The Terneuzen Birth Cohort

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.\textsuperscript{1,2} It is anticipated that in the near future more people will die from the complications of overnutrition than from starvation.\textsuperscript{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,\textsuperscript{5} leading to an intergenerational cycle of obesity.\textsuperscript{5} In addition, overweight often persists throughout life, referred to as tracking.\textsuperscript{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.\textsuperscript{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. 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. For international comparisons, overweight and obesity in children are defined according to the age and sex-specific international IOTF criteria. 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.

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. 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. 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. 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}

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.

Cardiometabolic risk and metabolic syndrome

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 homeostatis.\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 cm for males and >88 cm for 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.  

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. 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).

Interventions aimed at metabolic syndrome

The effects of overweight on later cardiometabolic risk amplify with age, leading to irreversible precursors of diabetes and cardiovascular disease already detectable in young persons. 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. 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.

 PRIMARY PREVENTION

As a consequence of the increased prevalences of overweight and obesity in children, and the tracking of overweight, 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. 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), and that it varies substantially according to the degree of body fatness. 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, 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. 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, and is a strong predictor of coronary heart disease in young adulthood. 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. 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, of which a few assessed this relationship up until adulthood. 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. 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. Dietary factors likely play a mediating role in this relationship.
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


