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
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.