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School of Health and Welfare


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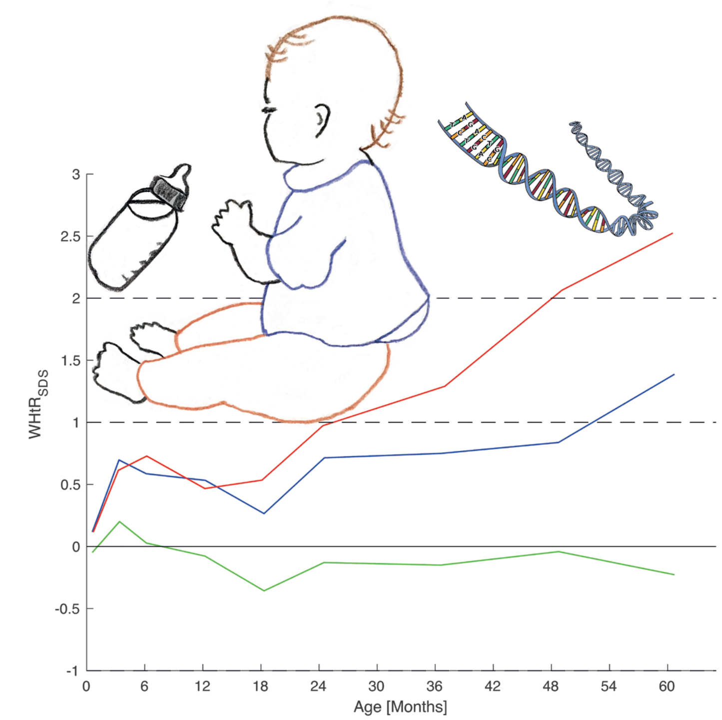
OVERWEIGHT AND OBESITY IN PRESCHOOL CHILDREN, EARLY RISK FACTORS AND EARLY IDENTIFICATION

ANNELIE LINDHOLM

Halmstad 2019

DOCTORAL THESIS




# Overweight and obesity in preschool children, early risk factors and early identification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*“I am among those who think that science has great beauty.”*
— *Marie Curie*

*To Philip and Victor*

# ABSTRACT

BACKGROUND: Overweight and obesity in children has reached epidemic proportions in recent decades, and even the youngest age groups are affected. Excess weight during childhood often follows the child into adulthood and is associated with diseases such as cardiovascular diseases and type 2 diabetes mellitus. In addition, excess weight often leads to health problems already during childhood. Childhood obesity is therefore one of the greatest public health challenges of the 21st century.

AIM: The overall aim was to study growth patterns and early risk factors for overweight, obesity and an elevated waist-to-height ratio (WHtR) in preschool children. The specific aims were to: examine early body mass index (BMI) and WHtR growth patterns and their ability to predict overweight or obesity in children at 5 years of age (Paper I); examine if BMI and WHtR growth patterns from an early age could identify children with an elevated WHtR at 5 years of age by using standard deviation score(s) (SDS) in children classified according to $WHtR_{SDS}$ at 5 years of age. Another aim was to study the association between $BMI_{SDS}$ and $WHtR_{SDS}$ at 5 years of age (Paper II); examine nutrition- and feeding practice-related risk factors for rapid weight gain during the first 0–6 months and the following 6–12 months (Paper III); examine the association between potential early risk factors and an elevated WHtR, defined as $WHtR_{SDS} \geq 1$ at 5 years of age, and examine whether similar associations also were found for overweight or obesity at the same age (Paper IV).

METHODS: This study was part of the population-based birth cohort study the Halland Health and Growth Study, including 2,666 children born in the county of Halland in the southwestern part of Sweden between October 2007 and December 2008. Weight, height and waist circumference were measured at nine time points starting at birth. At every measurement point the parents filled in questionnaires regarding their child’s nutrition, health and lifestyle and also background information about the family.

RESULTS: We found that children with overweight or obesity at 5 years of age had significantly different BMI and WHtR growth patterns already from an early age in comparison with children with normal weight or underweight. BMI was sufficient for predicting overweight or obesity at 5 years of age and WHtR did not add any further information in this prediction.

Children with an elevated WHtR at 5 years of age had significantly different growth patterns from an early age in comparison with children without this elevation. When comparing WHtR and BMI at five years of age, 55% of the children with an elevated WHtR had normal BMI.

Rapid weight gain was more common during the first 6 months of the first year than during the next 6 months. Bottle-feeding and nighttime meals containing formula milk were associated with rapid weight gain between 0 and 6 months. Breastfeeding was negatively associated with rapid weight gain during the same period.

Rapid weight gain during 0–6 months and also maternal pre-pregnancy BMI and paternal BMI were associated with an elevated $WHtR_{SDS}$ at 5 years of age. Rapid weight gain during both 0–6 and 6–12 months and also maternal pre-pregnancy BMI, were associated with overweight or obesity at 5 years of age.

CONCLUSION: This thesis showed that BMI was sufficient for predicting overweight or obesity at 5 years of age, and WHtR did not add any further information to this prediction. For identification of an elevated WHtR, BMI classification missed every second child, indicating that WHtR adds value in children who may need further investigation regarding cardiometabolic risk factors. Risk factors operating before pregnancy and early in life increase the risk of early rapid weight gain, an elevated WHtR and overweight or obesity at 5 years of age and bottle feeding, nighttime meals, early rapid weight gain as well as parental overweight are potential modifiable risk factors in this development.
KEYWORDS: abdominal adiposity, adiposity rebound, body mass index, childhood obesity, childhood overweight, early growth patterns, infancy peak, preschool children, waist-to-height ratio.

# LIST OF PAPERS

This thesis is based on the following four papers, which are referred to in the text by their Roman numerals.

**I** **Annelie Lindholm**, Stefan Bergman, Bernt Alm, Gerd Almquist-Tangen, Jovanna Dahlgren, Josefine Roswall.
**Infant body mass index growth patterns predicted overweight at five years, waist-to-height ratio did not add to this predictivity.**
*Acta Paediatrica 2019;5:945-953.*

**II** **Annelie Lindholm**, Josefine Roswall, Bernt Alm, Gerd Almquist-Tangen, Ann Bremander, Jovanna Dahlgren, Carin Staland-Nyman, Stefan Bergman.
**Body mass index classification misses to identify children with an elevated waist-to-height ratio at 5 years of age.**
*Pediatric Research 2019;85:30–35.*

**III** **Annelie Lindholm**, Stefan Bergman, Bernt Alm, Ann Bremander, Jovanna Dahlgren, Josefine Roswall, Carin Staland-Nyman, Gerd Almquist-Tangen.
**Nutrition- and feeding practice-related risk factors for rapid weight gain during the first year of life.** *Submitted.*

**IV** **Annelie Lindholm**, Josefine Roswall, Bernt Alm, Gerd Almquist-Tangen, Ann Bremander, Carin Staland-Nyman, Jovanna Dahlgren, Stefan Bergman.
**Early life risk factors for an elevated waist-to-height ratio at 5 years of age.** *Manuscript.*

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# ABBREVIATIONS

| | |
|---|---|
| AGA | Appropriate for gestational age |
| BAT | Brown adipose tissue |
| BCPED | Box-Cox-Power Exponential Distribution |
| BMI | Body mass index |
| $BMI_{SDS}$ | Standard deviation score for body mass index |
| BW | Birth weight |
| CDC | United States Centers for Disease Control and Prevention |
| CHC | Child health care |
| CHCC | Child health care centre |
| CT | Computed tomography |
| CVD | Cardiovascular disease |
| DMT2 | Diabetes mellitus type 2 |
| DXA | Dual-energy x-ray absorptiometry |
| FFM | Fat-free mass |
| FM | Fat mass |
| GA | Gestational age |
| GH | Growth hormone |
| GWA | Genome Wide Association |
| $H^2GS$ | Halland Health and Growth Study |
| HDL | High-density lipoprotein |
| HOMA-IR | Homeostatic model assessment for insulin resistance |
| IOTF | International Obesity Task Force |
| LGA | Large for gestational age |
| MetS | Metabolic syndrome |
| MBR | Medical Birth Register |
| MGRS | Multicentre growth reference standard |
| MRI | Magnetic resonance imaging |
| Nw | Normal weight according to $BMI_{SDS}$ |
| Ob | Obesity according to $BMI_{SDS}$ |
| Ow | Overweight according to $BMI_{SDS}$ |
| RWG | Rapid weight gain |
| SAT | Subcutaneous adipose tissue |
| SDS | Standard deviation score/or z-score |
| SGA | Small for gestational age |
| Uw | Underweight according to $BMI_{SDS}$ |
| VAT | Visceral adipose tissue |
| $Weight_{SDS}$ | Weight standard deviation score |
| WC | Waist circumference |
| WHO | World Health Organization |
| WHtR | Waist-to-height ratio |
| $WHtR_{SDS}$ | Standard deviation scores for waist-to-height ratio |

# 1 INTRODUCTION

Childhood overweight and obesity are global problems that have grown dramatically over the last few decades, and even the youngest age groups are affected (1-4). In 2016, the World Health Organization (WHO) reported that over 41 million children less than five years of age had overweight or obesity (5). Excess weight during childhood often tracks into adulthood (6), and is associated with several chronic diseases such as cardiovascular disease and type 2 diabetes mellitus, and also a risk of premature death (7). Even during childhood, overweight and obesity may cause suffering and acute problems (8). According to the WHO, childhood obesity is one of the greatest public health challenges of the 21st century (5).

Excess weight is often established early in life, and the first 1,000 days, beginning at conception and ending at the second birthday, have been identified as an important period for this establishment (9). Preventive interventions might be more successful when introduced early in life, but only a few such early interventions exist (10). In order to introduce early interventions, early identification of children who are at risk is crucial. Several studies have shown that parents and health care professionals often fail to identify children with overweight or obesity (11, 12), which highlights the importance of good and reliable measurement tools. With better knowledge regarding early signs of excess weight in early growth patterns and better knowledge of early risk factors, health care professionals will have better opportunities to identify children who are at risk at an early stage, and introduce preventive interventions when needed.

Every child has the right to the best possible health (13), and early identification of children who are at risk of overweight or obesity is an important task for the child health care organization, both from an individual point of view and from a public health standpoint (14, 15). The aim of this thesis was to study early growth patterns in BMI and WHtR and their association with later overweight, obesity and an elevated WHtR, and also early risk factors that may be associated with this development.

# 2 BACKGROUND

## 2.1 Childhood overweight and obesity: a global challenge

Childhood overweight and obesity have increased to the extent that they constitute a public health problem in many parts of the world (16). The WHO has estimated that by 2020, 9% of all children under the age of five will suffer from overweight or obesity (1). Although childhood overweight and obesity are spread around the world, the following regions are especially affected: Europe, North America and parts of the western Pacific. This includes many countries: The United States, Canada, Brazil, Chile, Australia, Japan, Finland, Germany, Greece, Spain and the United Kingdom. Sub-Saharan Africa and some parts of Southeast Asia have the lowest prevalence (3), but despite the low prevalence in Southeast Asia, when considered as a continent, Asia has the largest number of preschool children with overweight or obesity. Although overweight and obesity are more common in the developed parts of the world, the majority of affected children live in developing countries, and it is also here that the greatest increases are seen (1).

In Sweden, childhood overweight and obesity vary with age and also between areas with different socioeconomic standards, with higher prevalence in areas with a lower socioeconomic standard (17, 18). One study on 12-year-old Swedish children found that the prevalence of overweight was stable between 2003 and 2011 and that the largest numbers were seen in boys, in children living in rural residential areas (19), and where parents had lower levels of education (20). In 2011, overweight in Swedish school children aged 7–9 years was reported to be 16.6% and the corresponding proportion for obesity was 3% (17). A report from 2018 on four-year-old children, with 17 Swedish regions represented, showed that 9.4% of the children had overweight (boys 7.9% and girls 10.6%), and 2.3% had obesity (boys 2%, girls 2.5%) (21). For children younger than 4 years, there is no nationally representative data. In comparison with other parts of Europe, Sweden has relatively low numbers of children with overweight or obesity. In Italy, Spain and Portugal, for example, around 25% of the children are affected (5).

Recent data suggests that childhood obesity has reached a plateau in western Europe, USA, Australia and Japan (4, 22, 23), but the accuracy of this finding has been questioned, since many studies that reported a plateau had short-follow up times and mainly reported BMI measurements (24). In any case, the number of children with overweight or obesity in the world is still very high, and although Sweden has relatively low numbers, they have doubled in a few decades (20, 25, 26). Furthermore, the elevated number of children with excessive weight in neighbourhoods with low socioeconomic status (27) indicates that the problem is greater in certain parts of Sweden.

## 2.2 Overweight and obesity in evolution and in a historical perspective

### 2.2.1 An evolutionary perspective on excess weight

All organisms–from the simplest prokaryotes to mammals like ourselves–have ways of storing lipids in order to survive during periods with limited amounts of nutrients (28). Overweight and obesity are therefore often considered to be normal responses to a changed environment (29), in combination with a genetic predisposition that has its roots in our evolutionary history (30). Three different hypotheses to explain the obesity epidemic have been suggested. In the thrifty gene hypothesis, developed by Neel in 1962, diabetes mellitus and later also obesity were considered to be genetic variations under positive selection. The capacity to efficiently store energy during a period with an abundance of food would prepare the organism for later periods of famine, and such traits today can lead to overweight (31). Those with opposing views often point out that if this was the case, it is problematic to explain why not all humans have overweight or obesity nowadays, and that during starvation, infections rather than starvation, are the most common cause of death. Another hypothesis, the maladaptive one, suggests that obesity is a by-product when another trait is positively selected. This hypothesis states that obesity never have been advantageous. One common example of this hypothesis is the difference in the efficiency of brown adipose tissue (BAT) to burn calories by thermogenesis that exist between individuals. These individual variations are thought to depend on for example different exposition to cold during our evolution. Since BAT also can be used to burn excess calories, a low capacity may lead to obesity during excess energy intake. The third hypothesis suggests that the genes that cause obesity are so-called drifting genes; they cause obesity in some individuals whereas other individuals become resistant (30).

### 2.2.2 A historical perspective on paediatric overweight

Childhood obesity has been known since ancient times. Hippocrates documented it in the following citation when describing the Scythians, nomads in what is now known as Iran: “The male children, until they are old enough to ride, spend most of their time sitting in the wagons and they walk very little since they are so often changing their place of residence. The girls get amazingly flabby and podgy” (32). Different definitions of childhood overweight or obesity both within and between countries makes comparisons between countries difficult (33). In the USA, national surveys concerning children’s BMI started in 1963. In those surveys, the BMI values were stable between 1960 and 1980, at which time they started to increase until the 2000s (34). According to the definitions by the IOTF, the prevalence of overweight increased from approximately 15% to 30% and the prevalence of obesity increased from 5% to 10% (35). In Europe, many studies focusing on childhood obesity have been cross-sectional and therefore unable to be used when tracking childhood obesity (33). When British children born in 1946 and in 1958 were compared, obesity had almost doubled in 1958 and between 1972 and 1994 triceps skinfold measurements had increased by 7–8%. In the Netherlands, the values remained relatively stable between the 1950s and 1980, and after that increases were seen. Similar increases (from the 1980s) have been observed in France and Switzerland.

## 2.3 Early growth patterns

Both pre-and postnatal growth patterns have been associated with later overweight, and a better understanding of early growth patterns would help the clinician in identification of children who would benefit from early interventions regarding excess weight (36). Growth starts *in utero* and continues throughout infancy, childhood, puberty and early adulthood (37). Hormones, genes, nutrition and environmental factors can affect growth (37, 38). In a mathematical model of growth (where biological factors were taken into account), the Infancy, Childhood and Puberty model, infant growth is seen as being mainly driven by nutrition and as being a continuation of foetal growth (39). Childhood growth is regulated by growth hormone (GH) and insulin like growth factor I (IGF-I). When puberty starts, sex steroids and GH are the main regulatory hormones of growth (40).

### 2.3.1 Intrauterine growth and development

The linear growth *in utero* peaks in velocity at 18 weeks of gestation; at that time point, the foetus grows four times more rapidly than at any other time after birth. The pattern of weight gain is the same, the difference being that it peaks at 34 weeks (37). During the last weeks of gestation, the growth rate declines substantially (37). Male foetuses often become larger than their female counterparts, probably by directly affecting maternal energy intake (41).
Optimal growth during the intrauterine period is a narrow balance between the risk of too large a foetus with problems associated with the delivery on the one hand and on the other the risk of the foetus being too small, which may be detrimental to the foetus itself (41). Foetal growth and size are dependent on the placenta for hepatic, respiratory and renal functions (42), and also on endocrine signals between the mother and the foetus (41). Foetal growth is a balance between foetal demand on the one hand which depends on its genetic potential and the maternal supply of nutrients on the other (43, 44). Furthermore, placental functioning, blood flow, maternal nutrition and metabolism determine the nutrition delivered to the foetus (44-46). Problems in functioning of the placenta, for example too few placental vessels, placenta praevia or uterine problems affecting placental function, may all lead to intrauterine growth restriction. Apart from that, maternal nutrition and caloric intake all are important regulators of intrauterine growth and size at birth (41). Parental genes are also important for intrauterine growth and development. Maternal genes, mostly those determining the mother's height, are important determinants of foetal size (47). Imprinted genes, epigenetically programmed genes with functions determined by which parent they came from, have also been shown to be of importance for normal foetal growth. Defects in imprinting could lead to several diseases such as obesity, Prader-Willi syndrome, diabetes mellitus, Silver-Russell syndrome, cancer and psychiatric disease (48).

Hormones that direct the development of the foetus are insulin, insulin like growth factors (IGFs) I and II, glucocorticoids and androgens. Insulin and the IGFs stimulate foetal growth whereas the glucocorticoids suppress it (49). Other factors that affect infant growth are maternal smoking and alcohol consumption; both smoking during pregnancy and alcohol consumption are associated with low birth weight in the child (50, 51).

During foetal life, each tissue has periods of increased growth and rapid cell division and the timing of these periods may differ between tissues. During these critical periods, the foetus is susceptible to the hormonal and nutritional environment, which may alter the expression of the foetal genome and affect lifelong health (52). This so-called foetal programming may change hormonal feed-back, and also lead to changes in cell type distribution, cell number and organ structure (53). An example of this is when–due to restricted nutrition during the foetal period–infants are born with a low birth weight, which is strongly associated with an increased risk of developing diseases later in life. This hypothesis, named the Barker hypothesis was proposed by Barker and his colleagues around 1990 when they found that children with low birth weight due to poor intrauterine growth had a higher risk of coronary heart disease in adult life (54, 55). The suggested link between low birth weight and later disease is a larger quantity of abdominal fat, which have been found in persons with poor foetal growth (56, 57). In 1994 Barker showed in animal models that a changed maternal diet could lead to long-term effects on postnatal growth, lipid metabolism and relative organ size (58).

### 2.3.2 Growth and development during infancy and childhood

During the first year, the infant grows approximately 25 cm in height followed by half of that during the second year. Then, growth declines further until a plateau of approximately 5.5 cm per year is reached before the start of puberty. During the first 6 months of life, boys have a higher height velocity than girls but after 1 year and until 4 years of age, girls have marginally higher height velocity. Thereafter, growth in height is rather similar between the genders until 9 years of age, when girls often reach their pubertal growth spurt (37, 59). Patterns of weight gain also show gender-specific differences. Boys gain weight slightly more rapidly during the first year, and thereafter both genders gain approximately 8 g per day during the next two years. In mid-childhood this number decreases to approximately 6–7 g per day. When entering puberty, weight gain velocity increases almost twofold (37).

When we look at the BMI curve of a typical growing child, BMI increases to a maximum around 7–9 months of age, the so-called infancy peak (IP) (60). The IP is followed by a steady decrease in BMI until it reaches a nadir around 6 years of age, the adiposity rebound (AR) (60, 61).

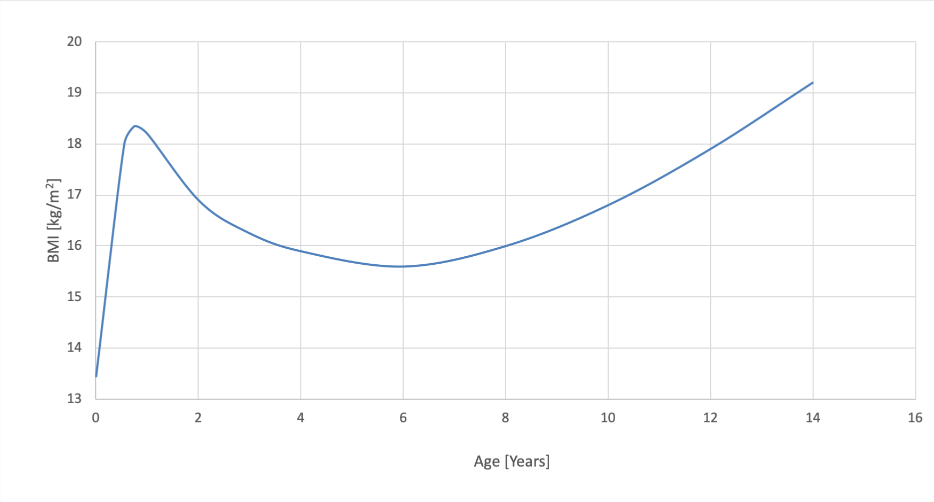


***Figure 1*** *Normal growth pattern of body mass index from birth to adolescence, showing the infancy peak and the adiposity rebound.*

Many studies have focused on the AR and have found that an AR before 5 years of age was associated with later adiposity (61-64). Fewer studies have focused on the IP and its association with later adiposity (65-67). Furthermore, it has been suggested that the IP does not correspond to the adiposity peak seen in infancy, and since BMI does not distinguish between fat mass (FM) and fat-free mass (FFM) it is unclear what the IP actually reflects (60). Even so, studies have found associations between the magnitude of the BMI peak and body composition at 3 years (67) and 5–6 years respectively (66) (and also blood pressure at 5–6 years). Also, the pre-peak velocity has been associated with body composition at 3 years (67). The timing of the peak has been positively associated with later overweight in some studies (68) but negatively associated with BMI in others (67).

### 2.3.3 Seasonal variations in growth

Effects of seasonal variations in both length and weight development have been shown in several studies (69-71), although there have also been studies with no evidence of such variations (72). The spring- and summer-time have been associated with higher length velocities (69, 71, 73). The reason behind the higher length velocity during spring and summer is not clear but the stimulatory effects of sunshine on vitamin D production and bone growth may be one explanation (74). Another reason may be seasonal variations in concentrations of IGF-I and its binding proteins, which were both found to increase with higher temperatures in a study from Gothenburg (75). The autumn- and winter-times have been associated with higher weight gain velocities. Also, in this case, contradictory results have been found (69). Dalskov *et al.*, suggested that the higher weight gain velocities observed in their study during spring-time may be due to an increased lean mass because of physical activity (69). In order to identify growth disorders, it is good to be aware of the normal fluctuations in growth during the different phases of childhood (71).

## 2.4 Paediatric body composition

When studying body composition, FM is differentiated from FFM or lean mass (76). At birth the human body is rather immature (77), and the volume of adipose tissue can vary between 0.3 and 1.7 L. This variation can possibly be explained by differences in sex, gestational age, glucose levels, maternal diabetes mellitus, ethnicity, maternal BMI and maternal gestational weight gain (78-83). During the first 6 months, weight gain is preferentially represented by a gain in FM (37). The infant may gain up to three times the FM during the first four months (84). Boys have more FFM than girls, and during mid-childhood they accumulate around 1 kg more FFM than girls do (37). Around the age of 9 months, the FM reaches a maximum (76); then it rapidly declines until a second increase at around 6–7 years of age. The FFM increases steadily throughout growth and development (76).

Almost any disease affecting children can induce changes in body composition (76) and *post mortem* and *in vivo* studies have shown that it is possible to change the total adiposity in neonates through nutritional intake, although the exact mechanisms for this remain unclear (85). Assessments of paediatric body composition aids the clinician in identifying and monitoring disease progress in children with overweight or underweight (86).

The definition of overweight or obesity is excess fat or adipose tissue associated with adverse health effects (87, 88). The development of this excess adipose tissue is complex and multifactorial and the mechanisms behind it are both genetic and non-genetic (8). Earlier research has suggested that obesity depends on a complex interplay between the environment and the body's predisposition to obesity, which is based on epigenetics and genetic programming (89). The first 1,000 days in a child's life, from conception until the age of 2 years, have been identified as an important period regarding risk factors for childhood overweight and obesity (9). Several early-life risk factors that may have an important role in this development have been suggested, and some of them are discussed further in the paragraphs below.

### 2.5.1 Biological and early life factors

#### *Genetic factors*

Despite the extensive research and better instruments, there are few explanations for obesity that involve single genes. Some monogenic disorders have been found that affect the leptin-signalling pathway and the regulation of food intake. Leptin deficiency leads to hyperphagia and obesity (90). These disorders are well-known but extremely rare causes of obesity (91, 92). There are also some rare genetic syndromes where obesity is a clinical feature, such as Prader-Willi syndrome (93), Barder-Biedet syndrome (94) and Wilm's tumour, aniridia genitourinary-abnormalities, and mental retardation syndrome (95). The genetics behind common obesity is still an enigma; several genetic loci have been identified by genome wide association (GWA) studies, but to date very little of the heritability of BMI has been satisfactorily explained (96). Even so, gene therapy has already gained great interest and future treatment of overweight and obesity will probably include such alternatives (97).

#### *Intrauterine factors*

The intrauterine environment of the foetus has been identified as an important period for BMI in later years and the development of adiposity in children. Pre-pregnancy BMI, gestational weight gain and high glucose levels during pregnancy have all been shown to lead to higher birth weight due to both general and abdominal FM accumulation (81-83). The so called "foetal overnutrition hypothesis" states that maternal obesity affects foetal appetite control, energy metabolism and endocrine functioning (98). Regarding maternal gestational weight gain, early- and mid-pregnancy have been identified as critical periods (99). During mid-pregnancy the foetus starts to develop adipose tissue (100), and a rapid maternal weight gain has been suggested to increase the amounts of free fatty acids that are delivered to the foetus (99, 101). An additional mechanism that has been suggested is lowered insulin sensitivity and lowered glucose tolerance in the mother, which may promote increased glucose transportation to the foetus (101). Both mechanisms mentioned above may lead to a permanent higher capacity of the foetus to produce adipocytes in postnatal life (81, 99). In the same way as a high maternal glucose concentration may lead to increased growth, a low glucose concentration leads to higher frequencies of children born small for gestational age (41). The mechanisms behind glucose concentration or diabetes and childhood overweight are not yet fully understood, but intrauterine exposure to a diabetic environment is an important risk factor (102). It has also been suggested that the reasons behind childhood overweight and obesity are related to genetic and lifestyle factors that the offspring inherits from both its parents. Therefore, the effects of both the maternal and the paternal BMI have been investigated. Pre-pregnancy BMI in the mother has been shown to be associated with childhood overweight or obesity in several studies (9, 103). Regarding paternal BMI and offspring adiposity, associations have been found (104, 105) but the results are somewhat inconclusive (9).

### Size and weight at birth

Size at birth is related to the gestational age, and the average weight and length measurements for Swedish children are 3.5 kg and 50 cm ± 1 SD. In general, girls are 7 mm shorter and 135 g lighter than boys (106). The mean birth weight has increased, and the reasons behind this may be a lower frequency of smoking in women, higher maternal BMI and greater gestational weight gain (107). According to birth size, children can be considered to be large for gestational age (LGA); defined as being ≥ 2 SDS in weight or length, small for gestational age (SGA); ≤ −2 SDS or appropriate for gestational age (AGA) (108). The association between birth weight and later adiposity and cardiometabolic risk factors like type 2 diabetes mellitus seems to be U-shaped (109). Children born LGA and with no so-called "catch-down growth" (a period of slower growth), children with a high birth weight and children born SGA with so-called "catch-up growth" are prone to a number of metabolic disorders later in life: obesity, type 2 diabetes mellitus and cardiovascular disease (9, 109-112). One mechanism behind SGA and later disease may be fat deposition, since children born SGA have been shown to accumulate more FM (113), and abdominal fat (112-114), in comparison with their AGA counterparts, and this also in the absence of overweight (115). Children born LGA are larger than children born AGA, but both groups have more FFM than FM and lower levels of FM than children who are born SGA (112, 114). Although, also in the LGA group, an early FM accumulation have been proposed to be one explanation behind the increased risk of later disease (116).

### Catch up growth and rapid weight gain

Rapid infancy growth in weight or height, was first observed and described by Bauer and Prader, both in children exposed to illness or starvation and in children born SGA or after intra uterine growth restriction (117, 118). In those cases, children regained their genetic growth trajectory after a period of less growth. This compensatory growth was described as ”catch-up growth" (119). However, rapid growth may occur even in the absence of periods of less growth, and it is then called unhealthy rapid growth or overgrowth (74). Although rapid growth has been shown to be crucial for neurocognitive development and brain structure in children born preterm, it has also been associated with central adiposity, insulin resistance and cardiovascular disease later in life (117, 119, 120), showing that rapid growth comes at a cost (117). Rapid weight gain (RWG) during the first two years of life, usually defined as a change > 0.67 in weight SDS, and representing the distance between two adjacent centile lines in standard childhood and infant weight growth charts (121), has been associated with later overweight or obesity in a number of studies (9, 121). This postnatal weight gain has therefore been identified as an important period to target for the avoidance of later obesity and associated disease (122). Children with RWG during this period have been found to have 3.66 times higher odds of developing overweight or obesity between 2 and 46.5 years (121). Several studies have tried to establish the exact period during these two years that best predicts later overweight or obesity but they came to mixed conclusions (121).

Catch-up growth early in life has been shown to be associated with an accumulation of fat mass rather than fat free mass. Dulloo et al., suggested in his "thrifty catch-up fat phenotype" that catch-up growth during the first years of life leads to fat mass accumulation and is associated with the development of insulin resistance (123). This fat mass accumulation is suggested to depend on a more efficient metabolism. A similar pattern of catch up fat- growth have been observed in a small sample of Ethiopian children with low birth weight when early body composition growth patterns were analysed (124).

### *Nutrition- and feeding practice-related factors*

In has been known for some time that breastfed infants gain weight at a slower pace than formula fed infants (125-127). Formula-fed children have a higher protein intake and energy intake than their breastfed counterparts (127). Both the protein quality and the high protein content in formula milk compared to that in breast milk have been considered to be important reasons behind the association between formula feeding and a steeper weight gain trajectory (128). Several of the studies of growth associated with formula milk feeding were performed with formula containing the higher protein content recommended before 2004. Newer formula milk products with a lower protein content and a better protein quality have been developed (129). Formula milk with a protein content similar to that of breast milk was found to result in similar weight gain patterns like that experienced in breastfed infants (130). One suggested mechanism behind the protein content in formula milk and the more rapid growth is the hormonal regulation associated with this growth (131). IGF-I levels have been shown to be lower in breastfed infants than in their formula fed counterparts (131, 132). In the study with low-protein formula milk mentioned above, infants given formula with a high protein content had higher IGF-I levels and experienced more weight gain until 2 years of age, than those fed on formula with a lower protein content. The lowest levels of IGF-I were found in the breastfed control group (130, 133). Apart from the lower protein levels, breast milk contains hundreds of bioactive and nutritional components (134, 135). One example would be the human milk oligosaccharides, which support the development of a microbiome with favourable microorganisms (135). These factors that differ in their composition between women have also been found to affect infant body composition and growth (136). However, more research regarding how growth is affected by these and other factors in human breast milk is needed (134, 136).

Other recent research has suggested that it is important to study not only the type of milk (formula versus breast milk) but also the mode of feeding (breastfeeding versus bottle feeding) when investigating associations between RWG and later adiposity (137, 138). Bottle-feeding has been associated with RWG regardless of whether the bottle contained formula milk or expressed breast milk (138). It has been hypothesized that bottle-feeding gives more control to the caregiver than to the infant, and that bottle-feeding facilitates a more pressuring feeding style where the caregiver is more responsive to contextual cues such as the content of the bottle than to the infant's satiety response (139, 140). Breastfeeding, on the other hand, has been suggested to give more control to the infant and to support the development of responsive feeding, which means feeding in response to the infant's satiation or hunger cues (139, 141). The hypothesis behind breastfeeding and support of responsive feeding is that since the mother cannot measure how much milk the infant consumes, she has to trust the infant's hunger and satiety cues (141). Although several studies have found that breastfeeding protects against later adiposity (142), there is no consensus (9). Studies with opposing views often refer to the PROBIT study (143) from Belarus, where this was not found to be the case (128). It has, however, been suggested that the children in that setting gained fewer gastrointestinal and respiratory tract infections when they were breastfed, something that could be one explanation to why they gained more weight (128), indicating that the slower weight gain trajectory in breastfed infants may be more relevant in westernized settings (128).

Apart from formula milk, the milk cereal drink (MCD) that is recommended from the age of six months in Sweden may be a risk factor for RWG and adiposity (144). MCD is made from grains and dehydrated skimmed milk, and before serving it is mixed with hot water (144). The protein content of MCD is 2.7 g per 100 mL. Because of the relatively limited use of MCD outside Sweden, only a few studies have investigated it in connection with overweight or obesity, but positive associations have been found (144-146). Another association between nutrition during childhood and overweight or obesity that have been found involves a high intake of sugar-sweetened drinks (147). Furthermore, low levels of the micronutrient vitamin D have been linked to obesity and the metabolic syndrome (148, 149).

## *The gut microbiome*

Contrary to earlier beliefs, the bacterial colonization already occurs during gestation (150). Microbes have been located in the amniotic fluid (151), meconium (152), and placenta (153). During delivery the child becomes further colonized. Vaginally born children get their mother's vaginal bacteria and children born by Caesarean section get microbes from the surface of the skin instead (92, 154). Between the ages of 18 and 36 months, the child's microbiome takes on its mature form (150). Disturbances in the intestinal flora are called dysbiosis, and may result from antibiotic treatment or disease (150). Antibiotics has been suggested to disrupt the microbiome leading to obesity and associated disease (155). In animal models, it has been shown that the gut microbiota may affect glucose metabolism and that it causes inflammation in adipose tissues (156). Although there are hypotheses regarding the same associations in humans, there is no such evidence yet (157). However, the bacterial diversity of the gut (158) and the ratio between *Bacteroides* and *Firmicutes* species have been suggested to have a possible role in the development of overweight and obesity. Humans with obesity have lower proportions of *Bacteroides* (159). Furthermore, it has been shown that the gut microbiota in individuals with obesity, have less diversity and different metabolic pathways and genes from its counterpart in individuals with normal weight (92, 160).

### 2.5.2. Epigenetic factors

Epigenetics describe heritable changes in gene expression that do not alter the genetic code. These changes are reversible and include processes such as DNA methylation, nucleosome positioning, chromatin modifications and alterations in non-coding RNA profiles (161). Epigenetic factors involve, for example, diet, environment and sleep patterns, and although more insight into epigenetic explanations is needed regarding obesity, recent studies have shown interesting results. In *Drosophila* flies, it was found that a change in the father's diet for only two days was capable of inducing obesity in the offspring. Sugar in the father's diet could suppress variegation and lead to desilencing of chromatin-state defined domains in mature sperm and offspring embryos. There is some evidence that similar systems exist in humans (162). Another example is the Trim28 gene complex in mice, which has been shown to be able to trigger obesity in a randomly selected on/off manner. Mutant isogenic mice have been found to be either obese or non-obese without any intermediates; even here similar systems have been found in humans (163). Epigenetic factors affecting the parents or the child will probably play an important role in future obesity prevention and in the treatment of overweight and obesity.

### 2.5.3 Socioeconomic factors

Besides the risk factors for overweight and obesity described in the preceding sections, the development of excess weight may depend on social determinants of health (164). Determinants of health in a population can almost be likened to a rainbow where some factors are possible to change through policy, society or by the individual, whereas other factors are fixed. Examples of fixed factors are age and gender. Examples of factors that may be changed are behavioural factors, social and community networks, and general socioeconomic, cultural and environmental conditions. These factors can be positive, negative or riskful for the individual (165). Both childhood obesity and obesity in the overall population affect the poorest and lowest educated in society to a greater degree (91, 166, 167), at least in westernized settings. In a study including eight European countries it was shown that overweight in children and socioeconomic status were inversely related in countries with higher human development index while there was no such association in countries with less development (168).

The reported plateau regarding overweight and obesity observed in many countries (169) is not as strong in families of lower socioeconomic status (170, 171). Globally, it has been shown that there is a higher frequency of overweight in urban areas than in the rural counterparts (3). Two Swedish studies in four-year-old children have found that the occurrence of overweight and obesity differed according to socioeconomic status (172) and neighbourhood purchasing power (18). The reasons for this may vary but in one of the Swedish studies it was found that mothers in areas with lower purchasing power tended to terminate breastfeeding earlier than mothers in areas with higher purchasing power (173). It has also been shown that children living in an area with low income who move to an area with better circumstances have a higher risk of getting cardiac infarction as adults. Even socioeconomic standard of the grandmother during her childhood has in one study been found to be important for her sons' children of female gender who had a higher risk of cardiovascular death, probably driven by epigenetic mechanisms (174). Early risk markers for these diseases which may be present already during childhood have also been shown to be associated with socioeconomic status. In a recent Danish study with 8- to 11-year-old children, the children of parents with the lowest education had higher levels of triglycerides and were more insulin resistant than the children of parents with the highest education (175).

Behavioural factors coupled to health–also known as lifestyle–can be changed. Lifestyle is, however, also strongly associated with socioeconomic status. Throughout the world, smoking, sedentary lifestyle and unhealthy diets are more common in individuals with the lowest education (176). Morbidity and mortality in a population has been shown to be related to socioeconomic positions (74, 177). Both nationally and internationally, children's, health, growth and development are closely associated with social (dis)advantages and (in)equalities (74).

## 2.6 Consequences of childhood overweight and obesity

Overweight or obesity in childhood often tracks into adulthood (6), and is associated with adverse health effects later in life such as cardiovascular disease and type 2 diabetes mellitus (178). However, obesity in children may lead to health problems and great suffering already in childhood (8). As a consequence of the obesity epidemic, diseases rarely seen in children before, such as hypertension, type 2 diabetes mellitus and dyslipidaemia, are now often seen in children with obesity (8, 179). Other diseases that are associated with childhood obesity are sleep apnoea, asthma, musculoskeletal disorders, polycystic ovary syndrome, menstrual irregularities, early puberty and steatohepatitis (7, 180). However, the most widespread health-related consequences of childhood obesity are psychosocial problems. Obese children often become systematically discriminated from an early age (7). In a study in which 10- to 11- year-old children were asked about who they would rather be friends with, obese children were the ones that other children chose least (181). From a global standpoint, obesity can be seen as a public health crisis that apart from the associated diseases also affects quality of life and national health care budgets (182).

## 2.6.1 Paediatric metabolic syndrome and abdominal adiposity

Metabolic syndrome is defined as a number of cardiometabolic risk factors: hypertension, obesity (predominantly abdominal), insulin resistance, dyslipidaemia and glucose intolerance, and it is closely related to an increased risk of cardiovascular disease and type 2 diabetes mellitus (183, 184). Abdominal visceral adiposity has in adults been identified as the most prevalent of the cardiometabolic risk markers, that when present is a sign of disturbed fat metabolism (185). In the lipid-overflow ectopic fat model, it has been suggested that during excess energy intake the extra energy can be stored in healthy subcutaneous and insulin- sensitive adipose tissue but in the absence of such tissue, it is stored as ectopic fat in liver, skeletal muscle, endocardium and visceral adipose tissue which may lead to the metabolic syndrome and its related risks of cardiovascular disease and type 2 diabetes mellitus (Figure 2). Metabolic syndrome has traditionally been associated with adulthood (183, 184), but cardiometabolic risk factors have been identified already during preschool age (186), and may have their origins *in utero* (187). These risk factors have been detected in

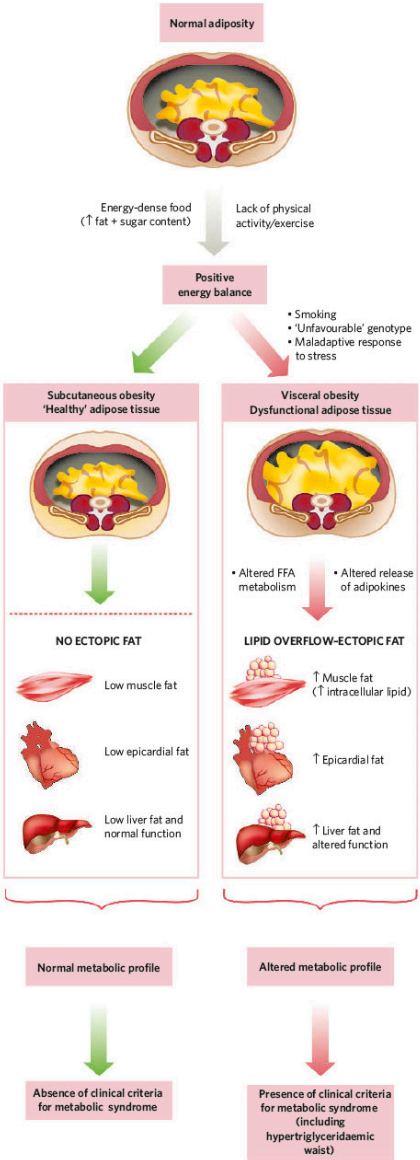


**Figure 2** *The lipid overflow-ectopic fat model. Picture published from article: Abdominal Obesity and Metabolic Syndrome by Despres J and Lemieux J. Published in Nature 2006. 14; 444 :881-887. Permission to print the picture in this thesis has been obtained.*

children of preschool age even at the onset of overweight or obesity, suggesting that screening for individuals who are at risk of later disease is needed early in life (186). Although sometimes present in children with normal weight, children with overweight or obesity are at higher risk of developing metabolic syndrome, and the higher numbers of individuals with this syndrome appear to be a consequence of the obesity epidemic (188, 189). According to a recent update, approximately 10% of children and adolescents are affected by metabolic syndrome (190). There is no consensus regarding the diagnosis of metabolic syndrome in children, but in 2007 the International Diabetes Federation presented one definition regarding children and adolescents between 6 and ≥ 16 years. For adolescents > 16 years, the adult's criteria were suggested, abdominal adiposity and also at least two of the following risk factors: elevated plasma glucose, elevated blood pressure, elevated triglycerides and low high- density lipoprotein (HDL) levels were required (191). In children between 10 and ≤ 16 years, some modifications were made to the adult criteria. In children less than 10 years of age, monitoring of abdominal adiposity as well as weight reduction was recommended instead of diagnosing the metabolic syndrome (191). In another definition by Ahren*s et al.*, children as young as 2 years were included. In their definition, special weighting was given to abdominal adiposity and the other criteria were elevated blood pressure, elevated triglycerides or lowered HDL as well as elevated fasting glucose or elevated model assessment for homeostatic insulin resistance HOMA-IR (192). Besides these two definitions, several others exist (188).

Similar associations between abdominal adiposity and disturbed fat metabolism found in adults have also been observed in children (193-196). However, the relationship between abdominal adiposity and cardiometabolic risk factors in children of preschool age is poorly understood. Insulin sensitivity has been found to be negatively associated with SAT in children of prepubertal age with overweight or moderate obesity, suggesting that the subcutaneous adipose tissue (SAT) rather than the visceral adipose tissue (VAT) is associated with cardiometabolic risk factors at younger ages (197). SAT has different characteristics than VAT both in lean and obese individuals. In lean individuals, VAT has less and larger adipocytes as well as non-differential adipokine secretion in comparison with SAT. When weight gain is induced, the adipocytes of VAT get hypertrophic, their cell size increases rapidly and they start to produce proinflammatory agents and recruit immune cells (Figure 3). Similar processes take place in SAT but to a lesser extent, leading to a healthier expansion. If the same processes are active in preschool children with or without overweight or obesity is unclear, and therefore studies regarding these associations are needed in this population (192, 198).

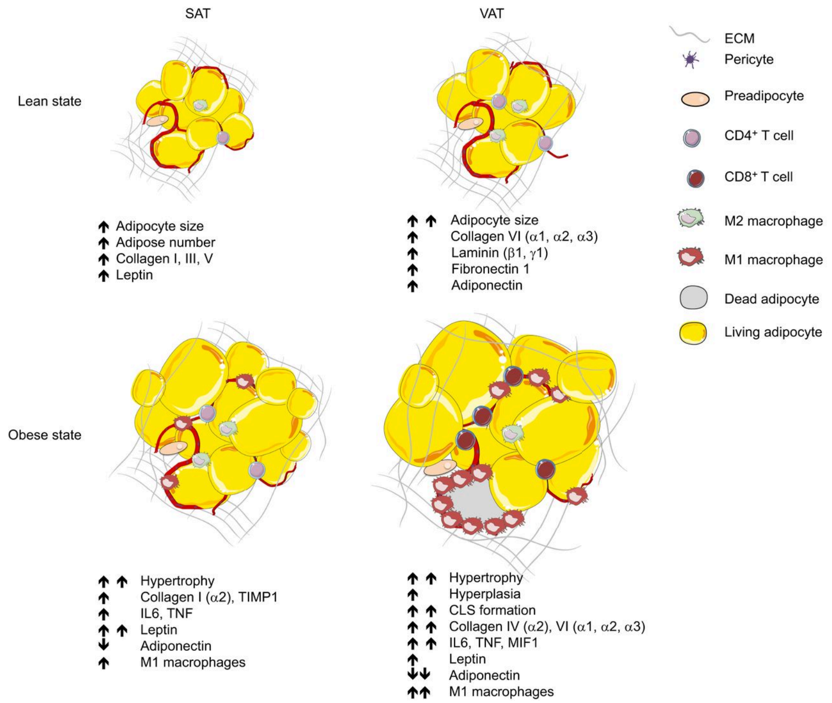


**Figure 3** *Different characteristics of subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT)in individuals with normal weight and obesity respectively. This picture was originally published in* article: *Heterogeneity of adipose tissue in development and metabolic function by Schoettl, T., Fischer, IP and Ussa, S. published in Journal of Experimental Biology 2018 221: jeb162958 doi: 10.1242/jeb.162958. Permission to print the picture in this thesis has been obtained.*

# 2.7 Measuring of childhood growth

Human growth has interested us from the early ages. The first documented statement was made by the Greek poet Solon in the sixth century BC, who described male development from birth until death (199). The study of growth is called Auxology, which comes from the Greek word *axuesis*, meaning to increase or grow, and the word *logos,* meaning to study. As Tanner wrote in 1986, childhood growth is a mirror of health (74), and together with neonatal death rate, birth rate and breastfeeding (200, 201) it is also important from a public health point of view (74). This monitoring of children's health is important regarding the children's rights and because child health is important for the health of future populations (202). To follow growth and development by anthropometric measurements is not only important for identifying children with overweight, but also children with poor growth, which is often a sign of disease or psychosocial problems (74, 203).

To be able to assess growth and body composition for the identification of children with excess weight and a risk of associated disease, it is crucial to have good and relevant measurement-and screening-tools. The desired technique should be gentle for the child, have little margin for error, should be easy to perform, be cost-effective and should be easy to compare with reference values. Currently, no method covers all of these (204). The most accurate methods for assessment of adipose tissue and its distribution are different imaging techniques such as magnetic resonance imaging (MRI) and computed tomography (CT) (205-207). MRI is preferable in children and in longitudinal studies, because of the absence of the ionizing radiation that is associated with CT (208). Due to their relatively high cost, these methods are mostly used in the scientific context. In clinical practice, the only well-established methods for measurements of body composition are anthropometry and air-displacement plethysmography (86, 209).

### 2.7.1 Body mass index and abdominal adiposity

The most widely used anthropometric variable for following children's weight gain in relation to height in clinical practice is sex- and age-specific body mass index (BMI) (kg/m$^2$) (210, 211). BMI is a relatively simple and well-established technique. Disadvantages of BMI are that it does not differentiate FM from FFM (210) and the low correlation between BMI and the distribution of the fat (212).

Anthropometric measures have been suggested as good alternatives to blood tests in the screening of children who may need further evaluation regarding cardiometabolic risk factors (213, 214). As earlier mentioned, abdominal adiposity has been identified as the most prevalent of the cardiometabolic risk factors in adults and associations between abdominal adiposity and cardiometabolic risk factors has been identified in school-age and preschool children (196) (see section 2.6.1), although more studies are needed, especially in the preschool population. However, concerning the disadvantages of BMI, a measure that better relates to abdominal adiposity might be preferable when assessing overweight, obesity and associated cardiometabolic risk factors in children.

### 2.7.2 Waist circumference and waist-to-height ratio

Waist circumference (WC) and waist-to-height ratio (WHtR) WC (cm)/length (cm), have been suggested as good surrogate measures of abdominal adiposity and associated cardiometabolic risk factors in children and adolescents (194, 215-218). Measures of WC were also given special weighting in the IDEFICS-definition of metabolic syndrome, including children as young as 2 years (192). Both methods are easy to perform and no advanced equipment is needed (204, 219). Disadvantages of these techniques that have been pointed out are that the reliability of measurement of WC has been lower than that of measurement of height and weight; furthermore, great inter-observational differences between

WC measurements have been found (217). Another disadvantage is that there are no internationally accepted reference values for children under 6 years of age (204, 217). By standardizing these measurements and educating health care professionals regarding the correct measuring technique, some of these errors might be avoided (217).

**Figure 4** *How to measure waist circumference in an infant in supine position. The measurement tape is placed midway between the lowest rib and the top of the iliac crest and the measurement takes place at the end of a gentle expiration, Photo: Peter Korpi/ Hallandsposten, Halmstad.*

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***Figure 5*** *How to measure waist circumference in a child in a child in standing position. Photo: Eivor Kjellberg Department of Paediatrics, Halmstad Hospital.*

### 2.7.3 Growth references and growth charts

The first documentation of a growth chart is the one made by Count Philibert de Montbeillard (1720–1785) who followed the growth of his own son for several years (220). Now growth charts are essential tools in clinical practice for following growth and development, and for observing signs of growth deviations. A growth reference describes how children do grow and represents the summary of the statistical distribution of an anthropometric measure, usually visualized as growth charts in clinical practice (74, 220, 221). Growth standards are almost the same as growth references, but instead describe how children should be growing (220). Growth standards are therefore developed in populations raised under optimal conditions. Several different growth references and standards exist, both nationally and internationally, but the three most frequently used for assessing health risks associated with weight are the ones created by the WHO, the International Obesity Task Force (IOTF), and the Unites States Centers for Disease Control and Prevention (CDC) (222). Apart from these three, several countries have developed their own reference curves that better fit their own population (74).

The WHO growth standards were released in 2006. They were generated from the WHO multicentre growth reference study (MGRS), which was conducted between 1997 and 2003. Six different countries–Brazil, Ghana, India, Norway, Oman and the United States–and 8,440 children took part in the study. The choice of countries was based on availability of the necessary epidemiological data, geographical distribution, national or international funds, and the presence of collaborative institutions that could implement the protocol (223). The children were raised under optimal conditions, meaning that they were exclusively or predominantly breastfed for more than four months, and until at least 12 months with complimentary foods added from six months. In addition, they were immunized, lived in smoke-free environments and received health care when needed. Both a longitudinal part from 0–24 months and a cross-sectional part from 18–71 months were constructed (224). A study from 1977 with American children, 5−19 years old, has later been added to the first one (225). Based on approximations of BMI when the children were 19 years old (226), children with BMI > the 84th percentile is defined as having overweight and > the 97.7th percentile as having obesity (224). This standard is recommended by the International Pediatric Association and the European Childhood Obesity Group.

The IOTF growth references were constructed by Cole *et al*., in 2000 and were based on children 2−18 years old, from six nationally representative surveys performed in middle-income and high-income countries; Brazil, Great Britain, Hong Kong, the Netherlands, Singapore, and the United States. Each of the studies had > 10,000 subjects (227). When extrapolated to the definitions of adult overweight, BMI ≥ 25, and obesity, BMI ≥ 30, age-and gender-specific cut-off values were created. When these cut-offs are used, children of preschool age with a BMI ≥ the 91st percentile are considered to have overweight and ≥ the 99th percentile are considered to have obesity (228). Since the age-and gender-specific cut-off values are different from adult BMI values they are named Iso BMI values in Sweden (21). One disadvantage of using these cut-offs was that they were not expressible as BMI centiles. Thus in 2012, Cole *et al*., published new definitions of overweight and obesity with minor changes from the older ones (229).

The CDC growth charts from 2000 were based on five different health and nutritional surveys in American children, conducted between 1963 and 1994 (230). They comprise charts for weight-for-age, recumbent length-for-age, head circumference for age, and weight-for-recumbent length for infants, 0–36 months old, and a set of charts for children and adolescents, 2–20 years old (230). Based on approximations of BMI when the children were 19 years old (226). A BMI at or above the 85th percentile defines overweight and a BMI at or above the 95th percentile defines obesity.

All the references described above have been questioned regarding their accuracy (231). In the WHO standard, for example, the children were relatively light at birth and then gained weight rapidly–which has been suggested to be counter-productive regarding encouragement of breastfeeding (232). Furthermore, the children in the WHO standard had relatively small head circumferences making this standard less optimal for example in Swedish children. There is no international consensus regarding which reference to use (231), and there are no signs that there will be such a universal reference in the near future. The lack of consensus concerning one reference complicates comparisons between studies and also precludes any consensus regarding cut-off values for overweight, obesity and associated health risks (233).

In the Swedish child health care, growth charts based on a longitudinal study of 3,650 full term infants–called Gothenburg 1974–are used. These children were born in Gothenburg between 1973 and 1975 and were followed from 0–18 years of age (234).

A newer Swedish study, Sweden 1981, included 3,158 children 0–19 years born in Sweden during 1981 (235). In the development of the latter charts, the same methods as WHO used when developing their growth standard for children between 0 and 5 years of age were used. In order to reduce the risk of mis-classification of children with growth deviations, children with overweight or obesity were excluded in the material from the age of 2 years (21).

Several countries have WC reference charts for children (236), but only a few cover the preschool population (237-239). Regarding WHtR, the number that covers children of preschool age is also limited (240, 241), especially in children younger than five years (242-244). A WHtR cut-off value of 0.5 has been suggested as a sign of abdominal adiposity associated with an increased risk of disease (245, 246), but this limit does not seem to be as suitable in preschool children. In a cross-sectional study from the county of Halland in Sweden, reference values for WHtR were created for children between 0–5 years. Median values of WHtR were found to be above 0.5 until the age of 4.5 years (247). Age and sex-specific reference values of WHtR has also been suggested in a recent German study including 22,113 children aged 3–18 years (248) and in a study from Japan with 19,233 children and adolescents 6–18 years (249). The values varied substantial according to age and sex.

## 2.8 Early prevention of childhood overweight and obesity

The early establishment of excess weight highlights the importance of interventions in infants and toddlers (10). Although no consensus exists, it has been suggested that children establish their eating habits, food preferences, and dietary intake patterns already by the age of 2 years (10, 250). The first 1,000 days in a child's life, beginning at conception may be an important time to intervene against later excessive weight gain, but only a few interventions during these early ages exist (251).

### 2.8.1 The Swedish child health care

The Swedish child health care has existed since 1937. In the sixties, it mainly monitored health and identified disabilities in children. From 1970, the parents' role in the child's development became more of a consideration. In 1980, parent education programmes were introduced both in child health care and in the antenatal care (252). Child health care in Sweden aims to support children in gaining the best possible physical, psychological and social health and it is an important part of the public health strategy, where one goal is "secure and equal growth conditions" (15, 252). This is achieved by supporting the health of children, prevent diseases and to identify children who may need extra support. The UN Convention on the Rights of the Child, Article 24 describes: "the right of the child to the enjoyment of the highest attainable standard of health and to facilities for the treatment of illness and rehabilitation of health." (13). In 2018 it was decided that the convention in its complete form would be incorporated into Swedish law from January 1, 2020 (13).

In Sweden, children are offered free health care at the Swedish Child Health Care Centers (CHCCs) from birth until they start school. This health care has a coverage of approximately 98% (253), which gives it an important function regarding surveillance of child health. The frequency of visits ranges from every week after birth, followed by monthly visits and then annual visits from the age of three until five years. Four visits are managed by paediatric physicians and the other ones are managed by trained child health care nurses. The CHCCs offer vaccinations, health monitoring which includes measurements of length, weight and head circumference and advice in areas such as nutrition, physical activity and sleep. The parents are offered individual consultation, group consultation and written information (252).

### 2.8.2 The Swedish antenatal care

The antenatal care (ANC) in Sweden was established during the 1930s and almost 100% of all Swedish women visit any of the private or public ANC-units which is free of charge. The ANC is regulated by local and national guidelines, and the main tasks regarding pregnant women include surveillance of maternal and foetal health and referral for obstetric assessment if complications arise. The ANC-units also support the parents for labour, birth and their future role as parents (254, 255).

### 2.8.3 Prevention of overweight and obesity in young children

According to the WHO, health is: “a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity” (256). Overweight and obesity may affect lifelong health since it is related to problems both during childhood and in the longer perspective (7). When tackling excess weight in preschool children, family-based interventions have been recommended. At this young age, clinicians are recommended to focus on the parents own behaviours (257). The parents are the so-called gatekeepers of their children’s health. They decide everything from what food to eat, the amount of health care received, the amount of physical activity, the degree of emotional support to the environment around the child. These decisions have been found to be based on the parents’ own knowledge, education, socioeconomic status and environment (258). In the Ottawa charter for health promotion, the goal is to let people take control over their own health (259), and in the case with preschool children the family can take control. Because of the regular health visits and their high degree of coverage, the health care professionals at the CHCCs have good opportunities to support the parents’ in their role of establishing a healthy lifestyle for their young children (260).

### 2.8.4 The child as part of a system

Since every child is part of a context, a system theoretical approach may be helpful when trying to understand and prevent childhood overweight and obesity (261). The ecological systems theory of the Russian developmental psychologist Urie Bronfenbrenner (1925–2005) can then be used. According to his theory, the child can be seen as the centre of a system consisting of macro-, exo-, meso- and microsystems. The child is surrounded by different microsystems like his or her immediate family, school/day-care center, and playground area. The connection between these different microsystems is called the mesosystem and these interactions between the microsystems are important parts of the theory. The exosystem in turn, surrounds the micro- and mesosystems and consists of microsystems that is not in direct contact with the child, for example the parent’s workplace, extended family and neighbours. In the outermost layer surrounding the child the macrosystem is found. In this system, laws, culture, social conditions and economic factors are important parts. The child does not take active part in the macrosystem but is affected by it (262).

When studying health and disease with a systems theoretic approach, systems can be both the cause and the solution to health problems (263). In the case of a child with overweight or obesity, the problems may originate from, for example, the family and its diet habits, which may be affected by the neighbourhood, and the culture. The neighbourhood may in turn be dependent on policy decisions regarding, for example, resources to that neighbourhood. From this view point, problems may depend on one or several levels in the system and in the same way, the solutions to the problems may need interventions at more than one level.

As mentioned before, a family-based approach is recommended when targeting childhood overweight or obesity (257). Murray Bowen (1913–1990), an American psychiatrist, developed the family systems theory. Bowen saw the family not as members constituting a group but rather as individuals who are interdependent. The family can be seen an open system where the individuals can affect each other as well as be affected by adjacent systems like health care systems and other parts of the society (264, 265). If one individual in a family changes his behaviour, the other family members will get affected by it and they in turn will influence him (264, 266). Besides that, the systems surrounding the family may also have an impact and support or hinder the induced change. Bowen established eight concepts including sibling position, triangulation, family projection process, nuclear family emotional system, emotional cut off, multigenerational and differentiation of self, which are all factors that may affect how the family respond to advice regarding behavioural changes. Bowens family systems theory have been used in family-based approaches working against childhood obesity (265, 266).

# RATIONALE OF THIS THESIS

There is much evidence that indicates that childhood overweight and obesity are established already early in life and with the adverse health consequences associated with excess weight, early identification of affected children is an important priority for maternal and child health care systems. It has been found in studies that parents and health care professionals often fail to identify overweight or obesity in children, so good and reliable measurement tools are needed. BMI is the most widely used measure for following weight gain in relation to height in children, but BMI does not describe fat deposition in the body and it does not discriminate fat mass from fat-free mass. Since obesity-associated diseases are related to fat deposition, especially abdominal fat, measurements that better relate to abdominal fat such as WC and WHtR have been suggested to be better than BMI for identification of adiposity and cardiometabolic risk factors in both children and adults. However, the number of studies regarding WHtR in children under 6 years of age is limited.

There is evidence that the first two years of life is an important window for the establishment of later overweight or obesity. This information has led to a large body of research regarding early-life risk factors associated with development of excess weight. In several studies rapid weight gain has been found to be associated with adiposity later in childhood and in adulthood. Early nutrition and feeding practices have also been identified as important factors for the regulation of early growth and adverse health consequences later in life. In order to ensure a more balanced weight gain trajectory in children, parents and health care professionals need more information regarding risk factors for overweight and obesity, and also about the effects of different nutritional alternatives and the best feeding practices. Only a few studies have examined risk factors for the development of abdominal adiposity specifically in children of preschool age. In order to prevent this development, knowledge regarding early risk factors are needed.

Health care professionals at child health care centres are in a good position to reach children early in life who are at risk of overweight, obesity and an elevated WHtR and they have the possibility to introduce preventive interventions, but there is a need for more knowledge regarding early growth patterns, early risk factors and reliable and evidence-based measures to identify children who are at risk of developing overweight, obesity and abdominal adiposity.

# 3 AIMS

## Overall aim

The overall aim was to study growth patterns and early risk factors in the development of overweight and obesity and an elevated waist-to-height ratio in preschool children

## Specific aims

To examine early BMI and WHtR growth patterns and their ability to predict overweight or obesity in children at five years of age.

To examine if BMI and WHtR growth patterns from an early age could identify children with an elevated WHtR at 5 years of age by using standard deviation score(s) (SDS) in children classified according to $WHtR_{SDS}$ at 5 years of age. The second aim was to study the association between $BMI_{SDS}$ and $WHtR_{SDS}$ at 5 years of age, with the hypothesis that an elevated WHtR partly identifies other children than an elevated BMI does.

To examine nutrition- and feeding practice-related risk factors for RWG during the first 0–6 months and the following 6–12 months, adjusted for biological, socioeconomic and parental health-related risk factors for RWG or childhood overweight or obesity.

To examine the association between potential early risk factors and an elevated WHtR, defined as $WHtR_{SDS} \geq 1$ at five years of age. A second aim was to examine if similar associations also were found for overweight or obesity at the same age.

# Hypotheses

BMI and WHtR differs from each other regarding their ability to identify children with overweight or obesity at five years of age and WHtR together with BMI would be more informative in this identification than BMI alone.

An elevated WHtR partly identifies other children than an elevated BMI does

Nutrition- and feeding practice-related risk factors lead to rapid weight gain early in life

Child- parent- and nutrition related risk factors are associated with an elevated WHtR and overweight or obesity at five years of age

# 4 SUBJECTS AND METHODS

## 4.1 Subjects and design

### 4.1.1 The Halland Health and Growth Study

This project was part of the ongoing population-based birth cohort study, the Halland Health and Growth Study ($H^2GS$), including 2,666 children (1,349 boys and 1,317 girls) born in the southwestern part of Sweden between October 1, 2007 until December 31, 2008, with the aim of studying factors that affect health and growth in children. All children born during this time period, 3,860 were eligible to take part in the study without any exclusions. The families were recruited at their first visit to any of the local CHCCs; in Halland, these CHCCs see about 98.4% of the children living in the county (267). During this period, there were 3,860 births in Halland; 69.2% (2,666) of the families agreed to participate in the study, 9.7% choose not to participate and 21.1% did not answer (267). Measurements of height, weight and waist circumference were carried out by trained child health care nurses at 9 measurement points beginning at birth. In connection with the measurements, the parents filled in questionnaires regarding their child's food, lifestyle and background data.

## 4.1.2 The population in this thesis

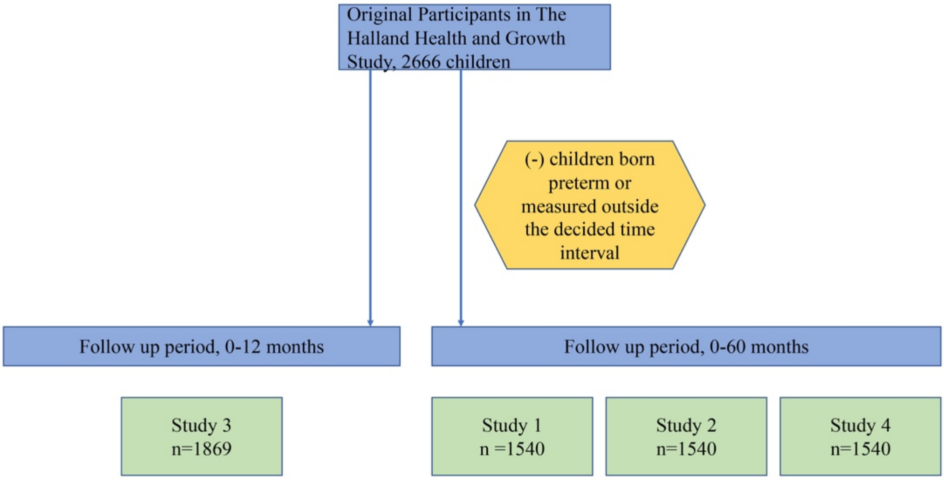


**Figure 6** *Overview of the subjects included in the four papers of this thesis. The sign (-), indicates the excluded children.*

### *Paper I–IV*

The studies were population-based birth cohort studies. The participants were children with measurements of waist circumference, weight and length at five years of age as well as information regarding gestational age (Paper I, II and IV). Children born preterm or measured outside the decided time period of 0–45 days for measurement point 0–1 month, ± 1.5 month at 3–4 and 6 months of age and ± 2.5 months thereafter were excluded from the study. Altogether, 1,540 children were included in the studies. In Paper III, the participants were children with measurements of waist circumference, weight and length at 0, 6 and 12 months. A total of 1,869 children were included in that study.

The children were classified at five years as having overweight/obesity or normal weight/underweight according to the IOTF criteria (229).

***Table 1*** *Characteristics of the children enrolled*

| | **Normal weight/underweight** | **Overweight/obesity** |
|---|---|---|
| Number of participants | 1365 | 175 |
| Gender M/F | 675/690 | 75/100 |
| MBW M/F (g) | 3633/3477 | 3879/3713*** |
| | | |
| SGA (n) | 106 | 12 |
| AGA (n) | 1159 | 143 |
| LGA (n) | 99 | 20 |
| Missing (n) | 1 | 0 |
| Gestational age | | |
| $37^0$-$37^6$ (n) | 61 | 8 |
| $38^0$-$40^6$ (n) | 999 | 127 |
| $41^0$-$43^5$ (n) | 305 | 40 |
| Maternal age | | |
| <25 (n) | 134 | 16 |
| 25-35 (n) | 906 | 115 |
| ≥35 (n) | 311 | 43 |
| Missing (n) | 14 | 1 |

*MBW, mean birth weight; M/F, males/females; SGA, small for gestational age; AGA, appropriate for gestational age; LGA, large for gestational age; $BMI_{SDS}$ body mass index standard deviation scores; $WHtR_{SDS}$, waist-to-height ratio standard deviation scores, ***$p < 0.001$.*

The children were classified as having ≥ 1 or < 1 in $WHtR_{SDS}$ at five years of age according to Swedish reference values (247), and as having overweight/obesity or normal weight/underweight according to the IOTF criteria (229).

**Table 2** *Characteristics of the children enrolled*

| $WHtR_{SDS}$ | < 1 SD | ≥ 1 SD |
|---|---|---|
| *Number of participants* | 1309 | 231 |
| *Gender* | | |
| Male/Female | 651/658 | 99/132 |
| *At birth* | | |
| MBW M/F (g) | 3685/3546 | $3654^{ns}/3499^{ns}$ |
| *Size for gestational age* | | |
| SGA (n) | 98 | 20 |
| AGA (n) | 1115 | 187 |
| LGA (n) | 95 | 24 |
| Missing (n) | 1 | 0 |
| *Gestational age* | | |
| $37^0$–$37^6$ (n) | 56 | 13 |
| $38^0$–$40^6$ (n) | 958 | 168 |
| $41^0$–$43^5$ (n) | 295 | 50 |
| *Maternal age* | | |
| <25 (n) | 129 | 21 |
| 25–35 (n) | 865 | 156 |
| ≥35 (n) | 303 | 51 |
| Missing (n) | 12 | 3 |
| *At 60 months, mean ± SD* | | |
| BMI ($kg/m^2$) | 15.35 ± 1.1 | 17.36 ± 1.6*** |
| $BMI_{SDS}$ | -0.31 ± 1.0 | 1.16 ± 0.9*** |
| WHtR (cm/cm) | 0.47 ± 0.0 | 0.53 ± 0.0*** |
| $WHtR_{SDS}$ | -0.32 ± 0.8 | 1.57 ± 0.5*** |

*For mean values in birth weight, BMI, $BMI_{SDS}$, WHtR and $WHtR_{SDS}$ the groups with $WHtR_{SDS}$ ≥1 at five years of age were compared with the groups with <1, ***p <0.001, ns, non-significant. MBW, mean birth weight; SD, standard deviation; SGA, small for gestational age; AGA, appropriate for gestational age; LGA, large for gestational age; $BMI_{SDS}$, body mass index standard deviation scores; $WHtR_{SDS}$, waist-to-height ratio standard deviation scores.*

The children were classified according to having rapid weight gain (RWG) or non-rapid weight gain (nRWG) during 0–6 months or 6–12 months based on a change > 0.67 SDS in weight growth charts, representing the difference between two adjacent centile lines in regular weight growth charts.

**Table 3** *Characteristics of the children enrolled*

| | **RWG 0–6m/RWG 6–12m** | **nRWG 0–6m/nRWG 6–12m** |
|---|---|---|
| Number of participants | 865/142 | 1004/1727 |
| Gender | | |
| Boys | 461/70 | 487/878 |
| Girls | 404/72 | 517/849 |
| Birth weight[a] | | |
| MBW (g) | 3438/3543 | 3699***/3581[ns] |
| Size for gestational age | | |
| SGA (n) | 38/5 | 19/52 |
| AGA (n) | 812/132 | 913/1593 |
| LGA (n) | 15/4 | 70/81 |
| Missing (n) | 0/1 | 2/1 |

*RWG, rapid weight gain; nRWG, non-rapid weight gain; months, m; MBW, mean birth weight; SD, standard deviation; ns, non-significant; SGA, small for gestational age; AGA, appropriate for gestational age; LGA, large for gestational age.*

*[a]For mean values in birth weight, the groups with RWG was compared with the groups with nRWG, ***p < 0.001; ns, non-significant.*

The children were classified at five years as having a $WHtR_{SDS} \geq 1$or < 1 according to Swedish reference values (247) and as having overweight/obesity or normal weight/underweight according to the IOTF criteria (229).

***Table 4*** *Characteristics of the children enrolled and divided by BMI and WHtR*

| | Ow/Ob | Nw/Uw | WHtR ≥ 1 SD | WHtR < 1 SD |
|---|---|---|---|---|
| *Number of children* | 175 | 1365 | 231 | 1309 |
| Male/Female | 99/76 | 691/674 | 99/132 | 651/658 |
| *At birth* | | | | |
| MBW ± SD (g) | 3785 ± 420 | 3553 ± 479 *** | 3605 ± 458 | 3575 ± 482 $^{ns}$ |
| *Size for gestational age* | | | | |
| SGA (n) | 4 | 44 | 20 | 98 |
| AGA (n) | 160 | 1265 | 187 | 1115 |
| LGA (n) | 10 | 54 | 24 | 95 |
| Missing (n) | 1 | 2 | 0 | 1 |
| *Gestational age* | | | | |
| $37^0$-$37^6$ (n) | 8 | 61 | 13 | 56 |
| $38^0$-$40^6$ (n) | 127 | 999 | 168 | 958 |
| $41^0$-$43^5$ (n) | 40 | 305 | 50 | 295 |
| *Maternal age* | | | | |
| <25 (n) | 16 | 134 | 21 | 129 |
| 25-35 (n) | 115 | 906 | 156 | 865 |
| ≥35 (n) | 43 | 311 | 51 | 303 |
| Missing (n) | 1 | 14 | 3 | 12 |
| *At 60 months, mean ± SD* | | | | |
| BMI ($kg/m^2$) | 18.37 ± 1.2 | 15.30 ± 1.0*** | 0.53 ± 0.0 | 0.47 ± 0.0*** |
| $BMI_{SDS}$ | 1.82 ± 0.6 | -0.33 ± 0.9*** | 1.57 ± 0.5 | -0.32 ± 0.8*** |

*For mean values in birth weight, BMI and $BMI_{SDS}$, the group with overweight/obesity according to $BMI_{SDS}$ was compared with the group with normal weight, ***p < 0.001, ns, non-significant.*
*MBW, mean birth weight; SD, standard deviation; SGA, small for gestational age; AGA, appropriate for gestational age; LGA, large for gestational age; $BMI_{SDS}$, body mass index standard deviation scores; $WHtR_{SDS}$, waist-to-height ratio standard deviation scores.*

## 4.2 Outcome measures

Weight, height and waist circumference were measured by trained child health care nurses when the children were 0–1, 3–4, 6, 12, 18, 24, 36, 48 and 60 months old (Figure 3). Until two years of age, stadiometers were used for measuring height in supine position, and thereafter height was measured in standing position (without shoes). Children were weighed without any clothes, or when older, in underpants. Infants under 15 kg were weighed in supine position on baby scales, and thereafter on step scales, mechanical or electronic. BMI was calculated as weight (kg)/ height$^2$ ($m^2$). Waist circumference was measured without clothes and midway between the lowest rib and the top of the iliac crest at the end of a gentle expiration. Children younger than 2 years of age were measured in supine position, and thereafter in standing position. Within the framework of the project, the inter- and intra-operator reliability for WC has been studied in children mainly under 24 months. The intra-class correlation coefficients were 0.98 both within and between those who made the measurements, although one of the persons had less experience. WHtR was calculated as waist circumference (cm)/ height (cm). Crude BMI and WHtR values were transformed to standard deviation scores according to Swedish reference values (163, 179). In *Paper I, II* and *IV*, measurements of weight height and waist circumference were used and in *Paper III*, measurements of weight were used.

## 4.3 Explanatory measures

Maternal weight before pregnancy, maternal weight at delivery, paternal weight at the first measurement point, maternal age, parental smoking, parental education, and parental diabetes mellitus or cardiovascular disease were all reported by the parents at the first measurement point. Birth weight and gestational age were collected from the Swedish Medical Birth Register MBR. Parental weights were reported to the nearest kg. Regarding parental smoking the answering alternatives were "yes" or "no". Parental education had four alternatives: elementary school, upper secondary, school university and other education. Parental diabetes mellitus and cardiovascular disease had the alternatives yes or no. Breastfeeding and bottle feeding were reported by the parents at every measurement point. Consumption of milk cereal drink (MCD) was reported from 6 months and nighttime meals were reported from 3–4 months. Breastfeeding had the alternatives "yes" or "no" and the parents who answered "yes", were asked about the frequency–with three answering alternatives: 1–5 times a day, 6–10 times a day and >10 times a day. Bottle-feeding, MCD consumption and nighttime meals had "yes" or "no" as alternatives. Parents who answered "yes" to giving nighttime meals were asked about the content of these meals and the alternatives were: breast milk, formula milk (at the first and second measurement point, and thereafter MCD), water, juice, the with sugar or rosehip juice or other (with free-text answer).

The questionnaires were constructed for this study, but some of the questions came from the Nordic Epidemiological sudden infant death study (268). Before the start of this study, a pilot study with 80 participating families was carried out whereby the face validity in the questionnaires were tested.

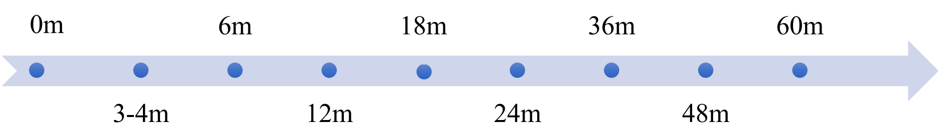


**Figure 7** *Measurement points for anthropometric measures and questionnaires between 0–60 months at the child health care centres.*

## 4.4 Statistical methods

### *Paper I*

All children with BMI and WHtR values at five years of age and also information regarding gestational age (n = 1,540) were classified as either having overweight/obesity or normal weight/underweight at five years of age according to the IOTF (229). Charts of $BMI_{SDS}$ and $WHtR_{SDS}$ growth patterns were constructed. Student's t-tests were performed to compare mean values of $BMI_{SDS}$ and $WHtR_{SDS}$ at the different measurement points in children with overweight/obesity or normal weight/underweight, and also differences in $BMI_{SDS}$ and $WHtR_{SDS}$ between 0–1 and 12 months, 18 and 48 months and 18 and 60 months. Univariable and multivariable logistic regression analyses were performed to study predictors of overweight/obesity at 60 months of age. All statistics were obtained separately for boys and girls. Any p value <0.05 was considered to be statistically significant in all analyses.

### *Paper II*

All children with BMI and WHtR values at five years of age (n = 1,540) and also information regarding gestational age were classified as having < 1 or ≥ 1 SDS in WHtR according to Swedish WHtR reference values (247) and as having overweight/obesity or normal weight/underweight according to the IOTF (229). Charts over $BMI_{SDS}$ and $WHtR_{SDS}$ growth patterns were constructed. Student's t-tests were performed to compare the mean values of $BMI_{SDS}$ and $WHtR_{SDS}$ at the different measurement points between children classified as having $WHtR_{SDS}$ ≥ 1 or < 1 at five years of age. At the five-year measurement point, associations between $WHtR_{SDS}$ and $BMI_{SDS}$ were examined by Chi-squared tests. In all statistical analyses except the Chi-squared tests, boys and girls were analysed separately. Any p value <0.05 was considered to be statistically significant in all analyses.

### *Paper III*

All children with measurements of weight at 0–1, 6 and 12 months and also information regarding gestational age (n = 1,869) were classified as having had rapid weight gain (RWG) or nonRWG during the time periods 0–6 months and 6–12 months. RWG was defined as change > 0.67 SDS in weight growth charts. Logistic regression models successively adjusted for biological, socioeconomic or parental health-related risk factors were made to study associations between nutrition- and feeding practice related risk factors and RWG. Any p value <0.05 was considered to be statistically significant in all analyses.

All children with measurements of weight, height and WC at five years of age and also information regarding gestational age (n = 1,540) were classified as having a $WHtR_{SDS} \geq 1$ or $< 1$ at five years of age according to Swedish reference values (247), and as having either overweight/obesity or normal weight/underweight according to the IOTF (229). Univariable and multivariable logistic regressions analyses concerning potential risk factors for a $WHtR_{SDS} \geq 1$ or $< 1$ at five years and also whether the same risk factors were associated with overweight/obesity at the same age were examined. A p value $< 0.05$ was considered to be statistically significant in all analyses. IBM SPSS statistics (v.20.0; IBM corp, Armonk, New York, USA) was used for the statistical analyses in *Papers I* and *II*. Version 25.0 was used in *Papers III* and *IV*. Conversions of crude values to $BMI_{SDS}$ and $WHtR_{SDS}$, and also the construction of graphs were done using Matlab (v.9.0.0.341360R2016a; The MathWorks, Natick, Massachusetts, USA).

## 4.5 Ethical considerations

Children can be considered to be a vulnerable group and in the declaration of Helsinki it is expressed that research in a vulnerable group is permissible only if special care is taken regarding the needs of the group, and provided that the same research cannot be done in a group that is not considered to be vulnerable (269). Measurements of weight and height are included in the regular tasks at the CHCCs. Only the addition of measurements of waist circumference was new. Given the routine regarding the other measurements, this was not considered to be a significant change from the regular routine. Detailed information regarding voluntary participation and the possibility of leaving the project at any time without any further questions was given to the parents of all the participating children. This project was approved by the regional ethical review board in Lund, Sweden (Study number: 299/2007). Written informed consent was obtained from the parents of all the children who participated. Approval from one caregiver was sufficient but if the other one disapproved, the child was not included in the project.

# 5 RESULTS

## 5.1 Growth patterns in children classified according to BMI (Paper I)

Of the 750 boys, 1.5% had obesity, 8.5% had overweight, 87.6% had normal weight and 2.4% had underweight at 5 years of age. The corresponding proportions for the 790 girls were 3.0%, 9.6%, 85.7% and 1.6%. Children of both genders with overweight or obesity had a significantly higher mean birth weight than children with normal weight or underweight: 3,879 ± 451 g for boys and 3,713 ± 381 g for girls, respectively, versus 3,633 ± 492 g and 3,477 ± 453 g, ($p < 0.001$ for all).

### 5.1.1 $BMI_{SDS}$ growth patterns

Even from an early age, children with overweight or obesity at 5 years of age had significantly higher mean $BMI_{SDS}$ than children with normal weight or underweight at the same age ($p < 0.001$ for all) (Figure 8 a and b). Boys with overweight or obesity crossed the +1 SD line between 30 and 36 months and girls with overweight or obesity crossed it between 24 and 30 months. Children with normal weight or underweight remained relatively stable in $BMI_{SDS}$ at all measurement points without any upward SD line crossing.

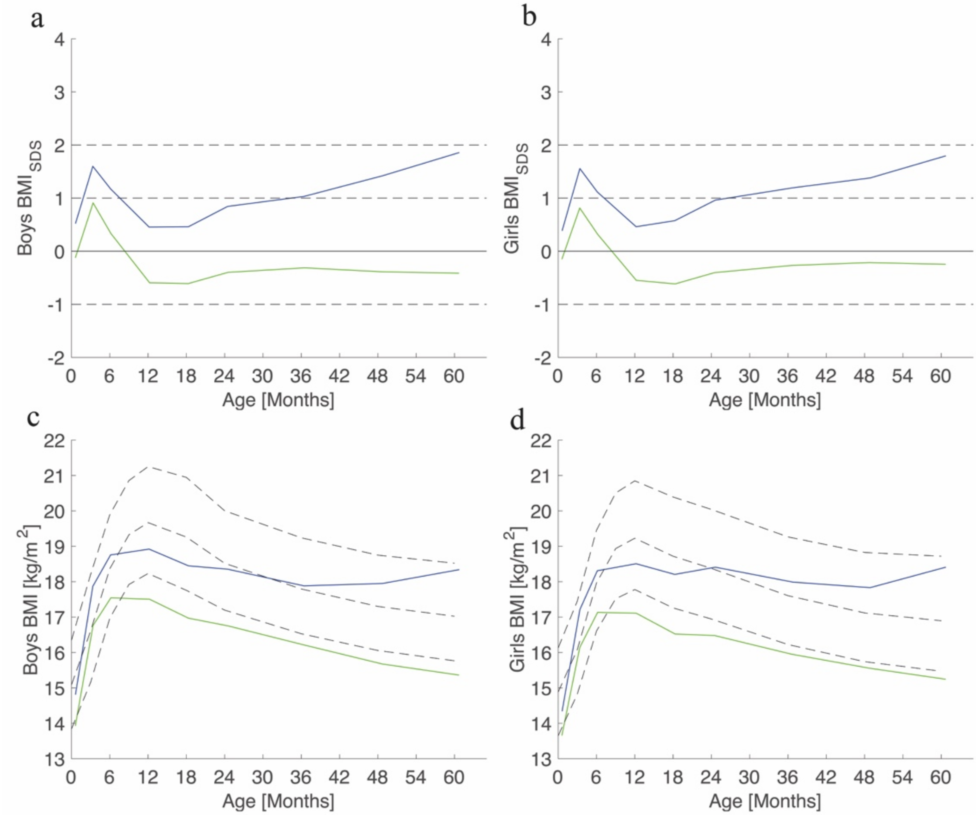


***Figure 8*** *Growth patterns for children with overweight/obesity and for normal weight/underweight, with mean $BMI_{SDS}$ values in boys **(a)** and girls **(b)** aged 0–1 to 60 months and classified by BMI cut-off values according to the IOTF at 60 months of age (229). Blue lines represent children with overweight/obesity and green lines, children with normal weight/underweight. Growth patterns for children with overweight/obesity and for normal weigh/underweight, with mean BMI values in boys **(c)** and girls **(d)**, aged 0–1 to 60 months, classified by BMI cut-off values according to the IOTF at 60 months of age (229), and including Swedish BMI reference values for mean, +1 SD and +2 SD (247). Blue lines represent children with overweight/obesity and green lines, children with normal weight/underweight. Lindholm et al., Acta Paediatrica 2019.*

### 5.1.2 Adiposity rebound

Children with overweight or obesity reached adiposity rebound (AR) earlier than children with normal weight (Figure 8 c and d). This finding was based on mean values of BMI and on one measurement point per year. Boys with overweight or obesity reached AR at 36 months, in contrast to boys with normal weight or underweight who had not reached it at 60 months. The girls had similar patterns; girls with overweight or obesity reached AR at 48 months, while girls with normal weight had not reached it at 60 months. Figure 9 shows the growth patterns when the children were separated in three weight groups instead of two.

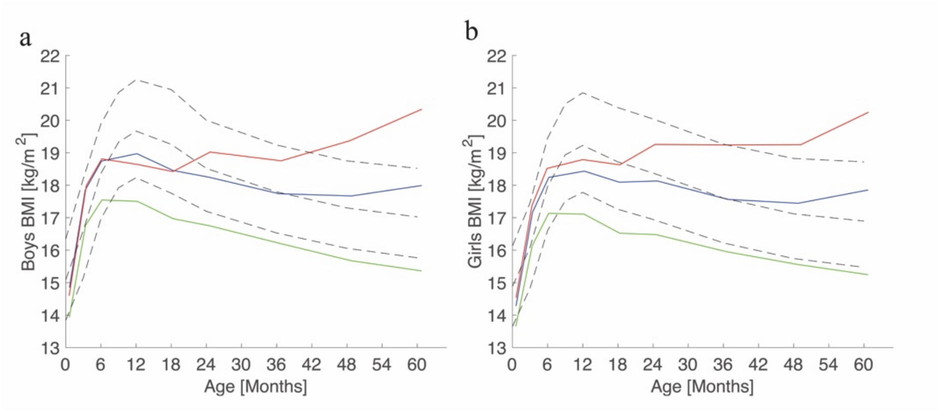


***Figure 9*** *Growth patterns for overweight, obesity and for normal weight/underweight, with mean BMI values in boys (c) and girls (d), aged 0–1 to 60 months, classified by BMI cut-off values according to the IOTF at 60 months of age (229), and including Swedish BMI reference values for mean, +1 SD and +2 SD (247). Red lines represent, children with obesity, blue lines, children with overweight and green lines, children with normal weight/underweight.*

### 5.1.3 WHtR$_{SDS}$ growth patterns

Even from an early age, children with overweight or obesity at 5 years of age had significantly higher mean WHtR$_{SDS}$ than children with normal weight or underweight at the same age ($p < 0.01$ for boys and $p < 0.05$ for girls) (Figure 10 a and b). Boys with overweight or obesity crossed the +1 SD line between 54 and 60 months and the girls crossed it between 42 and 48 months. Children with normal weight or underweight remained relatively stable in WHtR$_{SDS}$ at all measurement points without any upward SD line crossing. The graphs with crude WHtR values (10 c and d) showed that children with overweight or obesity at five years of age had WHtR values above +1 SD.

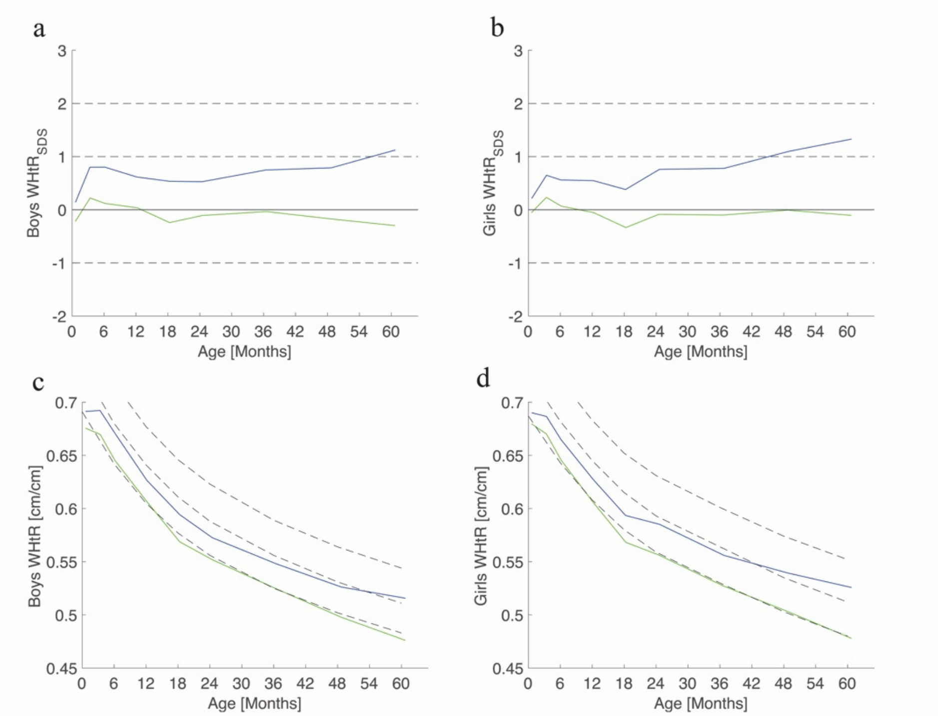


***Figure 10** Growth patterns for children with overweight/obesity or normal weight/underweight at five years of age, with mean waist-to-height ratio standard deviation scores ($WHtR_{SDS}$) in boys **(a)** and girls **(b)**, aged 0–1 to 60 months and classified by BMI cut-off values according to the International Obesity Task Force (IOTF) at 60 months of age (229). Growth patterns for overweight/obesity and for normal weight/underweight with mean WHtR values in boys **(c)** and girls **(d)** aged 0–1 to 60 months, and classified by BMI cut-off values according to the IOTF at 60 months of age (229), and including Swedish WHtR reference values for median, +1 SD and +2 SD (247). Blue lines represent children with overweight/obesity and green lines children with normal weight/underweight. Lindholm et al., Acta Paediatrica 2019.*

### 5.1.4 Prediction of overweight or obesity

$BMI_{SDS}$ at 0–1 month, $BMI_{SDS}$ between 0–1 and 12 months and $BMI_{SDS}$ between 18 and 48 months predicted overweight or obesity at five years of age ($p < 0.001$ for all). $WHtR_{SDS}$ did not add any information with regard to $BMI_{SDS}$, except for a negative association between 18 and 48 months in the boys ($p = 0.040$) (Table 5).

**Table 5** *Odds ratios and 95% confidence intervals for children with overweight or obesity versus children with normal weight or underweight, classified by BMI cut-off values at 60 months of age*

| | Univariable logistic regressions[a] | | | Multivariable logistic regressions[b] | | |
|---|---|---|---|---|---|---|
| Boys, Ow/Ob- Nw/Uw[c] | | | | | | |
| BMI-SDS 0–1 | 1.97 | (1.51–2.57) | **<0.001** | 7.15 | (3.76–13.61) | **<0.001** |
| ΔBMI-SDS 0–1–12 | 1.35 | (1.09–1.67) | **0.006** | 5.06 | (2.86–8.93) | **<0.001** |
| ΔBMI-SDS 18–48 | 3.53 | (2.41–5.18) | **<0.001** | 8.14 | (4.40–15.03) | **<0.001** |
| ΔWHtR-SDS 0–1 | 1.45 | (1.13–1.87) | **0.004** | 0.92 | (0.54–1.57) | 0.766 |
| ΔWHtR-SDS 0–1–12 | 1.14 | (0.94–1.39) | 0.181 | 0.90 | (0.60–1.35) | 0.613 |
| ΔWHtR-SDS 18–48 | 1.11 | (0.86–1.44) | 0.427 | 0.67 | (0.46–0.98) | **0.040** |
| Girls, Ow/Ob-Nw/Uw | | | | | | |
| BMI-SDS 0–1 | 1.69 | (1.36–2.11) | **<0.001** | 4.61 | (2.80–7.58) | **<0.001** |
| ΔBMI-SDS 0–1–12 | 1.41 | (1.17–1.68) | **<0.001** | 4.25 | (2.66–6.79) | **<0.001** |
| ΔBMI-SDS 18–48 | 1.54 | (1.14–2.07) | **0.005** | 3.00 | (1.84–4.88) | **<0.001** |
| WHtR-SDS 0–1 | 1.23 | (1.02–1.48) | **0.027** | 1.05 | (0.64–1.70) | 0.854 |
| ΔWHtR-SDS 0–1–12 | 1.24 | (1.04–1.48) | **0.017** | 0.99 | (0.64–1.54) | 0.955 |
| ΔWHtR-SDS 18–48 | 1.26 | (0.99–1.59) | 0.062 | 1.03 | (0.74–1.44) | 0.845 |

*OR, odds ratios; 95% CI, 95% confidence interval; p, p value; Ow/Ob, overweight/obesity; Nw/Uw, normal weight/underweight; $BMI_{SDS}$, body mass index standard deviation scores; $WHtR_{SDS}$, waist-to-height ratio standard deviation scores.*
*[a]The univariable logistic regression analyses included each of the independent variables separately, and in the [b]multivariable logistic regression analyses they were all controlled for each other. No other variables were included in the models than those presented in the table.*
*[c]The children were classified as having overweight or obesity or as having normal weight or underweight according to BMI cut-off values by the International Obesity Task Force (229).*
*Lindholm et al., Acta Paediatrica 2019.*

## 5.2 BMI and WHtR in children classified according to WHtR (Paper II)

Of the boys, 86.8% had $WHtR_{SDS} < 1$ and 13.2% had values ≥ 1 at five years. The corresponding values for the girls were 83.3% and 16.7%. $WHtR_{SDS} \geq 1$ at 5 years corresponded to crude WHtR values between 0.51 and 0.59 in the boys and between 0.51 and 0.66 in the girls. $BMI_{SDS}$ classification showed that among the boys, 2.4% had underweight, 87.6% had normal weight, 8.5% had overweight, and 1.5% had obesity. The corresponding values for the girls were 1.6%, 85.7%, 9.6%, and 3.0%. Mean values of BMI and $BMI_{SDS}$ at 5 years were significantly higher in children with $WHtR_{SDS} \geq 1$ than in children with $WHtR_{SDS} < 1$ ($p < 0.001$). There were no significant differences in mean birth weight (MBW) and in the proportion of children born SGA or LGA between the different $WHtR_{SDS}$ groups.

### 5.2.1 $BMI_{SDS}$ growth patterns

Children with $WHtR_{SDS} \geq 1$ at 5 years of age had at every measurement point significantly higher mean $BMI_{SDS}$ than children with < 1 in $WHtR_{SDS}$ (p <

0.001, except at the first measurement point; $p < 0.01$ for the boys and $p < 0.05$ for the girls). The boys passed the +1 SDS line at ~48 months and the girls passed it at ~54 months (Fig 12). Children with <1 in $WHtR_{SDS}$ remained relatively stable at all measurement points without any upward SDS line crossing.

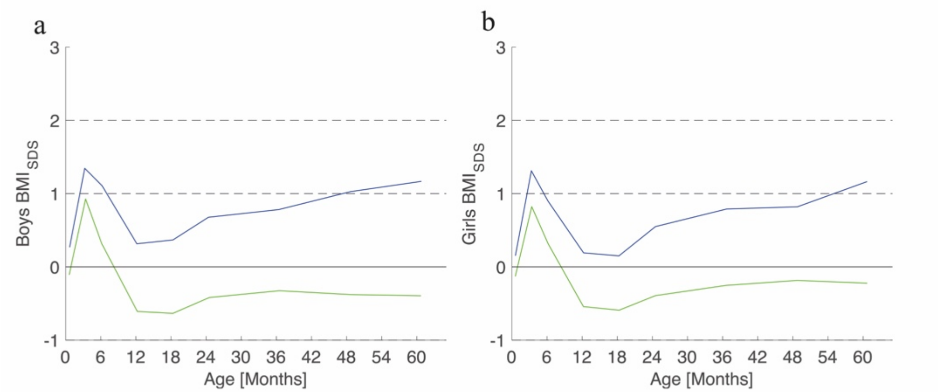


***Figure 12*** *Growth patterns based on mean body mass index standard deviation scores ($BMI_{SDS}$) for boys **(a)** and girls **(b)** from 0–1 to 60 months, classified according to Swedish $WHtR_{SDS}$ reference values at 60 months of age (247). Blue lines represent children with $WHtR_{SDS} \geq 1$ and green lines, children with $WHtR_{SDS} < 1$ at 5 years. Lindholm et al., Pediatric Research 2019.*

## 5.2.2 $WHtR_{SDS}$ growth patterns

Children with $WHtR_{SDS} \geq 1$ at five years of age had at every measurement point significantly higher mean $WHtR_{SDS}$ than children with < 1 in $WHtR_{SDS}$ ($p < 0.001$ except at the first measurement point in the girls $p = 0.131$. The boys crossed the +1 SDS line between 36 and 48 months and the girls crossed it at ~48 months (Figure 13). Children with < 1 in $WHtR_{SDS}$ remained relatively stable at all measurement points without any upward SDS line crossing.

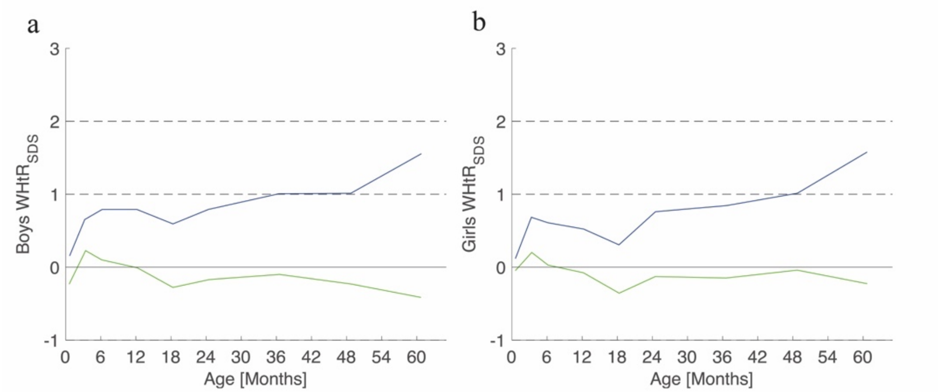


***Figure 13*** *Growth patterns based on mean waist-to-height ratio standard deviation scores ($WHtR_{SDS}$) for boys **(a)** and girls **(b)** from 0– 1 to 60 months, classified according to Swedish*

*$WHtR_{SDS}$ reference values at 60 months of age (247). Blue lines represent children with $WHtR_{SDS}$ $\geq 1$ and green lines, children with $WHtR_{SDS}$ <1 at 5 years. Lindholm et al., Pediatric Research 2019.*

### 5.2.3 Association between $BMI_{SDS}$ and $WHtR_{SDS}$

Overweight/obesity according to $BMI_{SDS}$ was to a high degree associated with an elevated $WHtR_{SDS}$. Of 175 children with overweight or obesity according to $BMI_{SDS}$, 104 (59%) had $WHtR_{SDS} \geq 1$. However, 127 (9%) of 1,365 children with normal weight or underweight according to $BMI_{SDS}$ had ≥ 1 in $WHtR_{SDS}$, representing 55% of all children with $WHtR_{SDS} \geq 1$ ($p < 0.001$). In this 55% of the children, the crude WHtR values were between 0.51– 0.56 in comparison to 0.51–0.66 in the group with overweight/obesity and $WHtR_{SDS} \geq 1$.

**Table 6** *Correlation between $WHtR_{SDS}$ and $BMI_{SDS}$ in children at 60 months of age*

| **$WHtR_{SDS}$[a]** n = 1540 | **< 1SD** n = 1309 | **≥1 SD** n = 231 |
|---|---|---|
| $BMI_{SDS}$ Nw[b] (n) | 1,238 (94.6%) | 127 (55%) |
| $BMI_{SDS}$ Ow/Ob (n) | 71 (5.4%) | 104 (45%) |

*$WHtR_{SDS}$, waist-to-height ratio standard deviation scores; $BMI_{SDS}$, body mass index standard deviation scores; Nw, normal weight; Ow/Ob, overweight/obesity. [a]Chi-squared tests of the association between $BMI_{SDS}$ and $WHtR_{SDS}$. [b]Including children with underweight. The children were classified as having< 1 or ≥ 1 in $WHtR_{SDS}$ according to Swedish reference values at 60 months of age (247), and as having $BMI_{SDS}$ for overweight/obesity or normal weight/underweight at 60 months of age, according to BMI cut-off values by the International Obesity Task Force (229). Lindholm et al., Pediatric Research, 2019.*

In further analyses, the subgroup of children with normal weight according to $BMI_{SDS}$ and with ≥ 1 in $WHtR_{SDS}$ at 5 years was compared with the children with overweight or obesity and ≥ 1 in $WHtR_{SDS}$ at the same age. We found that the group of children with normal $BMI_{SDS}$ and elevated $WHtR_{SDS}$ had a significantly lower mean birth weight, 3,504 g versus 3,725 g ($p < 0.001$), and 56% of the children were girls as compared to 59% girls in the group with overweight or obesity and an elevated $WHtR_{SDS}$ ($p = 0.143$) (Table 7). When comparing the WHtR growth patterns between 0 and 5 years in the two groups, we found that the mean $WHtR_{SDS}$ values in the two groups differed significantly first at the last two measurement points where the group with overweight or obesity and an elevated $WHtR_{SDS}$ had higher values ($p < 0.05$) (Figure 14).

**Table 7** Comparison of *characteristics of the 127 children with elevated $WHtR_{SDS}$ and normal $BMI_{SDS}$ and those with overweight/obesity and normal $WHtR_{SDS}$*

| | **≥1 SD Nw/Uw** (n = 127) | **≥1 SD and ow/Ob** (n = 104) |
|---|---|---|
| *At birth* | | |
| MBW ± SD (g) | 3504 ± 0.49 | 3725 ± 0.38 |
| Missing (n) | 8 | 3 |
| *Size for gestational age* | | |
| SGA (n) | 12 | 8 |
| AGA (n) | 103 | 84 |
| LGA (n) | 12 | 12 |
| Missing (n) | 0 | 0 |
| *Gestational age* | | |
| $37^0$–$37^6$ (n) | 9 | 4 |
| $38^0$–$40^6$ (n) | 93 | 75 |
| $41^0$–$43^5$ (n) | 25 | 25 |
| Missing (n) | 0 | 0 |
| *Maternal age* | | |
| <25 (n) | 11 | 10 |
| 25-35 (n) | 87 | 69 |
| ≥35 (n) | 26 | 25 |
| Missing (n) | 3 | 0 |
| *At 60 months, mean ± SD* | | |
| WHtR (cm/cm) | 0.51–0.56 | 0.51–0.66 |

*For mean values in birth weight, the children with ≥1 in $WHtR_{SDS}$ and normal weight/underweight according to BMI were compared to the children with <1 in $WHtR_{SDS}$ and Overweight/Obesity according to BMI, ***p <0.001.*
*Nw/Uw, Normal weight/underweight; Ow/Ob, Overweight/Obesity; MBW, mean birth weight; SD, standard deviation; SGA, small for gestational age; AGA, appropriate for gestational age; LGA, large for gestational age; $BMI_{SDS}$, body mass index standard deviation scores; $WHtR_{SDS}$, waist-to-height ratio standard deviation scores.*

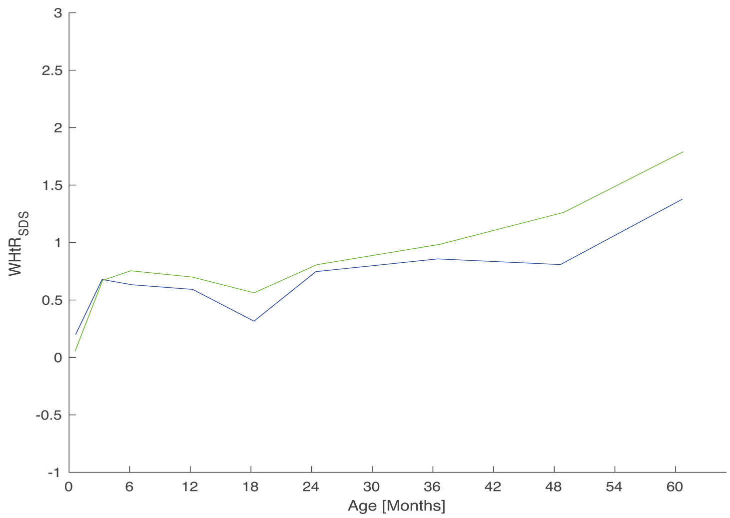


***Figure 14*** *Mean $WHtR_{SDS}$ values during the different measurement points for the children with normal weight according to $BMI_{SDS}$ and $\geq 1$ in $WHtR_{SDS}$ (green lines) as well as children with overweight/obesity according to $BMI_{SDS}$ and $\geq 1$ in $WHtR_{SDS}$ (blue lines).*

# 5.3 Nutrition, feeding-practices and rapid weight gain (Paper III)

When the children were analysed regarding RWG or nRWG during the first year, it was found that 46% of the children had RWG during the first 6 months and 8% the next 6 months.

## 5.3.1 Nutrition and feeding practices and RWG

RWG during 0–6 months was positively associated with bottle feeding at birth, 3–4 months and 6 months in all three regression models used. Breastfeeding at 3–4 months and 6 months and nighttime meals at 3–4 months in model 1 and at 6 months in all three models were negatively associated with RWG during the same time period (Table 8). When specifically studying the content of the night meals, it was found that breast milk was negatively associated with RWG whereas a positive association was found for formula milk at 3–4 months. Milk cereal drink (MCD) given at night at 6 months was positively associated with RWG when adjusted for birth weight and gender, but not in the other models (Table 9).

Only bottle-feeding at 3–4 months was associated with RWG between 6–12 months in all three models (OR 1.90, 95% CI 1.05,3.44; $p < 0.05$).

**Table 8** *Nutrition- and feeding practice-related risk factors for rapid weight gain during the first 6 months*

| | RWG/nRWG (n) | Model 1 OR | 95% CI | p | Model 2 OR | 95% CI | p | Model 3 OR | 95% CI | p |
|---|---|---|---|---|---|---|---|---|---|---|
| *Breastfeeding* | | | | | | | | | | |
| 0 months | | | | | | | | | | |
| No | 55/51 | 1 | Ref | | 1 | Ref | | 1 | Ref | |
| Yes | 800/943 | 0.83 | 0.55, 1.26 | 0.388 | 0.82 | 0.53, 1.28 | 0.384 | 0.79 | 0.49, 1.28 | 0.333 |
| 3–4 months | | | | | | | | | | |
| No | 621/783 | 1 | Ref | | 1 | Ref | | 1 | Ref | |
| Yes | 198/159 | 0.65 | 0.50, 0.83 | **0.001** | 0.63 | 0.48, 0.82 | **0.001** | 0.59 | 0.44, 0.79 | **<0.001** |
| 6 months | | | | | | | | | | |
| No | 381/336 | 1 | Ref | | 1 | Ref | | 1 | Ref | |
| Yes | 435/625 | 0.63 | 0.52, 0.78 | **<0.001** | 0.64 | 0.51, 0.79 | **<0.001** | 0.63 | 0.50, 0.80 | **<0.001** |
| *Bottle-feeding* | | | | | | | | | | |
| 0 months | | | | | | | | | | |
| No | 551/771 | 1 | Ref | | 1 | Ref | | 1 | Ref | |
| Yes | 262/183 | 2.02 | 1.60, 2.55 | **<0.001** | 2.11 | 1.65, 2.70 | **<0.001** | 2.23 | 1.70, 2.92 | **<0.001** |
| 3–4 months | | | | | | | | | | |
| No | 198/292 | 1 | Ref | | 1 | Ref | | 1 | Ref | |
| Yes | 448/379 | 1.74 | 1.37, 2.21 | **<0.001** | 1.71 | 1.32, 2.21 | **<0.001** | 1.70 | 1.29, 2.25 | **<0.001** |
| 6 months | | | | | | | | | | |
| No | 160/266 | 1 | Ref | | 1 | Ref | | 1 | Ref | |
| Yes | 689/724 | 1.65 | 1.30, 2.08 | **<0.001** | 1.67 | 1.30, 2.14 | **<0.001** | 1.63 | 1.24, 2.13 | **<0.001** |
| *Nighttime meals* | | | | | | | | | | |
| 3–4 months | | | | | | | | | | |
| No | 188/186 | 1 | Ref | | 1 | Ref | | 1 | Ref | |
| Yes | 630/760 | 0.78 | 0.61, 0.99 | **0.041** | 0.78 | 0.61, 1.02 | 0.065 | 0.82 | 0.62, 1.09 | 0.165 |
| 6 months | | | | | | | | | | |
| No | 342/321 | 1 | Ref | | 1 | Ref | | 1 | Ref | |
| Yes | 510/673 | 0.72 | 0.58, 0.88 | **0.001** | 0.72 | 0.58, 0.89 | **0.002** | 0.72 | 0.57, 0.91 | **0.007** |

*MCD, milk cereal drink, RWG, rapid weight gain; nRWG; non-rapid weight gain; n, number of subjects; OR, odds ratio; 95% CI, 95% confidence interval; p, p value.*
*Model 1, adjusted for birth weight and gender; Model 2, additionally adjusted for maternal and paternal education and maternal and paternal smoking; Model 3 additionally adjusted for maternal weight before pregnancy, maternal weight gain during pregnancy, paternal weight at the first measurement point and maternal and paternal diabetes mellitus and cardiovascular disease.*

***Table 9*** *Logistic regression analyses of content of nighttime meals and rapid weight gain during the first months*

| RWG/nRWG | | Model 1 | | | Model 2 | | | Model 3 | |
|---|---|---|---|---|---|---|---|---|---|
| (n) | OR | 95% CI | p | OR | 95% CI | p | OR | 95% CI | p |
| **Nighttime meals 3-4 months** | | | | | | | | | | |
| *Breastmilk* | | | | | | | | | | |
| No 499/654 | 1 | Ref | | 1 | Ref | | 1 | Ref | |
| Yes 319/292 | 0.69 | 0.56, 0.85 | **<0.001** | 0.67 | 0.54, 0.84 | **0.001** | 0.66 | 0.52, 0.84 | **0.001** |
| *Formula milk* | | | | | | | | | |
| No 656/827 | 1 | Ref | | 1 | Ref | | 1 | Ref | |
| Yes 162/119 | 1.68 | 1.28, 2.22 | **<0.001** | 1.74 | 1.30, 2.34 | **<0.001** | 1.87 | 1.36, 2.58 | **<0.001** |
| *Water* | | | | | | | | | |
| No 816/944 | 1 | Ref | | 1 | Ref | | 1 | Ref | |
| Yes 2/2 | 1.25 | 0.17, 9.45 | 0.83 | 1.15 | 0.16, 8.49 | 0.89 | 1.23 | 0.17, 9.07 | 0.84 |
| **Nighttime meals 6 months** | | | | | | | | | |
| *Breastmilk* | | | | | | | | | |
| No 492/466 | 1 | Ref | | 1 | Ref | | 1 | Ref | |
| Yes 360/528 | 0.63 | 0.52, 0.77 | **<0.001** | 0.64 | 0.52, 0.78 | **<0.001** | 0.61 | 0.49, 0.77 | **<0.001** |
| *Milk cereal drink* | | | | | | | | | |
| No 723/873 | 1 | Ref | | 1 | Ref | | 1 | Ref | |
| Yes 129/121 | 1.41 | 1.06, 1.88 | **0.020** | 1.29 | 0.94, 1.76 | 0.114 | 1.38 | 0.99, 1.93 | 0.061 |
| *Water* | | | | | | | | | |
| No 833/975 | 1 | Ref | | 1 | Ref | | 1 | Ref | |
| Yes 19/19 | 1.46 | 0.73, 2.90 | 0.282 | 1.38 | 0.65, 2.90 | 0.401 | 1.31 | 0.60, 2.86 | 0.504 |

*MCD, milk cereal drink, RWG, rapid weight gain; nRWG; non-rapid weight gain; n, number of subjects; OR, odds ratios; 95% CI, 95% confidence interval; p, p value*
*Model 1, adjusted for birth weight and gender; Model 2, additionally adjusted for maternal and paternal education and maternal and paternal smoking; Model 3, additionally adjusted for maternal weight before pregnancy, maternal weight gain during pregnancy, paternal weight at the first measurement point and maternal and paternal diabetes mellitus and cardiovascular disease.*

## 5.4 Early life risk factors for an elevated WHtR (Paper IV)

Of the 1540 children, 85% had $WHtR_{SDS} < 1$ and 15% $WHtR_{SDS} \geq 1$ at 5 years of age. At the same age 9% had overweight, 2% obesity and 89% normal weight or underweight. In the total population, 3% were born SGA, 93% AGA and 4% LGA.

## 5.4.1 Risk factors for an elevated WHtR

In univariable logistic regression analyses, child-related risk factors positively associated with a $WHtR_{SDS} \geq 1$ at 5 years of age were RWG during 0–6 months and during 6–12 months (Table 10).

**Table 10** *Univariable logistic regressions analyses over potential child-related risk factors for an elevated WHtR at five years of age*

| Child related risk-factors | WHtR≥1 SDS/< 1SDS | OR | 95% CI | p |
|---|---|---|---|---|
| *Gender* | | | | |
| **Male** | 99/651 | 1 | Ref | |
| **Female** | 132/658 | 1.32 | 1.00, 1.75 | 0.054 |
| *Birth weight in kg* | n/a | 1.14 | 0.85, 1.54 | 0.392 |
| *Rapid weight gain 0–6 months* | | | | |
| **No** | 74/588 | 1 | Ref | |
| **Yes** | 105/473 | 1.76 | 1.28, 2.43 | **0.001** |
| *Rapid weight gain 6–12 months* | | | | |
| **No** | 157/983 | 1 | Ref | |
| **Yes** | 22/78 | 1.77 | 1.07, 2.92 | **0.026** |

*OR, odds ratio; 95% CI, 95% confidence interval; p, p value.*

When examining parental health-related risk factors, maternal pre-pregnancy BMI and paternal BMI were found to be positively associated with a $WHtR_{SDS} \geq 1$ at five years of age (Table 11).

**Table 11** *Univariable logistic regression analyses of potential parental health-related risk factors for an elevated WHtR at five years of age*

| Parental risk factors | | WHtR ≥ 1 SDS/< 1SDS | | |
|---|---|---|---|---|
| | | OR | 95% CI | p |
| *Maternal pre-pregnancy BMI* | n/a | 1.07 | 1.03,1.10 | **<0.001** |
| *Maternal weight gain during pregnancy* | n/a | 1.00 | 0.97,1.03 | 0.930 |
| *Paternal BMI* | n/a | 1.09 | 1.02,1.16 | **0.007** |

*OR, odds ratios; 95% CI, 95% confidence intervals; p, p value*

Regarding nutrition- and feeding practice-related risk factors, MCD consumption at 24 months and also bottle-feeding at 12 and 24 months were negatively associated with a $WHtR_{SDS} \geq 1$ at five years of age (Table 12).

In multivariable logistic regression analyses, RWG between 0–6 months, maternal pre-pregnancy BMI and paternal BMI were significantly associated with an elevated $WHtR_{SDS}$ at five years of age (Table 13).

**Table 12** *Univariable logistic regression analyses of potential nutrition-related risk factors for an elevated WHtR at five years of age*

| Risk factors related to nutrition and feeding-practices | WHtR≥1 SDS/< 1SDS | OR | 95% CI | p |
|---|---|---|---|---|
| *Milk cereal drink consumption* | | | | |
| 24 months | | | | |
| No | 60/281 | 1 | Ref | |
| Yes | 105/718 | 0.69 | 0.49, 0.97 | **0.032** |
| *Bottle-feeding* | | | | |
| 12 months | | | | |
| No | 27/103 | 1 | Ref | |
| Yes | 165/1007 | 0.63 | 0.40, 0.99 | **0.043** |
| 24 months | | | | |
| No | 60/268 | 1 | Ref | |
| Yes | 110/748 | 0.66 | 0.47, 0.93 | **0.017** |

*OR, odds ratio; 95% CI, 95% confidence interval; p, p value.*

**Table 13** Comparison of *odds ratios and 95% CI for children with an elevated WHtR and children with normal WHtR at five years of age*

| [c]$WHtR_{SDS} \geq 1$ vs | Univariable logistic regressions[a] | | | Multivariable logistic regressions[b] | | |
|---|---|---|---|---|---|---|
| $WHtR_{SDS} < 1$ | OR | 95% CI | p | OR | 95% CI | p |
| RWG 0-6 mo | 1.76 | 1.28-2.43 | **0.001** | 1.90 | 1.23, 2.95 | **0.004** |
| Rapid weight gain 6-12 mo | 1.77 | 1.07-2.92 | **0.026** | 1.85 | 0.93, 3.69 | 0.081 |
| Pre-pregnancy BMI | 1.07 | 1.03-1.10 | <**0.001** | 1.06 | 1.01, 1.11 | **0.019** |
| Paternal body mass index | 1.09 | 1.02-1.16 | **0.007** | 1.11 | 1.01, 1.21 | **0.028** |
| Milk cereal drink 24 mo | 0.69 | 0.49-0.97 | **0.032** | 0.86 | 0.38, 1.93 | 0.713 |
| Bottle-feeding 12 mo | 0.63 | 0.40-0.99 | **0.043** | 0.85 | 0.41, 1.76 | 0.668 |
| Bottle-feeding 24 mo | 0.66 | 0.47-0.93 | **0.017** | 0.65 | 0.28, 1.49 | 0.308 |

*OR, odds ratio; 95% CI, 95% confidence interval; p, p value; $WHtR_{SDS}$, waist-to-height ratio standard deviation scores; vs, versus; mo, months. [a]The univariable logistic regression analyses included each of the independent variables separately, and in the [b]multivariable logistic regression analyses they were all controlled for each other. No other variables than those presented in the table were included in the models. [c]The children were classified as having a $WHtR_{SDS} \geq 1$ or <1 according to Swedish reference values (247).*

### 5.4.2 Risk factors for overweight or obesity at five years of age

When examining the variables that were positively associated with a $WHtR_{SDS} \geq 1$ at five years, regarding their association with overweight or obesity at five years, in univariable logistic regression analyses, three of them were found to be associated with overweight or obesity at five years: RWG between 0 and 6 months (OR 1.95, CI:1.36,2.81, p < 0.001), RWG between 6 and 12 months (2.03, 1.19, 3.47, p < 0.01) and maternal pre-pregnancy BMI (1.12, 95% 1.09,1.16, p < 0.001). In multivariable regression analyses, the same variables were positively associated with overweight and obesity: RWG between 0 and 6 months (2.53, 1.53, 4,20, <0.001), RWG between 6 and 12 months (2.82, 1.37, 5.79, <0.01) and maternal pre-pregnancy BMI (1.12, 1.06,1.17, p <0.001).

# 6 GENERAL DISCUSSION

## 6.1 Main findings and interpretations

This thesis contributes with information regarding early growth patterns in BMI and WHtR associated with overweight, obesity and an elevated WHtR in 5-year-old children. In *Paper I*, it was shown that early growth patterns in BMI and WHtR were different in children with overweight or obesity at 5 years of age in comparison with children with normal weight or underweight at the same age. BMI was sufficient in the prediction of later overweight or obesity and WHtR did not add any further information with regard to BMI. In the identification of children with abdominal adiposity measured by WHtR, *Paper II* showed that BMI classification missed every second child with an elevated WHtR at 5 years, suggesting that BMI alone is not sufficient for identification of all children with abdominal adiposity.

Concerning early risk factors for rapid weight gain during the first year, *Paper III* showed that bottle-feeding and nighttime meals containing formula milk were risk factors for rapid weight gain during the first 6 months while breastfeeding was negatively associated with this development. It was also shown that rapid weight gain was more common during the first 6 months of the first year than during the next 6 months. Rapid weight gain during the first 6 months of life together with parental BMI was associated with an elevated WHtR at 5 years of age (*Paper IV)* and rapid weight gain during both 0–6 and 6–12 months and also maternal pre-pregnancy BMI was associated with overweight or obesity at 5 years.

### 6.1.1 BMI and WHtR growth patterns in identifying excess adiposity

The finding that children with overweight or obesity at 5 years had significantly higher $BMI_{SDS}$ and $WHtR_{SDS}$ already from an early age is largely consistent with the results of several other studies in children (270-272), but most of these studies have focused on school-age children and adolescents, and only a few have focused on children of preschool age. Given the growing body of evidence regarding the early establishment of overweight and obesity (9), a larger focus on infant growth patterns and early signs of excessive weight gain could lead to interventions already at the onset of overweight or obesity. This may also prevent the development of cardiometabolic risk factors which have been shown to be present in preschool children already when the overweight or obesity starts (186).

We found that BMI between 0 and 12 months predicted overweight or obesity at 5 years of age. At or around 9 months of age, the IP in BMI normally occurs but its association with later overweight has been questioned (230). In our study we did not have any measurement point at or near 9 months of age so it is unclear if the association we found depended on the magnitude or the timing of the IP, if it rather was a sign of rapid growth during the first year or depending on other reasons.

In *Paper I*, it was shown that on a group level, children with overweight or obesity at 5 years had an earlier AR than children with normal weight. This result is consistent with several earlier studies (61, 62, 273). The AR normally occurs when the child is between 3–7 years, and a rebound before 5.5 years has been associated with adiposity later in life. Although one study claimed that its rather a sign of centile crossing than a critical period *per se* (274). In recent decades there has been a trend towards an earlier AR in entire populations, and mean ages at AR less than 5 years have been reported (275). In this child cohort, it was children with overweight or obesity that had an AR before the age of 5 years and we did not see any signs of the AR at 60 months in children with normal weight or underweight. Many studies examining early growth pattern have used population-based cohorts, including children with overweight or obesity, which probably leads to curves with an earlier AR than the ones that truly apply to children with normal weight. This raises the question of the use of standardized curves in relation to reference curves, and the importance of being aware of any differences between the population that a specific growth chart is based on and the one in which it will be used. From a research point of view, the lack of consensus regarding one international reference curve makes it difficult to compare studies with each other. Children who are identified as having overweight or obesity in one curve may be classified as having normal weight in another curve This is confusing and probably counterproductive regarding preventive interventions against childhood overweight and obesity (233).

### 6.1.2 BMI and WHtR growth patterns in identifying an elevated WHtR

The number of studies on WHtR in children of preschool age is even more limited than those on BMI in this age group. Both WC and WHtR are surrogate measures of abdominal adiposity, but we chose to examine WHtR since it apart from being a measure of the waist circumference also relates to the height of the child, which during these ages may differ by several centimetres between children. In *Paper II* it was shown that BMI classification missed every second child with an elevated WHtR at 5 years of age. Whether or not an elevated WHtR in preschool children also represents an increased risk of other cardiometabolic risk markers needs to be investigated further. However, abdominal adiposity was given special weighting in the IDEFICS diagnosis criteria for metabolic syndrome in children as young as 2 years (192), and WHtR values corresponding to the ones found in our study have been associated with such risk factors in 5-year-old children also in previous research (196). WHtR has been shown to correlate to SAT rather than to VAT in preschool children (276) and insulin resistance, one of the components of metabolic syndrome has been shown to be inversely associated with SAT in the youngest children (277). However, associations between abdominal adiposity and cardiometabolic risk factors need to be further examined in this population. If future research confirms that these associations exist in children during the preschool years, WHtR needs to be validated in this age group, and relevant age-and gender-specific cut-off values corresponding to these risks need to be developed. Worth to mention is that the measurements and calculations needed for WHtR are relatively easy to perform and reproduce, and WHtR has been suggested as a good and cost-effective alternative to blood tests, in screening for cardiometabolic risk markers in children (213, 214).

### 6.1.3 Growth patterns in clinical practice

The finding that overweight and obesity at 5 years could be identified in BMI and WHtR growth patterns already from an early age, together with the reported higher prevalence of overweight or obesity in preschool children nowadays (9), highlight the value of the repeated measurements of growth and development performed at the Swedish CHCCs at the regular health check-ups during the preschool years. With their coverage of almost 100% of all preschool children, the health care professionals at local CHCCs are in good position for early identification of children who may need closer monitoring or preventive interventions against excessive weight gain. Childhood overweight and obesity are associated with adverse health consequences, both in childhood and adulthood, and an early identification of children at risk of this development has the possibility to support their lifelong health. This is also in line with the Convention on the Rights of the Child, which states that “a child has the right to the best attainable health” (13).

*Paper I* and *II* confirmed that BMI and WHtR, which represent well established techniques, are good tools in the identification of children at risk of excessive weight gain during the preschool ages. In the Swedish child health care, length, weight and head circumference (the last, followed until 18 months) are followed during the preschool years, but neither WHtR, nor WC are used on a regular basis (21).

The growth curves used in the Swedish child health care are based on children born in Gothenburg between 1973 and 1975 (234), and although they were based on values from Swedish children, differences exist between that child cohort and the children born nowadays. One example is that the number of breastfed children were lower in Sweden during that time. At 2 months of age, only 20% of the children were breastfed (278), compared to 87% at birth and 64% at 3–4 months in our child cohort. Apart from this reference, both nationally and internationally alternatives exist. A study comparing four different growth references regarding definitions of overweight/obesity and thinness in Swedish children showed great variations based on which reference that was used (279). When using a certain growth reference, it is important to be aware of the population that it was based on and the context in it was created.

Another important consideration regarding the benefit of repeated measurements performed in preschool children is that several studies have shown that parents (11), as well as health care professionals (12), often underestimate overweight or obesity in children. Growth charts where every child's value is noted and followed over time may therefore be a helpful instrument in showing parents and health care professionals whether a child might need more frequent measurements or further investigation. Not only children with risk of overweight, but also children with poor growth, which is often associated with disease, deviate from the normal patterns (74). When discussing excess weight with parents, starting from a value in a chart may also be one way for health care professionals to play down the sometime sensitive issue of discussing overweight or obesity in a child with the parents. Since parents often get worried when their child's growth deviates from the expected growth pattern, it is important to emphasize that not all deviations need to be investigated further (74).

### 6.1.4 Risk factors for rapid weight gain

In *Paper III*, it was shown that bottle- feeding and nighttime meals containing formula milk were associated with rapid weight gain during the first 6 months of life, whereas breastfeeding was negatively associated with this development. Several studies have examined rapid weight gain and its association with later overweight or obesity (121, 280), but fewer studies have investigated risk factors behind this accelerated weight gain (281). A weakness of our study was that we only had limited information regarding the content of the bottle during the different measurement points. However, recent research has shown that bottle-fed children experienced rapid weight gain irrespective of whether the bottle contained expressed breast milk or formula milk (137, 138). This suggests that not only the type of milk but also the mode of feeding may have an effect on rapid weight gain. In this study bottle-feeding was found to be significantly associated with rapid weight gain at all measurement points, and when adjusted for several risk factors for rapid weight gain or overweight/obesity, whether these associations depend on mode of feeding, or milk type in the bottle needs to be examined further.

In *Paper III* it was also shown that breastfeeding was negatively associated with rapid weight gain during the first year. It is known since some time that breastfed children gain weight at a slower pace than infants who are fed on formula (127). Whether breastfeeding also has an impact on later adiposity has been debated (128). Apart from that, recent research has shown that the meaning of breastfeeding has changed. Today, many children are fed with expressed breast milk from a bottle, and the communication regarding breastfeeding in both research and clinical practice is not so clear anymore (282). Breast milk fed from a bottle may lose nutritional value and the bioactive agents may lose their functions when the milk is handled or stored (135). Therefore, the consequences of drinking breast milk from a bottle instead of directly from the breast would be interesting to examine.

Several earlier studies have shown that children born SGA or with low birth weight are more prone to rapid postnatal weight gain or so called "catch up growth"(117, 120). In this child cohort, only a small proportion of children with rapid weight gain were born SGA. Catch-up growth due to this could therefore not be the major explanation behind the associations found.

### 6.1.5 Risk factors for an elevated WHtR at 5 years of age

In *Paper IV*, it was found that rapid weight gain during the first 0–6 months of life was associated with an elevated WHtR at 5 years of age. Abdominal adiposity has been suggested to be the link between rapid weight gain and associated adverse health outcomes (121). Maternal pre-pregnancy BMI and paternal BMI was also associated with an elevated WHtR. Pre-pregnancy BMI has been associated with an elevated WHtR in older children and hypotheses regarding a shared low socioeconomic status and eating habits associated with a high BMI in the mother have been suggested (283). In animal studies, a high maternal BMI at conception has been shown to lead to early programming during the intrauterine development (284). Associations between a high paternal BMI and an increased risk of children born SGA have been found in earlier research (285) but due to the population-based design in this study, only a few of the children were born SGA, and therefore such associations were not examined in this child cohort. It was however interesting to notice that 85% of the children born SGA had fathers with a BMI greater than or equal to 25.

In the univariable models, only bottle-feeding at 12 and 24 months and milk cereal drink consumption at 24 months showed significant associations with an elevated WHtR later in life and in the multivariable analyses they did not reach significance as risk factors. Perhaps the nutrition- and feeding-practice related factors exert their effect on rapid weight gain early in life and when the children become older the fact that they have experienced rapid weight gain, as well as other risk factors, become more important for an elevated WHtR.

### 6.1.6 Prevention of childhood obesity and associated disease

Even during the prenatal period, it is possible to intervene regarding later overweight or obesity. The antenatal care, has an important role in identifying risk factors that can affect intrauterine growth and development. Regarding obesity, maternal weight, gestational weight gain, nutrition, smoking and alcohol consumption all represent modifiable risk factors that are possible to affect. Regarding non-modifiable risk factors such as diabetes mellitus, gestational diabetes and hormonal disturbances, close monitoring and further investigation may be needed.

Besides following growth and development during the preschool ages, health care professionals at the CHCCs are in good position to reach new parents with information regarding risk factors for overweight or obesity such as rapid weight gain, as well as the latest recommendations regarding early nutrition and feeding practices. A family-based approach has been recommended in preventive interventions regarding childhood overweight and obesity. During the preschool ages the child is dependent on his or her immediate environment regarding how advices coupled to healthy growth and weight gain will be implemented. Murray Bowen described families as systems and that when changes are implemented in one family member, the other members may also be affected (265). This may be good to keep in mind when meeting the families.

However, even if the parents get the information, they may be unable or unwilling to follow the advice. When considering overweight and obesity from a system theoretic perspective, every child with his or her family is part of a system (261). Several parts of the system may be involved in the family's possibilities and willingness to change behaviours: the neighbourhood the family lives in, the parents' education, economic situation, eating habits, relatives and friends surrounding the family, the possibility to find healthy food in the local store, are examples of factors that may support or counteract the given advice. Interventions on different levels and the knowledge that not only the closest family but also people that surrounds the family may affect whether an intervention becomes successful or not.

## 6. 2 Methodological considerations

### 6.2.1 Study design and participating population

Epidemiological studies can have either an experimental or an observational design. Although the work described in this thesis had an observational design, we wanted to investigate causes of overweight, obesity and an elevated WHtR by examining associations between early growth patterns and overweight or obesity at five years of age, and also risk factors for overweight, obesity and an elevated WHtR at the same age. The study was population-based and longitudinal, making it suitable for the investigations that we wanted to conduct. The same population, children from the $H^2GS$ cohort, was used in all four papers, although the number of children included was greater in *Paper III*. Comparisons between the $H^2GS$ cohort and both regional and national material from the National Board of Health and Welfare regarding gender, short gestational age, birth weight and parental smoking were done. No significant differences were found, with the exception that paternal smoking was slightly less common in the $H_2GS$ cohort (267). This indicate that the study population was representative of both Halland and Sweden.

### 6.2.2 Internal validity

The internal validity can be affected by confounding, chance and bias. The latter can be further divided into selection bias, mis-classification bias and information bias. Each factor is described below.

### *Bias*

*Selection bias*

Our cohort consisted of children born in the county of Halland between October 2007 and December 2008. All the children born during that time period, 3,860, were eligible to take part in the study without any exclusions. The proportion of families that did not answer regarding participation, the ones that dropped out and the ones that we had to exclude because of missing growth data may have caused a possible bias. The families that chose not to participate may have been the most socially disadvantaged families with the highest frequency of children with overweight or obesity, since it has been shown in other studies that such families often decline to take part in research studies (286). The lack of data from these children may represent a possible bias that could not be controlled for. However, for the children with growth data missing, comparisons with the children included were made regarding gender, birth weight, maternal age, maternal weight before pregnancy, parental smoking and parental education, but no significant differences were found.

The population-based design led to a relatively limited number of children with obesity, and since that caused problems regarding statistical power, this group was analysed together with children with overweight.

*Information bias*

There was a risk of measurement error, mis-classification and error in the transmission of data to the data files. These kinds of mistakes were not expected to be systematic, and were therefore not considered to lead to bias. Regarding the measurements of weight, height and waist circumference, trained child health care nurses with experience of these kind of measurements performed all the measurements, using standardized methods, which reduced the risk of errors. Measurements of waist circumference (WC) have been shown to be less reliable than measurements of height and weight; furthermore, great inter-observational differences have been shown between WC measurements (135). Within the framework of this project, the inter- and intra-operator reliability for waist circumference was studied in children who were mainly younger than 24 months. The intra-class correlation coefficients were 0.98 both between and within those who made the measurements, although one of them had less experience.

Regarding recall bias, the questionnaires were completed at the CHCCs in connection with each of the nine measurement points and recall-bias should therefore not be a great problem.

### *Confounding*

In our comprehensive questionnaires we tried to collect information about several of the known risk factors for overweight, obesity and an elevated WHtR. In the analyses we used both univariable (non-adjusted and adjusted) and multivariable analyses in order to identify variables that affected each other.

### *Chance*

With repeated logistic regressions and Student's t-tests there is a risk that some of the associations found may be explained by chance. However, in many of the associations, the p value was $< 0.001$ which reduces the risk of chance. However, for associations near the $p < 0.05$ level interpretations should be made with caution.

## 6.2.3 External validity

Given that the study population was derived from a population that was considered to be representative of children in both Halland and Sweden, and since we used standardized measurements, we consider that our results can be generalized to other children in the same age groups who were born during the same time period.

# 7 CONCLUSIONS

Children with overweight or obesity at 5 years of age could be identified already from an early age by $BMI_{SDS}$ and $WHtR_{SDS}$ growth patterns.

BMI was sufficient for predicting overweight or obesity as measured by BMI at 5 years of age, and WHtR did not add any further information to this prediction.

Children with an elevated $WHtR_{SDS}$ at 5 years of age could be identified already from an early age by $BMI_{SDS}$ and $WHtR_{SDS}$ growth patterns.

Every second child with an elevated $WHtR_{SDS}$ at 5 years had normal $BMI_{SDS}$, showing that WHtR partly identifies other children than BMI does.

The findings suggest that BMI is sufficient for early identification of children with a risk of overweight or obesity at 5 years of age. For the identification of children with an elevated WHtR, the use of BMI alone misses every second child that may need further investigation regarding cardiometabolic risk factors.

Rapid weight gain was more common during the first 6 months of life than during the next 6 months.

Bottle feeding and nighttime meals containing formula milk during the first 6 months of life was associated with rapid weight gain during 0–6 months. Breastfeeding was negatively associated with this development.

Rapid weight gain during 0–6 months as well as maternal pre-pregnancy BMI and paternal BMI were associated with an elevated $WHtR_{SDS}$ at 5 years of age.

Rapid weight gain during 0–6 and 6–12 months as well as maternal pre-pregnancy BMI were associated with an increased risk of overweight or obesity at 5 years of age.

Risk factors operating before pregnancy and early in life increase the risk of early rapid weight gain, an elevated WHtR and overweight or obesity at 5 years of age and bottle feeding, nighttime meals, early rapid weight gain as well as parental overweight are potential modifiable risk factors in this development.

# 8 FUTURE PERSPECTIVES

Excess weight during childhood has consequences both for the affected child, the family and for society as a whole. Given the complex and multifactorial background of childhood overweight and obesity, the saying that “we know so much and yet so little” is quite appropriate.

Regarding future studies, it would be interesting to do follow-up studies of the children in the $H_2GS$ cohort to examine whether those who had overweight, obesity or an elevated WHtR, at five years of age also have it later in life.

Interventions based on the risk factors found in this thesis would be interesting to develop and follow up in children of preschool age.

It would also be interesting to examine whether children with an elevated WHtR during the preschool years also have cardiometabolic risk markers, to determine further whether WHtR is a relevant measure of cardiometabolic risk in children.

Epigenetic reasons behind overweight or obesity would be interesting to examine. The development of treatment methods directed at epigenetic changes has just begun, and promising results have already emerged.

# SAMMANFATTNING PÅ SVENSKA

Övervikt och fetma hos barn har ökat världen över under de senaste decennierna och även de yngsta barnen är drabbade. Forskning har visat att övervikten kan vara etablerad redan i tvåårsåldern och den följer ofta med barnet upp i vuxen ålder. Hos vuxna är övervikt och fetma förknippade med en ökad risk för kroniska sjukdomar såsom hjärt-kärlsjukdomar och typ 2 diabetes mellitus samt en för tidig död. Övervikten kan dock leda till hälsoproblem redan under barndomen. Den tidiga etableringen av övervikt och fetma påvisar behovet av tidiga preventiva interventioner, dock förekommer endast få sådana insatser i nuläget. Tidiga interventioner förutsätter kunskaper om de riskfaktorer som är förknippade med utvecklingen av övervikt och fetma samt tillgång till bra mätmetoder för att redan tidigt i livet kunna identifiera barn med risk för denna utveckling.

Det övergripande syftet med denna avhandling var att studera tillväxtmönster i body mass index (BMI) och waist-to-height ratio (WHtR) associerade med övervikt, fetma och en förhöjd WHtR vid fem års ålder, samt tidiga riskfaktorer för denna utveckling

De specifika syftena var följande:
I) Undersöka om tidiga tillväxtmönster i BMI och WHtR redan från en tidig ålder kunde identifiera barn med övervikt eller fetma mätt med BMI vid 5 års ålder. II) Undersöka om tidiga tillväxtmönster i BMI och WHtR redan från en tidig ålder kunde identifiera barn med förhöjt midjemått mätt med WHtR vid 5 års ålder, samt om de båda metoderna identifierade samma barn. III) Undersöka samband mellan tidiga nutrition- och matningsrelaterade riskfaktorer för en snabb viktökning under de första 0–6 och 6–12 månaderna av livet. IV) Undersöka riskfaktorer för en förhöjd WHtR vid fem års ålder samt om samma riskfaktorer även har samband med övervikt eller fetma.

Avhandlingen baseras på 2666 barn, födda i Region Halland mellan oktober 2007 och december 2008 och deltagare i Tillväxtprojektet. Från födelsen har barnens längd, vikt och midjemått uppmätts vid nio olika tidpunkter. Vid varje mät-tidpunkt har föräldrarna fyllt i frågeformulär med frågor avseende barnets nutrition, livsstil och bakgrundsdata om familjen.

Artikel I visade att tillväxtmönster i BMI och WHtR kunde användas för att redan tidigt i livet identifiera barn med övervikt eller fetma vid 5 års ålder men att WHtR inte tillförde någon information utöver den som erhölls med BMI.

I samband med identifieringen av barn med en ökad WHtR vid 5 års ålder fann vi att mer än hälften av barnen med ökad WHtR vid 5 års ålder hade ett normalt BMI (Artikel II).

I artikel III fann vi att flaskmatning och nattmål innehållande bröstmjölksersättning ökade risken för en snabb viktökning mellan 0–6 månader. Amning var negativt associerat med denna utveckling.

Artikel IV visade att snabb viktökning under barnets första 6 månader, mammans BMI innan graviditeten såväl som pappans BMI hade samband med en förhöjd WHtR vid 5 års ålder. En snabb viktökning mellan 0–6 och 6–12 månader och mammans BMI innan graviditeten hade samband med övervikt eller fetma vid 5 års ålder.

Sammanfattningsvis så har denna avhandling visat att BMI var tillräckligt för att identifiera barn med övervikt eller fetma vid fem års ålder. För att identifiera en förhöjd WHtR räcker det dock inte med BMI då denna mätmetod missade hälften av barnen med ökad WHtR. Riskfaktorer som uppkommer redan innan födelsen eller tidigt i livet ökar risken för en tidig snabb viktökning samt för övervikt/fetma och en ökad WHtR vid fem års ålder. Flaskmatning, tidig snabb viktuppgång samt föräldrarnas BMI är exempel på faktorer som bör utredas vidare.

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