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.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.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.9-12 Our results are in line with the findings in the New Delhi Birth Cohort.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.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,14 which is supposed to have a protective effect against cardiometabolic risk.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.\textsuperscript{16} 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,\textsuperscript{5} 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%).\textsuperscript{17} The prevalences of metabolic syndrome in young adults in the Terneuzen Birth Cohort were comparable to the prevalences in another Dutch study.\textsuperscript{18} 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).\textsuperscript{17} 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 R² 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/m², 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/m², 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, 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 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.

**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.
Chapter 8

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/m²), converted to age-specific standard deviation scores (BMI SDS) based on Dutch reference data from 1996-7, 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. 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. 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 is caused by a rapid elevation in the deposition of body fat rather than lean tissue mass. Nonetheless, the age dependency of the extent to which fat is stored in either the visceral or the subcutaneous fat depots might have influenced our results.

Definition of metabolic syndrome

Several definitions of metabolic syndrome exist. In contrast to the WHO and EGIS criteria, the NCEP ATPIII and IDF definition underline central obesity as an essential component of the metabolic syndrome 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, this definition has been chosen in our study. Several studies have shown that
the concordance between definitions is modest,\textsuperscript{35} although the predictive value of future cardiovascular diseases for the NCEP ATPIII, IDF and WHO definition are of the same magnitude.\textsuperscript{36} 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.\textsuperscript{36} 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 \textit{per se}, but rather the change in BMI level that is related to risk of overweight and obesity and its comorbidity.\textsuperscript{37} 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.\textsuperscript{38} 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.\textsuperscript{39} 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).\textsuperscript{40}
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.41 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.
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