>parity (% first-born)</td>
<td>642</td>
<td>60.3</td>
</tr>
<tr>
<td>breakfast (% not daily)</td>
<td>604</td>
<td>6</td>
</tr>
<tr>
<td>consumption of snacks (% at least twice a week)</td>
<td>608</td>
<td>5</td>
</tr>
<tr>
<td>physical sports participation (% less than twice a week)</td>
<td>642</td>
<td>0</td>
</tr>
<tr>
<td>consumption of sugar-sweetened beverages and/or fruit juice (% every day)</td>
<td>605</td>
<td>27</td>
</tr>
<tr>
<td>television watching (% at least 3 hours / day)</td>
<td>472</td>
<td>6</td>
</tr>
<tr>
<td>smoking behaviour (% at least one cigarette/week)</td>
<td>604</td>
<td>6</td>
</tr>
</tbody>
</table>
Table 2. The odds-ratio's (95% CI) of independent variables for metabolic syndrome according to NCEP ATPIII in a univariable logistic regression analysis.

<table>
<thead>
<tr>
<th>continuous independent variables</th>
<th>Unit</th>
<th>Odds ratio for continuous variables per unit increase</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>age participant</td>
<td>Years</td>
<td>1.13</td>
<td>1.02-1.25</td>
</tr>
<tr>
<td>age of mother at birth</td>
<td>Years</td>
<td>1.02</td>
<td>0.95-1.10</td>
</tr>
<tr>
<td>BMI young adult</td>
<td>kg/m$^2$</td>
<td>1.51</td>
<td>1.37-1.66</td>
</tr>
<tr>
<td>BMI mother</td>
<td>kg/m$^2$</td>
<td>1.13</td>
<td>1.06-1.20</td>
</tr>
<tr>
<td>BMI father</td>
<td>kg/m$^2$</td>
<td>1.19</td>
<td>1.07-1.32</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Digitomous independent variables</th>
<th>categories (1 vs 2)</th>
<th>Odds ratio for second versus first category</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>1 males</td>
<td>1.31</td>
<td>0.71-2.41</td>
</tr>
<tr>
<td></td>
<td>2 females</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Firstborn</td>
<td>1 yes</td>
<td>2.08</td>
<td>1.06-4.07</td>
</tr>
<tr>
<td></td>
<td>2 no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breakfast consumption</td>
<td>1 not daily</td>
<td>0.46</td>
<td>0.24-0.89</td>
</tr>
<tr>
<td></td>
<td>2 daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Snacks consumption</td>
<td>1 less than twice a week</td>
<td>0.72</td>
<td>0.33-1.60</td>
</tr>
<tr>
<td></td>
<td>2 at least twice a week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>1 less than one cigarette/week</td>
<td>2.59</td>
<td>1.36 - 4.92</td>
</tr>
<tr>
<td></td>
<td>2 at least 1 cigarette / week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical sports</td>
<td>1 less than twice a week</td>
<td>0.59</td>
<td>0.318-1.083</td>
</tr>
<tr>
<td></td>
<td>2 at least twice a week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sugar-sweetened beverages and fruit juice</td>
<td>1 not every day</td>
<td>1.18</td>
<td>0.616-2.246</td>
</tr>
<tr>
<td></td>
<td>2 every day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Television watching</td>
<td>1 less than 3 hours a day</td>
<td>6.05</td>
<td>0.812 - 45.10</td>
</tr>
<tr>
<td></td>
<td>2 at least 3 hours a day</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Multivariable logistic regression model of the presence of metabolic syndrome according to the NCEP ATPIII definition and assigned risk scores

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Regression coefficients (SE)</th>
<th>OR</th>
<th>95% CI</th>
<th>Risk scores**</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>0.45 (1.5)</td>
<td>1.57</td>
<td>1.41-1.74</td>
<td>1</td>
</tr>
<tr>
<td>having breakfast</td>
<td>-0.66 (0.06)</td>
<td>0.52</td>
<td>0.24-1.10</td>
<td>-1</td>
</tr>
<tr>
<td>smoking behaviour</td>
<td>0.79 (0.39)</td>
<td>2.20</td>
<td>1.02-4.75</td>
<td>2</td>
</tr>
<tr>
<td>sports activity</td>
<td>-0.67 (0.39)</td>
<td>0.51</td>
<td>0.24-1.10</td>
<td>-1</td>
</tr>
<tr>
<td>parity</td>
<td>0.79 (0.42)</td>
<td>2.21</td>
<td>0.98-5.00</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Ap+</th>
<th>Bc+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slope</td>
<td>1.00</td>
<td>0.94</td>
</tr>
<tr>
<td>AUC</td>
<td>0.90</td>
<td>0.89</td>
</tr>
<tr>
<td>R-squared (%)</td>
<td>0.43</td>
<td>0.40</td>
</tr>
</tbody>
</table>

* Each coefficient is multiplied with the shrinkage factor of 0.90 and subsequently the new intercept of -13.12 was determined for the shrunken model. The linear predictor of this model is: -13.12 + 0.42 BMI - 0.62*breakfast + 0.74*smoking – 0.62 * sports + 0.74 *parity. ** Risk scores were determined by dividing each coefficient of the model after shrinkage through the lowest one and rounding to the nearest integer. Ap = apparent and Bc is bootstrap corrected performance.

This means that the risk model is only slightly optimistic. By replacing the self-reported BMI by measured BMI, the apparent AUC was 0.91 and the explained variation was 45%. After correction for optimism, the AUC and the explained variation were 0.90 and 42% respectively. Thus using measured BMI is better than self-reported BMI, but the difference in the performance of the risk models is very small. We also determined the performance of the MRS after we transformed the regression coefficients in easy-to-use risk scores. The performance of the MRS is equal to the performance of the model after backward logistic regression, with an AUC of 0.91 and an explained variation of 43%. Young adults with a MRS value above the chosen cut-off point have a high risk of metabolic syndrome. Table 5 shows the sensitivity, specificity, PPV and NPV at various cut-off points. For example at a cut-off of 25, the sensitivity is 0.88, whereas the specificity is 0.73, the PPV is 0.21 and the NPV is 0.99.
Table 4. The calculation of the Metabolic Risk Score (MRS)

<table>
<thead>
<tr>
<th>Questions and answer possibilities</th>
<th>Calculation of the MRS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>What is your height?</strong> .......... cm</td>
<td>calculate Weight / (Height)^2 = BMI</td>
</tr>
<tr>
<td><strong>What is your weight?</strong> .......... kg</td>
<td></td>
</tr>
<tr>
<td><strong>How many days a week do you have breakfast?</strong> .......... days a week</td>
<td>if less than 7 days a week 0 if every day -1</td>
</tr>
<tr>
<td><strong>How many cigarettes do you smoke in a week?</strong></td>
<td>if less than 1 cigarette a week 0 if at least 1 cigarette a week 2</td>
</tr>
<tr>
<td>☐ 0</td>
<td></td>
</tr>
<tr>
<td>☐ less than 1 cigarette a week</td>
<td></td>
</tr>
<tr>
<td>☐ 1 cigarette a week</td>
<td></td>
</tr>
<tr>
<td>☐ more than 1 cigarette a week</td>
<td></td>
</tr>
<tr>
<td><strong>How often do you have sports every week?</strong> .......... times/ week</td>
<td>if less than twice a week 0 if at least twice a week -1</td>
</tr>
<tr>
<td><strong>Were you the oldest child of your mother?</strong></td>
<td>if yes 0 if no 2</td>
</tr>
<tr>
<td>☐ yes</td>
<td></td>
</tr>
<tr>
<td>☐ no</td>
<td></td>
</tr>
</tbody>
</table>

Metabolic Risk Score (MRS) = sum of the BMI and the other scores
Table 5. The sensitivity, specificity, positive predictive value (PPV), negative predicted value (NPV) of the MRS at different cut-off points, and the related percentage of the young adults to whom medical evaluation would have been offered while they do not have MetS.

<table>
<thead>
<tr>
<th>Cut-off point</th>
<th>Number of cases with MetS</th>
<th>sensitivity</th>
<th>specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Subjects without MetS, to whom further medical evaluation is offered as percentage of the young adult population (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>48</td>
<td>1.00</td>
<td>0.00</td>
<td>0.08</td>
<td>1.00</td>
<td>93</td>
</tr>
<tr>
<td>19</td>
<td>48</td>
<td>1.00</td>
<td>0.05</td>
<td>0.08</td>
<td>1.00</td>
<td>88</td>
</tr>
<tr>
<td>21</td>
<td>48</td>
<td>1.00</td>
<td>0.22</td>
<td>0.09</td>
<td>1.00</td>
<td>72</td>
</tr>
<tr>
<td>23</td>
<td>47</td>
<td>0.98</td>
<td>0.47</td>
<td>0.13</td>
<td>1.00</td>
<td>49</td>
</tr>
<tr>
<td>25</td>
<td>42</td>
<td>0.88</td>
<td>0.73</td>
<td>0.21</td>
<td>0.99</td>
<td>25</td>
</tr>
<tr>
<td>27</td>
<td>37</td>
<td>0.77</td>
<td>0.87</td>
<td>0.32</td>
<td>0.98</td>
<td>12</td>
</tr>
<tr>
<td>29</td>
<td>30</td>
<td>0.63</td>
<td>0.95</td>
<td>0.49</td>
<td>0.97</td>
<td>5</td>
</tr>
<tr>
<td>31</td>
<td>18</td>
<td>0.38</td>
<td>0.98</td>
<td>0.56</td>
<td>0.95</td>
<td>2</td>
</tr>
<tr>
<td>33</td>
<td>12</td>
<td>0.25</td>
<td>0.99</td>
<td>0.71</td>
<td>0.94</td>
<td>1</td>
</tr>
<tr>
<td>35</td>
<td>8</td>
<td>0.17</td>
<td>0.99</td>
<td>0.89</td>
<td>0.94</td>
<td>1</td>
</tr>
<tr>
<td>37</td>
<td>5</td>
<td>0.10</td>
<td>1.00</td>
<td>1.00</td>
<td>0.93</td>
<td>0</td>
</tr>
<tr>
<td>39</td>
<td>3</td>
<td>0.06</td>
<td>1.00</td>
<td>1.00</td>
<td>0.93</td>
<td>0</td>
</tr>
<tr>
<td>41</td>
<td>2</td>
<td>0.04</td>
<td>1.00</td>
<td>1.00</td>
<td>0.93</td>
<td>0</td>
</tr>
<tr>
<td>43</td>
<td>1</td>
<td>0.02</td>
<td>1.00</td>
<td>1.00</td>
<td>0.93</td>
<td>0</td>
</tr>
</tbody>
</table>
DISCUSSION

The MRS is an easy-to-use score to detect MetS in a population of young adults. The discriminatory performance is high. At a cut-off of 25, its sensitivity is 0.88, the specificity 0.73, the PPV 0.21 and the NPV is 0.99. A particular feature of the scale is that the MRS provides a refinement of risk assessment on top of BMI. This makes it easy to connect the MRS to clinical practice. The individual's MRS can vary between BMI minus 2 and BMI plus 4, so the upward detecting potential is large, equal to ‘4 BMI points’. In practice, the score could be used with either self-reported BMI or measured BMI.

It is somewhat remarkable that including age did not improve the risk estimation. It might be the case that the age range of 18-28 years in our study is too narrow to bring out the age effect. Gender also had no impact on the performance, which might be due to the sex-specific cut-offs of two of the five components of metabolic syndrome according to the NCEP ATPIII definition, i.e. waist circumference and HDL cholesterol.29

For research purposes the MRS could be used as a continuous score of MetS risk. In practice, one may want to choose one or more cut-off points, corresponding to different actions. In choosing a cut-off for a risk estimation instrument, a good balance should be struck between the sensitivity, specificity, PPV, NPV and the implications of the test results for individuals and society. A person with a MRS above the cut-off could be invited for further medical evaluation with the aim of excluding or diagnosing MetS. We propose using 25 as the cut-off of the MRS, with a percentage of false positives and false negatives of respectively 27% and 12%. In Table 5 it is shown that at the cut-off MRS=25 the young adults without MetS to whom further medical evaluation would be offered represent 25% of the total population. This implies that most young adults will not be invited for further diagnostic assessment. In populations with a higher prevalence of MetS, the percentage of the total population that will wrongly be offered further diagnostics will even be lower. At the cut-off MRS=25 in 1 out of the 5 persons who were invited for further diagnostics, MetS is assessed. This seems reasonable for the use of the risk score as a first detection instrument in the general population of young adults. Of course, the final decision on the cut-off should
depend on the perceived burden of the diagnostic tests by individuals, and on the costs and benefits of different possible interventions.

The MRS might turn out to be useful within a stepwise diagnostic process, as described in a previous study. After being detected as a person at high cardiometabolic risk by the MRS, a few additional measurements (e.g. waist circumference, blood pressure) could be performed before deciding on the necessity for blood tests. Such an approach minimizes the diagnostic burden since taking blood is only needed for those who also have high values on the additional measures.

To date, no risk estimation instrument which is based solely on information from questionnaires is available to assess the risk of MetS. A risk estimation instrument for older populations is the Diabetes Risk Score (DRS), which has been developed to detect 35- to 64-years olds with increased risk of the onset - within 10 years - of type 2 diabetes. The ultimate goal of the DRS is to prevent the transition from normoglycemia to impaired glucose tolerance and to overt diabetes. The DRS is also based on a history of blood pressure medication and/or high blood glucose, which both occur only rarely at younger ages. Thus, the DRS may not perform as well in younger age groups. Additional work is needed to bridge the gap between ages 28 and 35 years.

An advantage of the MRS is the small risk of recall bias because none of the items calls upon the memory of the young adult and/or his family. In the Netherlands a population-based screening for MetS in 20-70 years olds by self-measurement of waist circumference appeared to be feasible. In favour of this method is that only information on one parameter measurement is needed from the subjects. However, in this study, a relatively low percentage of MetS was detected in young adults (<1%). This could mean that for adults who are younger than 30 years of age, the self-measurement of waist circumference by itself does not comply as a screening instrument. As we have no data on the self-measurement of waist circumference, its additional value to the performance of the MRS should be determined in future research.

Except from self-measured waist circumference, we have not included all other possible metabolic risk factors as candidate predictors, i.e. a family history of diabetes
or cardiovascular disease,\textsuperscript{31,42} alcohol consumption, or socioeconomic status. Although the performance of the risk model is already high, adding these variables might potentially improve the performance. However questions about family history of diabetes or cardiovascular disease might lead to too many missing answers and/or misjudgements by the young adults. Alcohol consumption seems hard to quantify on the basis of one simple question, as its severity should not only be based on the mean consumption per time interval but also on the frequency and severity of binge drinking.\textsuperscript{32} Socioeconomic status may already have been mediated through other predictors included in the model.\textsuperscript{43} Extending the instrument with more variables might improve diagnostic accuracy, but also at the expense of a more complicated model. We think that the MRS strikes a good balance between accuracy and simplicity.

One of the strengths of our study is that the risk model is based on the data from a general population, which are – except for gender – representative of the original birth cohort. Because gender is not an effect modifier, this probably has not influenced the results of the analyses. However, the MRS should be externally validated in other cohorts before it can be implemented. Because our study population consisted of Caucasians, validation and possibly adaptation in other ethnic groups is warranted before it can be implemented on a larger scale. Also we recommend the investigation of the possible surplus value of adaptation of the MRS by combining the MRS with the self-measurement of waist circumference.

By detecting young adults with metabolic syndrome, lifestyle interventions or – if necessary – medical treatment can be offered with the aim to prevent overt type 2 diabetes and cardiovascular diseases. If maintained in the long term, lifestyle modification based on behavior therapy is the most important and effective strategy to manage the metabolic syndrome.\textsuperscript{44} Long-term effects for more than 4 years have been shown of diet and exercise prescription to adults with impaired glucose tolerance in the prevention of type 2 diabetes.\textsuperscript{45,46} Also evidence exists for beneficial lipid changes due to chronic physical activity for especially HDL cholesterol and triglycerides, and for blood pressure reduction.\textsuperscript{47,48}

Because the MRS is based on only six simple questions it seems easily applicable within settings where young people often spend their time together, such as at work,
school, and sport (events). In this way we can offer young adults, who are often difficult to reach, a short check-up. The MRS might contribute to a cost-effective and practical way of identifying young adults at increased risk of later type 2 diabetes and cardiovascular disease.

ACKNOWLEDGMENTS

We gratefully thank all participants for their time and efforts, the assistants for their contribution to the research work, the laboratory of the Community Hospital in the city of Terneuzen (especially Dr Ruud Muusze), and the Municipal Health Services of Terneuzen for their support and cooperation. The study was funded by the Health Research and Development Council of the Netherlands (ZONMw Grants no.2100.0092). The researchers are non dependent of the funder.
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The Terneuzen Birth Cohort

Longer exclusive breastfeeding duration is associated with leaner body mass and a healthier diet in young adulthood

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ABSTRACT

Background
Breastfeeding (BF) is protective against overweight and is associated with dietary behaviour. The aims of our study were to assess the relationship between exclusive BF duration and BMI, waist circumference (WC) and waist-hip ratio (WHR) at adulthood, and to study whether dietary behaviour could explain the relationship between BF duration and the proxies of fat mass.

Methods
In 2004-2005, 822 subjects from the Terneuzen Birth Cohort (n=2,604), aged 18-28 years, filled in postal questionnaires including sociodemographic factors and aspects of dietary behavior; 762 subjects also underwent anthropometric measurements of weight, height, and waist and hip circumference. The relationship between exclusive BF duration and dietary outcomes was investigated by logistic regression analysis. The relationships of BF duration with the anthropometric measures were investigated by linear regression analyses. All results were corrected for age, gender and possible confounders. Finally, regression analyses were performed to investigate if diet factors had a mediating effect on the relationship between BF duration and fat mass.

Results
A significant inverse dose-response relationship of BF duration was found for BMI (β -0.13, SE 0.06), WC (β -0.39, SE 0.18) and WHR (β -0.003, SE 0.001), after correction for age, gender and confounders. The odds ratio (OR) of exclusive BF duration in months for a breakfast frequency of at least 5 times a week was 1.16 (95%CI 1.06-1.27), and for snack consumption of less than twice a week was 1.15 (95%CI 1.06-1.25). Both ORs were corrected for age, gender and confounders. For other dietary outcomes, the results point in the same direction, i.e. a positive relationship with BF duration, but these were not statistically significant. A mediating effect of the diet factors on the association between BF and anthropometric outcomes was not shown.

Conclusions
Exclusive BF duration had a significant inverse dose-response relationship with BMI, WC and WHR at young adulthood. BF duration was positively related to a healthier diet at adulthood, but this did not explain the protective effect of BF against body fat. Our results underline the recommendation of the WHO to exclusively breastfeed for 6 months or longer.
BACKGROUND

Children with overweight or a relatively rapid weight gain during growth tend to become overweight adults\(^1,2\) with an associated high risk of cardiovascular diseases, type 2 diabetes and cancer.\(^3,4\) Exclusive breastfeeding (BF) for at least 4 months not only protects the infant against adverse health outcomes, such as eczema\(^6\) and asthma,\(^7\) but also against overweight and obesity.\(^8,9\) Several studies have also shown a dose-response relationship between BF and overweight at later ages,\(^9-12\) of which two studies assessed this relationship up until adulthood.\(^10,12\) In these studies overweight was defined on the basis of body mass index (BMI) or weight by height. It is not clear how BF is related to waist circumference (WC) and waist-hip ratio (WHR). These are both proxies of visceral fat, which is considered to be extremely harmful to health.\(^12\)

Dietary behaviour, which is often developed at a young age, is an important predictor of overweight.\(^13\) Therefore, generally more and more attention is being paid to promoting the development of healthy dietary habits from birth onwards. Breast milk comprises flavors that reflect foods consumed by the mother, and therefore breastfed infants are more accepting than formula-fed infants of new solid foods when they are offered in a later phase of life.\(^14\) BF and parental consumption of fruit and vegetables.\(^15-18\) are both correlated to children's consumption of fruit and vegetables. Two studies have showed that BF is associated with a variety of diet factors at the ages of 12 months and 7 years.\(^16,19\) At both ages breastfed children consumed fruit and vegetables more frequently than non-breastfed children. These studies did not assess the relationship of BF with other dietary habits such as eating breakfast or having a regular eating pattern. Moreover, it is not known whether the relationship between BF and consumption of healthy food products still exists at young adulthood, or whether this relationship partly explains the relationship between BF duration and accumulation of fat mass.

The aims of our study were 1.) to assess the relationship between exclusive BF duration and anthropometric measures approximating body fat or visceral fat, i.e. BMI, WC and WHR, and dietary behaviour at young adulthood, and 2.) to determine to what extent dietary behaviour explains the relationship of BF duration with body and/or visceral fat mass.
METHODS

Study population and study design
We analyzed data from the Terneuzen Birth Cohort (n=2,604). A more detailed description of the study population and study design has been given previously.\textsuperscript{2,20} In 2004-2005, 822 subjects with an age range of 18-28 years (31.6\%) participated in a follow-up study at young adulthood: they completed questionnaires and 762 subjects of them also participated in anthropometric measurements. The questionnaires included data on sociodemographic characteristics and dietary behaviour. These adults’ mothers also completed a questionnaire. After excluding children with missing data for BF (n=12), the data for 810 young adults were used for statistical analyses. These subjects were representative of the original cohort regarding birth weight and parity of the mother ($p>0.05$). However, significant differences with the original cohort existed for gender (42\% males vs. 55\% in the original cohort), the duration of exclusive BF (mean duration 53 days vs. 45 days in the original cohort), and the age of the mothers (mean 26.9 vs. 26.6 years in the original cohort). 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 the participants.

Physical examinations
Physical examinations were performed by two assistants who received standardized training at the Municipal Health Services in Terneuzen, the Netherlands. Weight was measured, with the subject in underwear, to the nearest 0.1 kg on an electronic self-zeroing scale. Standing height was measured to the nearest 0.1 cm with the aid of a stadiometer. WC was measured mid-way between the lower side of the lowest rib and the upper side of the pelvis, on bare skin, after a normal expiration, and with muscles relaxed.

Independent variables: BF duration and confounders
Data about BF were prospectively collected from birth until the age of 6 months during the visits by the mothers and their babies to the Child Health Care clinics of the Municipal Health Services in Terneuzen. These visits took place at 1, 2, 4, 8, 10, 14 weeks and 5 and 6 months of age. At each visit it was recorded if the baby received exclusive BF, a combination of BF and formula milk, or only formula milk. Also the
date of the introduction of formula milk and the last day of BF were recorded. The duration of BF was defined as the duration of exclusive BF, and was categorized as 0-15, 16-45, 46-74, 75-104, 105-134, 135-164 and ≥ 165 days. This corresponds to 0, 1, 2, 3, 4, 5 and 6 months respectively (rounded to integer figures), which makes it possible to use these categories as a quantitative variable in regression analyses. Parity, birth weight, and the BMI of the subject and the educational level of the mother were studied as possible confounders because they are known to be related, as well as BF duration, to body fat mass in later life.\textsuperscript{21,22} During the first visit to the Child Health Care clinics the birth weight of the subject and the age and parity of the mother were recorded. Data on the BMI and educational level of the mother were obtained from the mothers by questionnaires. Educational level was categorized as low, medium or high, which was categorized on the basis of the highest level of the education completed by the mother ('low' is primary school and/or secondary school; 'medium' is vocational education and 'high' is higher vocational education and/or university).

**Outcome variables**

The BMI (in kg/m\(^2\)), WC (in cm) and WHR were analyzed as continuous outcome variables. Characteristics of the dietary behaviour were obtained by postal questionnaires, composed on the basis of validated questionnaires.\textsuperscript{23,24} They concern the frequency of eating breakfast and meals, the consumption of fruit, vegetables, oil-fried snacks such as French fries and croquettes, energy-rich snacks, and the drinking of sweet beverages and alcohol. Sweet beverages are defined as soda or fruit juice, because both contain a lot of sugars.\textsuperscript{25} Energy-rich snacks are defined as the consumption of French fries, cakes or candy bars, all containing at least 200 kilocalories per 100 grams: they are among the foods with the highest percentage of saturated fats.\textsuperscript{25} The characteristics of the dietary behaviour were dichotomized in healthy and non-healthy outcomes, according to the criteria of the Dutch Nutrition Center (Table 1).

**Statistical analyses**

Mean and frequency differences in the characteristics of the young adults by gender were examined using \( t \)-tests and \( \chi^2 \)-tests. Logistic regression analysis was applied to
Table 1. Dichotomization of outcome variables of dietary behaviour at young adulthood*.

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Unhealthy outcome</th>
<th>Healthy outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breakfast frequency</td>
<td>&lt;5 times/week</td>
<td>≥5 times/week</td>
</tr>
<tr>
<td>Meal frequency</td>
<td>&lt;3 times/day</td>
<td>3 times/day</td>
</tr>
<tr>
<td>Consumption of fruit</td>
<td>&lt;7 days/week</td>
<td>7 days/week</td>
</tr>
<tr>
<td>Consumption of vegetables</td>
<td>&lt;7 days/week</td>
<td>7 days/week</td>
</tr>
<tr>
<td>Consumption of fruit or vegetables</td>
<td>&lt;7 days/week</td>
<td>7 days/week</td>
</tr>
<tr>
<td>Consumption of fried snacks</td>
<td>&gt; 1 time/week</td>
<td>≤1 time a week</td>
</tr>
<tr>
<td>Consumption of other energy-rich snacks</td>
<td>every day</td>
<td>not every day</td>
</tr>
<tr>
<td>Consumption of types of snacks</td>
<td>every day</td>
<td>not every day</td>
</tr>
<tr>
<td>Consumption of sweet beverages</td>
<td>every day</td>
<td>not every day</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>&gt;2 glasses/day</td>
<td>≤2 glasses/day</td>
</tr>
</tbody>
</table>

* based on the criteria of the Dutch Nutrition Center (http://www.voedingscentrum.nl/nl/eten-gezondheid)

study the relationship between the duration of exclusive BF and several aspects of the dietary behaviour. We used linear regression to predict BMI, WC and WHR at adulthood from BF duration at infancy. Analyses were adjusted for gender and age by including them in the regression model. A variable is considered to be a confounder if by adding the variable the regression coefficient of the independent variable changes by more than 10%. As the studied population was not representative of the original population for gender, for the mother’s age at the birth or for BF duration, the interaction of these variables with the other independent variables have been studied as well. Statistically significant interaction terms (if $p<0.05$) were retained in the final model. In addition, we examined whether adding the quadratic term of the BF duration significantly improved the description of the relationship of BF duration with the outcome variables at a level of $p=0.05$. If significant, this means that the protective effect of BF duration gradually increases (a positive sign of the regression coefficient) or gradually decreases (a negative sign of the regression coefficient). Finally, the aspects of the diet that were found to have a statistically significant relationship with BF were added to the model that explained BMI, WC and WHR, to assess if these aspects mediated the relationship between BF and body fat or visceral fat, according to
Longer exclusive breastfeeding duration is associated with leaner body mass and a healthier diet in young adulthood

Table 2. Demographic background variables, BF duration and dietary factors by gender (n=810)

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Males (n=340)</th>
<th>Females (n=470)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Age</td>
<td>340</td>
<td>23.2 (2.9)</td>
</tr>
<tr>
<td>Birth weight</td>
<td>340</td>
<td>3520.6 (501.6)</td>
</tr>
<tr>
<td>Age of mother at birth</td>
<td>340</td>
<td>27.2 (4.2)</td>
</tr>
<tr>
<td>BMI of mother</td>
<td>306</td>
<td>25.1 (4.0)</td>
</tr>
<tr>
<td>BMI at adulthood</td>
<td>307</td>
<td>23.0 (3.3)</td>
</tr>
<tr>
<td>WC at adulthood</td>
<td>307</td>
<td>84.3 (9.6)</td>
</tr>
<tr>
<td>WHR at adulthood</td>
<td>307</td>
<td>0.86 (0.08)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Educational level of the mother</th>
<th>289</th>
<th>405</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>46.4</td>
<td>53.1</td>
</tr>
<tr>
<td>Medium</td>
<td>37.7</td>
<td>30.9</td>
</tr>
<tr>
<td>High</td>
<td>15.9</td>
<td>16.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Firstborn*</th>
<th>340</th>
<th>470</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>43.2</td>
<td>38.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusive BF duration in days (months, in rounded figures)</th>
<th>340</th>
<th>470</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-14 (0)</td>
<td>48.5</td>
<td>47.9</td>
</tr>
<tr>
<td>15-44 (1)</td>
<td>13.2</td>
<td>16.0</td>
</tr>
<tr>
<td>45-74 (2)</td>
<td>10.0</td>
<td>8.9</td>
</tr>
<tr>
<td>75-104 (3)</td>
<td>3.8</td>
<td>5.1</td>
</tr>
<tr>
<td>105-134 (4)</td>
<td>4.7</td>
<td>3.4</td>
</tr>
<tr>
<td>135-164 (5)</td>
<td>3.2</td>
<td>3.0</td>
</tr>
<tr>
<td>≥ 165 (6)</td>
<td>16.5</td>
<td>15.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dietary factors at adulthood</th>
<th>Males (n=340)</th>
<th>Females (n=470)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Having breakfast ≥ 5 times a week**</td>
<td>337</td>
<td>73.0</td>
</tr>
<tr>
<td>Having meals 3 times a day **</td>
<td>335</td>
<td>44.2</td>
</tr>
<tr>
<td>Consumption of fruit 7 days a week**</td>
<td>334</td>
<td>26.9</td>
</tr>
<tr>
<td>Consumption of vegetables 7 days a week*</td>
<td>336</td>
<td>52.7</td>
</tr>
<tr>
<td>Consumption of sweet beverages, not every day **</td>
<td>332</td>
<td>74.1</td>
</tr>
<tr>
<td>Consumption of snacks such as French fries and croquettes less than once a week**</td>
<td>340</td>
<td>63.8</td>
</tr>
<tr>
<td>Other energy-rich snacks, such as candy bars, cake and French fries, not every day**</td>
<td>335</td>
<td>16.7</td>
</tr>
<tr>
<td>Alcohol ≤ 2 consumptions a day **</td>
<td>310</td>
<td>42.6</td>
</tr>
</tbody>
</table>

Differences between males and females by t-tests and $\chi^2$-tests: * non-significant, ** p<0.05
the causal steps approach of Baron and Kenny. All the statistical analyses were performed with the help of SPSS 15.0.

**RESULTS**

In Table 2 characteristics of the population are shown by gender. The mean age of the young adults was 23.1 years (SD 2.9). WC and WHR at adulthood were significantly different for males and females. Dietary behaviour at adulthood also differed significantly for males and females. For most outcomes females show a healthier dietary pattern, except for the consumption of sweet beverages and the consumption of ‘other energy-rich snacks’, such as candy bars, cake and French fries.

In Table 3 the relationship between BF duration in months and dietary outcomes at young adulthood are shown. A significant dose-response relationship for exclusive BF was found with breakfast frequency and the consumption of snacks such as French fries and croquettes, also after correction for age, gender and possible confounders, with an OR of respectively 1.16 (95% CI 1.06-1.27), and 1.20 (95% CI 1.12-1.30). In none of the investigated relationships did gender or age appear to be effect modifiers. Adding the quadratic function of the BF duration did not improve the models ($p>0.05$).

In Table 4 the relationship between the BF duration in months and BMI, WC and WHR are shown. In addition, the effects of adding the variables breakfast frequency and snack consumption on the regression coefficients of the BF duration are shown. As breakfast frequency and snack consumption had no significant relationship with BMI, WC and WHR ($p>0.05$), and adding these variables did not significantly influence the explained variance, no mediation could be shown for breakfast frequency or snack consumption. As these variables did not fulfill the third condition to be defined as mediator, the fourth step of the causal steps approach was not performed.
Table 3. Odds ratios (OR) of exclusive BF duration (in months) for favorable dietary outcomes at young adulthood (n=810)

<table>
<thead>
<tr>
<th>Favorable dietary outcomes at young adulthood for:</th>
<th>Crude OR 95% CI</th>
<th>Adjusted OR for age and gender 95% CI</th>
<th>Adjusted OR for confounders 95% CI</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Having breakfast</td>
<td>1.16 1.06-1.26</td>
<td>1.16 1.06-1.27</td>
<td>1.16 1.06-1.27</td>
<td>1.06-1.27</td>
</tr>
<tr>
<td>Having 21 meals a week</td>
<td>1.03 0.96-1.09</td>
<td>1.01 0.95-1.08</td>
<td>1.03^A 0.96-1.11</td>
<td>0.96-1.11</td>
</tr>
<tr>
<td>Consumption of fruit</td>
<td>1.05 0.98-1.12</td>
<td>1.05 0.98-1.13</td>
<td>1.05^B 0.95-1.10</td>
<td>0.95-1.10</td>
</tr>
<tr>
<td>Consumption of vegetables</td>
<td>1.08 1.02-1.15</td>
<td>1.07 1.00-1.14</td>
<td>1.07^A 0.98-1.13</td>
<td>0.98-1.13</td>
</tr>
<tr>
<td>Consumption of sweet beverages</td>
<td>1.00 0.93-1.06</td>
<td>1.02 0.96-1.10</td>
<td>1.02^B 0.91-1.06</td>
<td>0.91-1.06</td>
</tr>
<tr>
<td>Consumption of snacks such as French fries</td>
<td>1.12 1.05-1.19</td>
<td>1.20 1.12-1.30</td>
<td>1.20^A 1.06-1.25</td>
<td>1.06-1.25</td>
</tr>
<tr>
<td>Consumption of energy-rich snacks, such as candy</td>
<td>1.02 0.93-1.12</td>
<td>1.06 0.96-1.17</td>
<td>1.06^B 0.90-1.13</td>
<td>0.90-1.13</td>
</tr>
<tr>
<td>cake</td>
<td>1.02 0.96-1.09</td>
<td>1.05 0.98-1.14</td>
<td>1.05^B 0.99-1.15</td>
<td>0.99-1.15</td>
</tr>
</tbody>
</table>

Significant relationships ($p<0.05$) are printed in bold

Effect modification by gender, BF duration and age of the mother were not significant in any of the investigated relationships

-- no additional confounders found, ^ adjusted for educational level mother, ^B adjusted for BMI mother and educational level of mother
### Table 4. Relationship between exclusive BF duration (in months) and a. BMI, b. WC, c. WHR at young adulthood in linear regression analyses (n=710)

<table>
<thead>
<tr>
<th>Model</th>
<th>n</th>
<th>BMI</th>
<th>WC</th>
<th>WHR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>β (SE)</td>
<td>P</td>
<td>Adj. R²</td>
</tr>
<tr>
<td>1. Univariate</td>
<td>710</td>
<td>-0.19 (0.01)</td>
<td>&lt;0.001</td>
<td>0.01</td>
</tr>
<tr>
<td>2. Model 1 adjusted for gender and age</td>
<td>710</td>
<td>-0.19 (0.06)</td>
<td>0.002</td>
<td>0.02</td>
</tr>
<tr>
<td>3. Model 2 adjusted for confounders*</td>
<td>605</td>
<td>-0.13 (0.06)</td>
<td>0.042</td>
<td>0.08</td>
</tr>
<tr>
<td>4. Model 3 and adjustment for breakfast</td>
<td>601</td>
<td>-0.14 (0.06)</td>
<td>0.033</td>
<td>0.08**</td>
</tr>
<tr>
<td>5. Model 3 and adjustment for snack consumption</td>
<td>605</td>
<td>-0.13 (0.06)</td>
<td>0.044</td>
<td>0.08**</td>
</tr>
<tr>
<td>6. Model 3 and adjustment for breakfast and snack consumption</td>
<td>601</td>
<td>-0.14 (0.06)</td>
<td>0.034</td>
<td>0.08**</td>
</tr>
</tbody>
</table>

* The models were adjusted for birth weight, BMI of the mother and educational level of the mother; interactions had no significant relationship with the outcomes.

** No significant changes in explained variance in comparison to model 3, so no effect modification was shown.
DISCUSSION

Our results show a negative dose-response relationship for the exclusive BF duration with all three outcomes, BMI, WC and WHR. This consistently confirms the hypothesis that the duration of exclusive BF is protective against fat mass in later life. For every month of exclusive BF the BMI, WC and WHR decreased by respectively 0.14 kg/m², 0.42 cm and 0.003. This implies that for young adults who have been breastfed for 6 months or longer, the BMI, WC and WHR are on average respectively 0.84 kg/m², 2.52 cm and 0.018 lower than for those who have not been breastfed at all. Our findings confirm the results of several studies that assessed the effect of BF on BMI at a later age [9,10, 27-31]. The protective effect of BF against overweight may be small, but it is remarkable that the relationship with BF still exists at adulthood, and even protects against visceral obesity. Moreover, at a population level even small effects of BF on fat mass or visceral fat mass may still be relevant for the prevalences of comorbidity of overweight or obesity. We have also shown that the duration of exclusive BF has a dose-response relationship with breakfast frequency and snack consumption at adulthood. Although the relationships between BF duration and the other dietary factors were not statistically significant, all results point to a positive relationship between BF duration and healthy dietary outcomes. However, we could not show that breakfast frequency or snack consumption mediated the relationship between BF duration and fat mass. Remarkably, a significant difference has been found for males and females for several dietary factors. This possibly refers to gender peer effects, which has also been found by others.32

Only a few studies have been carried out on the relationship between BF and dietary behaviour at later ages or on the mediating effects of dietary behaviour on the relationships of BF with anthropometric variables.15,19,33-35 As far as we know, only one other cohort study reported on the relationship between BF and dietary behaviour for young adults.35 In this cohort study, no relationship was shown between BF duration and dietary behaviour at 18 years of age and no mediating effect of dietary behaviour was shown on the relationship between BF duration and measures of overweight. Notwithstanding the high number of included subjects in this cohort, the effects of BF might have been masked by the frequent early introduction of teas, herbal drinks and fruit juices, impeding the study into the effects of exclusive BF.35
Although most relationships between BF duration and healthy dietary outcomes at adulthood in our study were not statistically significant, they all point to a positive relationship between BF duration and healthy dietary outcomes. This is in line with studies that revealed relationships between BF and several healthy dietary outcomes at later ages: it has been shown that BF is positively related to fruit and vegetable intake at 2-6 years and at 8 years, to fruit intake by 6-14 year olds, and negatively related to the intake of sweetened drinks and added sugars at 12 months of age, and intake of white bread, carbonated soft drinks, chocolate bars and fried snacks at 8 years of age. As we studied the relationships until adulthood, it might be that other exposures during later phases in life masked these associations. There are several explanations for the relationships between BF (duration) and healthy dietary outcomes. They might be due to a confounding effect of a higher health consciousness in mothers that breastfeed their child, implying that these mothers will offer a more healthy diet to their children in general. Another explanation may be that food preferences may partly be induced by the variety of flavors offered by breast milk, and the resulting easier acceptance of fruit and vegetable flavors and new solid food by breastfed children in later life, while children that received formula milk accept non-sweet flavors less easily.

Finally, our study results are also in line with another Dutch study that also did not show mediation by dietary factors on the BMI at the age of 7. The reasons for these similar findings might be that a mediating effect of dietary factors does not exist, that the effects of the mediators are so small that very large study samples are needed to show them, or that the dietary factors studied were too much of a simplification of the dietary behaviour as a whole.

One of the strengths of our study is that the data were prospectively collected from birth onwards, which excludes the possibility of recall bias. Another strength was that we could focus entirely on the exclusive BF duration, implying that the duration of mixed feeding (BF and bottle feeding) could not affect the results. In addition our data enabled us to study proxies of visceral fat, which also appeared to have a dose-response relationship with BF duration. As visceral fat mass is associated with metabolic syndrome and type 2 diabetes, a longer exclusive BF duration could be one of the first steps in the primary prevention of these comorbidities.
A limitation of our study was that the value of the collected data on food frequency is limited as they possibly only partly reflect caloric and nutrient intake and the total consumption of fatty food, both of which are highly correlated with fat mass. Therefore we recommend initiating research in which the feeding pattern is studied on the basis of a validated food questionnaire, such as the Food Frequency Questionnaire.\textsuperscript{40} Also we had to deal, as a consequence of loss to follow-up, with the fact that the subjects included in this study were not representative of the original cohort with regard to gender, the duration of exclusive BF and the age of the mothers. However, this probably will not have influenced the results as no effect modification has been shown for these variables.

**CONCLUSION**

Our study results indicate that a significant protective dose-response effect of the exclusive BF duration exists on outcomes that approximate total body fat mass as well as visceral fat mass. Although the protective effect is small, on a population level the impact on prevalences of type 2 diabetes and cardiovascular diseases may still be relevant. Because mediation of diet factors were not shown, it should not be precluded that the beneficial effects of BF on later body composition and dietary behaviour evolve by different pathways. Our study results underline the health recommendations by the WHO\textsuperscript{41} to exclusively breastfeed children for a duration of at least 6 months.

**ACKNOWLEDGEMENTS**

We gratefully thank all participants for their time, the assistants for their contribution in the field work, and Guus A. de Jonge, PhD, professor emeritus, for laying the foundations of this study in 1977-1986. The study was funded by the Health Research and Development Council of the Netherlands (ZONMw Grants no.2100.0092). The researchers are not dependent on the funder.
REFERENCES


The Terneuzen Birth Cohort

General Discussion
The aim of this thesis is to contribute to the identification and prevention of (adult) overweight and its related cardiometabolic risk in the earliest possible phases of life. In order to achieve this aim, we have
1. identified at which age intervals children are most susceptible to developing adult overweight and related cardiometabolic risk,
2. investigated how young adults with increased cardiometabolic risk can be detected efficiently in a general population, and
3. assessed the relationship of exclusive breastfeeding duration with BMI, waist circumference and waist-hip-ratio at young adulthood.

**MAIN RESULTS AND CONCLUSIONS**

**Age intervals most predictive of developing adult overweight and cardiometabolic risk**

With data from the Terneuzen Birth Cohort we identified the age intervals most predictive of developing adult overweight (Chapter 2) and cardiometabolic risk (Chapter 3), based on serial BMI SDS changes. We found that the age interval between 2 and 6 years (2-6y) is the earliest and most critical period for adult overweight. The BMI SDS increase between the ages of 10 and 18 years (10-18y) has also a significant — albeit weaker — relationship with adult overweight. We studied the following cardiometabolic factors: waist circumference, skinfold thickness, systolic and diastolic blood pressure, triglycerides, HDL cholesterol, glucose and hsCRP. From 2 years onward the age intervals 2-6y, 6-10y and 10-18y are predictive for all these cardiometabolic risk factors, the age interval 2-6y being the most predictive. BMI SDS changes in all age intervals from birth onwards are related to waist circumference and skinfold thickness. However, the relationships of BMI SDS changes before the age of 2 years with other cardiometabolic risk factors at young adulthood are not significant, except for the relationship with hsCRP. For the various age intervals, we have found different relationships with various cardiometabolic risk factors. The BMI SDS change 2-6y is most strongly related to waist circumference, systolic and diastolic blood pressure and hsCRP, and the BMI SDS change 10-18y is most strongly related to HDL cholesterol and triglycerides. The age interval 6-10y showed weaker associations with cardiometabolic risk factors compared to the age intervals 2-6y and 10-18y. Adult
HDL cholesterol had an inverse relationship with the BMI SDS changes in all the age intervals, except for the age interval 6-10y. Metabolic syndrome, a constellation of metabolic risk factors, is significantly related to the BMI SDS changes at 2-6y and 10-18y with odds ratios of 3.39 (95%CI 2.33-4.94) and 2.84 (95%CI 1.94-4.15), respectively.

In line with our results, several studies have assessed the relationship between upwards centile crossing of the BMI between 2 to 5 or 6 years of age and adult overweight or obesity.\textsuperscript{3-7} Also relationships have been reported between BMI SDS changes before the age of 2 years and overweight and/or cardiovascular risk factors in childhood, adolescence or adulthood.\textsuperscript{8-12} However, we found only weak evidence for these relationships with BMI SDS changes before the age of 2. This may be due to differences in study design, such as the age at which the predictors or outcomes were measured or the inclusion of specific populations such as children being small for gestational age.\textsuperscript{9-12} Our results are in line with the findings in the New Delhi Birth Cohort.\textsuperscript{13} They also found that the BMI SDS changes from 2 years onward are associated with overweight and cardiometabolic risk.

Finally, the relation of BMI SDS changes during adolescence for developing adult overweight, which may be attributed to changes in visceral fat mass has also been reported before.\textsuperscript{14} If confirmed in another study, the opposite association of adult HDL with the BMI SDS change in the age interval 6-10 needs to be studied further. A possible explanation may be that during this age interval subcutaneous fat contributes more to the BMI increase than visceral fat,\textsuperscript{14} which is supposed to have a protective effect against cardiometabolic risk.\textsuperscript{15}

Our results indicate that it is important to develop strategies for prevention of overweight and cardiometabolic risk in children from 2 years onward. We believe prevention aimed at the age interval 2-6 years to be the most promising.
Prediction tool for identifying 2-6 years olds at risk of adult overweight

We developed a practical tool for the age interval 2-6 years to predict adult overweight. The tool consists of several risk score diagrams, all based on two measurements of the BMI. The diagrams show the risk of adult overweight based on the BMI development between 2 and 4 years, and 2 and 6 years of age, respectively. The explained variance of adult BMI by the BMI SDS change between 2 and 6 years is high: 48%. The ROC plots of the risk score diagrams suggest cut-off values at approximately 25% with 30% of false positive results. A cut-off at 50% seems more sensible, as it is associated with only 8% of false positive results. Simultaneously with the development of our risk score diagrams, in another (non-Caucasian) cohort risk diagrams were constructed on the basis of serial BMI SDS measurements. Their risk score diagrams were meant to identify children at risk of metabolic syndrome and diabetes at adulthood, whereas our aim was to identify children at increased risk of adult overweight.

Detection of metabolic syndrome in young adults

In the Terneuzen Birth Cohort the overall prevalence of metabolic syndrome was 7.5% (n=642). The prevalence was highest in young adults with obesity (50.0%) and lowest in subjects with a normal weight (1.7%). The prevalences of metabolic syndrome in young adults in the Terneuzen Birth Cohort were comparable to the prevalences in another Dutch study. These prevalences underline the need to detect young adults with metabolic syndrome and offer them a lifestyle intervention with the aim of preventing type 2 diabetes and cardiovascular diseases. Because it is costly to invite all young adults for a medical examination including blood tests, we have developed two ways to detect metabolic syndrome in young adults from a general Caucasian population without the necessity to perform these more elaborate tests in all subjects.

By tree regression analysis, we found that in clinical practice most young adults with metabolic syndrome can be identified or excluded without blood tests by a simple and stepwise diagnostic process, based on the measurement of BMI, waist circumference and blood pressure (Figure 1). Based on the results of this analysis we have found that in 89.6% of the young adults, blood tests seem to be unnecessary to diagnose or
Figure 1. Decision tree to assess the necessity to perform blood tests in young adults in a general population to detect metabolic syndrome.
exclude metabolic syndrome (Chapter 6). This figure indicates that blood tests are not necessary to diagnose metabolic syndrome if the BMI ≥35, as all subjects with this BMI have metabolic syndrome. For those with a BMI <35, as well as normal waist circumference and normal blood pressure, blood tests are not needed as none of these subjects have metabolic syndrome. In the group with BMI<30 and an increased waist circumference or increased blood pressure, we recommend not performing blood tests as the prevalence of metabolic syndrome is lower than in the general population. According to our data, blood tests to diagnose or exclude metabolic syndrome seem only necessary if, according to the NCEP ATP III criteria:

- waist circumference and/or blood pressure are raised in subjects with 30 ≤ BMI <35
- the waist circumference and blood pressure both are raised in subjects with a BMI<30

Also, we have developed the Metabolic Risk Score (MRS), a risk score to detect metabolic syndrome in young adults in the general population. The MRS is an easy-to-use score and is based on six simple questions about weight, height, having breakfast, smoking behaviour, participation in physical sports, and being firstborn. Unlike the stepwise diagnostic process as obtained by the tree regression analysis, the MRS does not require a preventive healthcare consultation. The scores of the answers of the MRS sum up to a total score. The individual MRS can vary between BMI minus 2 and BMI plus 4 (Chapter 6). After internal validation, the MRS has a high discriminatory performance (AUC 0.89, Nagelkerke $R^2$ 0.40). Replacing the reported BMI by measured BMI gives an even better performance, although the difference is small. The advantage of the MRS is that recall bias plays no or hardly any role.

To date, no efficient diagnostic process is available to detect metabolic syndrome in young adults in a general population. For older populations, the Diabetes Risk Score (DRS) has been developed to detect 35- to 64-years olds with increased risk of the onset - within 10 years - of type 2 diabetes. Another feasible instrument, which has been developed in the Netherlands as well, is a population-based screening for metabolic syndrome in 20-70 years olds based on one single parameter, namely the self-measurement of waist circumference. Using this instrument in 20-30 year olds, a percentage of lower than 1% was identified with metabolic syndrome. This percentage
was not verified by blood tests or physical measurements. This percentage was much lower than in our study and in another Dutch study (ARYA), which had a prevalence of around 7.5%. Therefore it seems that testing by self-measurement of waist circumference alone may lead to a significant number of false negatives in young adults. However, this method might provide additional value to the predictive value of the MRS.

In conclusion, the stepwise approach and the MRS both offer possibilities to detect metabolic syndrome in young adults without the necessity to perform blood tests in all subjects. The first method can be applied in preventive health care settings as a stepwise diagnostic process, the second can be applied in schools and other settings where many young adults spend time together. A next step might be the combination of the MRS with the stepwise approach. After assessing increased risk of metabolic syndrome by the MRS, a stepwise diagnostic process, further medical examination and lifestyle intervention may be offered.

**Breastfeeding duration and adult BMI, waist circumference and waist-hip ratio**

In the Terneuzen Birth Cohort we found an inverse dose-response relationship between exclusive breastfeeding duration and BMI at adulthood. Moreover, this inverse dose response relationship existed also with proxies of visceral fat, i.e. waist circumference (WC) and waist-hip ratio (WHR) (Chapter 7). After correction for the educational level and BMI of the mother, for every month of exclusive breastfeeding the BMI, WC and WHR at adulthood decreased by respectively 0.14 kg/m$^2$, 0.42 cm and 0.003 (p<0.05). This implies that for young adults who have been breastfed for 6 months or longer the BMI, WC and WHR are on average respectively 0.84 kg/m$^2$, 2.52 cm and 0.018 lower than for those who have not been breastfed at all. We also found a positive relationship between breastfeeding duration with a healthy breakfast frequency (≥5 times a week) and snack consumption (<2 times a week) at adulthood. However, breakfast frequency and snack consumption did not mediate the relationships with BMI, WC and WHR (Chapter 7).

Our results are in line with several studies that showed that the duration of breastfeeding has an inverse dose-response relationship with the BMI at later ages.23-25
To our knowledge there are no other studies that have shown that exclusive breastfeeding also has an inverse dose-response relationship with proxies of visceral fat, i.e. waist circumference and waist-hip ratio. With respect to dietary behaviour, our results are also in line with another Dutch study,\(^2\) that did not show a mediating effect of dietary factors on the BMI at the age of 7.

The pathways of the beneficial effects of breastfeeding on later body composition still have to be elucidated. Nonetheless, our results indicate that a longer duration of exclusive breastfeeding could be one of the first steps in the primary prevention of cardiometabolic diseases. Our results endorse the health recommendations of the WHO\(^2^7\) to exclusively breastfeed children for at least 6 months. The prevalences of adult overweight and related cardiometabolic risk are high, implying that even a small protective effect of exclusive breastfeeding at an individual level may have a considerable public health impact. In particular, increasing the exclusive breastfeeding duration may have a high public health impact in countries such as the Netherlands with a low percentage of children that is exclusively breastfed for 6 months or longer. In 2005, in the Netherlands this percentage was 15%, in contrast to, for instance, Nordic European countries where 80% of infants are being breastfed for 6 months or longer.\(^2\)

**METHODOLOGICAL CONSIDERATIONS**

Within this thesis the research questions are answered on the basis of analyses of the Terneuzen Birth Cohort data. Some methodological issues that might have influenced our results are discussed in this paragraph. These are the data sample and definitions of important variables and concepts used.

**The Terneuzen Birth Cohort**

The strength of the present cohort study is the unselected and large population-based sample. The Terneuzen Birth Cohort consists of all newborns in Terneuzen, in the south-west of the Netherlands, born between 1977 and 1986 (n=2,604). These subjects had an average of 21 (SD 9.5) growth measurements taken between birth and young adulthood. As we had the opportunity to use growth data that were prospectively
measured by the CHC according to protocol, we were able to perform longitudinal analyses over a much longer follow-up time than the duration of the present study. The measurements in adulthood have been performed according to a protocol by specially trained personnel. Another strength was that the CHC professionals prospectively and accurately collected data about the duration of breastfeeding and formula feeding during regular visits until the age of 6 months. This implies that the risk of recall bias is minimal. Finally, baseline characteristics at birth have been collected for all subjects, enabling us to assess the representativeness of the subjects in the follow-up study.

**Internal validity**
We aimed to maximize the follow-up rate of the participants at young adulthood by incentives, such as combining measurements at young adulthood with a free admission reunion party, 'TOP Dance'. Nevertheless there was – as in most cohorts - a loss to follow-up. However, selection bias is unlikely. First, the subjects who participated were representative with regard to the baseline characteristics of the original cohort except for gender. As the analyses did not show any effect modification for gender, this is unlikely to have influenced the results. Second, for this within-sample analysis, there is no reason to assume that participation in the study is related to the found relationships. It cannot be excluded that socially desirable response tendencies have played a role in answering questions about health-related behaviour. This might have influenced the performance of the metabolic risk score and/or the results regarding the relationships between breastfeeding and dietary behaviour at young adulthood. By using more objective and/or standardized measurement methods, this bias could be reduced.

**External validity**
The Terneuzen Birth Cohort is a Caucasian cohort born between 1977 and 1986 in Terneuzen. The percentage of mothers that breastfed their children in Terneuzen was of the same magnitude as in other parts of the Netherlands for the period 1977-1986. This gives an indication of the external validity of our results for other Caucasians in the Netherlands. Also, we should be aware that cohort effects may be possible. As we are living in a more and more obesogenic society, our results need to be validated in younger cohorts as well. Finally, validation in other ethnicities is warranted.
Conceptual framework

Within this thesis several definitions and concepts were used. We discuss the definitions and concepts applied that are essential in their possible implications for our study results.

Definition of overweight
Overweight during childhood was defined with the BMI values (kg/m\(^2\)), converted to age-specific standard deviation scores (BMI SDS) based on Dutch reference data from 1996-7,\(^{30}\) as these are most comparable to our study population. Using international instead of national reference data in longitudinal analyses probably would have generated less accurate results, as the ages between which critical periods tend to occur, e.g. adolescence, differ by ethnicity.\(^5\) We have chosen to use the BMI SDS scale, mainly because it eliminates the relatively large variation of the BMI resulting from ageing, including the fall and rise of the BMI around the adiposity rebound.\(^{31}\) This simplifies the interpretation of the results, without affecting them. Within the Terneuzen Birth Cohort data we had serial BMI measurements at our disposal. The BMI is the most common measure used to estimate body fat. Our results might have been influenced by the fact that the BMI (SDS) not only reflects body fat mass, but also lean mass (Chapter 1). Therefore, a relatively high BMI SDS increase during the age interval 2-6 years may be due to an increase in muscular and/or bone tissue. However, several studies have shown that an upwards centile crossing of the BMI just before the age of 6 years\(^{31}\) is caused by a rapid elevation in the deposition of body fat rather than lean tissue mass.\(^7\) Nonetheless, the age dependency of the extent to which fat is stored in either the visceral or the subcutaneous fat depots\(^{14}\) might have influenced our results.

Definition of metabolic syndrome
Several definitions of metabolic syndrome exist. In contrast to the WHO and EGIR criteria, the NCEP ATPIII and IDF definition underline central obesity as an essential component of the metabolic syndrome\(^{32,33}\) and do not require the assessment of insulin resistance or a glucose tolerance test (GTT). Consequently, the latter two definitions are most suitable for population-based studies and are best applicable in primary health care for early detection. Because the NCEP ATPIII definition is most commonly used,\(^{34}\) this definition has been chosen in our study. Several studies have shown that
the concordance between definitions is modest, although the predictive value of future cardiovascular diseases for the NCEP ATPIII, IDF and WHO definition are of the same magnitude. The present attempts to harmonize the definition of the metabolic syndrome are based on several principles that are largely met by the NCEP ATPIII definition. Nevertheless, a different definition as outcome variable might have yielded other results.

**Critical period and age intervals**
Indications exist that it is not the BMI level *per se*, but rather the change in BMI level that is related to risk of overweight and obesity and its comorbidity. Dietz defined a critical period for the development of obesity and its complications as a developmental stage in which physiologic alterations increase the later prevalence of obesity and related comorbidity more than in other periods. In our study we consider the BMI SDS change as the physiologic alteration. Usually, BMI SDS changes during growth are not studied in relation to the development stage of an individual child, but in relation to his or her age. Using age intervals as a proxy of development stage has the practical advantage that preventive interventions can be based on age, which is easier to measure and register. Therefore we made the assumption that a critical period is equivalent to the age interval in which the developmental stage is supposed to occur. We have chosen the age intervals in relationship to developmental stages as described in literature (Chapter 2). Nevertheless, this assumption might have attenuated the relations with later overweight. Also the width of the age intervals may have influenced the study results. By combining subsequent age intervals, the relationship with the outcome variable will be an average of the relationships of these age intervals.

**The broken stick model**
In our study we had to deal with irregular spacing between measurements and missing growth data. We solved the problem of the varying number and timing of the measurements between individuals, by fitting each individual BMI SDS trajectory by a piecewise linear model, known as the broken stick-model. Figure 2 contains longitudinal trajectories of height, weight and BMI SDS from 6 individuals from the Terneuzen birth Cohort, showing that the individual broken sticks consistently capture all relevant aspects of the individual data (Figure 2).
The broken stick model will shrink the trajectory of persons with only a few measurements towards the global mean. This implies that any test of differences will be conservative, and possibly underestimates the effects of BMI SDS changes in periods with fewer measurements. As the mean number of measurements (≈1.6) in the period 6-10y are about half the number (≈2.7) in the age interval 2-6y, the relationships of BMI SDS in the age interval 6-10y with adult overweight and cardiometabolic risk might have been underestimated. However, the age intervals 2-4y and 4-6y have approximately the same number of measurements (≈1.3) as the age interval 6-10y, and the BMI SDS changes within both age intervals, 2-4y and 4-6y, are strong predictors of adult BMI and cardiometabolic risk.

IMPLICATIONS AND RECOMMENDATIONS

The results of this thesis offer several possibilities to improve primary prevention of overweight and obesity, and its comorbidity in both young children and young adults. In this paragraph, we will describe the possible practical implications and recommendations for future research.

Practical implications

Primary prevention of overweight in children

Primary prevention of overweight and related cardiometabolic risk targeted at individuals should especially focus on preventing upwards centile crossing in the age interval 2-6 years. Currently, targeted prevention against overweight is offered to those children that are overweight according to the IOTF cut-offs. The developed prediction tool, diagrams based on two measurements of the BMI, may lead to the early detection of young children at high risk of adult overweight. These diagrams could help the professional to indicate how the BMI of a child should develop from 2 years of age to respectively 4 and 6 years of age to minimize the risk of adult overweight. At the age of 4 years, a mid-term estimate of risk of adult overweight can be calculated with the help of the diagram for 2-4y. Based on this risk estimation the professional could make the decision whether or not tailored preventive interventions should be offered. In this way, also children without overweight but with a relatively strong increase in their BMI may be selected. On the other hand, the professional may decide not to offer a
preventive intervention to children with overweight if a relatively decline of the BMI in the preceding period has been observed. In addition, the tool may be helpful in sustaining professionals to motivate parents to adhere to a healthy lifestyle. If interventions are offered before the age of 6 years with the aim of preventing overweight, the effects of these interventions can be monitored and evaluated on the basis of the risk assessment by the same risk diagrams (Chapter 5). We suggest that the estimated risk should be taken as the primary outcome, instead of BMI (SDS). Of course, before implementing the tool within CHC, it should be validated and possibly adapted to variables such as ethnicity.

Detection of young adults with metabolic syndrome in a general population
By detecting young adults with metabolic syndrome, lifestyle interventions can be offered, which could yield high health gain at the population level. Because most young adults are still in the beginning of their reproductive life phase, future generations will also benefit from their lifestyle modifications. Before we have the opportunity to intervene, we should know how to identify the group at highest risk. Both strategies we have developed offer opportunities to detect metabolic syndrome in young adults without the necessity to perform blood tests. The stepwise approach, which is based on the assessment of BMI, WC and blood pressure, enables the omission of blood tests in most young adults (Chapter 5). The Metabolic Risk Score is a simple questionnaire which seems easily applicable within settings where young people often spend their time together, such as at work, school, and sport events (Chapter 6). After deciding on cut-offs for the MRS, a person with a MRS above the cut-off could be invited for further medical evaluation with the aim of excluding or diagnosing metabolic syndrome. It seems reasonable to use a cut-off of 25. For this cut-off the percentages of false positives and false negatives are respectively 27 and 12%, whereas the percentage of the total population in the Terneuzen Birth Cohort that is offered medical evaluation without having metabolic syndrome is 25%.

Both strategies, the stepwise strategy and the MRS, have potential to be implemented by CHC after validation in other populations.

Reinforcement of promotion of exclusive breastfeeding of 6 months or longer
The results from the Terneuzen Cohort Study show an inverse dose-response relationship of the duration of exclusive breastfeeding with BMI, WC and WHR at
adulthood, which appeared to be independent of age, gender and BMI and educational level of the mother. Our results reinforce the World Health Organization’s recommendation to exclusively breastfeed for the first 6 months of life in order to achieve optimal growth, development and health (Chapter 7). These results may be an extra reason, in addition to all other beneficial effects of breastfeeding, for professionals in their advisory role to the parents to stimulate a longer duration of exclusive breastfeeding.

Implementation within the Child Health Care (CHC) in the Netherlands
In the Netherlands, the improvements in primary preventive care, as suggested on the basis of this thesis, may be embedded in the Child Health Care practice. The Dutch CHC offers a nationwide program, free of charge and supported by the government. The CHC in the Netherlands reaches more than 90% of all Dutch infants from birth onward after birth and at set ages until the age of 19 years. This implies that the Dutch CHC has the potential to be successful in offering primary preventive interventions. This has been demonstrated by the decline of the incidence of sudden unexpected infant death since 1987. During the CHC check-ups, the height and weight of each child are measured until the age of 14 years. Where needed, the growth of an individual child is also measured more frequently and at later ages.

The CHC system has excellent opportunities to implement the risk diagrams and to subsequently offer primary prevention of overweight targeted at individual children at high risk of developing overweight. For the use of the risk score diagrams to predict adult overweight, relevant ages at which growth is routinely monitored by the CHC are 18 months, and 2, 3, 3.9 and 5.5 years. At the age of 18 months or 2 years the risk estimation tool might be introduced to the parents as a new monitoring instrument. Especially children with a high risk of overweight, e.g. children from parents with an increased BMI, may benefit from these risk estimations. After the subsequent ages of 3, 3.9 and 5.5 years, the BMI development might be monitored with the help of the diagrams. At the chosen cut-off or if the estimated risk of adult overweight increases, the child can be offered preventive interventions, before the child is actually overweight. By assessing the risk of adult overweight at each following visit to the CHC, the results of the intervention can be evaluated. Based on these longitudinally-
performed risk assessments the professional might decide to continue or to change her advice or intervention.

Several policy makers and Child Health Care professionals have pleaded for the extension of the age span of the target population of CHC to 23 years. If this is realized, the CHC may also play a role - in cooperation with other professionals - in the early detection of metabolic syndrome in young adults, with the ultimate goal of also offering them targeted preventive interventions. After assessing the risk of metabolic syndrome with the help of the MRS, (Chapter 6) these young adults might be invited for a further (stepwise) evaluation as described in Chapter 5. If metabolic syndrome is diagnosed, an effective lifestyle intervention should be offered, aimed at exercise and dietary behavior.41

**Recommendations for future research**

The results and used methods in our research lead to several recommendations for future research.

**BMI and other methods in monitoring overweight development**

The measurement of the BMI is simple to perform and is used worldwide by professionals in preventive and curative health care. However, the BMI reflects total body mass, including bone and muscular tissue, and not only fat mass. Therefore several measurements have been compared with BMI in estimating body composition, especially BIA, skinfold thickness, and DXA.44 In addition, it has been shown that waist circumference and even neck circumference45,46 give more precise information about the presence of fat depots that are specifically harmful to health.47 The changes in BMI during growth, however, give more information than the BMI at a particular point in time. This supports the hypothesis that serial measurements of BMI during growth can be used to approximate the change in total fat mass.5 This is based on the assumption that for each individual child the optimal and thus healthy ratio of fat, bone and muscle mass is genetically determined. Although the optimal ratio between fat, bone and muscle mass changes with age, large variations of the BMI SDS are not expected, unless affected by an unhealthy increase of fat mass, or - highly unlikely - abnormal increase of bone or muscular mass, as induced by intensively playing sport.
Figure 2. Broken stick trajectories for height, weight and BMI SDS from six individuals from the Terneuzen Birth Cohort. Subjects 1259 and 7019 have a fairly common pattern, subject 2447 has a dip near the age of 4 months, subject 7460 has a change in the height/weight proportions during the 1st year, subject 8046 has an increase during infancy and subject 7646 has an unusually large increase in BMI between birth and puberty.
Therefore, serial measurements of BMI might be as reliable as serial measurements of other variables, such as waist circumference, in estimating the risk for later overweight and its comorbidity. As long as the surplus value of serial measurements of other variables is not shown, this might imply that searching for other measurements than BMI to monitor abnormal changes in total body fat mass in growing children is not necessary.

Feasibility and validation of the overweight prediction tool
Professionals are calling for a more objective guidance in providing preventive interventions against overweight. Currently, the decision to offer preventive interventions is based on the IOTF criteria. These criteria are not related to a risk estimation of developing overweight and cardiometabolic risk. After validation and possible adaptation, we recommend an implementation and evaluation study into the feasibility of using the risk score diagrams as a decision tool in combination with preventive interventions such as the Transition plan, which is used by most CHC centers. In the Netherlands this study can easily be carried out within the CHC practices. In addition, the relative contributions of BMI SDS changes between birth and young adulthood to adult overweight and metabolic risk should be confirmed in other ethnicities and in younger cohorts, living in an increasingly obesogenic society. If confirmed in other studies, the underlying mechanism of the predictive value of the age interval 2-6y should be elucidated. The diagrams for the age interval 2-6y to predict adult overweight should be validated in younger cohorts as well. Beyond validation, adapting the tool to populations from another ethnicity, to the BMI SDS development before the age of 2 years or to other risk factors, such as parental weight status, might be necessary. A more advanced digitized tool can be developed by exploring the use of longitudinal prediction models based on the repeated measurements of BMI at different ages.

Finally, the predictive value of subsequent age intervals for cardiometabolic risk as found in our study gave rise to research questions that remain to be answered. We found that the BMI change in the age interval 0-1y and adult hsCRP is positively related, and that the BMI change in the age interval 6-10y is negatively associated with adult HDL cholesterol. If replicated in other studies, our hypotheses about the underlying mechanisms (Chapter 4) need profound investigation.
Development and evaluation of a lifestyle intervention for young adults with metabolic syndrome

The prevalence of metabolic syndrome in young adults is around 7.5%, and is higher in young adults with a higher BMI. Lifestyle modification has been proven effective in diminishing cardiometabolic risk in older adults. However, until now no interventions have been evaluated for this young age group with metabolic syndrome. Therefore, we recommend the development and evaluation of a lifestyle intervention for young adults with metabolic syndrome.

Validation of the stepwise approach and the Metabolic Risk Score to assess metabolic syndrome

After validation of both the stepwise approach and the MRS, they both offer possibilities to detect metabolic syndrome in young adults without the performance of blood tests in all subjects. In addition to validation, we also recommend an investigation into the possible surplus value of adaptation of the MRS by combining the MRS with the self-measurement of waist circumference. The investigation of the efficiency of combining the two strategies, the MRS with the stepwise approach, is a logical next step to assess if the efficiency of the diagnostic process can be further increased.

The influence of breastfeeding duration

We could not show that dietary factors were a pathway of the beneficial effects of breastfeeding to later body composition. However, our data partly reflect caloric, nutrient and fat intake. Moreover also epigenetic influences of breastfeeding may play a role, which are related to the maternal diet during lactation. Another Dutch study showed that lower risk of overweight at 7 years of age in relation to the non-exclusive breastfeeding duration is already achieved at 1 year of age. In this study, the included period of mixed infant feeding might have attenuated the found relationship after the age of 1 year. However, others found that infant weight change between birth and 6 months of age did not mediate association of breastfeeding with BMI at the age of 3 years. For a better understanding of the protective effects of (a longer) exclusive breastfeeding (duration) we recommend prospective research into the effects of breastfeeding (duration) on several (changes in) anthropometrical and cardiometabolic outcomes at subsequent ages during growth. Herewith, the feeding pattern of the
mother during lactation as well as the child should be taken into account, to be assessed by validated instruments.

**Cohort studies on the basis of data collected by Child Health Care:**
Our study shows that it is feasible to conduct longitudinal studies over a long life span on the basis of data that are prospectively collected by the Dutch CHC professionals. In the Terneuzen Birth Cohort detailed data on breastfeeding duration and baseline characteristics of all members of the cohort were available, enabling a study into the representativeness of the adult study population for the original study population. In the future performing cohort studies on the basis of CHC data will even be more feasible, as collected data will be digitized and standardized throughout the Netherlands. Connections with the data of the Dutch Perinatal Registration (PRN), which are data from midwives, gynecologists and pediatricians, will enhance the study into the baseline characteristics and the influence of perinatal risk factors. By extending the age span to the prenatal phase (–9 months) and to young adulthood (23 years of age), the duration of follow-up by the CHC will increase from the prenatal phase until young adulthood. This will even offer opportunities to study transgenerational effects on the health of children.

The longitudinal care by CHC is primarily meant to guarantee and protect the health of each individual child throughout its life course. The Terneuzen Birth Cohort study has proven that the longitudinally-collected data also offer valuable - time and effort saving - opportunities to generate more knowledge about targets and methods for prevention. In the future we should take more and more advantage of these possibilities as generated by the CHC system.
Highlights of this thesis

An increasing BMI SDS during the age interval 2-6 years is most predictive of adult overweight and cardiometabolic risk. Primary prevention of overweight and cardiometabolic risk may be possible by preventing a BMI SDS increase between 2 and 6 years.

A prediction instrument based on the BMI changes between 2 and 6 years of age is promising to assess the risk of adult overweight.

By a stepwise diagnostic strategy based on the measurement of BMI, waist circumference and blood pressure, in most young adults blood tests are superfluous to exclude metabolic syndrome.

By a risk score, based on six simple questions, identification of young adults with increased risk of metabolic syndrome is feasible.

Exclusive breastfeeding has an inverse dose response relationship with adult BMI, waist circumference and waist-hip-ratio, proxies of visceral fat. This adds evidence to promote exclusive breastfeeding up to 6 months at least.

This thesis illustrates that data from routine child health care are suitable for scientific research.
REFERENCES


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Summary

The Terneuzen Birth Cohort
Detection and Prevention of Overweight and Cardiometabolic Risk from Infancy Onward
In **Chapter 1** the background, relevance, definitions, concepts used and the outline of the thesis are described.

The aim of this thesis is to contribute to the early identification and prevention of overweight and related cardiometabolic risk. The ultimate goal is to offer primary prevention at the right time to those who need it most. The major research questions are:

1. During which age intervals are children most susceptible to adult overweight and its related cardiometabolic risk?
2. How can we detect young adults with metabolic syndrome in a general population?
3. What is the relationship of exclusive breastfeeding duration with BMI, waist circumference and waist-hip-ratio at young adulthood?

We have used data from the Terneuzen Birth Cohort (n=2,604). Data on breastfeeding duration were prospectively collected from birth until 6 months of age in all children born in 1977-1986 in Terneuzen. Data on growth, collected by the Child Health Care, were yielded for 1,701 subjects. The subjects were invited to participate in the follow-up study in 2004-2005. We received 822 questionnaires, and performed measurements of weight, height, waist circumference, blood pressure and skinfold thickness in 762 subjects. We determined glucose, HDL cholesterol, triglycerides and high-sensitivity C-reactive protein (hsCRP) in fasting blood samples from 642 subjects. These subjects were representative of the original cohort regarding most baseline characteristics, e.g. age, birth weight, parity, and breastfeeding.

The objective of **Chapter 2** was to assess which age intervals during childhood are most predictive of adult overweight, and the identification of the earliest critical growth period for adult overweight. In total, data from 762 subjects on growth with an average of 21 measurements per subject from birth until 18 years were analyzed. The main outcome measure was the BMI standard deviation score (SDS) at young adulthood. For each subject the BMI SDS trajectory was fitted by the broken-stick model, which gave an estimation of the BMI SDS at 8 different ages between birth and 18 years. The age intervals 2-6y and 10-18y were predictive for adult BMI SDS. The largest rise in correlation between estimated BMI SDS and measured adult BMI SDS occurs during the period 2-6y, resulting in a high sensitivity and specificity at the age of 6 years. The
BMI SDS change between 2 and 6 years of age has relatively the largest contribution to adult overweight. These findings indicate that primary prevention of overweight should be especially directed towards upwards centile crossing in the age interval 2-6 years.

The aim of Chapter 3 was to determine which age intervals are predictive of cardiometabolic risk at young adulthood. Data were used from 642 subjects from the Terneuzen Birth Cohort for whom data on growth, physical examination and blood tests were available. The main outcomes are the components of the metabolic syndrome according to the NCEP ATPIII definition, skinfold thickness and the level of hsCRP. All BMI SDS changes from birth onwards were related to waist circumference and skinfold thickness in young adults. BMI SDS change between 2 and 6 years was strongly related to the outcome variables, especially to waist circumference, systolic blood pressure, diastolic blood pressure and hsCRP at young adulthood. The BMI SDS change between 10 and 18 years was most strongly related to HDL cholesterol and triglycerides. To a lesser degree the BMI SDS changes 6-10y were also related to most outcome variables. Fasting blood glucose was not predicted by any BMI SDS change at all. BMI SDS changes 2-6y and 10-18y were significantly related to metabolic syndrome in young adulthood. We conclude that BMI SDS changes from the age of 2y onwards were related to cardiometabolic risk at young adulthood, the age interval 2-6y being the most predictive.

In Chapter 4 we describe the development of a tool to identify 2-6 years old children at high risk of adult overweight. The prediction models included gender and the BMI SDS at 2 and 4 years, at 2 and 6 years, at 4 and 6 years and at 2, 4 and 6 years of age, respectively. Risk models for adult overweight are shown for the age intervals 2-4y and 2-6y as risk score diagrams, given the BMI at the start and the end of the age intervals. The choice of a cut-off at 50% seems sensible as this is associated with only 8% of false positive results. Our tool might support preventive healthcare professionals in the early detection of young children at high risk of adult overweight. Moreover the tool can be used for primary prevention by informing parents about the risks of upwards centile crossing during the age interval 2-6 years. After external validation, a wider adoption of this tool might enhance primary prevention of overweight during a sensitive period in human growth.
Because blood tests necessary for the identification of MetS are an invasive and costly procedure, the objective in Chapter 5 was to develop an efficient and simple stepwise strategy to identify metabolic syndrome in young adults. Data were used from 642 subjects of the Terneuzen Birth Cohort. The overall prevalence of MetS according to the NCEP ATPIII was 7.5%. Tree regression was used to determine the optimal decision strategy to identify metabolic syndrome. Results show that if BMI <30, refining the BMI-categories was of no additional value in estimating the risk of MetS. However, risk estimates improved by dividing the category BMI ≥30 in two categories. Depending on the accepted level of error, between 50% and 90% of blood tests are superfluous for the diagnosis of metabolic syndrome. Also in less frequent combinations, such as a BMI between 30 and 35 and a normal WC and BP (5.6% of the persons with this BMI), the omission of blood tests may have an important impact at population level. The stepwise diagnostic procedure may contribute to the development of more efficient and less invasive way to assess the presence of metabolic syndrome in young adults in general practice.

The objective in Chapter 6 was to develop a risk score to detect metabolic syndrome (NCEP ATPIII) in young adults in a general population. Data were used from 642 subjects of the Terneuzen Birth Cohort. Predictors were selected if they are known risk factors for cardiometabolic-related health problems, and if they can easily be determined by the individuals themselves. After backward multiple logistic regression, the final prediction model retained the following variables: BMI, having breakfast, smoking behaviour, participation in physical sports, and being firstborn. After internal validation, the regression coefficients were transformed into easy-to-use risk scores. The sum of the risk scores, the Metabolic Risk Score (MRS), can be used as a prediction instrument in general practice. We propose using a cut-off of 25. With the MRS, primary prevention of type 2 diabetes and cardiovascular diseases will become realistic for young adults with MetS, even for those with an apparently normal BMI.

The objective of Chapter 7 was to assess the relationship between exclusive breastfeeding duration and BMI, waist circumference and waist-hip ratio at young adulthood, and to study if dietary behaviour mediated these relationships. We used the data of 822 subjects who filled in postal questionnaires in 2004-2005, including 762 subjects that underwent anthropometric measurements. By linear regression analysis
Summary

and after correction for age, gender and possible confounders a significant inverse dose-response relationship was found between breastfeeding duration (in months) and BMI, waist circumference and waist-hip-ratio. Exclusive breastfeeding duration was also significantly related to a breakfast frequency of at least 5 times a week, and snack consumption less than twice a week. Mediation of diet factors was not shown. The results underline the health recommendations of the WHO to exclusively breastfeed children for at least 6 months.

In Chapter 8 the main results of this thesis, some methodological considerations such as the definition of overweight, obesity and cardiometabolic risk, and possible limitations of the broken stick method are described. This chapter ends with recommendations for clinical practice and for future research.

In conclusion, conducting longitudinal scientific studies over a long life span on the basis of data that are prospectively collected by the Dutch Child Health Care professionals is feasible. Our results may contribute to improving primary prevention of overweight and related cardiometabolic risk by the Child Health Care organizations.
Samenvatting

Het Terneuzen Geboortecohort
Detectie en Preventie van Overgewicht en Cardiometabool Risico vanaf de Geboorte
Samenvatting

In **Hoofdstuk 1** worden de achtergrond, relevantie, gebruikte definities en concepten, en de opbouw van de thesis beschreven.

Het doel van dit proefschrift is om bij te dragen aan de vroege herkenning en preventie van overgewicht en hieraan gerelateerd cardiometaboool risico. Het uiteindelijke doel is om op het juiste moment primaire preventie aan te bieden aan diegenen die dit het hardst nodig hebben. De belangrijkste onderzoeksvragen zijn:
1. Gedurende welke leeftijdsintervallen tijdens de groei zijn kinderen het meest gevoelig voor het ontstaan van overgewicht en hieraan gerelateerd cardiometaboool risico op volwassen leeftijd?
2. Hoe kunnen we jong-volwassenen met metabool syndroom opsporen in een algemene populatie?
3. Welke relatie bestaat er tussen exclusieve borstvoedingsduur en BMI, middelomtrek en middel-heup-ratio op jong-volwassen leeftijd?

We hebben de gegevens gebruikt van het Terneuzen Geboorte Cohort (n=2.604). Van alle kinderen die in 1977-1986 in Terneuzen zijn geboren, werden prospectief vanaf de geboorte tot de leeftijd van 6 maanden gegevens verzameld over de borstvoeding. Van 1.701 personen werden de groeigegevens verkregen, die zijn vastgelegd door de Jeugdgezondheidszorg. Deze personen werden uitgenodigd om deel te nemen aan een vervolgonderzoek in 2004-2005. We ontvingen van 822 personen vragenlijsten, en hebben bij 762 personen gewicht, lengte, middelomtrek, bloeddruk en huidplooidikte gemeten. Bij 642 personen hebben we de nuchtere bloedgehaltes bepaald van glucose, HDL cholesterol, triglyceriden en high-sensitive C-reactive protein (hsCRP). Deze personen waren representatief voor het originele cohort wat betreft de meeste achtergronddeterminanten, namelijk leeftijd, geboortegewicht, pariteit en borstvoeding.

Het doel van **Hoofdstuk 2** was om vast te stellen welke leeftijdsintervallen tijdens de groei het meest voorspellend zijn voor overgewicht op volwassen leeftijd, en om de vroegst kritische groeiperiode voor overgewicht op volwassen leeftijd te identificeren. Groeigegevens van in totaal 762 personen zijn geanalyseerd met een gemiddeld aantal van 21 metingen van lengte en gewicht per persoon vanaf de geboorte tot aan de leeftijd van 18 jaar. De uitkomstmaat was de BMI standaard deviatie score (SDS) op

Het doel van Hoofdstuk 3 was om vast te stellen welke leeftijdsintervallen voorspellend zijn voor cardiometabool risico op volwassen leeftijd. Hiertoe werden gegevens geanalyseerd van de 642 personen van het Terneuzen Geboorte Cohort van wie groeigegevens en gegevens van lichamelijk onderzoek en bloedtesten beschikbaar waren. De belangrijkste uitkomstvariabelen waren de componenten van het metabool syndroom volgens de NCEP ATPIII definitie, de huidplooidikte en het hsCRP gehalte in het bloed. Het bleek dat alle BMI SDS veranderingen vanaf de geboorte gerelateerd waren aan middelomtrek en huidplooidikte bij jongvolwassenen. De BMI SDS verandering tussen 2- en 6-jarige leeftijd was sterk gerelateerd aan de uitkomstvariabelen, vooral aan middelomtrek, systolische bloeddruk, diastolische bloeddruk en hsCRP op volwassen leeftijd. De BMI SDS verandering tussen 10- en 18-jarige leeftijd was het sterkst gerelateerd aan HDL cholesterol en triglyceriden. Ook de BMI SDS verandering tussen 6- en 10-jarige leeftijd was gerelateerd aan de uitkomstvariabelen, zij het in mindere mate. Nuchtere bloedglucose werd door geen enkele BMI SDS verandering tijdens de groei voorspeld. BMI SDS veranderingen tussen 2- tot 6-jarige leeftijd, en 10- tot 18-jarige leeftijd waren significant gerelateerd aan het metabool syndroom op jongvolwassen leeftijd. We concluderen dat BMI SDS veranderingen vanaf de leeftijd van 2 jaar gerelateerd waren aan cardiometabool risico op jongvolwassen leeftijd, waarbij het leeftijdsinterval 2-6 jaar het meest voorspellend bleek te zijn.
In Hoofdstuk 4 wordt beschreven hoe we een instrument hebben ontwikkeld om hoog risico op overgewicht op volwassen leeftijd te voorspellen voor 2- tot 6-jarige kinderen. De predictiemodellen bevatten geslacht en de BMI SDS op respectievelijk 2- en 4-jarige leeftijd, op 2- en 6-jarige leeftijd, op 4- en 6-jarige leeftijd en 2-, 4- en 6-jarige leeftijd. In risicoscore-diagrammen zijn op basis van de BMI aan het begin en op het einde van het leeftijdinterval de risicomodellen voor overgewicht op volwassen leeftijd weergegeven voor de leeftijdsintervallen 2-4 jaar en 2-6 jaar. De keuze voor een afkapwaarde van 50% lijkt redelijk, aangezien deze is geassocieerd met slechts 8% vals-positieve resultaten. Ons instrument zou professionals die werkzaam zijn in de preventieve gezondheidszorg kunnen ondersteunen bij de vroege detectie van jonge kinderen met een hoog risico op overgewicht op volwassen leeftijd. Bovendien kan het instrument worden gebruikt voor primaire preventie door ouders te informeren over de risico's van een relatief sterke BMI toename tijdens het leeftijdinterval 2-6 jaar. Na externe validatie, zou het op brede schaal toepassen van het instrument de primaire preventie kunnen bevorderen gedurende een erg gevoelige periode in het menselijk leven.

Omdat voor het vaststellen van het metabool syndroom de noodzakelijke bloedtesten invasief en kostbaar zijn, was het doel van Hoofdstuk 5 een efficiënte en stapsgewijze strategie te ontwikkelen om het metabool syndroom bij jongvolwassenen vast te stellen. Er zijn gegevens gebruikt van 642 personen van het Terneuzen Geboorte Cohort. De prevalentie van het metabool syndroom in het totale cohort bedroeg 7.5%. Tree regressie analyse werd gebruikt om de optimale beslissingsstrategie vast te stellen om het metabool syndroom te diagnostiseren. Het bleek dat als BMI <30, een verdere verfijning van de BMI-categorieën geen additionele waarde had om het risico op metabool syndroom te schatten. Risicoschattingen verbeterden echter wel door de categorie 'BMI ≥30' in tweeën te delen. Afhankelijk van het geaccepteerde niveau van error, bleek tussen de 50 en 90% van de bloedtesten overbodig te zijn om het metabool syndroom te diagnostiseren. Ook in minder voorkomende gevallen, zoals de combinatie van een BMI tussen de 30 en 35 met een normale middelomtrek en bloeddruk (bij 5.6% van de personen in deze BMI categorie), zou het weglaten van de bloedtesten een belangrijke impact kunnen hebben op populatieniveau. Deze stapsgewijze diagnostische procedure kan in de algemene praktijk bijdragen aan een
efficiëntere en minder invasieve manier om het metabool syndroom vast te stellen bij jongvolwassenen.

Het doel in Hoofdstuk 6 was om een risicoscore te ontwikkelen om het metabool syndroom (NCEP ATPIII) vast te stellen bij jongvolwassenen in de algemene populatie. Van 642 personen van het Terneuzen Geboorte Cohort zijn de gegevens geanalyseerd. Kandidaatpredictoren werden geselecteerd als ze bekende risicofactoren zijn voor cardiometabool gerelateerde gezondheidsproblemen en ze gemakkelijk door de jongvolwassenen zelf kunnen worden vastgelegd. Na backward multiple logistische regressie, bevatte het definitieve risicomodel de volgende variabelen: BMI, ontbijten, rookgedrag, deelname aan fysieke sport en het eerstegeboorene zijn. Na interne validatie werden de regressiecoëfficiënten getransformeerd tot gemakkelijk bruikbare risicoscores. De som van de risicoscores, de Metabole Risico Score (MRS), kan worden gebruikt als een risicoinstrument in de algemene praktijk. We stellen voor om 25 als afkappunt te gebruiken. Met de MRS, zal primaire preventie van type 2 diabetes en cardiovasculaire ziekten bij jongvolwassenen met metabool syndroom realistisch worden, zelfs voor diegenen met een ogenschijnlijk normale BMI.

Het doel van Hoofdstuk 7 was om de relatie tussen exclusieve borstvoedingsduur met BMI, middelomtrek en midden-heup-ratio vast te stellen, en om te bestuderen of dieetgedrag (één van) deze relaties medieert. We gebruikten de gegevens van 822 personen van het Terneuzen Geboorte Cohort die per post verstuurde vragenlijsten invulden in 2004-2005. Van hen hebben 762 personen antropometrische metingen ondergaan. Door lineaire regressie analyse na correctie voor leeftijd, geslacht en mogelijke confounders, vonden we een omgekeerde dosis-respons relatie tussen borstvoedingsduur (in maanden) en BMI, middelomtrek en midden-heup-ratio. Exclusieve borstvoedingsduur was ook significant gerelateerd aan een ontbijtfrequentie van minstens 5 keer per week, en snack-consumptie van minder dan 2 keer per week. Mediatie van deze dieetfactoren kon niet worden aangetoond. De resultaten onderstrepen de aanbevelingen van de WHO om kinderen gedurende ten minste 6 maanden exclusieve borstvoeding te geven.

In Hoofdstuk 8 worden de belangrijkste resultaten van de thesis, sommige methodologische aspecten, zoals de definitie van overgewicht, obesitas en
Samenvatting
cardiometabool risico, en de mogelijke beperkingen van de ‘broken stick’ methode beschreven. Dit hoofdstuk eindigt met aanbevelingen voor de klinische praktijk en toekomstig onderzoek.

De conclusie is dat het uitvoeren van wetenschappelijke studies die een lange leeftijdsspanne overbruggen haalbaar zijn op basis van prospectief verzamelde gegevens door professionals die werkzaam zijn bij de Jeugdgezondheidszorg. Onze resultaten kunnen bijdragen aan de verbetering van de primaire preventie door de Jeugdgezondheidszorg van overgewicht en hieraan gerelateerd cardiometabool risico.
**LIST OF ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>Adj $R^2$</td>
<td>adjusted explained variance</td>
</tr>
<tr>
<td>AO</td>
<td>adult overweight</td>
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<td>AR</td>
<td>adiposity rebound</td>
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<tr>
<td>AUC</td>
<td>area under the curve</td>
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<td>BF</td>
<td>breastfeeding</td>
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<td>BMI</td>
<td>body mass index</td>
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<td>BMI SDS</td>
<td>BMI standard deviation score</td>
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<tr>
<td>BP</td>
<td>blood pressure</td>
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<tr>
<td>CHC</td>
<td>Child Health Care (synonym of Youth Health Care)</td>
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<tr>
<td>DBP</td>
<td>Diastolic Blood Pressure</td>
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<tr>
<td>DRS</td>
<td>Diabetes Risk Score</td>
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<tr>
<td>EGIR</td>
<td>European Group for the Study of Insulin Resistance</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>GGD</td>
<td>Gemeentelijke Gezondheidsdienst (in English: Municipal Health Services)</td>
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<tr>
<td>HDL</td>
<td>high-density lipoprotein</td>
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<tr>
<td>hsCRP</td>
<td>high-sensitivity C-reactive protein</td>
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<tr>
<td>IDF</td>
<td>International Diabetes Federation</td>
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<tr>
<td>IOTF</td>
<td>International Obesity Task Force</td>
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<tr>
<td>LMS</td>
<td>least mean square</td>
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<tr>
<td>MetS</td>
<td>metabolic syndrome</td>
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<tr>
<td>MRS</td>
<td>Metabolic Risk Score</td>
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<tr>
<td>NCEP ATPIII</td>
<td>National Cholesterol Education Program Adult Treatment Panel III</td>
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<tr>
<td>NPV</td>
<td>negative predictive value</td>
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<tr>
<td>OR</td>
<td>odds ratio</td>
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<tr>
<td>PPV</td>
<td>positive predictive value</td>
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<tr>
<td>PRN</td>
<td>Perinatal Registration of the Netherlands</td>
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<tr>
<td>ROC</td>
<td>Receiver Operating Characteristic</td>
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<tr>
<td>SBP</td>
<td>Systolic Blood Pressure</td>
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<tr>
<td>SD</td>
<td>standard deviation</td>
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<tr>
<td>SE</td>
<td>standard error</td>
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<tr>
<td>SES</td>
<td>social economic status</td>
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<tr>
<td>y</td>
<td>years(s)</td>
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<tr>
<td>YHC</td>
<td>Youth Health Care (synonym of Child Health Care)</td>
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<tr>
<td>WC</td>
<td>waist circumference</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>WHR</td>
<td>waist hip ratio</td>
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<tr>
<td>ZonMw</td>
<td>Zorgonderzoek Nederland en Medische Wetenschappen (in English: Care research of the Netherlands and Medical Science)</td>
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DANKWOORD

De weg naar de voltooiing van dit proefschrift was inspirerend en leerzaam. Op deze weg heb ik met veel mensen te maken gehad die ik dankbaar ben voor hun bijdrage en hun steun.


Heel in het bijzonder gaat mijn dank uit naar de volgende personen.

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Maria Louisa Antonia (Marlou) de Kroon was born on 6 April 1961 in The Hague, the Netherlands. She completed Gymnasium β in Eindhoven, Augustinianum, in 1979 (cum laude), and started her study medicine at the Catholic University of Nijmegen, the Netherlands. After her graduation in 1987, she participated in scientific research projects at the Daniel den Hoed-cancer clinics and the Erasmus University Rotterdam. She was registered as an epidemiologist A in 1993. Because of her love and interest for children and preventive health care, she decided to become a practicing Child Health Care physician and was registered in 1998. Finally, she decided to combine her love for children with her affinity for epidemiologic research. Between 2000 and 2002 she was Child Health Care physician and epidemiologist at the Municipal Health Services in Delft. In 2002 she wrote a grant application for the Terneuzen Birth Cohort Study, at the request of Professor dr. Remy A HiraSing. After the application was granted by ZonMw in 2003, she conducted the research in her spare time, in addition to her job as middle manager at the Municipal Health Services, The Hague. Since 2009 she has been the coordinator of The Academic Collaborative Center Child Health Care Northern Holland (VU University Medical Centre), with the challenging aim of strengthening collaboration between researchers and practitioners and to make Child Health Care professionals enthusiastic about evidence based preventive medicine. She is married to Frank Driessen and is the mother of Sep, born in 1991.