Early feeding practices and weight-related outcomes in childhood

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associations in different ethnic groups in the Netherlands

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EARLY FEEDING PRACTICES AND WEIGHT-RELATED OUTCOMES IN CHILDHOOD

associations in different ethnic groups in the Netherlands

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Contents

Glossary of terms and abbreviations

BMI	Body mass index
WHO	World Health Organization
IOTF	International Obesity Taskforce
SDS	Standard Deviation Score
WFL	Weight for Length
EBF	Exclusive breastfeeding
CF	Complementary feeding
ESPGHAN	European Society for Paediatric Gastroenterology Hepatology and Nutrition
EFSA	European Food Safety Authority
ABCD	Amsterdam Born Children and their Development cohort study
GECKO	Groningen Expert Center for Kids with Obesity cohort study
BF	Breastfeeding
SPSS	Statistical Package for Social Sciences
CI	Confidence Interval
OR	Odds Ratio
YHC	Youth Health Care
LCMM	Latent Class Mixed Effect Model
LMR	Linear Mixed Regression
FFQ	Food Frequency Questionnaire
PCA	Principal Components Analysis
SSB	Sugar-sweetened beverages

Chapter 1

General introduction

Childhood overweight and obesity

Epidemiology of childhood overweight and obesity

Childhood overweight and obesity are among the most serious global public health concerns [1]. Children with overweight and obesity are at risk of developing obesity later in life [2,3] as well as noncommunicable diseases such as type 2 diabetes and cardiovascular diseases [4,5]. Children with obesity have also an increased risk of psychological comorbidities, such as depression, which may continue into adult life [6]. Due to the several short- and long-term comorbidities and the fact that obesity is difficult to reverse, prevention of childhood overweight and obesity is crucial.

Over the past four decades, mean body mass index (BMI) and the prevalence of overweight and obesity among 5–19 year-old children and adolescents have increased in most countries[7]. The latest global estimates suggest that 38 million children under the age of 5 and more than 340 million children and adolescents aged 5–19 years have overweight [8]. Worldwide, the number of children and adolescents with obesity has increased 10-fold between 1975 and 2016 [9]. Furthermore, the proportion of children with overweight has increased from 10.3% in 2000 to 18.4% in 2018 [10]. In the Netherlands, latest estimates indicate that 14% of 4 to 20 year-old children and adolescents have overweight or obesity [11,12]. Since 1980, there has been a two to three fold increase in prevalence of overweight and four to six fold increase in obesity among children and adolescents in the Netherlands [13]. However, recently, in several high-income countries, such as in the Netherlands, the prevalence of overweight and obesity seem to have stabilized [7].

Despite of the fact that in certain countries the overweight and obesity estimates seem to be plateauing, there are large and growing ethnic inequalities in overweight and obesity [14-16]. Populations with a certain ethnic minority backgrounds are found to have a relatively high prevalence of overweight and obesity. In the Netherlands, an overall decrease in overweight and obesity has been observed from 1999 through 2011 in children of Dutch ethnic descent, while during the same period the rates for children of Moroccan or Turkish descent were still increasing [17]. It is of importance to note that these ethnic differences, appearing already during the first years of life, remain largely unexplained [18,19]. Hence, early detection and prevention of overweight and obesity may require a better understanding of the early determinants in different ethnic groups.

Text box 1: Ethnicity

Ethnicity is a term that describes a group of people whose members identify with one another through shared culture - the practices, values, and beliefs [19]. This might include commonalities such as shared language, religion and traditions. In the Netherlands, country of birth is a widely used classification of ethnicity [20]. Although the country of birth does not capture the multidimensional character of ethnicity, it is considered as the most objective and stable measure. In the studies described in this thesis, ethnicity of the mother and her infant was defined as the country of birth of the mother or maternal grandmother to include first- and second generation immigrants [21].

Defining overweight and obesity in children using BMI

According to the WHO, overweight and obesity are defined as 'abnormal or excessive fat accumulation that presents a risk to health [23]. Currently, a global consensus on how to define overweight and obesity in (young) children is still lacking. The most commonly used measure for overweight and obesity both in children and adults, is based on measures of relative body weight such as the body mass index (BMI), defined as weight divided by height squared (kg/m^2) [24]. Although BMI is not meant for assessing fat accumulation of individuals, it is widely utilized as a screening tool for individual diagnoses of overweight and obesity in clinical practice. In epidemiological studies, the BMI is considered as the most feasible, non-invasive and inexpensive assessment of the prevalence of overweight and obesity. Indeed, most studies assessing obesity in adults and children have used BMI as an outcome measure [25]. In children, age- and sex-specific BMI reference cut-off values, such as the ones published by the WHO and the International Obesity Task Force (IOTF), are used to define overweight and obesity. According to the WHO definition, among 0-5 year old children overweight is defined as >2 and obesity as >3 standard deviation scores (sds) above the median for age and sex [26]. However, in children under 2 years of age, the threshold to define overweight or obesity remains a debate as well as the use of BMI as an indicator to detect 'abnormal or excessive fat accumulation' during infancy. In children and adolescents 5-19 years of age, the WHO defines overweight as

>1 sds and obesity as >2 sds above the median for age and sex [26]. It needs to be re-emphasized that BMI is an indirect proxy of body fatness based on body weight. Hence, it is not possible to use BMI to distinguish fat mass from lean mass and it is therefore a less accurate compared to direct methods [25]. However, although the accuracy of BMI varies according to the degree of body fatness [27], it is shown to be moderately sensitive and a specific indicator of excess weight among children [28].

Importance of the early life period

The causes of childhood overweight and obesity are complex and multifaceted. The most common causes are genetic factors, lack of physical activity, unhealthy eating patterns, or a combination of these factors [29]. An increasing amount of evidence suggests that the early life period, starting from conception until early childhood, is a critical period in the development of health and disease [30]. According to the concept of *metabolic programming*, environmental factors during early life influence the development of cardiovascular, neuroendocrine and metabolic systems and, if suboptimal, may predispose the individual to later life diseases [31]. Several biological and lifestyle determinants during the early life period may increase the risk for developing childhood overweight and obesity, such as high BMI of the parents or low/high birthweight of the infant [32,33]. Furthermore, increasing evidence suggests that type of feeding exposures during the first years of life have a crucial role in the development of childhood overweight and obesity [34,35].

Growth during early childhood

Growth references during 0-5 years

Measurements of weight, length, weight-for-length (WFL) or BMI can be used to monitor the growth of the child. In this thesis, the focus is on weight-related measures of growth, specifically on BMI. Growth measurements at specific time-points can be compared against age- and sex- specific growth charts, such as the WHO standards, to assess the growth of an individual child over time. During infancy (0-2 years), WFL percentile curves are often used to assess growth. However, WFL charts do not reflect age-dependent variation of weight or length. To overcome this limitation, the WHO has provided BMI-for-age references to monitor growth of children between 0-5 years of age. The WHO BMI-for-age growth references are based on a strict inclusion criteria, including a selected group of children whose mothers complied with the following feeding recommendations: exclusive breastfeeding for ≥4–6 months, continued partial breastfeeding to ≥12 months and introduction of complementary foods between 4-6 months of age [36]. Although WFL is currently the preferred measure for the assessment of weight status in children younger than 2 years, few recent studies suggested that WFL and BMI provided similar estimates for later overweight and obesity risk [37,38].

Early childhood growth patterns

Growth during the first years of life is faster than during any other period in life, including puberty [39]. Between birth and 3 years of age, body height doubles and body weight increases fivefold. The individual growth measurements of a child may represent a distinct growth pattern i.e., trajectory which provide an important perspective on growth velocity in addition to just assessing size at one point in time. The 'expected' growth rate of a child is seen when the growth measurements closely follow a certain percentile line on the growth chart.

There is increasing evidence that patterns in growth, such as development of weight and BMI during infancy or early childhood are strongly associated with later overweight and obesity and cardiometabolic health [35,40,41]. Particularly, excessive body weight or rapid growth (weight or BMI increase) during the first years of life seem to be strongly associated with subsequent overweight and obesity [35,42,43]. Rapid growth, defined as a change in weight, WFL or BMI of >0.67 sds-score, corresponds to an upward centile crossing on the growth chart. Growth rate is strongly dependent on birth weight and infants with a low birth weight tend to show rapid (catch-up) growth during early postnatal life [44]. Furthermore, recent findings suggest that different BMI trajectories especially during the first 2 years of life are more predictive of body composition and obesity in later childhood than a single time point assessment of BMI [45,46].

Childhood growth patterns are influenced by several factors, including genetics, intrauterine exposures, infant feeding and other factors, such as hormones [47,48]. Feeding during the early life period is suggested as one of the key determinants of growth with potential long-term health consequences. During the early life period feeding is gradually changing, nevertheless the role of different (or combinations of) feeding practices on early growth patterns and later overweight and obesity are not fully understood [49].

Diet during early childhood

Current recommendations and practices

Breastfeeding

Breastfeeding confers many important short and longer-term health benefits for both infant and the mother. Breast milk is recognized as the preferred source of nutrition during infancy. The WHO and UNICEF recommend exclusive breastfeeding (EBF), defined as providing only breast milk without any other liquids or solids, from birth until six months of age [50]. From 6 months onwards, when complementary feeding (CF) has been introduced, breastfeeding on demand is recommended to be continued up to 2 years of age or beyond [50]. In the Netherlands, it is advised to provide EBF at least until the age of 4 months, after which CF can be introduced.

It has been estimated that, globally, around 44% of infants between 0–5 months of age are provided EBF and this has increased over the past years [51]. In the Netherlands, the prevalence of women providing EBF has also increased during the last years [52]. Recent data shows that at 6 months, a larger percentage of Dutch mothers provide exclusive formula feeding (49%) compared to EBF (39%) (here EBF is irrespective of CF introduction) [52]. Interestingly, there are large differences in breastfeeding practices across populations. Exclusive breastfeeding is found to be more common among high- compared with low educated mothers [53,54]. Furthermore, mixed feeding (combined breast- and formula feeding) is highly common in certain ethnic minority populations already during the first months of life [55]. In the Netherlands, mothers with certain ethnic minority background have been reported to provide EBF or mixed feeding for a longer duration compared to Dutch mothers [56,57]. In addition, certain ethnic minority populations appear to give more frequent milk feedings throughout the day [58].

Complementary feeding

CF is known as the period of transition from a fully milk-based diet (either breast milk or infant formula) to family foods. Typically this covers the period from when solid foods are introduced into the diet, around 4-6 months, until the child has fully transitioned to the family diet, usually around 24 months [50].

Timing of complementary feeding

Around the age of 4-6 months, an infant's need for energy and nutrients starts to exceed what is provided by breast milk (or infant formula) and CF, in addition to breast milk, is needed to meet these increasing needs [50]. Complementary foods are also required to develop the ability to bite, chew and swallow food. CF is defined as solid foods and liquids other than breast milk or infant formula. Currently, there are different recommendations on the appropriate timing of CF. According to the WHO, CF should begin after 6 months of EBF. However, the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) recommends to provide CF between 4-6 months of age [59]. Furthermore, the European Food Safety Authority (EFSA) considers it safe to start CF introduction between 17-26 weeks, depending on the individual child's characteristics and development [60]. The recommendations in the Netherlands, provided by The Netherlands Nutrition Centre (Voedingscentrum) has adopted the recommendations from ESPGHAN and EFSA, suggesting to start providing CF during the period of 4 to 6 months [61]. Some recent evidence suggests that there is a critical time window for introduction of new foods, in terms of acceptance or allergy prevention [62,63]. Although most evidence suggests to introduce CF during 4-6 months, the age at which CF should be introduced, remains controversial [64].

Globally it has been estimated that nearly a third of 4-5 month old infants are already fed complementary foods [65]. Studies in the Netherlands have shown that 38% of infants receive CF before 6 months and 21% already before 3 or 4 months [66,67]. Factors such as low maternal educational level, maternal overweight and obesity and no/short duration of breastfeeding are associated with early introduction of CF [66].

Amount, frequency and type of complementary feeding

Apart from the timing of CF, recommendations on other aspects of CF are less detailed. Most recommendations state that the introduction of foods should be a gradual process, starting with small quantities of healthy foods alongside breastfeeding (or formula), gradually increasing while the intake of breastmilk decreases. CF should provide an increasing amount of energy to cover the energy- and nutrient needs which are no longer covered by breastfeeding [68]. The variety and frequency of foods should increase as the infant gets older, adapting to the infant's requirements and abilities. In addition, the consistency of the foods should gradually increase, from providing pureed food to mashed and semi-solid foods.

Most recommendations, including from the WHO, indicate that the amount of CF should be based on the principles of responsive feeding according to the hunger cues of the infant [68]. The frequency of CF is recommended to increase from 2–3 times per day at 6–8 months to 3–4 times per day at 9–24 months of age. The Dutch recommendations give advice for different periods of CF [61]. From 4 to 6 months, CF should be provided as small 'taste portions', i.e., 3-4 spoons 1-2 times per day to get introduced to new tastes. From 6 months onwards it is recommended to provide CF as full meals alongside milk feedings, and from 8 months onwards milk feedings can be fully replaced by complementary feedings. There are no specific recommendations for later CF periods; progressive introduction of healthy and varied CF is recommended during the dietary transition towards healthy family meals. This should continue until all the milk feedings have been replaced by meals and the child eats together with the rest of the family.

No detailed recommendations exist on the types of foods that should be provided during CF. The Dutch recommendations indicate that any ''healthy'' product is suitable to start CF, such as fruit, vegetables, potatoes, fish, porridge or bread [61]. There is increasing scientific evidence suggesting that a repeated exposure of vegetables at the start of the CF process may promote the acceptance and increase the intake of vegetables later during childhood [69].

According to studies in the US, fruits, vegetables and mixed dishes are the predominant types of complementary foods provided during the early CF phase (6-8 months) [70]. Thereafter, consumption of milk, whole grains and whole fruits seems to decline from 9-11 months onwards, whereas the intake of sugar-sweetened beverages, added sugars, and salty snacks seems to increase [71]. Already from 6 months onwards, diet quality is shown to already decline rapidly [71] and by the age of 2 years, sweets and snacks provide nearly 20% of total energy intake [70]. In the Netherlands, early introduction and frequent intake of non-recommended foods is also common. At 6 months of age, 20% of all infants were found to have consumed sweet beverages daily and 17% of infants had consumed snack foods, such as cookies, chocolate and candy daily [66]. Furthermore, a large proportion of Dutch children aged 2 to 6 years do not consume recommended amounts of vegetables, fruit, fish and fibre [72].

Early childhood diet and weight related outcomes in childhood

The effect of type of milk feeding

There are marked differences in early growth patterns of infants based on the different milk feeding types; EBF, mixed- or formula feeding [73]. EBF is associated with 'slower' weight gain during the early years [74]. Compared with formula-fed infants, breastfed infants tend to achieve faster weight-for-age during the first 1-4 (or 6) months of life, followed by slower weight gain during the 2nd half of infancy, resulting in a lower BMI at 1 year of age [73]. In addition to the differences in weight and weight-gain during infancy, breast- and formula fed children also present different growth patterns during childhood [75,76]. Although several studies suggest that breastfeeding has a moderate protective effect on childhood overweight and obesity, the evidence is mainly from observational studies [77] and was not supported by a randomized intervention study in Belarus [78]. Therefore, it has been proposed that the protective effect of breast feeding against overweight and obesity found in observational studies may reflect uncontrolled bias caused by confounding and selection.

There are also large discrepancies between the findings across studies depending on the type of milk feeding provided [77]. Although mixed feeding has been assumed to provide a small protective effect on excess weight gain [79,80], other studies suggested that mixed-fed infants have a higher energy intake [81] and a higher risk for overweight [82] compared to EBF infants. Furthermore, several studies did not distinguish between EBF and mixed feeding [77]. Certain studies also suggested that associations of the type of milk feeding and growth outcomes may vary across different ethnic populations [83,84].

Complementary feeding and dietary patterns

In comparison with the inconclusive effects of the type of milk feeding on the risk of obesity in infancy, there is currently even less knowledge about the importance of other early dietary factors on weight-related outcomes. Most studies have focused on the timing of CF, showing conflicting findings [85]. Although some studies indicated that early CF (<4 months or <6 months) is associated with rapid infant weight gain [79] or later overweight and obesity [86], other studies did not report this [87,88]. Furthermore, some studies suggested that these associations may vary depending on the type of milk feeding [89,90].

Evidence regarding other aspects of early childhood diet, such as types of foods and feeding frequency in relation to weight-related outcomes, is currently limited and inconclusive

[91]. From 4-6 months of age, weight gain appears not to be sensitive to the frequency or types of CF in healthy infants [92] yet there are no long-term studies. However, some evidence suggests that during early childhood, high intakes of food with high levels of animal protein such as meat and dairy products, or sugar-sweetened desserts and beverages are associated with a higher BMI-sds and risk of overweight and obesity in childhood [91,93,94]. In addition to single foods, specific dietary patterns are shown to be associated with later health outcomes, such as overweight and obesity [95,96]. Studies among older children and adults have shown that diets high in energy-dense, high-fat and low-fibre foods seem to predispose to overweight and obesity [97], yet evidence in younger children is scarce and conflicting [98,99].

Outline of this thesis

The overall aim of this thesis is to investigate associations of infant milk feeding and CF practices as well as toddler dietary patterns with weight-related outcomes during early childhood. A particular focus is to study the associations among different ethnic populations in the Netherlands.

Prevalence of obesity is relatively low among young children in the Netherlands; in 2009 the prevalence of obesity among 5-year-old boys and girls was 2.0% and 3.3%, respectively [13]. In order to reach adequate numbers for sufficient statistical power in the analyses, this thesis specifically focuses on overweight (including obesity) as an outcome.

In **Chapter 2,** associations between timing of CF and EBF duration with childhood BMI-sds and overweight are studied among groups of children at varying risk of overweight according to maternal characteristics: ethnicity, education, pre-pregnancy BMI and neighbourhood. Then, in **Chapter 3** associations between specific infant feeding patterns (i.e. milk feeding type combined with timing of CF) and BMI trajectories during the first year of life are investigated. Furthermore, potential ethnic differences in these associations are studied. Subsequently, in **Chapter 4,** the role of several infant feeding practices (BF duration, milk feeding frequency as well as timing, frequency and variety of CF) in explaining possible ethnic differences in BMI-sds during 2 to 5 years of age are explored. In **Chapter 5**, dietary patterns among 3-year-old Dutch children are identified and their associations with overweight and BMI-sds development during 3 to 10 years of age are analyzed. Finally, **Chapter 6** provides a discussion of the findings and the methodological considerations as well as implications for future research and public health.

Data sources

In order to address the aforementioned research aims, data from multiple Dutch population studies were used. These include: the Amsterdam Born Children and their Development (ABCD) cohort, the TIBET study and the GECKO cohort. The design of each study is described shortly below.

The ABCD cohort

The ABCD cohort is a large prospective population-based cohort which examines the association between maternal lifestyle, medical, psychosocial and environmental conditions during pregnancy, and children's health at birth as well as in later life, with specific attention paid to ethnic inequalities [100]. From January 2003 until March 2004 all pregnant women living in Amsterdam (12, 373) were invited to participate in the study at their first antenatal visit by their general practitioner, midwife or gynecologist. Three months after giving birth, the mothers who gave permission for follow-up received a questionnaire concerning the baby's health, development and growth; and the mother's lifestyle during and after pregnancy. Specially trained Youth Health Care (YHC) nurses conducted an average of 14 standardized routine measurements to monitor the growth and feeding patterns of the child until the children were 4 years old. When the children reached the age of 5 years, the mothers received an invitation for a health check of their child. Recently, the 5th study phase of the ABCD study was completed at the age of 15-16 years.

The TIBET study

The TIBET study is a prospective population-based study on infants of Turkish and Dutch descent born between August 2009 and March 2010 [58]. The main aim of the study was to assess the relation of nutrition with infancy growth among the study population and to explore the potential modifying role of ethnicity and socio-cultural factors. Infants of Turkish and Dutch descent born in the following five (former) districts of Amsterdam were invited to participate in the study: Baarsjes, Bos en Lommer, Geuzenveld/Slotermeer, Osdorp and Slotervaart. Data collection during infancy included three home visits (1, 4 and 6 months after birth) which assessed the following factors: demography, infant health, nutrition (comprehensive qualitative and quantitative aspects), infant Behavioral Questionnaire, social participation and language adequacy, perception of infant growth and feeding as well as information and support. Measurements collected during regular visits at the YHC at 1, 4 and 6 months were used which included: height, weight and head circumference. In total, 368 mothers were asked to participate, of whom 300 (150 Dutch and 150 Turkish) agreed (81.5%). The final study sample consisted of 286 participants (143 Dutch and 143 Turkish).

The GECKO cohort

The Groningen Expert Center for Kids with Obesity (GECKO) Drenthe study is a population-based, birth-cohort study of children born during a 1-year period in Drenthe, one of the northern provinces of The Netherlands [101]. The overall aim of the GECKO Drenthe cohort is to study the prevalence and early risk factors for the development of childhood overweight and fat distribution at very young age [102]. Within this birth cohort the growth of the children is closely followed, from birth until adulthood. At birth, cord blood was sampled and stored for (epi)genetic analysis and biomarkers. During the first 9 months of life, the children were measured every month (incl. questionnaire), thereafter this frequency decreased to once every 2 years from 3 years of age onwards. The following risk factors for childhood overweight and obesity are monitored: nutrition, physical activity, biological, epigenetic, social and environmental factors. The information is collected by using questionnaires filled out by the parents. During the regular visits to the YCF, the length, weight, head circumference and hip and waist circumference are measured. Furthermore, physical activity is measured using accelerometers.

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Chapter 2

Prospective associations of age at complementary feeding and exclusive breastfeeding duration with body mass index at 5-6 years within different risk groups

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Abstract

Background: Children with overweight or obesity are at risk for developing obesity in adulthood. Certain maternal characteristics, such as ethnicity, education, body mass index (BMI) or neighbourhood are determinants for childhood overweight risk. There are large variations in how mothers differing in these characteristics feed their infants. Therefore, associations of age at complementary feeding, exclusive breastfeeding duration with childhood overweight may differ in these groups. Understanding these associations would be essential to develop overweight prevention strategies.

Objectives: Study the associations of age at complementary feeding, exclusive breastfeeding duration with BMI-SDS at 5-6 years within risk groups.

METHODS: Using data from the Amsterdam Born Children and their Development (ABCD study), a population-based birth cohort (n=4495), we formed groups of children at varying risk of overweight according to maternal characteristics of ethnicity, education, pre-pregnancy BMI and neighbourhood. Linear and logistic regression analyses were conducted.

Results: Complementary feeding ≥5 months of age was associated with lower BMI-SDS in children of mothers of: Dutch ethnicity (B:-0.12; 95% CI:-0.21, -0.04), medium level education (-0.19; -0.30, -0.08), normal BMI (-0.08; -0.16, -0.01) and high risk neighbourhood (-0.16; -0.29, -0.02). Compared to exclusive breastfeeding for <3 months, exclusive breastfeeding for ≥6 months was associated with lower BMI-SDS in groups of medium level education (-0.28; 0.44, -0.11), normal BMI (-0.18; -0.29, -0.08) and medium (-0.18; -0.33, -0.04) and high-risk (-0.22; -0.42, -0.02) neighbourhoods.

Conclusions: Associations between infant feeding practices and childhood BMI may differ between risk groups, implying that overweight prevention strategies should be group-specific.

Introduction

Increasing evidence suggests that early life growth and development can have an influence on long-term health outcomes. Overweight (including obesity) during childhood is a risk factor for later obesity and obesity-related diseases, such as coronary heart disease [1,2]. As obesity in adulthood is also associated with several other comorbidities and is difficult to reverse, it is thus important to maintain normal weight trajectories during childhood [3]. It has been estimated that in 2020, 60 million preschool children worldwide will have overweight [4]. Although some developed countries have reported recent stabilization in the prevalence of childhood overweight [5], inequalities in the prevalence of overweight between certain groups, such as different socio-economic and ethnic populations, seem to be growing [6,7]. In the Netherlands, an overall decrease in overweight has been observed in children of Dutch origin, whereas the rates for children of Moroccan or Turkish origin are still increasing, from as early as two years of age [7]. This suggests that current intervention strategies may not be effective for all groups. Thus, there is a strong rationale to investigate early determinants for overweight in groups at varying risk of overweight.

Certain characteristics of the mother, such as ethnicity [8], education [9], BMI [10] or neighbourhood [11] predict a child's risk of becoming overweight. Underlying determinants for overweight may be different for children whose mothers differ in these characteristics, being partly (epi)genetical as well as behavioural, related to dietary habits or physical activity. Infant feeding practices i.e. (exclusive) breastfeeding and age at complementary feeding, have been suggested to have a moderate protective effect on childhood overweight [12,13]. However, conflicting evidence exists and residual confounding remains an issue in these studies. Many previous studies have conducted analyses within a single population, correcting for certain factors such as education and ethnicity. Yet, there are considerable differences in how mothers of different education or ethnic backgrounds feed their infants [14,15]. This suggests that maternal factors should be considered as potential effect modifiers, rather than confounders. Consequently, associations between exclusive breastfeeding duration as well as timing of complementary feeding may be different across populations. Such findings could suggest that interventions to target overweight that focus on infant feeding practices may have limited impact in certain groups. Furthermore, understanding potential differences in these associations between certain populations could aid the development of group-specific strategies to prevent overweight.

Therefore, the objective of this study was to examine the associations of age at complementary feeding and exclusive breastfeeding duration with BMI-standard deviation scores (SDS) at 5 - 6 years of age within groups of children at varying risk of overweight. We based our selection of risk groups on several maternal characteristics that are associated with childhood overweight [8-11], including pre-pregnancy BMI, education level, ethnicity and neighbourhood. We hypothesized that the associations between infant feeding practices and BMI in childhood may differ between the risk groups.

Methods

Participants

Data were obtained from the Amsterdam Born Children and their Development (ABCD) study, a large Dutch prospective birth cohort in the city of Amsterdam [16]. Between January 2003 and March 2004, all pregnant women (n= 12,373) living in Amsterdam were invited to participate in this study by completing a pregnancy questionnaire (Figure S1). Of these women, 8266 women completed the questionnaire (at 12 - 14 week of pregnancy) and 7863 women gave birth to live singleton infants. Weight and height data for a total of 4495 children at 5 - 6 years of age was obtained either from the Youth Health Care (YHC) (n= 3404) or from the ABCD health check (n= 1091). Participants with missing data on age at complementary feeding or duration of exclusive breastfeeding were excluded, leaving n= 4133 for age at complementary feeding and n= 4080 for duration of exclusive breastfeeding.

Risk groups

From the available data, we formed several risk groups based on four maternal characteristics: pre-pregnancy BMI, maternal education level, ethnicity and neighbourhood (Table SII). Data on pre-pregnancy BMI (weight and height data), education level, ethnicity and neighbourhood (in the city of Amsterdam) were all self-reported by the mother. All maternal data were obtained through the pregnancy questionnaire. Pre-pregnancy BMI was calculated from the weight and height data and categorized as follows: normal weight (including underweight) BMI <25 kg/m^2; overweight 25 - 29.9 kg/m^2; or obese ≥30 kg/m^2. Education level was defined as years of education after primary school: low (0 - 5 years of education); medium (6 - 10) years; or high (>10 years) [17]. Ethnicity was defined as the country of birth of the mother or her mother (to include first- and second generation immigrants), categorized as: Dutch, Turkish, Moroccan or Surinamese [18]. Numbers in groups of other ethnicities were too small for separate analyses. Neighbourhood was defined as the area of residence in Amsterdam (based on four digit postal code) where the mother was living at the time of completing the questionnaire. Neighbourhoods were categorized according to previously reported prevalence of child overweight (including obesity) at 5 years in Amsterdam as following: low (reported prevalence of child overweight in the area <15%), medium (15 - 20%) or high risk of overweight (> 20%) [19].

Measurements

Infant feeding practices

Information on age at complementary feeding and duration of exclusive breastfeeding were collected prospectively during the YHC evaluations, which parents are routinely invited to complete for their children at 1, 2, 3, 4, 6, 7.5, 9 and 11 months of age [20]. To complete missing data, information on infant feeding was also obtained with a questionnaire administered when children were 5-years of age (23.7% of the data for age at complementary feeding and 19.9% for exclusive breastfeeding). These data have been reported to be reliable by means of an intra-class correlation coefficient, showing sufficient validity [20]. Age at complementary feeding was defined as the child's age (in months) at which other foods and beverages were introduced to the previously exclusively breast- or formula-fed infant. For the current analysis this was categorized as either <5 months or ≥5 months. We also performed sensitivity analysis using 6 months as a cut-off for complementary feeding age; this showed only slight changes in the estimates in comparison to using a 5-month cut-off. The duration of exclusive breastfeeding was defined as duration of breastfeeding (in months) without any other milk, solids or fluids. The following categories were used: <3 months, 3 - 5.9 months and ≥6 months. Duration of any breastfeeding was defined as non-exclusive breastfeeding duration, categorized as <3 months, 3-5.9 months and ≥6 months.

Outcome

The primary outcome was the child's BMI-SDS at age 5 - 6 years. For this, weight and height data were obtained from the YHC registry or the ABCD health check, which was conducted by trained research assistants. Height was measured to the nearest millimetre with a Leicester portable height measure (Seca, Hamburg, Germany) and weight was measured to the nearest 100 g with a calibrated Marsden M-4102 scale (Oxfordshire, UK) [16]. BMI was calculated from the height and weight data as weight in kilograms divided by the square of height in meters. BMI scores were converted to age- and sex-adjusted SDSs relative to WHO 2007 growth standards [21] using the Growth Analyser 3.0 (Dutch Growth Research Foundation, Rotterdam, The Netherlands). We also obtained odds ratios (ORs) for overweight, for which children were dichotomised into either having 'no overweight' or 'overweight' (including obesity) according to sex- and age specific BMI cut-off values defined by the International Obesity Task Force (IOTF) [22].

Statistical analysis

Differences in mean BMI-SDS (continuous outcome) at 5 - 6 years between the risk groups were tested using ANOVA. The ORs for overweight (dichotomous outcome) for each risk group were obtained using logistic regression analyses. Risk groups with lowest overweight prevalence were used as the reference group. Firstly, we examined the associations between age at complementary feeding and duration of exclusive breastfeeding with BMI-SDS by unadjusted linear regression analyses, using BMI-SDS as a continuous outcome. Second, we used logistic regression analyses using dichotomized BMI cut-off values to examine the associations with overweight. We conducted stratified analyses (planned a priori the basis of previous literature) [8-11] according to each risk group (ethnicity, education, BMI, neighbourhood). Interaction between exclusive breastfeeding duration and age at complementary feeding was tested by adding a product term of these two variables to the main linear regression model [23]. Additional adjusted linear regression models were performed (Table SII and SIII) to assess the robustness of the crude analyses. In model 2, analyses were adjusted for the other risk group variables to test whether the associations were confounded by other maternal characteristics. In model 3, analyses were adjusted for birth weight SDS (age- and sex-adjusted relative to the WHO 2006 growth standards) [24], and in the analysis of age at complementary feeding, adjusted for duration of any breastfeeding [12]. These adjustments were made instead of model 2 covariates. Results are presented as B, OR and 95% CI using the following reference groups: age at complementary feeding <5 months and exclusive breastfeeding <3 months. Statistical analyses were conducted using SPSS, version 23.0 (SPSS Inc., Chicago IL).

Results

BMI-SDS and overweight according to risk groups

In all risk groups, mean BMI-SDS was significantly higher than in the reference group (Table I). The largest contrasts in mean BMI-SDS within the risk groups were found for ethnicity and pre-pregnancy BMI, with the highest BMI-SDS values for Turkish children (mean BMI-SDS: 0.80; SD: 1.3) and children of mothers with obesity (0.75; 1.3). Children of Turkish ethnicity had a greater than six-fold risk of overweight (OR: 6.38; 95% CI: 4.71, 8.64) compared to children of Dutch ethnicity. Children from mothers with obesity had a greater than four-fold risk (OR 4.06; 95% CI: 3.09, 5.33) compared to children from mothers with normal BMI.

Table 1. BMI-SDS, overweight and ORs for overweight at 5 - 6 years of age according to risk groups

Maternal characteristics	% (N)	BMI-SDS mean (SD)	Overweight % (N)	OR for overweight (95% CI)
Ethnicity				
Dutch	58.0 (2607)	0.13 (0.9) (ref)	7.8 (203)	(ref)
Turkish	6.9 (238)	0.80 (1.3)***	35.0 (83)	6.38 (4.71, 8.64)***
Moroccan	8.5 (384)	0.57 (1.1)***	23.2 (89)	3.57 (2.71, 4.71)***
Surinamese	6.6 (298)	0.26 (1.2)*	16.8 (50)	2.40 (1.71, 3.35)***
Education level				
Low	20.0 (892)	0.47 (1.2)***	21.5 (191)	3.49 (2.76, 4.42)***
Medium	37.1 (1656)	0.23 (1.1)***	13.3 (220)	1.96 (1.57, 2.45)***
High	42.9 (1916)	0.04 (0.9) (ref)	7.3 (139)	(ref)
Pre-pregnancy BMI				
Normal	76.4 (3424)	0.07 (1.0) (ref)	9.3 (317)	(ref)
Overweight	16.8 (754)	0.52 (1.1)***	19.9 (150)	2.44 (1.97, 3.02)***
Obese	6.8 (305)	0.75 (1.3)***	29.3 (89)	4.06 (3.09, 5.33)***
Neighbourhood				
Low risk	27.2 (1221)	0.10 (0.9) (ref)	7.5 (91)	(ref)
Medium risk	43.8 (1966)	0.19 (1.1)*	12.7 (249)	1.8 (1.40, 2.30)***
High risk	29.1 (1305)	0.29 (1.2)***	16.7 (218)	2.5 (1.93, 3.23)***

*p<0.05, **p<0.01, ***p<0.001

Associations between age at complementary feeding and BMI-SDS at 5-6 years

When compared to complementary feeding <5 months, complementary feeding >5 months was associated with 0.11 lower BMI-SDS at 5 - 6 years of age (Table 2). When stratified by risk group, a significant association was found in groups of Dutch ethnicity (B: -0.12; 95% CI: -0.21, -0.04), medium education (-0.19; -0.30, -0.08), normal BMI (-0.08; -0.16, -0.01) and high risk neighbourhood (-0.16; -0.29, -0.02). In line with the linear regression, logistic regression analyses indicated a significantly lower risk for overweight in these groups when complementary feeding >5 months (except for the group with normal BMI, Table 2).

In the additional adjusted linear regression models 2 and 3 (Table S3), adjustment for confounders somewhat attenuated the associations in several risk groups but did not drastically change the results.

Table 2. Crude linear and logistic regression analyses between age at complementary feeding and BMI-SDS and overweight at age 5 - 6 years by risk groups

	Linear regression		Logistic regression	
	B for BMI-SDS when complementary feeding ≥ 5 months	(95% CI)	OR for overweight when complementary feeding ≥ 5 months	(95% CI)
All	**-0.11****	(-0.18, -0.04)	**0.81***	(0.66, 0.99)
Ethnicity				
Dutch	**-0.12****	(-0.21, -0.04)	**0.71***	(0.52, 0.97)
Turkish	0.04	(-0.39, 0.48)	1.22	(0.59, 2.52)
Moroccan	-0.12	(-0.40, 0.16)	0.86	(0.48, 1.55)
Surinamese	-0.04	(-0.35, 0.26)	0.84	(0.43, 1.63)
Education level				
Low	-0.09	(-0.27, 0.09)	0.95	(0.66, 1.37)
Medium	**-0.19****	(-0.30, -0.08)	**0.62****	(0.45, 0.84)
High	0.02	(-0.08, 0.12)	1.33	(0.85, 2.11)
Pre-pregnancy BMI				
Normal	**-0.08***	(-0.16, -0.01)	0.87	(0.66, 1.13)
Overweight	-0.17	(-0.34, 0.01)	0.77	(0.51, 1.15)
Obese	0.07	(-0.24, 0.38)	0.96	(0.55, 1.66)
Neighbourhood				
Low risk	-0.08	(-0.21, 0.04)	1.12	(0.65, 1.95)
Medium risk	-0.07	(-0.18, 0.04)	0.91	(0.67, 1.24)
High risk	**-0.16***	(-0.29, -0.02)	**0.70***	(0.50, 0.96)

*p<0.05, **p<0.01. B represents change in BMI-SDS and OR represents odds for overweight when complementary feeding at 5 months or later (compared to complementary feeding < 5 months).

Association between duration of exclusive breastfeeding and BMI-SDS at 5-6 years

When compared to exclusive breastfeeding for <3 months, exclusive breastfeeding for ≥6 months was associated with 0.18 lower BMI-SDS at 5 - 6 years. A significant association was observed in groups of medium education (B: -0.28; 95% CI: -0.44, -0.11), normal BMI (0.18; -0.29, -0.08), medium- (-0.18; -0.33, -0.04) and high-risk neighbourhood (-0.22; -0.42, -0.02). Logistic regression analyses were in line with these results, indicating a lower risk for overweight when infants were exclusively breast fed for ≥ 6 months compared to < 3 months except for the group from high-risk neighbourhoods (Table 3).

After additional adjustment for confounders, significant associations observed in the crude linear regression analysis remained, except in the group of low education (Table SIV).

There was no evidence of an interaction between age at complementary feeding and duration of exclusive breastfeeding (p = 0.78).

Table 3. Crude linear and logistic regression analyses between duration of exclusive breastfeeding and BMI-SDS and odds of overweight at age 5 - 6 years by risk groups

	Linear regression (reference group: < 3 months)		Logistic regression (reference group: < 3 months)	
	3 - 5.9 months B (95% CI)	≥ 6 months B (95% CI)	3 - 5.9 months OR (95% CI)	≥ 6 months OR (95% CI)
All	-0.06 (-0.13, 0.01)	**-0.18***** (-0.28, -0.09)	0.83 (0.67, 1.02)	**0.58**** (0.42, 0.81)
Ethnicity				
Dutch	-0.05 (-0.13, 0.03)	-0.10 (-0.21, 0.02)	0.83 (0.60, 1.14)	**0.53*** (0.31, 0.91)
Turkish	0.02 (-0.37, 0.341)	-0.06 (-0.60, 0.47)	1.12 (0.60, 2.12)	1.01 (0.42, 2.48)
Moroccan	0.14 (-0.17, 0.44)	-0.20 (-0.56, 0.16)	1.32 (0.71, 2.45)	1.20 (0.58, 2.50)
Surinamese	-0.05 (-0.47, 0.36)	-0.42 (-1.03, 0.18)	0.47 (0.16, 1.41)	0.25 (0.03, 1.95)
Education level				
Low	0.10 (-0.12, 0.32)	-0.25 (-0.52, 0.02)	1.20 (0.79, 1.83)	0.72 (0.40, 1.31)
Medium	-0.06 (-0.18, 0.06)	**-0.28**** (-0.44, -0.11)	0.84 (0.60, 1.17)	**0.50*** (0.28, 0.89)
High	0.03 (-0.06, 0.12)	-0.02 (-0.15, 0.10)	1.08 (0.74, 1.58)	0.65 (0.35, 1.20)
Pre-pregnancy BMI				
Normal	-0.05 (-0.13, 0.02)	**-0.18**** (-0.29, -0.08)	0.88 (0.67, 1.14)	**0.52**** (0.33, 0.82)
Overweight	0.13 (-0.06, 0.32)	-0.16 (-0.40, 0.09)	1.05 (0.68, 1.61)	0.73 (0.40, 1.33)
Obese	-0.06 (-0.42, 0.29)	0.02 (-0.48, 0.52)	0.83 (0.44, 1.57)	0.65 (0.25, 1.70)
Neighbourhood				
Low risk	-0.04 (-0.15, 0.07)	-0.11 (-0.27, 0.05)	0.90 (0.57, 1.42)	**0.35*** (0.14, 0.89)
Medium risk	-0.08 (-0.18, 0.03)	**-0.18*** (-0.33, -0.04)	0.73 (0.53, 1.00)	**0.58*** (0.36, 0.93)
High risk	-0.01 (-0.16, 0.14)	**-0.22*** (-0.42, -0.02)	1.08 (0.76, 1.54)	0.78 (0.46, 1.32)

*p<0.05, **p<0.01

Discussion

In this large, population-based cohort study of 5-6 year-old children, we found that associations of age at complementary feeding and exclusive breastfeeding duration with BMI differed between groups at varying risk of overweight. Compared to complementary feeding before 5 months, complementary feeding after 5 months of age was associated with lower BMI and lower risk of overweight in groups of Dutch ethnicity, medium education, normal BMI and high risk neighbourhood. These associations, except for the group of normal BMI, were supported by logistic regression analyses and remained significant after adjusting for confounders. Furthermore, we found that when compared to exclusive breastfeeding for less than 3 months, exclusive breastfeeding for 6 months or longer was associated with lower BMI and lower risk of overweight at age 5 - 6 years in risk groups of medium education, normal BMI and medium risk neighbourhood. Associations in groups of medium education and normal BMI remained significant after adjustment for confounders.

Previous studies on age at complementary feeding and overweight in childhood have reported inconsistent results [12]. These studies varied by several factors; categorization of age at complementary feeding, definition of the outcome (overweight/obesity) and timing of outcome measurement. Furthermore, most studies included different populations, such as mix of ethnicities, which were analysed as one population and corrected for certain factors such as ethnicity. Different associations between populations, as observed in the current study, could explain the inconsistencies in previous findings. Only one previous study examined differences in associations between age at complementary feeding and obesity between populations [25]. In this particular study, early (<3 months) complementary feeding was more strongly associated with childhood obesity in groups of white/European ethnicity and of higher income than in black, Asian, middle- or low-income groups. This seems to be in agreement with our findings of a stronger association in Dutch ethnicity than in other ethnicities. Also previous studies with Turkish children reported no association between age at complementary feeding and overweight in childhood or excess weight gain during infancy [20,26].

A number of studies have reported a moderate protective effect of exclusive breastfeeding duration on overweight [13,27,28]. We observed that, compared to exclusive breastfeeding for less than 3 months, exclusive breastfeeding for 6 months or longer was associated (after adjustment for confounders) with lower BMI and lower risk of overweight at age 5 - 6 years in risk groups of medium education, Dutch ethnicity (indicated by logistic regression and adjusted linear regression models) and normal BMI. Similar to our study, studies in the US and Sweden stratified their analyses by maternal ethnicity and concluded that the protective effect of breastfeeding (any duration, non-exclusive) on overweight/obesity or BMI development was limited to children of white mothers and not observed in blacks, Hispanics or non-Swedish immigrants [29-32]. One of these studies also examined a low-income population in which the effect was limited only to white children who were breastfed at least for 4 months and whose mothers did not smoke [31]. In our study, breastfeeding for 3 - 5.9 months was not significantly associated with lower BMI-SDS in the crude analyses in any of the risk groups. Results on exclusive breastfeeding duration for 6 months or longer showed a similar protective effect in most of the risk groups.

There are several possible explanations why we found differences in associations between age at complementary feeding or exclusive breastfeeding duration with overweight between the risk groups. Firstly, there may be other factors which play a more important role on development of overweight than age at complementary feeding or exclusive breastfeeding duration. One such factor might be diet quality and quantity, for which we lacked information [33,34]. We found that age at complementary feeding and exclusive breastfeeding duration were weakly associated with child's BMI in groups with Turkish ethnicity, high education or maternal obesity. Turkish parents have been reported to supplement breastfeeding with additional formula and to feed uncommon complementary foods such as sweetened yogurt, bread and confectionery compared to mothers of Dutch origin [14]. Furthermore, mothers with obesity have been found to provide higher proportions of "adult" foods to their infants than mothers with normal weight [35]. The observed associations could also have been attenuated by differences in dietary practices during early childhood.[36] Secondly, absence of statistical significance for some associations could be also due to the limited number of participants in certain risk groups. Numbers in the groups of non-Dutch ethnicity (each group <10% of total population), and mothers with overweight (17%) or obesity (7%) were relatively small. Finally, we cannot exclude the possibility that the observed associations represent chance findings. Therefore, our results should be interpreted with caution.

The strength of our present study was the large population-based cohort, which included many non-Dutch participants, who were followed from early pregnancy until childhood. Unlike most previous studies, we conducted separate analyses within several risk groups. Yet, some limitations should be addressed. First, as mentioned, our analysis may have lacked statistical power to detect a true effect in some of the risk groups. However, our sample sizes were larger than some previous studies [12]. Second, information on age at complementary feeding and breastfeeding were mainly prospectively collected during the regular YHC visits, but partly retrospectively collected at 5 years of age, which relied on parental recall. The reliability between the sources has been previously reported [20].

To conclude, these results suggest that associations between infant feeding practices and BMI in childhood differ between risk groups, implying that strategies to prevent childhood overweight should be group-specific. Future studies should include higher numbers of participants from specific risk groups as well as information on both quantity and quality of the complementary foods.

Supplementary information

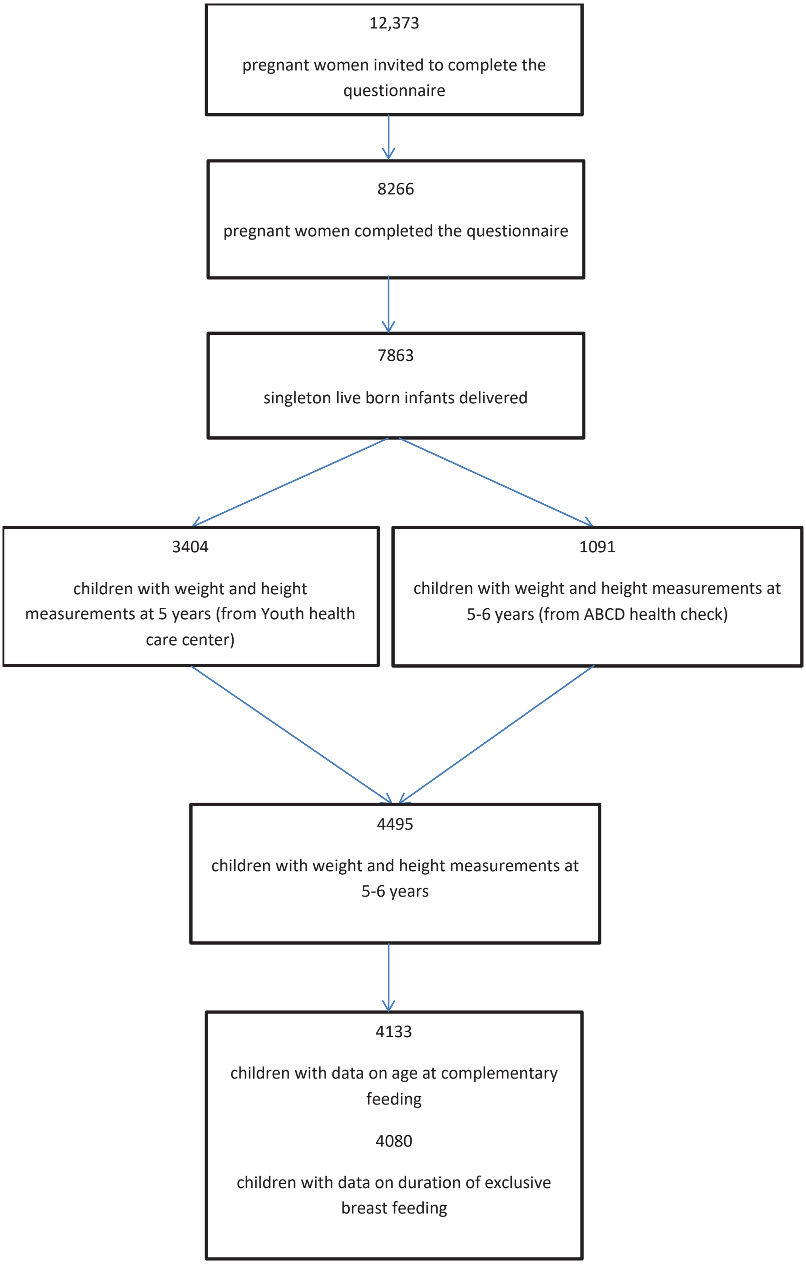

Figure S1. Selection of the study population

Table S1. Risk groups by age at complementary feeding (N=4133) and duration of exclusive breastfeeding (N=4080)

	Age at complementary feeding		Duration of exclusive breastfeeding		
	< 5 months (N=1094)	**≥ 5 months (N=3039)**	**0-2.9 months (N=2223)**	**3-5.9 months (N=1321)**	**≥ 6 months (N=536)**
Ethnicity % (N)[1]					
Dutch	26.8 (652)	73.2 (1783)	51.3 (1237)	35.3 (851)	13.4 (323)
Turkish	20.6 (43)	79.4 (166)	52.7 (109)	33.8 (70)	13.5 (28)
Moroccan	23.9 (80)	76.1 (255)	63.5 (207)	21.8 (71)	14.7 (48)
Surinamese	34.6 (90)	65.4 (170)	78.6 (202)	14.8 (38)	6.6 (17)
Educational level % (N)[2]					
Low	30.1 (241)	69.9 (559)	68.0 (534)	20.0 (157)	12.0 (94)
Medium	29.4 (443)	70.6 (1065)	58.6 (874)	29.5 (440)	11.9 (177)
High	22.6 (405)	77.4 (1389)	45.0 (798)	40.4 (716)	14.6 (259)
Pre-pregnancy BMI % (N)[2]					
Normal	25.3 (797)	74.7 (2347)	52.5 (1628)	34.4 (1066)	13.2 (408)
Overweight	28.7 (200)	71.3 (496)	58.8 (405)	27.1 (187)	14.1 (97)
Obese	33.3 (94)	66.7 (188)	65.8 (183)	23.7 (66)	10.4 (29)
Neighbourhood % (N)[2]					
Low-risk	21.0 (234)	79.0 (878)	46.8 (513)	39.3 (431)	13.9 (152)
Medium risk	26.9 (492)	73.1 (1336)	55.4 (1003)	31.4 (569)	13.1 (238)
High-risk	30.9 (368)	69.1 (822)	60.3 (707)	27.2 (319)	12.5 (146)

[1]Total N=3601 due to exclusion of ‘’other’’ ethnicities (N=894 for age at weaning, N=879 exclusive breast feeding). [2]Missing data per risk group: educational level 31 (0.7 %), pre-pregnancy BMI 11 (0.3 %), neighbourhood 3 (0.1 %).

Table S2. Associations between age at complementary feeding and BMI-SDS at age 5-6 years by risk groups, linear regression, adjusted models

	Model 2[1]		**Model 3[2]**	
	B	(95% CI)	B	(95% CI)
All	**-0.09***	(-0.17, -0.01)	**-0.10****	(-0.17, -0.03)
Ethnicity				
Dutch	**-0.10***	(-0.18, -0.02)	**-0.10***	(-0.19, -0.02)
Turkish	0.03	(-0.44, 0.50)	0.09	(-0.36, 0.54)
Moroccan	-0.12	(-0.41, 0.17)	-0.14	(-0.45, 0.16)
Surinamese	-0.05	(-0.36, 0.26)	-0.01	(-0.32, 0.29)
Educational level				
Low	-0.14	(-0.36, 0.08)	-0.13	(-0.33, 0.06)
Medium	**-0.15***	(-0.28, -0.03)	**-0.18****	(-0.30, -0.06)
High	-0.02	(-0.12, 0.09)	0.04	(-0.06, 0.14)
Pre-pregnancy BMI				
Normal	-0.06	(-0.15, 0.02)	-0.07	(-0.15, 0.01)
Overweight	-0.19	(-0.39, 0.01)	-0.18	(-0.37, 0.01)
Obese	-0.16	(-0.55, 0.22)	0.05	(-0.28, 0.39)
Neighbourhood				
Low-risk	-0.06	(-0.20, 0.08)	-0.04	(-0.16, 0.09)
Medium risk	-0.04	(-0.16, 0.08)	-0.06	(-0.17, 0.05)
High-risk	**-0.17***	(-0.32, -0.02)	**-0.17***	(-0.32, -0.02)

[1]Model 2 is adjusted for all other risk group variables. [2] Model 3 is adjusted for birth weight and duration of any breastfeeding. *p<0.05, **p<0.01

Table S3. Associations between duration of exclusive breastfeeding and BMI-SDS at age 5-6 years by risk groups, linear regression, adjusted models

	Model 2[1]		**Model 3**[2]	
	3-5.9 months	**≥ 6 months**	**3-5.9 months**	**≥ 6 months**
	B (95% CI)	B (95% CI)	B (95% CI)	B (95% CI)
All	-0.02 (-0.01, 0.06)	**-0.13*** (-0.24, -0.02)	**-0.08*** (-0.15, -0.01)	**-0.22***** (-0.31, -0.12)
Ethnicity				
Dutch	-0.03 (-0.11, 0.05)	-0.10 (-0.22, 0.01)	-0.07 (-0.15, 0.01)	**-0.16**** (-0.27, -0.05)
Turkish	0.00 (-0.41, 0.41)	-0.16 (-0.74, 0.42)	-0.01 (-0.41, 0.40)	-0.08 (-0.64, 0.47)
Moroccan	0.09 (-0.22, 0.40)	-0.25 (-0.62, 0.13)	0.15 (-0.17, 0.46)	-0.24 (-0.60, 0.12)
Surinamese	0.03 (-0.40, 0.46)	-0.43 (-1.02, 0.17)	-0.15 (-0.57, 0.26)	-0.40 (-0.99, 0.19)
Educational level				
Low	0.05 (-0.21, 0.32)	-0.22 (-0.54, 0.09)	0.07 (-0.15, 0.29)	**-0.32*** (-0.59, -0.05)
Medium	-0.09 (-0.23, 0.05)	**-0.19*** (-0.38, -0.00)	-0.08 (-0.20, 0.04)	**-0.31***** (-0.47, -0.14)
High	0.03 (-0.07, 0.12)	-0.04 (-0.18, 0.09)	0.03 (-0.06, 0.11)	-0.04 (-0.16, 0.08)
Pre-pregnancy BMI				
Normal	-0.04 (-0.13, 0.04)	**-0.13*** (-0.25, -0.02)	-0.07 (-0.14, 0.01)	**-0.20***** (-0.31, -0.10)
Overweight	**0.22*** (0.00, 0.43)	-0.07 (-0.34, 0.20)	0.11 (-0.08, 0.30)	-0.21 (-0.45, 0.04)
Obese	-0.31 (-0.76, 0.14)	-0.30 (-0.90, 0.31)	-0.06 (-0.43, 0.30)	-0.04 (-0.55, 0.47)
Neighbourhood				
Low-risk	0.03 (-0.09, 0.14)	-0.09 (-0.27, 0.09)	-0.02 (-0.13, 0.09)	-0.13 (-0.29, 0.02)
Medium risk	-0.07 (-0.19, 0.05)	-0.10 (-0.26, 0.06)	-0.10 (-0.21, -0.01)	**-0.22**** (-0.36, -0.07)
High-risk	0.05 (-0.12, 0.21)	**-0.18*** (-0.40, -0.04)	-0.05 (-0.20, 0.10)	**-0.26*** (-0.46, -0.06)

[1]Model 2 is adjusted for all other risk group variables. [2] Model 3 is adjusted for birth weight. *p<0.05, **p<0.01, ***p<0.001

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Chapter 3

Feeding patterns and BMI trajectories during infancy: a multi-ethnic, prospective birth cohort

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Abstract

Background: Milk feeding type (exclusive breastfeeding [EBF], formula feeding or mixed feeding) and timing of complementary feeding (CF) have been associated with infant growth. However, studies evaluating their combined role, and the role of ethnicity, are scarce. We examined associations of feeding patterns (milk feeding type combined with timing of CF) with infant body mass index (BMI) trajectories and potential ethnic-specific associations.

Methods: Infant feeding and BMI data during the 1st year of life from 3524 children (Dutch n=2880, Moroccan n=404 and Turkish n=240) from the Amsterdam Born Children and their Development (ABCD) cohort were used. Six feeding patterns were defined: EBF/earlyCF, EBF/lateCF (reference), formula/earlyCF, formula/lateCF, mixed/earlyCF and mixed/lateCF. A covariate adjusted latent class mixed model was applied to simultaneously model BMI trajectories and associations with feeding patterns. Potential ethnic differences in the associations were studied in a separate model where interactions between ethnicity and feeding patterns were included.

Results: Four distinct BMI trajectories (low, mid-low, mid-high and high) were identified. Feeding pattern of formula/earlyCF was associated with lower odds for low (OR: 0.43; 95% CI: 0.25, 0.76) or mid-high (0.28; 0.16, 0.51) (ref: high) trajectory compared with EBF/lateCF pattern (ref). An ethnic-specific model revealed that among Dutch infants, formula/earlyCF pattern was associated with lower odds for low trajectory (0.46; 0.24, 0.87), whereas among Turkish/Moroccan infants almost all feeding patterns were associated with lower odds for the low trajectory (ref: high).

Conclusion: Infant feeding patterns are associated with early BMI trajectories with specific ethnic differences. Future studies should take the role of ethnicity into account in the associations between infant feeding and growth.

Background

Childhood overweight and obesity may track into adulthood and are associated with adverse health outcomes from childhood [1,2]. Rapid growth, i.e. excess weight gain or excess increase in BMI (kg/m^2), during 1st year of life is associated with increased risk of later life overweight [3-5]. Infant feeding is suggested as one of the most important modifiable factors associated with early growth trajectories and later overweight and obesity [6-8].

Milk feeding type, e.g. exclusive breastfeeding (EBF), formula feeding or a combination thereof (mixed feeding) has been associated with infant growth outcomes [9-11]. In general, (exclusive) breastfeeding has been associated with slower weight and length gain during infancy [12], lower BMI and lower risk of childhood overweight [13] compared with formula feeding. Yet some studies have reported no association between breastfeeding and growth outcomes during infancy [14], childhood [15,16] or adulthood [17,18]. Methodological differences across studies, i.e. adjustment for confounders or definitions of breastfeeding might explain these apparent discrepancies [13]. Several studies combined mixed-fed and EBF infants into one breastfed group [19,20] whereas, in other studies, mixed-fed infants were either considered as formula-fed [21] or excluded from the analysis [9]. In addition to milk feeding type, some evidence suggests that the timing of complementary feeding (CF) may influence body weight and BMI during childhood, yet evidence is mixed [22]. Later CF has been associated with lower prevalence of childhood and adult overweight [16,17]. Other studies suggested reverse causality [23] or no associations [24-26] between timing of CF and infant weight gain or childhood overweight.

Most previous studies investigating the associations of milk feeding type or timing of CF have mutually adjusted for these factors to evaluate their independent effects on later growth outcomes. However, some studies reported an interaction between these factors [27-29]. Early CF in formula- or mixed-fed infants has been associated with increased infant weight gain [27] or childhood overweight [28]. On the contrary, one study reported that late CF introduction among EBF infants was associated with an increased prevalence of overweight [29]. Therefore, the combination of different milk feeding types with timing of CF should be further investigated.
Considerable ethnic differences exist in infant feeding practices and childhood overweight prevalence [30-32]. In the Netherlands, mothers of Turkish or Moroccan ethnicity are reported to provide longer duration of EBF or mixed feeding than mothers of Dutch ethnicity [33,34]. However, children from Turkish or Moroccan ethnicities have a higher infancy weight gain and childhood overweight prevalence compared to children of Dutch ethnicity [32,33,35]. Hence, it is of interest to improve our understanding of potential ethnic differences in the association between infant feeding patterns and growth.

Our main objectives were: (i) examine associations of feeding patterns (i.e. milk feeding type during the first three months of life combined with timing of CF) with distinct infant BMI trajectories and (ii) determine potential ethnic differences in these associations. Additionally, we examined overweight prevalence at 5–6 years among the identified BMI trajectories.

Methods

Subjects

Data were obtained from the Amsterdam Born Children and their Development (ABCD) study, a large prospective birth cohort in Amsterdam, the Netherlands [36]. Between January 2003 and March 2004, all pregnant women (n=12 373) living in Amsterdam were invited to participate in this study by filling out a pregnancy questionnaire. Of these women, 8266 women completed the questionnaire during their 12–14th week of pregnancy and 7863 gave birth to a live singleton infant. For the purpose of the current study, infants from the three largest ethnic groups with at least one measurement of both body weight and length during the first year were included; Dutch (n=2998), Moroccan (n=437) and Turkish (n=270). Ethnicity of the mother and her infant was defined as the country of birth of the mother or maternal grandmother to include first- and second-generation immigrants [37]. Moroccan and Turkish ethnicities were of particular interest due to relatively high prevalence of overweight from early childhood onwards [35]. These ethnic groups were combined for the analysis because of the low number of participants in both groups and previously reported similarities in infant feeding and growth of the infants [33,34]. Children with missing values on feeding pattern (n=97) or at least one of the following covariates: maternal educational level (n=17), maternal pre-pregnancy BMI (n=10), maternal smoking during pregnancy (n=137), gestational age (n=3), birth weight (n=10) were excluded. The final study sample consisted of 3524 children (Figure 1). The ABCD study was approved by the Central Committee on Research Involving Human Subjects, the Medical Ethical Examining Committees of all Amsterdam Hospitals and the Municipal Privacy Protection Committee of Amsterdam and was developed in accordance with the Declaration of Helsinki. All participants provided written informed consent.

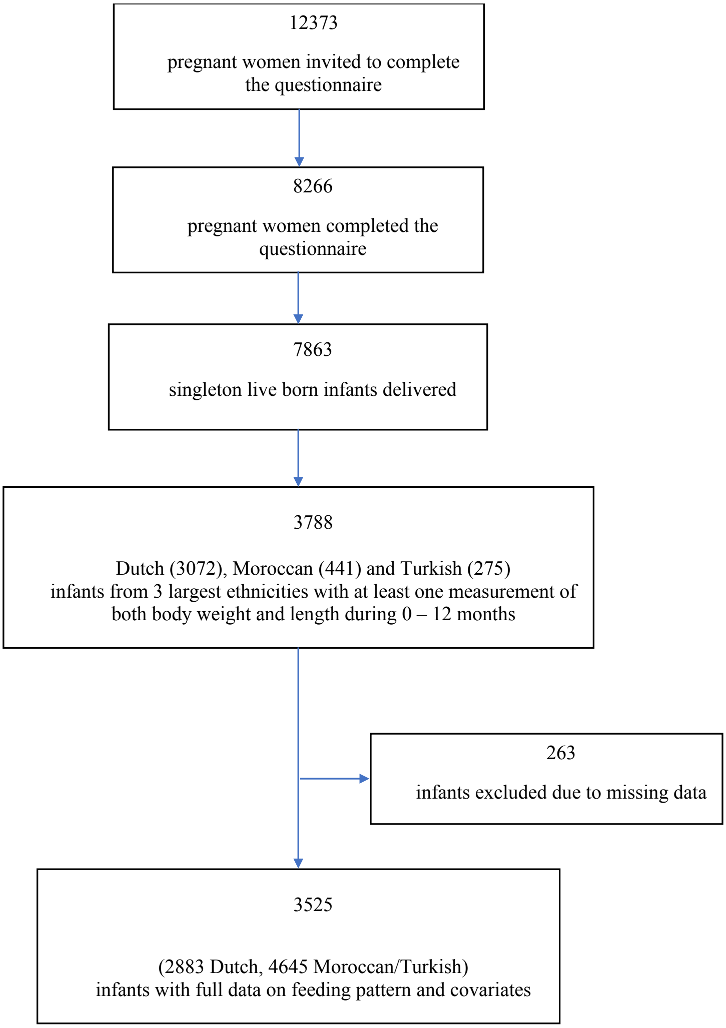

Figure 1. A flowchart of the selection of analysed study population.

Measures

Infant feeding pattern

Information about infant feeding (EBF duration and the child's age when receiving formula and CF) were collected by using a questionnaire, administered at the Youth Health Care (YHC) routine visits during the first year. These data were recorded in following categories: none, <1 month, 1-2.9 months, 3-5.9 months and >=6 months. More detailed description of the data collection procedure has been previously described [33]. EBF was defined as providing only breastmilk, no other solids/fluids except water. CF was defined as any solids or fluids other than breastmilk, infant formula or water.

From the available data, infant feeding patterns were defined based on the milk feeding type provided combined with the timing of CF introduction. We initially aimed to investigate feeding pattern during 0-6 months according to the World Health Organization (WHO) recommendations to give EBF until 6 months [38], however, the majority of women in the Netherlands discontinue EBF after 3 months [39]. One of the main reasons to discontinue EBF after 3 months is that it is common for women in the Netherlands to return to work after 3 months from the delivery. Prevalence of EBF ≥6 months in our study was only around 18%, close to the Dutch national estimates reported at the time of the study [40]. Therefore, for the milk feeding type, a period of 0-3 months was chosen and sensitivity analyses using the milk feeding type during 0-6 months were carried out. Three milk feeding categories during 0-3 months were established: 1) EBF, defined as exclusive breastfeeding from birth onwards; 2) formula feeding, defined as introducing full formula feeding within the first month after birth and 3) mixed feeding, as any other milk feeding combination which was not described above. Timing of CF was dichotomized as ”early” (<6 months) or ”late” (≥6 months) according to the WHO [38]. Although other recommendations exist to introduce CF between 4 and 6 months [41], the numbers for the feeding pattern combinations were not sufficient for the ethnic-specific analyses when using this categorization. In our dataset the vast majority (80 % of the mothers) introduced CF between 4-6 months, only around 5% before 4 months and 15% after 6 months.

By combining the three categories of milk feeding type and the two categories of CF timing, infants were classified into six feeding patterns: 1) EBF with late CF (EBF/lateCF); 2) EBF with early CF (EBF/earlyCF); 3) formula feeding with late CF (formula/lateCF); 4) formula feeding with early CF (formula/earlyCF); 5) mixed feeding with late CF (mixed/lateCF); and 6) mixed feeding with early CF (mixed/earlyCF). For the analyses, EBF/lateCF feeding pattern was chosen as the reference since this most closely reflects the WHO recommendations [38].

BMI measurements during infancy and at 5–6 years

Data on weight and length (BMI) during the first year were collected during the YHC routine visits where children are invited to at 1, 2, 3, 4, 6, 7.5, 9 and 11 months of age. These data were obtained from the YHC registry. During these visits, height was measured to the nearest millimeter with a Leicester portable height measure (Seca, Hamburg, Germany). Weight was measured to the nearest 100g with a calibrated Marsden M-4102 scale (Oxfordshire, UK) [36]. From these data, BMI was calculated as weight in kilograms divided by the square of height in meters. For deriving BMI trajectories, non-standardized BMI values were used. At 5–6 years of age, data on child's weight and height (for BMI) were obtained from the YHC registry (n=1235) or the ABCD health examinations (n=1868). The examinations were conducted by trained research assistants according to a standard protocol [33]. Age- and sex- specific BMI standard deviation (SD) scores were derived according to the WHO growth standards [42] using the Growth Analyzer Software, version 4.0 (Growth Analyzer BV). Overweight (including obesity) was defined as >+1SD above the median of the WHO growth standards.

Covariates

Data on predefined maternal covariates; pre-pregnancy BMI, educational level, parity and smoking (during pregnancy), were obtained through the pregnancy questionnaire and were self-reported by the mother. Pre-pregnancy BMI was dichotomized as normal weight (BMI<25 kg/m^2) or overweight (including obesity) (≥25 kg/m^2). Educational level was defined as years of education after primary school and categorized as either low: 0–5 years of education; medium: 6–10 years or high: >10 years [43]. Smoking (no/yes) and parity (primipara/multipara) were dichotomized. Infancy covariates included sex, birth weight (in kg) and gestational age which was dichotomized (term: ≥37 weeks and preterm: <37 weeks of gestational age). These data were obtained from the YHC registry. Height was not measured at birth and therefore BMI at birth could not be calculated. Trajectories were based on the first available BMI data (usually obtained in the first months after birth) and onwards.

Statistical analysis

A latent class mixed effect model (LCMM) was fitted to the BMI data during infancy [44]. With the LCMM model, we simultaneously estimated k BMI trajectories (i.e. latent classes) and the probability that an infant followed a particular BMI trajectory. The class membership of an infant i was defined by the unobserved discrete variable C_i, where $C_i = g$ if infant i followed BMI trajectory $g = 1, \dots, k$. Since it was not known before performing the analysis how many trajectories were present in the data, the number of BMI trajectories k was determined based on the Bayesian Information Criterion. The LCMM consists of two submodels; the linear mixed effect submodel describing each trajectory and the multinomial logistic regression submodel describing the associations between feeding patterns and the infant's probability to follow a particular trajectory.

Linear mixed effect submodel

The linear mixed effect submodel for BMI trajectory $g = 1, \dots, k$ was parameterized as follows. For the fixed effects, natural cubic spline functions with five degrees of freedom were used. The inner knots of the spline functions were placed at the corresponding percentiles of the data. Additionally, a trajectory specific random intercept and a trajectory specific random slope were used to capture the correlation between the BMI measurements from each infant. This led to the following submodel

$$Y_{ij}|_{C_i=g} = f\left(t_{ij}; \boldsymbol{\beta}_g\right) + b_{ig,1} + t_{ij} b_{ig,2} + \epsilon_{ij}$$

where y_{ij} is the j^{th} BMI measurement of infant i obtained at age t_{ij} and $\boldsymbol{f}(t_{ij}, \boldsymbol{\beta}_g)$ is the natural spline function describing the g^{th} BMI trajectory parametrized by the vector $\boldsymbol{\beta_g}$. In addition, $(b_{ig,1}, b_{ig,2})$ are the random slope and intercept for the g^{th} BMI trajectory and ϵ_{ij} is a residual term. In our model, the random effects $(b_{ig,1}, b_{ig,2})$ were assumed to follow a bivariate normal distribution with means zero and an unstructured covariance matrix Σ. The residual ϵ_{ij} was assumed to follow a normal distribution with mean zero and variance parameter σ.

Multinomial logistic regression submodel

The multinomial logistic regression submodel described the probability that infant i followed trajectory g. For the two main objectives of this study, two separate LCMM analyses were performed. First, to examine whether feeding patterns were associated with distinct infant trajectories, an additive relation was assumed for all covariates. In this model, we assumed that the effects of the six feeding patterns were the same in Dutch and non-Dutch (i.e. Turkish and Moroccan) infants. With this LCMM, referred to as model 1, the probability that infant i followed trajectory g was given by

$$Pr(C_i = g|\boldsymbol{x}_i) = \frac{\exp\left(\gamma_{g0} + x_{i1}\gamma_{g1} + x_{i2}\gamma_{g2} + x_{i3}\gamma_{g3} + \cdots + x_{ip}\gamma_{gp}\right)}{\sum_{j=1}^{k} \exp\left(\gamma_{j0} + x_{i1}\gamma_{j1} + x_{i2}\gamma_{j2} + x_{i3}\gamma_{j3} + \cdots + x_{ip}\gamma_{jp}\right)},$$

Second, to explore potential ethnic differences in the associations of feeding patterns with the trajectories, we combined the feeding patterns and the ethnicity variable into a dummy variable with pre-determined 12 unique values (i.e. 6 feeding patterns for Dutch and 6 feeding patterns for Turkish/Moroccan). In this model, referred to as model 2, the feeding patterns were allowed to have different effects in the Dutch and Turkish/Moroccan infants. In both models, the reference group were Dutch infants with EBF/lateCF pattern. All analyses were conducted using the statistical program R 3.5.2 with package lcmm [44].

Overweight at 5–6 years of age

Based on the fitted LCMM, we calculated the posterior probability of following a certain trajectory for each child. These probabilities were used as weighing of a child's contribution to each trajectory. For example, a child could contribute to 20%, 45% and 35% respectively, to the first, second, and third trajectory. Using the information on child's BMI at 5–6 years, we then derived the percentage of children with overweight (or obesity) within each trajectory, according to the child's weighted contribution to each trajectory.

Results

Participants

Table 1 shows the characteristics of the full study population as well as based on ethnicity or the pre-defined feeding patterns. Overall, the most common pattern was EBF/lateCF, including 30% of the participants. Among the Turkish/Moroccan mothers, mixed feeding or EBF/late CF introduction were the 3 largest groups. For Dutch mothers, most apparent feeding group was EBF/late CF with one third of mothers.

Classification of BMI trajectories

Four BMI trajectories during the first year of life were identified in models 1 and 2 (Figure 2). Both models resulted in similar trajectories with respect to the shape of the trajectories and the number of infants assigned to each trajectory. The trajectories were classified as low, mid-low, mid-high and high according to the WHO BMI reference percentiles [45]. The most prevalent trajectory, named as "low'', described a relatively stable BMI pattern with values below the median of the WHO growth standards through the 1st year of life. Trajectories "mid-low'' and "mid-high'' showed an ascending pattern in the BMI values close to or slightly above the median of the WHO growth standard. The trajectory "high'' showed a rapid BMI increase during the first 2 months of life and remained at a substantially high BMI value throughout the year, well-above the median of the WHO growth standard.

Associations of feeding patterns with BMI trajectories

Table 2 presents the results of model 1 describing the covariate adjusted associations between feeding patterns and BMI trajectories. Compared with the reference feeding pattern (EBF/lateCF), infants with a pattern of formula/earlyCF had lower odds of belonging to the low rather than to the high trajectory. Furthermore, formula/earlyCF and mixed/earlyCF were associated with lower odds of belonging to mid-high trajectory compared with the high trajectory.

Ethnic-specific associations of infant feeding patterns with BMI trajectories

The results from model 2 including the ethnic-specific associations (Table 3) revealed that compared with the reference group (EBF/lateCF, Dutch infants), formula/earlyCF pattern of Dutch infants was associated with lower odds for the low compared with the high trajectory. Interestingly, compared with the reference group, all feeding patterns of Turkish/Moroccan infants indicated lower odds of being in the low rather than high trajectory.

Sensitivity analyses including the milk feeding type during 0-6 months, where the reference feeding pattern (EBF/late CF) was defined as EBF≥6 months/CF≥6 months, showed comparable results for most feeding groups compared to our main results (Table S1). However, compared to the reference feeding pattern, mixed/late CF (i.e. either mixed feeding or EBF<6 months combined with CF≥6 months) was associated with higher odds for the low trajectory. Ethnic-specific model showed that among the Dutch both mixed/early CF and mixed/late CF were associated with higher odds for the low trajectory (Table S2).

Overweight at 5–6 years

The lowest percentage of overweight at 5–6 years of age was observed for the low trajectory (10.1%) whereas the highest was seen for the high trajectory (34.1%); the other groups were intermediate (Table 4). Compared with the Dutch children, percentage of Turkish/Moroccan children with overweight appeared to be higher in all trajectories.

Table 4. Overweight prevalence at age 5 – 6 years in the BMI trajectories (n = 2753)[1]

	% of overweight in each BMI trajectory			
	''low''	''mid-low''	''mid-high''	''high''
Total (n = 2753)	10.1	12.2	22.6	34.1
Dutch (n = 2253)	8.6	9.7	18.4	27.4
Turkish/Moroccan (n = 500)	23.6	26.4	38.5	45.0

[1]Overweight (including obesity): >+1 SD above the median of the age and sex-specific WHO 2007 growth standards.

Discussion

Our results showed that specific infant feeding patterns are associated with BMI trajectories during the first year of life and that there are apparent ethnic differences in these associations. Compared with infants who received EBF during the first three months with CF introduction after six months (reference), infants who were formula-fed with early CF introduction, had lower odds for being in the low rather than high trajectory. Ethnic-specific analyses revealed that Dutch infants with a feeding pattern of formula feeding and early CF had lower odds for being in the low trajectory rather than in the high. Among Turkish/Moroccan infants, all feeding patterns were associated (tended to) with lower odds for being in the low trajectory compared with the Dutch (reference) infants.

To our knowledge, three previous studies [27,46,47] investigated different combinations of milk feeding types or breastfeeding duration with timing of CF on growth outcomes during infancy. These studies showed inconsistent findings and used somewhat different feeding pattern definitions than our study. In line with our findings, Imai et al [46] reported greater weight gain during infancy and higher BMI at 6 years among infants who were formula-fed and introduced to CF early (≤5 months) compared to infants receiving EBF for 5 months. However, unlike our study, they did not investigate the group of EBF infants with early CF exposure. The other two studies investigated breastfeeding duration among (EBF or mixed feeding) with timing of CF. Baker et al found that a short duration (<5 months) of breastfeeding with early

CF (4 months) was associated with an increased infant weight gain compared to long duration (>10 months) of breastfeeding with late CF (≥4 months) [27]. Sun et al however reported that regardless of breastfeeding duration, early CF (<4 months) compared with late CF (≥4 months) was associated with above normal BMI at 1 year [47]. Furthermore, previous studies on feeding patterns and later overweight suggested that early (<4 months) compared with late (≥4 months) CF was associated with childhood overweight only in formula-fed/short breastfed infants [28,29,48,49]. Furthermore, two studies suggested that also delayed CF (>7 months) was associated with overweight in later life among children receiving EBF [29,47]. Differences in the study populations, definitions or cut-offs of the feeding exposures are likely to explain the mixed findings. Interestingly, in our sensitivity analyses including milk feeding during 0-6 months, compared to the reference pattern, mixed feeding/lateCF was associated with higher odds for the low trajectory. These results could be partly explained by differences in some characteristics between the reference groups (EBF≥6 months/lateCF vs. EBF≥3mo/lateCF in our main analysis). Mothers in EBF≥6 months/late CF group were less often highly educated (53.6 vs 59.1%), had more often overweight (22.2 vs 18.7%) and had Turkish/Moroccan ethnic background (17.2 vs 14.4%) compared with the reference group in our main analysis. Furthermore, the majority of mothers (51%) in the mixed/late CF group provided rather long duration of EBF (between 3-6 months). Due to some very small group sizes (i.e. Dutch EBF/earlyCF only 5.2%) these results should be interpreted with caution. We also cannot exclude the possibility of chance findings. Given the evidence both on the benefits of EBF ≥6 months [13,27] as well as introducing CF between the age of 4-6 months [41], future studies assessing growth outcomes should consider alternative categorization of feeding pattern.

In addition to the differences in feeding definitions, large differences exist in the adjustment for confounders across studies. Especially, previous studies on breastfeeding and childhood BMI showed that the associations were largely reduced after adjustment for family-based sociodemographic, or maternal/child lifestyle related factors (i.e. sedentary activities, sleep duration or dietary pattern in toddlerhood) [50,51]. Although the findings from previous studies on early growth or overweight are controversial and comparison of studies is difficult due to different feeding definitions, evidence from our and several other studies does suggest that especially the combination of formula feeding during early infancy with early CF introduction is associated with rapid infant growth or childhood overweight.

There are several explanations for the observed associations of feeding patterns on infant BMI in our study. Formula feeding is suggested to lead to a more rapid growth during infancy compared to breastfeeding [52]. Possible mechanisms include the composition of formula milk, e.g. higher protein content compared to breastmilk as well as differences in feeding style such as feeding on schema, which may lead to lower ability to self-regulate food intake [53]. Infants who are exposed to formula feeding and early CF may have higher energy and/or protein intakes compared with infants with EBF and late CF [54]. These higher intakes from both milks and foods may consequently lead to more rapid gains in weight (and length), explaining their lower odds for being in the low BMI trajectory [55,56]. However, we did not have information on the quantity and quality of diet during infancy which may explain the associations observed in our study [54,57]. It is also possible that our results may reflect reverse causality rather than causal associations; infants who grow more rapidly may have higher energy needs and demand for feedings. This could lead to parents switching from breastfeeding to formula feeding and to introducing CF earlier to these children [23]. However, we have no information on reasons as to why formula was chosen or why CF was introduced.

We observed substantial ethnic differences in the associations of feeding patterns with BMI trajectories, suggesting that ethnicity may modify this association. Nevertheless, irrespective of ethnicity, infants with formula/earlyCF pattern were consistently least likely to be in the low BMI trajectory. Interestingly, compared with the Dutch reference group, nearly all feeding patterns of the Turkish/Moroccan group were associated with lower odds for the low trajectory. In line with our results, previous study [30] found no association between EBF during the first 6 months and BMI development in immigrant (non-Swedish) children, whereas EBF was associated with lower BMI trajectory in Swedish children. These findings suggest ethnic specific associations between infant feeding and growth. This could be explained by differences in other infant feeding practices between certain ethnic groups, for which we lacked information, such as feeding frequency, diet quality or bottle feeding practices [31,58,59]. Especially, macronutrient intake after the breastfeeding period may influence the association between breastfeeding and body fat [60]. Also other determinants, such as genetic predisposition [61] or maternal factors such as gestational weight gain or diet during pregnancy are suggested to be important for the ethnic differences in childhood overweight [62].

Our study has several strengths. These include the use of prospective data on infant feeding and growth in a multi-ethnic population. To our knowledge, we are the first to examine associations of infant feeding patterns, including milk feeding type and CF timing, with BMI trajectories across ethnic groups. Unlike some previous studies [9,10], we modelled BMI trajectories using unstandardized BMI, which is shown to be better suited for longitudinal measures than z-scores [63]. Furthermore, we adjusted for several maternal and infant confounders. However, some limitations should be acknowledged. First, results are based on observational data and do not allow to make conclusions about causal effects of feeding on growth. Although our analyses were adjusted for birth weight, it cannot be ruled out that the observed BMI trajectories are the result of reverse causality. For instance, parents of children with low BMI early in life may respond to this by overfeeding the child (because the child's growth is below the norm used by YHC, hence extra feeding is advised). In that case a high BMI later in life is not simply caused by feeding itself but the underlying cause of this trajectory may be a response to a low BMI (or weight for height) earlier. Second, our study population included two ethnic minority groups which limits the generalizability of our results to all populations. Also, we conducted ethnic specific analyses (planned a priori) in which some of the feeding groups of Turkish/Moroccan children were of limited sample size. Therefore, these results should be interpreted with caution. Fourth, although we adjusted our analyses for several known confounders, some of the continuous covariates were categorized in order to avoid estimating non-linear associations, which would have further increased the model complexity. However, categorization of the continuous covariates may be considered suboptimal [64]. Finally, we lacked information on other potentially important maternal or infant related factors, such as gestational weight gain or the quantity and quality of the diet during infancy, which may have also explained some of the observed associations. Future studies should therefore include more detailed nutritional information on infant feeding.

Conclusions

Infant feeding patterns are associated with BMI trajectories during the first year of life with specific ethnic differences. Future studies should take the role of ethnicity into account in the associations between infant feeding and growth.

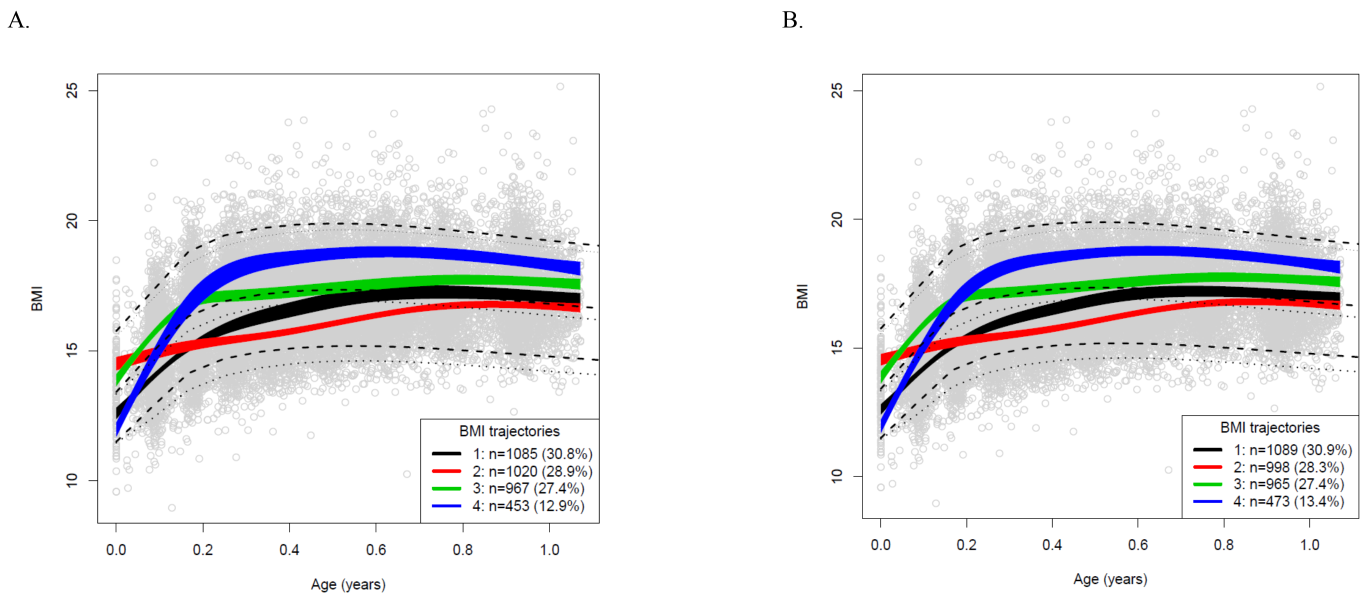

Figure 2. A. BMI trajectories identified by the LCMM, model 1. B. BMI trajectories identified by the LCMM, model 2.
Coloured lines represent the BMI–derived trajectories with 95% confidence intervals. Dotted lines represent the WHO 5th, 50th and 95th percentiles for BMI for age, boys (---) and girls (…). The number of subjects in each trajectory was calculated according to the subjects weighted contribution (based on the posterior probability derived from the LCMM) to each trajectory. Total n=3525 due to rounding.

3

Table 1. Characteristics of the study population by ethnicity and feeding pattern[1]

		Ethnicity		Feeding pattern					
		Dutch	Turkish/ Moroccan	EBF/ early CF	EBF/ late CF	Mixed/ early CF	Mixed/ late CF	Formula/ early CF	Formula/ late CF
	All (3524)			16.0 (562)	31.2 (1101)	16.2 (573)	16.9 (597)	11.5 (405)	8.1 (286)
Maternal characteristics									
Ethnicity[2]									
Dutch	81.7 (2880)			16.5 (475)	32.7 (943)	14.8 (428)	15.1 (436)	12.1 (348)	8.7 (250)
Turkish / Moroccan	18.3 (644)			13.5 (87)	24.5 (158)	22.5 (145)	25.0 (161)	8.8 (57)	5.6 (36)
Education									
Low	15.7 (554)	6.9 (199)	55.1 (355)	12.3 (69)	11.0 (121)	17.1 (98)	22.1 (132)	21.0 (85)	17.1 (49)
Medium	34.8 (1226)	33.9 (976)	38.8 (250)	33.3 (187)	30.0 (330)	39.1 (224)	33.8 (202)	41.0 (166)	40.9 (117)
High	49.5 (1744)	59.2 (1705)	6.1 (39)	54.4 (306)	59.1 (650)	43.8 (251)	44.1 (263)	38.0 (154)	42.0 (120)
Pre-pregnancy BMI									
Overweight	21.6 (761)	17.0 (491)	41.9 (270)	19.4 (109)	18.7 (206)	20.2 (116)	24.8 (148)	29.9 (121)	21.3 (61)
Parity									
Primiparous	57.0 (2010)	59.5 (1713)	46.1 (297)	52.3 (294)	52.6 (579)	60.9 (349)	58.1 (347)	60.0 (243)	69.2 (198)
Smoking									
Yes	6.6 (232)	6.6 (191)	6.4 (41)	5.2 (29)	4.9 (54)	7.2 (41)	5.9 (35)	10.4 (42)	10.8 (31)
Child characteristics									
Sex									
Boy	50.3 (1773)	49.5 (1426)	53.8 (347)	49.1 (276)	49.5 (545)	51.7 (296)	50.6 (302)	51.6 (209)	50.7 (145)
Preterm birth									
Yes	4.0 (140)	4.1 (118)	3.4 (22)	0.9 (5)	3.2 (35)	3.8 (22)	4.5 (27)	6.2 (25)	9.1 (26)
Birth weight (kg) *mean, SD*	3.51 (0.53)	3.52 (0.54)	3.44 (0.51)	3.58 (0.50)	3.54 (0.50)	3.49 (0.50)	3.45 (0.55)	3.49 (0.59)	3.43 (0.63)

[1]Values are *% (N), unless otherwise indicated.* [2]*The percentages for the different feeding patterns are within the Dutch or within the Turkish ethnicity.*

Table 2. Associations of infant feeding patterns with BMI trajectories[1-3]

	BMI trajectory					
	''low''		''mid-low''		''mid-high''	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Feeding patterns						
EBF/ early CF	0.86 (0.52, 1.42)	0.56	0.94 (0.50, 1.79)	0.85	0.75 (0.44, 1.28)	0.29
EBF/ late CF (reference)	-		-		-	
Mixed/ early CF	0.63 (0.35, 1.15)	0.12	1.71 (0.96, 3.03)	0.14	0.50 (0.29, 0.87)	0.01
Mixed/ late CF	0.62 (0.33, 1.17)	0.64	1.55 (0.80, 3.00)	0.13	0.47 (0.25, 0.89)	0.19
Formula/ early CF	0.43 (0.25, 0.76)	<0.01	0.76 (0.40, 1.44)	0.40	0.28 (0.16, 0.51)	<0.01
Formula/ late CF	0.63 (0.27, 1.48)	0.29	1.71 (0.73, 4.00)	0.22	0.50 (0.24, 1.07)	0.07

[1]Values are OR based on LCMM. [2]Reference BMI trajectory ''high''. [3]Adjusted for ethnicity, educational level, pre-pregnancy BMI, parity, smoking, sex, preterm birth, birth weight.

Table 3. Ethnic-specific associations of infant feeding patterns with BMI trajectories (model 2) (Dutch, Turkish/Moroccan)[1-3]

	BMI trajectory					
	''low''		''mid-low''		''mid-high''	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Feeding pattern						
Dutch						
EBF/ early CF	1.09 (0.59, 2.01)	0.79	1.14 (0.54, 2.41)	0.73	0.90 (0.46, 1.75)	0.75
EBF/ late CF (reference)	-		-		-	
Mixed/ early CF	0.62 (0.32, 1.22)	0.28	1.46 (0.74, 2.85)	0.12	0.54 (0.27, 1.08)	0.05
Mixed/ late CF	0.69 (0.32, 1.49)	0.70	1.72 (0.75, 3.95)	0.22	0.50 (0.21, 1.19)	0.35
Formula/ early CF	0.46 (0.24, 0.87)	0.02	0.79 (0.39, 1.57)	0.50	0.30 (0.15, 0.61)	<0.01
Formula/ late CF	0.62 (0.26, 1.49)	0.29	1.46 (0.58, 3.63)	0.42	0.54 (0.23, 1.24)	0.15
Turkish/Moroccan						
EBF/ early CF	0.14 (0.05, 0.42)	<0.01	0.15 (0.03, 0.68)	0.01	0.50 (0.21, 1.20)	0.12
EBF/ late CF	0.43 (0.20, 0.91)	0.03	0.32 (0.13, 0.82)	0.02	0.72 (0.33, 1.56)	0.41
Mixed/ early CF	0.14 (0.06, 0.33)	<0.01	0.39 (0.15, 1.00)	0.05	0.30 (0.14, 0.65)	<0.01
Mixed/ late CF	0.25 (0.11, 0.55)	<0.01	0.44 (0.18, 1.07)	0.07	0.41 (0.18, 0.94)	0.03
Formula/ early CF	0.11 (0.03, 0.39)	<0.01	0.22 (0.06, 0.80)	0.02	0.18 (0.05, 0.61)	0.01
Formula/ late CF	0.06 (0.00, 1.50)	0.09	0.92 (0.31, 2.73)	0.88	0.22 (0.04, 1.12)	0.07

[1]Values are OR based on LCMM. [2]Reference BMI trajectory ''high''. [3]Adjusted for covariates: educational level, pre-pregnancy BMI, parity, smoking, sex, preterm birth, birth weight.

Supplementary tables

Table S1. Associations of infant feeding patterns with BMI trajectories, sensitivity analysis based on the type of milk feeding provided during 0-6 months[1-3]

		BMI trajectory					
		''low''		''mid-low''		''mid-high''	
% (n)		OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
	Feeding pattern[4]						
5.4 (192)	EBF/ early CF	1.14 (0.57, 2.27)	0.71	0.66 (0.26, 1.65)	0.37	0.45 (0.21, 0.93)	0.03
13.0 (459)	EBF/ late CF (reference)	-		-		-	
26.7 (942)	Mixed/ early CF	1.71 (0.94, 3.10)	0.08	2.35 (1.21, 4.58)	0.01	0.73 (0.42, 1.28)	0.27
35.2 (1240)	Mixed/ late CF	2.45 (1.40, 4.27)	<0.01	2.17 (1.15, 4.11)	0.02	0.91 (0.53, 1.58)	0.74
11.5 (405)	Formula/ early CF	0.87 (0.45, 1.70)	0.69	1.09 (0.50, 2.36)	0.84	0.32 (0.16, 0.62)	<0.01
8.1 (286)	Formula/ late CF	1.34 (0.54, 3.31)	0.53	2.35 (0.90, 6.10)	0.08	0.61 (0.25, 1.47)	0.27

[1]Values are OR based on LCMM. [2]Reference BMI trajectory ''high''. [3]Adjusted for ethnicity, educational level, pre-pregnancy BMI, parity, smoking, sex, preterm birth, birth weight. [4]feeding patterns are based on the type of milk feeding provided during 0-6 months period.

Table S2. Ethnic-specific associations of infant feeding patterns with BMI trajectories (model 2) (Dutch, Turkish/Moroccan), sensitivity analysis based on the type of milk feeding provided during 0-6 months[1-3]

		BMI trajectory					
		''low''		''mid-low''		''mid-high''	
%[2] (n)		OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
	Feeding pattern[4]						
	Dutch						
5.2 (150)	EBF/ early CF	1.39 (0.57, 3.36)	0.47	1.05 (0.34, 3.24)	0.93	0.63 (0.22, 1.83)	0.40
13.2 (380)	EBF/ late CF (reference)						
26.1 (752)	Mixed/ early CF	2.12 (1.11, 4.07)	0.02	3.03 (1.43, 6.45)	0.00	0.86 (0.39, 1.90)	0.71
34.7 (1000)	Mixed/ late CF	2.69 (1.28, 5.65)	0.01	2.67 (1.17, 6.08)	0.02	1.03 (0.38, 2.81)	0.95
12.1 (348)	Formula/ early CF	0.99 (0.56, 1.76)	0.97	1.32 (0.61, 2.85)	0.49	0.37 (0.15, 0.89)	0.03
8.7 (250)	Formula/ late CF	1.42 (0.59, 3.45)	0.44	2.68 (1.04, 6.87)	0.04	0.68 (0.24, 1.88)	0.46
	Turkish/Moroccan						
6.5 (42)	EBF/ early CF	0.46 (0.16, 1.36)	0.16	0.06 (0.00, 3.37)	0.17	0.20 (0.05, 0.83)	0.03
12.3 (79)	EBF/ late CF	0.46 (0.12, 1.69)	0.24	0.65 (0.18, 2.41)	0.52	0.90 (0.30, 2.74)	0.85
29.5 (190)	Mixed/ early CF	0.27 (0.10, 0.69)	0.01	0.78 (0.31, 1.97)	0.59	0.51 (0.21, 1.21)	0.13
37.3 (240)	Mixed/ late CF	0.77 (0.35, 1.70)	0.52	0.75 (0.30, 1.87)	0.54	0.56 (0.23, 1.40)	0.22
8.9 (57)	Formula/ early CF	0.24 (0.07, 0.87)	0.03	0.38 (0.10, 1.44)	0.15	0.20 (0.05, 0.78)	0.02
5.6 (36)	Formula/ late CF	0.05 (0.00, 1.42)	0.59	1.15 (0.23, 1.42)	0.87	0.47 (0.10, 1.42)	0.32

[2]The percentages for the different feeding patterns are within the Dutch or within the Turkish ethnicity. [4]Feeding patterns are based on the type of milk feeding provided during 0-6 months period.

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Chapter 4

Infant feeding and ethnic differences in body mass index during childhood: a prospective study

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Abstract

Background: This study investigated ethnic differences in childhood body mass index (BMI) in children from Dutch and Turkish descent and the role of infant feeding factors (breastfeeding duration, milk feeding frequency, as well as the timing, frequency and variety of complementary feeding (CF)).

Methods: We used data from 244 children (116 Dutch and 128 Turkish) participating in a prospective study in the Netherlands. BMI was measured at 2, 3 and 5 years and standard deviation scores (sds) were derived using WHO references. Using linear mixed regression analyses we examined ethnic differences in BMI-sds between 2-5 years, and the role of infant feeding in separate models including milk- or CF factors or both (full model).

Results: Relative to Dutch children, Turkish children had higher BMI-sds at age 3 (mean difference:0.26;95%CI:0.04,0.48) and 5 (0.63;0.39,0.88), but not at 2 (0.08;-0.16,0.31). Ethnic differences in BMI-sds were somewhat attenuated by CF factors at age 3 (0.16;-0.07,0.40) and 5 (0.50;0.24,0.77) whereas milk feeding had minor impact. Of all factors, only CF variety was associated with BMI-sds in the full model.

Conclusion: CF factors, particularly CF variety, explain a small fraction of the BMI-sds differences between Dutch and Turkish children. The role of CF variety on childhood BMI requires further investigation.

Introduction

Childhood overweight (and obesity) remains an important and growing global public health issue[1]. In the Netherlands, overweight rates have slightly declined during recent years among children from Dutch descent while remaining high among children from Turkish descent[2,3]. Infants of Turkish descent have been reported to have a higher body mass index (BMI) already during the first year of life[4] and by 2 years of age, one out of five children of Turkish descent has developed overweight. Infant feeding has been suggested as one of the most important modifiable risk factors for long-term growth outcomes[5,6]. Hence, a better understanding of the role of infant feeding in explaining ethnic differences in childhood BMI is pivotal.

Previous studies on infant feeding have mainly focused on (exclusive) breastfeeding (BF) duration and the timing of introduction of complementary feeding (CF) with somewhat conflicting results[7]. Although some studies reported that a longer BF duration and later introduction of CF are associated with a lower BMI during childhood[6,8] others reported no association[9]. To our knowledge, only limited evidence exists on other infant feeding factors such as feeding frequency or food variety[10], i.e. the number of food groups consumed. Although a high (milk) feeding frequency has been associated with infant weight gain[11], no studies have assessed the long-term impact of either milk- or complementary feeding frequency during infancy on childhood BMI development. Moreover, although several aspects of milk- and CF feeding may play a role in the development of overweight, previous studies have not investigated their role independently of other feeding factors.

Large ethnic differences exist in infant feeding[12,13]. In the Netherlands, infants from Turkish descent generally receive longer duration of BF and are introduced to CF later than Dutch infants[13]. Although previous studies in the Netherlands including Dutch infants reported associations of BF duration and the timing of CF with infant weight gain[13] or higher BMI during childhood,[14] these studies found no associations among Turkish infants. Previously, in the cohort studied in the current study, Turkish infants were found to receive more frequent feedings and a higher variety of complementary foods than Dutch infants at 6 months of age. It is of interest to investigate long-term associations of infant feeding practices with childhood growth outcomes in these populations[15].

The aim of the current study was to investigate the contribution of infant feeding factors to the ethnic differences in BMI between 2 to 5 years in children of Dutch and Turkish descent. We examined the contribution of following infant feeding factors: BF duration, milk feeding frequency as well as timing, frequency and variety of CF. Our hypothesis was that infants of

Turkish descent would show increase in BMI development compared to infants of Dutch descent which would be largely explained by infant feeding factors related to CF.

Methods

Study population

The inclusion of the study population for the current study has been described previously in detail[15]. In short, the study population includes Turkish and Dutch mothers and their infants, born between August 2009 and March 2010 in the city of Amsterdam. Infants were considered of Dutch descent when both parents and the mothers' mother were born in the Netherlands. If at least one parent and the mothers' mother were born in Turkey, infants were considered of Turkish descent[15,16]. Inclusion criteria for participation were term gestational age (≥37 weeks), appropriate weight for gestational age (≥10th percentile of the Dutch national reference curves), singleton pregnancy, no maternal complications during pregnancy (e.g. no diabetes or hypertension) and no medical problems diagnosed during pregnancy or after birth (e.g. congenital malformations). Approximately 2 weeks after birth, when data on ethnicity, pregnancy, birth and neonatal health were recorded in the Child Health Care registration, mothers who met the inclusion criteria were contacted by phone and provided with verbal and written study information. Once participation was agreed, a home visit was made 4 weeks after birth during which written informed consent was obtained. In total, 368 mothers were asked to participate, of whom 300 (150 Dutch and 150 Turkish) agreed (81.5%) to participate in the follow-up, which included three home visits (1, 4 and 6 months after birth). Of these mothers, 286 completed the data collection during the home visits. The sociodemographic characteristics of the fourteen mothers that dropped out were similar to the characteristics of the participating mothers. Children with complete data on the feeding factors at 6 months and ≥1 measure of BMI-sds during 2-5 years of age were included in the analysis. The final study sample consisted of 244 children, 116 from Dutch and 128 from Turkish descent (Figure 1). The study protocol was approved by the Medical Ethical Committee of the Academic Medical Centre in Amsterdam, The Netherlands.

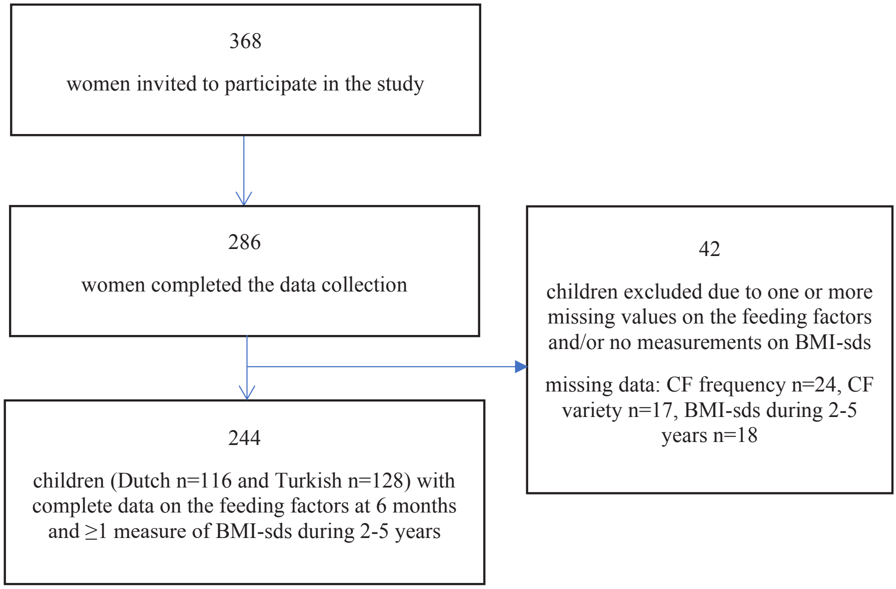

Figure 1. A flowchart of the selection of analysed study population.

Data collection

Data on maternal and infant characteristics as well as infant feeding were collected during home visits when infants were 1, 4 and 6 months old by means of a standardized questionnaire and a 24-h recall. Home visits were made by a team of ten medical students, who were carefully selected and trained to secure the quality of the data. Students were able to speak Turkish if requested by the mother.

Infant feeding

During every home visit at 1, 4 and 6 months, mothers were asked to provide information on the feeding of their infant by filling out a standardized questionnaire. A 24-h food recall was also performed to obtain data on feeding from the day preceding the visit. For duration of BF, questions during each home visit assessed whether the child had received either BF or formula feeding during the period preceding the visit and the duration in months. The duration of full BF (BF without additional formula feeding) was then defined based on the duration of full BF and the age of the child when formula feeding was introduced. For the present study, the duration of full BF was dichotomized as <6 months and ≥6 months. We chose to investigate full BF (defined as no formula, but other foods/drinks are allowed) instead of exclusive BF (no formula or other foods or drinks) because we were interested to study the role of full BF duration and the timing of CF as separate factors.

Regarding CF timing, during every home visit the mothers were asked if they had introduced complementary foods or drinks to their infant during the period preceding the visit. Complementary foods were defined as any other liquid or food other than breast milk, infant formula or water. For the present study, the timing of CF was dichotomized as <6 months and ≥6 months according to the WHO recommendations[17].

Data on milk and CF frequency was obtained via the 24-h recall at 6 months of age. Milk feeding frequency included all milk feedings, which were either infant formula or BF, including expressed breast milk fed from the bottle. Formula feedings with added rice flour were also considered as milk feedings. For the CF frequency we considered the number of times when liquids or foods other than breast milk, infant formula (with or without added rice flour) or water, were consumed. For both variables the frequency was defined as the number of times these liquids/foods were provided to the infant during the 24h recall period. CF variety was assessed by means of the questionnaire by asking mothers the types of complementary foods they had introduced to their infants according to the 6 months questionnaire. Additionally, information on types of complementary foods mentioned in the 24h-recalls was used to complement the data from the questionnaire. For the CF variety, all complementary foods offered to the infant were grouped into 5 food groups; 1) fruits and vegetables, 2) dairy products, 3) bread and cereals, 4) cookies and 5) savoury foods. Fruits and vegetables group included all food items consisting of vegetables or/and fruits only, including commercial jars. Dairy products included cow's milk, cheese and yogurt. Bread and cereals included breads and cereal based meals such as infant cereal products, rice crackers and breadsticks. Cookies included all types of cookies, including baby cookies. Savoury foods included all savoury meals and snacks which were not included in the other categories, such as meat and pizza. Each food group consumed was assigned with one point. CF variety score was then calculated for each infant as the number of food groups. For the purpose of the analysis, the score was categorized then as: 1, 2 or ≥3. All mothers had indicated to have started CF by the time of the 6 months home visit. In case no information from the questionnaire or 24h-recall was available on the types of foods, these data were considered missing.

BMI during childhood

Information on child's weight and height during childhood was obtained from the Youth Health Care (YHC) centers standard health examinations during which height and weight were measured. BMI values (on average 2.6 measurements per child) were calculated as weight in kilograms divided by the square of height in meters (kg/m^2) and transformed into standard deviation scores (BMI-sds) according to the WHO age- and sex-specific growth references for 2, 3[18] and 5[19] years of age. For this, Growth Analyser Software, version 4.0 (Growth Analyser BV) was used. Overweight was defined as >+1 SD above the median of growth references.

Covariates

We included the following covariates: maternal BMI, education, age, parity and smoking as well as infant's gestational age and birth weight. For maternal BMI, height and weight data were measured by physicians at Youth Health Care (YHC) centers during the regular 6-month examination which all children receive. Maternal BMI was dichotomized as normal weight (BMI<25 kg/m^2) or overweight (including obesity, BMI≥25 kg/m^2). Maternal educational level was recorded during the second home visit and categorized based on the years of education completed: low (< 6 years); medium (6-10) or high (≥10 years). Information on maternal age (years) was obtained from the YHC registration. Parity (primiparity/multiparity) and smoking during pregnancy (yes/no) were recorded during the first home visit. Data on infant's gestational age (in days), birth weight (in gram) and sex were obtained from the YHC registration. For birth weight, sds was calculated using the WHO reference values [20], using the Growth Analyser, version 4.0.

Statistical analysis

We used linear mixed regression (LMR) analysis, including both fixed and random effects (random intercept for each subject), to examine ethnic differences in BMI-sds between 2-5 years and the explanatory role of infant feeding factors. This analysis takes into account the repeated BMI-sds measurements per subject and overcomes challenges inherent to longitudinal studies: bias due to missing data and the requirement for all individuals to be measured at the same ages.

First, to answer our first research question, in model 1 (crude model) potential ethnic differences in BMI-sds between 2-5 years were estimated by including age and the ethnicity variables as the main effects. We also assessed whether ethnic differences in BMI-sds remain similar over time during the period of 2-5 years by including an interaction term between ethnicity and age in this crude model. In case of significant interaction, it was included in subsequent models and marginal means and 95% CI's were generated from the LMR models to demonstrate differences in BMI-sds at each age.

Second, to investigate the role of milk- and CF factors in explaining the association between ethnicity and BMI-sds, separate models (models 2-4) were applied. Model 2 included model 1 plus the milk feeding factors (full BF duration and milk feeding frequency). Model 3 included model 1 plus the CF factors; timing of CF, variety of complementary foods and CF feeding frequency. Model 4 included all feeding factors (models 1+ 2 + 3) to investigate the milk- and CF factors simultaneously and their independent association with BMI-sds.

We additionally examined potential ethnic differences in the associations between feeding factors and BMI-sds to understand whether the impact of feeding factors on BMI-sds are similar for both ethnic groups. This was done by including interaction terms between ethnicity and each feeding factor in models 2 and 3. Additionally, we considered whether associations between each feeding factors and BMI-sds vary by age. This was done by including interaction terms between each feeding factors and age in models 2 and 3. In case of significant interactions ($p<0.05$), these terms were included in the subsequent models.

An additional adjusted model (model 5, including model 4 + covariates) was fitted including the subset of population with complete data on the pre-defined maternal and infant covariates; maternal age, parity and smoking as well as infant's gestational age and birth weight-sds (n=229), Table S1. Maternal BMI was not included in model 5 analyses due to the substantial amount of missing data for maternal BMI (>30%). As a sensitivity analysis, in model 6 we assessed potential confounding by maternal BMI by including it in addition to model 5 covariates (Table S2). This was done in the subset of population with complete data on the covariates as well as maternal BMI (n=156). Maternal educational level was not included in models 5 and 6 due to high correlation with ethnicity [15].

4

Results

Population characteristics

Apparent differences between maternal and infant characteristics as well as in BMI and the prevalence of overweight at age 5 were observed between the two ethnic groups (Table 1).

Table 1. Characteristics of study population by ethnicity (n=244).
(All values are % (n) unless otherwise stated

	Dutch (n=116) % (n)	Turkish (n=128) % (n)
Maternal characteristics		
Age, years (mean, SD)	32.5 (4.4)	28.7 (4.7)
Parity, primipara	58.6 (68)	28.1 (36)
Smoking during pregnancy	9.5 (11)	21.1 (26)
BMI		
Normal weight	64.3 (54)	28.7 (25)
Overweight (including obesity)	35.7 (30)	71.3 (62)
Educational level		
Low	4.3 (5)	50.0 (64)
Medium	19.8 (23)	37.5 (48)
High	75.9 (88)	12.5 (16)
Infant characteristics		
Birth weight, grams (mean, SD)	3547 (473)	3537 (527)
Gestational age, days (mean, SD)	281 (8.9)	279 (8.1)
Sex, boy	48.3 (56)	52.3 (67)
Infant feeding factors		
Full breastfeeding duration, months		
<6 months	85.3 (99)	65.6 (84)
≥6 months	14.7 (17)	34.4 (44)
Milk feeding frequency per day at 6 months (mean, SD)	5.0 (1.4)	5.9 (2.2)
Complementary feeding frequency per day at 6 months (mean, SD)	1.6 (1.0)	2.1 (1.1)
Timing of complementary feeding introduction		
<6 months	72.4 (84)	64.8 (83)

≥6 months	27.6 (32)	35.2 (45)
Complementary feeding variety score at 6 months		
1	55.2 (64)	28.6 (38)
2	38.8 (45)	36.7 (47)
≥3	6.0 (7)	35.9 (46)
Types of complementary feeding at 6 months [a]		
Fruits and vegetables	91.8 (123)	85.7 (114)
Dairy products	6.7 (9)	44.4 (59)
Bread, cereals	26.9 (36)	29.3 (39)
Cookies	12.7 (17)	19.5 (26)
Other savoury foods	6.5 (6)	39.8 (53)
Childhood BMI and overweight		
2 years (n=250)		
BMI-sds, mean (SD)	0.53 (0.82)	0.56 (1.03)
Overweight[b]	5.3 (5)	6.2 (7)
3 years (n=248)		
BMI-sds, mean (SD)	0.18 (0.80)	0.53 (1.01)
Overweight[b]	4.3 (4)	11.5 (13)
5 years (n=206)		
BMI-sds, mean (SD)	-0.04 (0.83)	0.63 (1.04)
Overweight[c]	7.5 (7)	23.5 (25)

Missing data (n): maternal BMI (89), smoking (5), maternal age (9), gestational age (4).
[a] multiple types of CF can be reported.
[b]Defined as BMI >2+SD above the age- and sex-specific WHO 2006 Child Growth Standards median (19).
[c]Defined as BMI >+1SD above the age- and sex-specific WHO 2007 Child Growth Standards median (32).

Ethnic differences in BMI between 2 to 5 years and the role of infant feeding factors

There was significant interaction (p<0.001) between ethnicity and age, suggesting that ethnic differences in BMI-sds are age-specific. In addition, interaction term food variety and age was significant (p=0.007), suggesting that the association between food variety and BMI-sds differs depending on the age. Therefore, these interaction terms were included in the subsequent analyses. Results are shown as marginal means and 95% CI's, which were generated from the LMR to describe the associations at each age.

Table 2 shows the mean differences in estimated BMI-sds at age 2 years by ethnicity and feeding factors, derived from the LMR. Ethnic differences in BMI-sds were not present at 2 years (Table 2, crude model). The addition of milk- and CF factors in models 2 and 3 did not change the magnitude of the mean differences in BMI-sds between the ethnic groups. When examining the independent associations of all the feeding factors with BMI-sds in the full model (model 4), only CF variety was significantly associated with BMI-sds at age 2; children with a CF variety of ≥3 had 0.39 units higher BMI-sds than those with CF variety of 1.

At 3 years Turkish children had statistically significant 0.26 units higher BMI-sds compared to Dutch children (Table 3, crude model). Milk feeding factors slightly reduced the ethnic differences in model 2. In model 3, after the adjustment for CF factors, ethnic differences attenuated (0.10 sds units) and became non-significant. When all feeding factors were mutually adjusted for in model 4, CF variety of ≥3 (vs. CF variety of 1) was associated with BMI-sds (mean difference: 0.44; 95% CI: 0.10, 0.78) independent of other feeding factors and ethnicity. Ethnic differences in BMI-sds were even more apparent at 5 years of age, Turkish children had statistically significant 0.63 units higher BMI-sds compared to Dutch children (Table 4, model 1). Although CF factors attenuated the ethnic differences (0.13 sds units), ethnic differences remained significant also in models 3 and 4. In model 4 only CF variety (≥3 vs. 1) was significantly associated with BMI-sds (mean difference: 0.55; 95% CI: 0.17, 0.92) independent of other feeding factors and ethnicity.

Results from the sensitivity analyses including adjustment for maternal and infant covariates (model 5, Table S1) and additionally for maternal BMI (model 6, Table S2) showed further reduction in the ethnic differences in BMI-sds compared to model 4 results at each age (Tables 2-4). Furthermore, in models 5 and 6, adjustment for the covariates did not change the associations of the feeding factors with BMI-sds except for the slight attenuation of the estimates for full BF and CF variety.

Discussion

In this longitudinal study we found that relative to Dutch children, Turkish children had higher BMI-sds at age 3 and 5, but not at 2. A small fraction of the ethnic differences in BMI-sds were explained by CF factors, particularly CF variety, whereas milk feeding had minor impact.

We observed that the ethnic differences in BMI increased with age. Although previous studies in the Netherlands reported higher overweight prevalence at 2 years among children from Turkish descent compared to children from Dutch descent[21,22], we did not observe ethnic differences in BMI at this age. In our study ethnic differences in BMI were smaller than reported in a previous study from the city of Amsterdam [21]. Possible explanation for this may be differences in sample size as well as the inclusion criteria. The current study was relatively small and included singleton infants who were born term, with an appropriate weight for gestational age and mothers with no complications during pregnancy (e.g. diabetes or hypertension).

To our knowledge, our study is the first in examining the role of several infant feeding factors simultaneously, including CF variety, on ethnic inequalities in childhood BMI at different ages. We found that CF factors, especially CF variety, explained a small fraction of the ethnic differences in BMI at 3 and 5 years of age. CF variety was also strongly associated with BMI at 2, 3 and 5 years of age, independent of the other feeding factors examined and ethnicity. There was also some indication that this association increased with age, suggesting that the role of early nutrition may become more apparent at older ages. However, this was less clear in the adjusted models 5 and 6. Our results on CF variety and BMI are in line with a previous study on preschool children in the US that found that a higher food variety was associated with a larger annual increases in BMI-sds during a follow-up of 20 months [10]. Additionally, according to a study of Schack-Nielsen et al. [23], increasing number of types of foods introduced between the age of 3-6 months indicated a higher, although not significant, risk for adult overweight. One possible explanation for the association between food variety and BMI observed in our study is that infants exposed to a high food variety during early infancy may have an overall high food intake, which leads to excessive energy intake and subsequently to an increased weight gain [23]. The quality of foods may also be important as variety of non-recommended foods (i.e. sources of added sugars and solid fats) has been shown to increase the likelihood of excess adiposity in adults [24]. In the cohort studied in the current study, large differences were observed in the types of CF offered to the children [15]. When exploring the different types of CF provided among the children with a CF variety of ≥3, it was seen that a large majority had been provided with dairy products (81.6%) and savoury meals

(75.0%), whereas among the children with a CF variety of 1, these were only 8.4% and 6.4%, respectively (data not shown). It is thus possible that our associations on CF variety and BMI may be (partly) explained by the types of CF[25]. Currently the Dutch and the WHO guidelines on CF include only the timing on when it is appropriate to start CF. In light of the prevention of childhood obesity, information on the variety and the type of CF might be also needed.

Conflicting evidence exists in the association between breastfeeding duration and overweight during childhood [12,22,26]. In our study, BF duration did not explain the observed ethnic differences in BMI. These findings are in line with several other multi-ethnic studies which reported no association of BF and growth outcomes among ethnic minority children [27 28 13]. We also did not find evidence that the frequency of milk feedings contributed to the ethnic differences in BMI despite of the fact that Turkish infants were given more frequent milk feedings than Dutch infants. Although one previous study found an association between milk feeding frequency and increased infant adiposity[11], to our knowledge no previous studies investigated milk feeding frequency in relation to childhood growth outcomes.

In our study the timing or frequency of CF did not explain ethnic differences and was not associated with BMI at any age. Our findings on timing of CF are in line with previous studies in the United Kingdom and in the Netherlands [12 28 13]. Although some studies concluded no associations between timing of CF with overweight[7,29], other studies showed that later introduction of CF was associated with lower BMI or decreased risk for overweight[23,30]. CF feeding frequency has not been investigated in childhood, although a previous study reported that CF frequency was not associated with weight gain during infancy [31].

Important strengths of the present study include the prospective data on childhood BMI as well as information on several infant feeding factors collected during infancy. Moreover, our study population included an ethnic minority group with an increased childhood overweight risk. The fact that mothers were interviewed in their language of choice to account for differences in language proficiency, established a high response and low dropout rates. Nevertheless, some limitations should be considered. First, the final sample size available for the analyses may be considered small. Second, due to multiple testing, we also cannot exclude the possibility of spurious findings. Third, although we additionally adjusted for several potential maternal and infant related confounders, we did not include maternal BMI due to the large number of missing values. However, sensitivity analyses showed comparable results. Hence, future studies should include detailed information on CF, including intakes of energy and macronutrients across ethnic groups. Finally, dietary assessment including the period of 6 to 12 months may also be important to consider as it has been considered important for the dietary transition towards the family diet. Future studies should also include detailed composition and quantities of the foods and drinks provided, which may explain the associations between the feeding factors and BMI observed in this study.

To conclude, this study suggests that infant feeding at 6 months, and especially CF factors explain some of the ethnic differences in BMI between 2 to 5 years of age between children from Dutch and Turkish descent. Therefore, a better understanding of CF practices across ethnic groups is warranted in order to reduce ethnic inequalities in childhood BMI. Further investigation on the importance of CF variety on childhood BMI is required.

Table 2. Mean differences in estimated BMI-sds at age 2 years by ethnicity and feeding factors, derived from the LMR (models 1-4) and contribution of infant feeding factors

	Model 1[a] (Crude model)	Model 2[b] (Milk feeding factors)	Model 3[c] (Complementary feeding factors)	Model 4[d] (Model 2+3)
	Mean difference (95% CI)			
Ethnicity				
(Turkish vs. Dutch)	0.08 (-0.16, 0.31)	0.03 (-0.21, 0.27)	0.00 (-0.25, 0.25)	-0.08 (-0.35, 0.18)
Full breastfeeding duration				
(<6 months vs. ≥6 months)		-0.20 (-0.48, 0.08)		-0.18 (-0.46, 0.10)
Milk feeding frequency		0.01 (-0.06, 0.07)		0.02 (-0.05, 0.08)
Timing of complementary feeding				
(<6 months vs. ≥6 months)			-0.03 (-0.26, 0.21)	-0.01 (-0.23, 0.25)
Complementary feeding variety score				
(2 vs. 1)			0.04 (-0.23, -0.32)	0.06 (-0.22, 0.33)
(≥3 vs. 1)			0.37 (0.01, 0.72)*	0.39 (0.03, 0.75)*
Complementary feeding frequency			-0.08 (-0.19, 0.03)	-0.06 (-0.18, 0.05)

Data are least-square means and 95% CI. Linear mixed models were used to model mean differences in estimated BMI-sds at age 2 years by ethnicity and the feeding patterns.
* P<0.05.
[a]Model 1: crude model including variables age and ethnicity.
[b]Model 2: as model 1 and additionally adjusted for the milk feeding factors: full breastfeeding duration and milk feeding frequency
[c]Model 3: as model 1 and additionally adjusted for the complementary feeding factors; timing of complementary feeding, Complementary feeding variety score, complementary feeding frequency
[d]Model 4: all feeding variables (models 1+ 2 + 3)

Table 3. Mean differences in estimated BMI-sds at age 3 years by ethnicity and feeding factors, derived from the LMR (models 1-4) and contribution of infant feeding factors

	Model 1[a] (Crude model)	Model 2[b] (Milk feeding factors)	Model 3[c] (Complementary feeding factors)	Model 4[d] (Model 2+3)
	Mean difference (95% CI)			
Ethnicity				
(Turkish vs. Dutch)	0.26 (0.04, 0.48)*	0.22 (-0.01, 0.44)	0.16 (-0.07, 0.40)	0.10 (-0.15, 0.35)
Full breastfeeding duration				
(<6 months vs. ≥6 months)		-0.20 (-0.48, 0.08)		-0.18 (-0.46, 0.10)
Milk feeding frequency		0.01 (-0.06, 0.07)		0.02 (-0.05, 0.08)
Timing of complementary feeding				
(<6 months vs. ≥6 months)			-0.03 (-0.26, 0.21)	-0.01 (-0.23, 0.25)
Complementary feeding variety score				
(2 vs. 1)			0.03 (-0.23, 0.29)	0.05 (-0.22, 0.31)
(≥3 vs. 1)			0.42 (0.08, 0.76)*	0.44 (0.10, 0.78)*
Complementary feeding frequency			-0.08 (-0.19, 0.03)	-0.06 (-0.18, 0.05)

Data are least-square means and 95% CI. Linear mixed models were used to model mean differences in estimated BMI-sds at age 3 years by ethnicity and the feeding patterns.
* P<0.05.
[a]Model 1: crude model including variables age and ethnicity.
[b]Model 2: as model 1 and additionally adjusted for the milk feeding factors: full breastfeeding duration and milk feeding frequency
[c]Model 3: as model 1 and additionally adjusted for the complementary feeding factors; timing of complementary feeding, Complementary feeding variety score, complementary feeding frequency
[d]Model 4: all feeding variables (models 1+ 2 + 3)

Table 4. Mean differences in estimated BMI-sds at age 5 years by ethnicity and feeding factors, derived from the LMR (models 1-4) and contribution of infant feeding factors

	Model 1[a] (Crude model)	Model 2[b] (Milk feeding factors)	Model 3[c] (Complementary feeding factors)	Model 4[d] (Model 2+3)
	Mean difference (95% CI)			
Ethnicity (Turkish vs. Dutch)	0.63 (0.39, 0.88)***	0.59 (0.33, 0.84)***	0.50 (0.24, 0.77)***	0.47 (0.20, 0.75)**
Full breastfeeding duration (<6 months vs. ≥6 months)		-0.20 (-0.48, 0.08)		-0.18 (-0.46, 0.10)
Milk feeding frequency		0.01 (-0.06, 0.07)		0.02 (-0.05, 0.08)
Timing of complementary feeding (<6 months vs. ≥6 months)			-0.03 (-0.26, 0.21)	-0.01 (-0.23, 0.25)
Complementary feeding variety score				
(2 vs. 1)			0.01 (-0.28, 0.30)	0.02 (-0.27, 0.31)
(≥3 vs. 1)			0.53 (0.15, 0.90)**	0.55 (0.17, 0.92)**
Complementary feeding frequency			-0.08 (-0.19, 0.03)	-0.06 (-0.18, 0.05)

Data are least-square means and 95% CI. Linear mixed models were used to model mean differences in estimated BMI-sds at age 5 years by ethnicity and the feeding patterns.
** P<0.01. ***P<0.001
aModel 1: crude model including variables age and ethnicity.
bModel 2: as model 1 and additionally adjusted for the milk feeding factors: full BF duration and milk feeding frequency
cModel 3: as model 1 and additionally adjusted for the CF factors; timing of CF, variety of complementary foods and CF feeding frequency
dModel 4: all feeding variables (models 1+ 2 + 3)

Supplementary tables

Table S1. Mean differences in estimated BMI-sds at ages 2, 3 and 5 by ethnicity and feeding factors (n=229), derived from the LMR model 5

	Model 5[a]		
	2 years	3 years Mean difference (95% CI)	5 years
Ethnicity			
(Turkish vs. Dutch)	-0.13 (-0.42, 0.17)	0.03 (-0.26, 0.31)	0.33 (0.02, 0.64)*
Full breastfeeding duration			
(<6 months vs. ≥6 months)	-0.11 (-0.40, 0.17)	-0.11 (-0.40, 0.17)	-0.11 (-0.40, 0.17)
Milk feeding frequency	0.03 (-0.03, 0.10)	0.03 (-0.03, 0.10)	0.03 (-0.03, 0.10)
Timing of complementary feeding			
(<6 months vs. ≥6 months)	-0.05 (-0.29, 0.19)	-0.05 (-0.29, 0.19)	-0.05 (-0.29, 0.19)
Complementary feeding variety score			
(2 vs. 1)	0.11 (-0.16, 0.38)	0.11 (-0.15, 0.37)	0.12 (-0.17, 0.41)
(≥3 vs. 1)	0.37 (0.01, 0.73)*	0.41 (0.07, 0.76)*	0.49 (0.12, 0.87)*
Complementary feeding frequency	-0.05 (-0.16, 0.06)	-0.05 (-0.16, 0.06)	-0.05 (-0.16, 0.06)

Data are least-square means and 95% CI. Linear mixed models were used to model mean differences in estimated BMI-sds at age 2, 3 and 5 years by ethnicity and the feeding patterns.

* P<0.05.

[a] Adjusted for all infant feeding factors and the covariates (maternal: age, smoking, parity; child: sex, gestational age, birth weight-sds).

Table S2. Mean differences in estimated BMI-sds at ages 2, 3 and 5 years by ethnicity and feeding factors (n=156), derived from the LMR (model 6)

	Model 6[a]		
	2 years	3 years	5 years
	Mean difference (95% CI)		
Ethnicity			
(Turkish vs. Dutch)	-0.24 (-0.60, 0.12)	0.08 (-0.26, 0.43)	0.23 (-0.14, 0.60)
Full breastfeeding duration			
(<6 months vs. ≥6 months)	-0.22 (-0.58, 0.14)	-0.22 (-0.58, 0.14)	-0.22 (-0.58, 0.14)
Milk feeding frequency	0.02 (-0.06, 0.10)	0.02 (-0.06, 0.10)	0.02 (-0.06, 0.10)
Timing of complementary feeding			
(<6 months vs. ≥6 months)	-0.05 (-0.33, 0.22)	-0.05 (-0.33, 0.22)	-0.05 (-0.33, 0.22)
Complementary feeding variety score			
(2 vs. 1)	0.05 (-0.26, 0.37)	0.08 (-0.22, 0.38)	0.14 (-0.19, 0.48)
(≥3 vs. 1)	0.35 (-0.11, 0.81)	0.39 (-0.05, 0.83)	0.48 (0.01, 0.96)*
Complementary feeding frequency	-0.02 (-0.16, 0.12)	-0.02 (-0.16, 0.12)	-0.02 (-0.16, 0.12)

Data are least-square means and 95% CI. Linear mixed models were used to model mean differences in estimated BMI-sds at age 2, 3 and 5 years by ethnicity and the feeding patterns.

* $P<0.05$. [a]Model includes model 5 (all infant feeding factors and maternal: age, smoking, parity; child: gestational age, birth weight) and maternal BMI.

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Chapter 5

Dietary patterns in early childhood and the risk of childhood overweight: the GECKO Drenthe birth cohort

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Abstract

Background: Limited and inconsistent evidence exists on the associations between dietary patterns and overweight during childhood. The present study describes dietary patterns of 3-year-old Dutch children and associations between childhood overweight and body mass index (BMI) development between 3 and 10 years.

Methods: In the GECKO Drenthe birth cohort (N=1306), body height and weight were measured when children were around the ages of 3,4,5 and 10 years and overweight was defined according to Cole and Lobstein. Diet was measured at 3 years through a validated food frequency questionnaire (FFQ). Principal components analysis (PCA) was used to derive dietary patterns. Using logistic regression analyses, pattern scores were related to overweight at 3 and 10 years. A linear mixed-effects model was used to estimate BMI-sds development between 3 to 10 years according to quartiles of adherence to the pattern scores.

Results: Two dietary patterns were identified: 1)'minimally processed foods', characterized by a high intake of vegetables, sauces and savory dishes; and 2)'ultra-processed foods', characterized by a high intake of white bread, crisps and sugary drinks. A 1 SD increase in 'ultra-processed foods' pattern score increased the odds of overweight at 10 years (adjusted OR1.30,95%CI:1.08,1.57; p=0.006). The 'minimally processed foods' pattern was not associated with overweight. Although a high adherence to both the 'minimally processed' and 'ultra-processed foods' patterns was associated with a higher BMI-sds up to 10 years of age, a stronger association for the 'ultra-processed foods' pattern was observed (p<0.001).

Conclusion: A dietary pattern high in energy-dense and low-fibre ultra-processed foods at 3 years is associated with overweight and a high BMI-sds later in childhood.

Introduction

Childhood overweight and obesity are important public health challenges, because they are associated with an increased risk of obesity later in life [1] as well as other adverse health consequences [2]. Increasing evidence suggests that unhealthy diets during early childhood are key modifiable risk factors for the development of overweight and obesity [3-5]. Improving dietary habits is thus one of the crucial strategies for the prevention of overweight.

Dietary patterns represent a comprehensive picture of the whole diet and may thus give a better indication of a disease risk than by looking at the consumption of individual foods or nutrients [6]. There is growing evidence for adults and older children that dietary patterns that are high in energy-dense, nutrient-poor and low-fibre foods, predispose to later overweight and obesity [5, 7]. However, studies in young children (2 to 5 years) are limited and have shown inconsistent findings.

Most previous studies on dietary patterns including young children have identified two major dietary patterns. One pattern indicated a high intake of energy-dense, high-sugar/fat and low-fibre foods, labeled often as 'Unhealthy' or 'Processed' [8-18]. Although in several cross-sectional studies among 3 to 7 year-old children a high adherence to such pattern was associated with a higher risk of having obesity [8, 10, 12], other cross-sectional studies including younger children reported no associations [9, 11, 13]. Another dietary pattern identified across studies indicates high intake of fruits and vegetables, cereals and/or dairy products, and is named as 'traditional' [8, 9, 11] or 'healthy' [8-10, 12, 13]. Some of the cross-sectional studies reported no associations between these patterns and childhood obesity [9, 10] or body mass index (BMI) [13]; however, two studies [8, 11] reported that children with a higher adherence to a 'traditional' or 'healthy' pattern were less likely to have overweight or obesity. Interestingly, one study found that a higher adherence to a 'traditional' pattern was associated with a higher BMI [12].

Among prospective studies assessing diet among 2 to 5 year-old children, three found that a high adherence to a 'snacking' or 'energy-dense' pattern or 'processed foods' cluster was associated with an increase in BMI [14, 15] or excess fat mass [16]. However, two other prospective studies assessing diet in young children showed that a 'junk food' or 'energy-dense foods' pattern was not associated with obesity at age 7 [18] or an association with BMI at age 7 was found only among girls [17]. Furthermore, studies with the longest follow-up period (up to 5 years) reported either no or mixed associations between various dietary patterns at age 3 or 5 and weight-related outcomes later in childhood [18,19].

Based on the aforementioned findings, current evidence on the associations between dietary patterns of young children and the development of childhood overweight or obesity is conflicting and longer-term follow-up studies are lacking. As dietary habits are established early and track into later life [20-23], further knowledge on this topic is crucial for developing prevention strategies for overweight and obesity. Therefore, the objective of this study was to (1) identify dietary patterns of 3-year-old Dutch children by using principal component analysis (PCA) and (2) examine associations between dietary patterns and overweight cross-sectionally at 3 years and prospectively until 10 years. Additionally, we examined associations between dietary patterns and BMI-sds development between 3 and 10 years of age.

Subjects and methods

Subjects

Data were obtained from a Dutch population-based cohort study, embedded within the Groningen Expert Center for Kids with Obesity (GECKO), the GECKO Drenthe study. Details of the study design, recruitment and study procedures are described in detail elsewhere [24]. All pregnant women living in the province of Drenthe, the Netherlands, were invited to participate in this study during the third trimester of their pregnancy. Of the 5326 children born between April 2006 and April 2007, 2842 started active participation in the study. At 10 years, 2299 children still participated in the study. For the identification of dietary patterns among the study population, all children with complete data on the food frequency questionnaire (FFQ) at 3 years were included (N=1306). From these children, all children with complete data on the covariates and for whom height and weight measurements were obtained at 3 and 10 years were selected for the analysis on the associations between the dietary patterns and overweight (N=938, Figure S1). The majority of missing questionnaires at the age of 3 years was related to logistical issues. Characteristics and available BMI measurements of the children excluded from the analyses (because of the missing data on growth measurements or covariates) were similar, except for the educational status of the mother, which was slightly lower among those excluded. For the analysis on dietary patterns and BMI-sds development between 3 and 10 years, children with complete data on FFQ, covariates and at least one BMI measurement during the period of 3 to 10 years were included, N=1233. Written informed consent was obtained from the parents. The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Medical Ethics Committee of the University Medical Center Groningen. The cohort is registered at www.birthcohorts.net.

Dietary data

Information on the diets at 3 years was obtained through an FFQ, completed by the parents. This FFQ has been validated for energy intake against the doubly labelled water method in a group of 4 to 6-year-old children [25]. The FFQ assessed the frequency of weekly consumption of 71 food products over the past four weeks. Answer categories ranged from 'never' to '6-7 days a week'. For 27 food products, additional questions were included regarding the type or brand of the product consumed. Portion size was assessed using fixed units (e.g. slices of bread) or common household measures (e.g. cups, spoons). Parents were asked to measure the volume of glasses and cups used for different beverages. From these data, intake of each food product (in grams per day) was calculated. Daily energy and nutrient intakes were calculated based on the Dutch food composition database (2011) [26]. For the purpose of the current analysis, food intake data were collapsed into 33 food groups taking into account the nutrient composition, i.e. energy density, fat and fiber content, as well as the usage of each food item. These 33 food groups are listed in the Supplementary Table 1.

Growth measures during childhood

The weight and height of the children were measured at ages 3, 4, 5 and 10 years during routine health examinations by the staff of the Youth Health Care centers (YHC). Body weight was measured using an electronic scale and rounded to the nearest 0.1 kg. Height was measured in the standing position against a wall and rounded to the nearest 0.1 cm. For the analyses on overweight at 3 and 10 years, age- and sex- specific BMI standard deviation scores (sds) were derived using the WHO growth references [27, 28] using the Growth Analyzer Software, version 4.0 (Growth Analyzer BV). Since the number of children with obesity (n=17 and n=39 at 3 and 10 years, respectively) were too small to be analyzed separately, the outcome was defined as overweight including obesity (referred to as overweight in the methods and results section) and defined according to Cole and Lobstein [29]. To investigate the BMI-sds development between 3 and 10 years, all BMI measurements at ages 3, 4, 5 and 10 years were included. These were calculated according to the age- and sex- specific distributions of BMI derived from the Dutch growth reference (2010) [30]. This reference was selected as it covers the period of 0-21 years, (thus including the period between 3 and 10 years), whereas the WHO provides two separate standards for the periods of 0-5 [27] and 5-19 years [28].

Covariates

Maternal covariates included pre-pregnancy BMI, highest completed educational level, ethnicity, smoking during pregnancy (yes/no), age (continuous, years) and parity (primiparous/multiparous) [31-33]. The information on the maternal covariates was collected during the last trimester of pregnancy or shortly after birth by means of a questionnaire and maternity files. Pre-pregnancy BMI was calculated from the weight and height data and dichotomized as normal weight (BMI <25 kg/m^2) or overweight (≥25 kg/m^2). Educational level was categorized as low (no education, primary school, lower vocational or lower general secondary education), middle (intermediate vocational training or higher secondary education) or high (higher vocational or university education) [34]. Ethnicity was defined as the country of birth of the mother and dichotomized as Dutch (mother being born in the Netherlands) or non-Dutch [35]. Child covariates included gestational age (weeks) and birth weight (g), which was rounded to the nearest 5 g. These data were reported by the midwives and obtained through the YHC registry. Birth weight was standardized according to gestational age- and sex- specific reference values based on the WHO reference [36]. These were derived using the Growth Analyzer Software, version 4.0 (Growth Analyzer BV). For 59 children, data on at least one of the covariates was missing. Due to the low number of missing data on the confounders, we decided not to impute missing data.

Statistical analysis

Principal component analysis (PCA) with varimax rotation was used to identify dietary patterns among the total study population with valid dietary data (n=1306). The number of patterns was selected considering eigenvalues of >1.50, the scree plot and the interpretability of the patterns. We identified two dietary pattern components which had factor loadings >2 (2.76 and 2.02). The interpretability of the components was preferred over the second-best option, a five-component solution. In the scree plot a clear break was indicated after the second component, suggesting a two-component solution. Regarding the interpretability, the disadvantage of the five-component solution was that two components depicted meals rather than a diet (e.g. ‘breakfast’ with a high intake of food groups such as bread, butter/oil and sweet bread toppings). For the two identified dietary patterns, regression-based factor scores were created by summing the observed standardized consumption per food group, which were weighted according to the PCA loadings. These factor scores were derived for each child and indicated the adherence to each dietary pattern.

Logistic regression analyses were used to study the associations between the dietary pattern scores and overweight at 3 and 10 years (N=938). First, we carried out an analysis to estimate cross-sectional associations between the dietary patterns and overweight at 3 years. Then, we analysed prospective associations of the dietary patterns and overweight at 10 years. In both analyses the pattern scores for both dietary patterns were used as determinants simultaneously in order to adjust for the adherence to the other pattern. At both ages we estimated two models; a crude model including the dietary pattern scores, and a second adjusted model including the a priori selected child and maternal covariates. As sensitivity analyses, we also repeated the logistic regression analyses using the definition of overweight according to WHO (Tables S2 and S3). According to this definition, overweight is defined as +2 BMI-sds at 3 years [27] and +1 BMI-sds at 10 years [28].

To assess the association between dietary pattern scores and BMI-sds development between 3 to 10 years, a random effects linear regression model with robust standard errors, to correct for the nesting (several measurements per child), was used. These analyses included all children who had at least one BMI measurements available between 3 to 10 years (N=1233, see Table S4 and S5). On average, each child had 3.3 BMI measurements (min 1, max 4). We estimated one model including both dietary pattern scores and interactions between the dietary patterns and age (categorical: 3, 4, 5 and 10 years) to account for non-linearity between age and BMI-sds development. This model was adjusted for all covariates.

Descriptive data analysis and the logistic regression analyses were conducted using the statistical program SPSS, version 19 (Chicago Illinois, USA). The random effects linear regression model was conducted using Stata, version 16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).

Results

The mothers of the children in the study population were mainly Dutch, 28.6% had a low educational level and 38.5% had overweight (Table 1). The percentage of children with overweight (according to Cole and Lobstein) at 3 and 10 years were 13.6% and 16.4%, respectively.

Table 1. Characteristics of the study population (n=1306)

Maternal characteristics	n (%)[1]
Age, mean (SD)	31.2 (4.2)
Educational level	
Low	28.6 (368)
Middle	32.8 (422)
High	38.7 (498)
Ethnicity	
Dutch	97.5 (1259)
Other	2.5 (32)
Pre-pregnancy BMI, mean (sd)	24.8 (4.7)
Overweight % (n)	38.5 (494)
Parity	
Multiparous	39.6 (516)
Smoking during pregnancy	
Yes	11.7 (152)
Child characteristics	
Sex	
Male	660 (50.5)
Birth weight (g), mean (sd)	3563.6 (557.0)
Age at diet measurement (years), mean (sd)	3.1 (0.4)
Age at 3-year BMI measurement (years), mean (sd)	3.1 (0.1)
Age at 10-year BMI measurement (years), mean (sd)	10.6 (0.5)
BMI and overweight at 3 years (n=938)	
BMI, mean (sd)	16.0 (1.2)
Overweight (%, n)	
According to Cole and Lobstein [29]	13.6 (128)
According to WHO [27]	3.5 (33)
BMI and overweight at 10 years (n=938)	
BMI, mean (sd)	17.8 (2.8)
Overweight (%, n)	
According to Cole and Lobstein [29]	16.4 (154)
According to WHO [28]	22.3 (209)

[1] All values % (n) unless otherwise indicated. Missing values: education (n=18), smoking (n=3), ethnicity (n=15), pre-pregnancy BMI (n=23), birth weight (n=13), gestational age (n=13), parity (n=3), age of the mother (n=3).

Table 2 shows the two dietary patterns identified, their factor loadings and correlations with nutrients. The two patterns accounted for 14.5% of the variability in food consumption within our study population. For ease of description, we called these patterns ‘minimally processed foods’ and ‘ultra-processed foods’. The names were based on the characteristics of the foods that distinguished the two patterns. The first pattern ‘minimally processed foods’ was characterized by high intakes of vegetables, sauces, rice/pasta and savory dishes. The second pattern, ‘ultra-processed foods’, indicated high intakes of white bread, crisps, savory snacks and sugar-sweetened beverages (SSB), as well as low intakes of whole-grain bread.

Table 2. Factor loadings for the identified dietary patterns

	Factor loadings	
	Dietary pattern 1 'minimally processed foods'	Dietary pattern 2 'ultra-processed foods'
Water	0,20	-0,04
Vegetables	0,61	-0,17
Fruit	0,18	-0,22
Whole-grain bread	0,28	-0,65
Fish	0,30	0,01
Sauces	0,58	0,00
Potatoes, plain	0,41	0,14
Eggs	0,27	0,09
Fried and baked potatoes	0,40	0,18
Savoury dishes	0,48	-0,03
Chicken	0,32	0,03
Meat	0,43	0,29
Milk and buttermilk	0,12	-0,21
Dairy desserts	0,23	0,07
Crisps	0,26	0,41
Cheese	0,28	-0,18
Cakes and confectionery	0,22	0,26
Butter and oil	0,14	0,02
White bread	-0,15	0,64
Breakfast cereals	0,16	-0,12
Added sugar	0,16	0,17
Sweet bread toppings	0,05	0,05
Sugar-sweetened beverages	0,14	0,34
Cookies	0,24	0,27
Rice and pasta	0,53	-0,26
Vegetarian meat substitutes	0,02	-0,26
Porridge	0,11	0,02
Soya milk products	0,01	-0,11
Nuts and raisins	0,25	0,00
Crackers	0,12	0,00
Savory snacks	0,31	0,41
Dairy drinks with sugar	0,04	0,34
Light drinks	0,02	0,07
Nutrients	Pearson's correlation coefficient	
Total energy, mean (kcal/d)	0.7**	0.4**
Protein (E%)	0.3**	-0.2**
Fat (E%)	0.2**	0.1*
Carbohydrates (E%)	-0.3**	0.1*
Mono- and disaccharides (E%)	-0.2**	0.1**
Fibre (g/MJ)	0.7**	-0.1**

Extraction Method: Principal Component Analysis. Rotation Method: Varimax with Kaiser Normalization. Rotation converged in 3 iterations.
Factor loadings >±0.3 highlighted. ** p<0.01, *p<0.05

Cross-sectional and prospective associations between dietary patterns and overweight at 3 and 10 years

At 3 years no associations between the two dietary patterns and overweight were observed (Table 3). At 10 years (Table 4), a 1 SD higher score for the 'ultra-processed foods' pattern was positively associated with 1.36 times (95% CI: 1.14, 1.61) higher odds for overweight (crude model). This association remained statistically significant after adjusting for confounders (OR 1.30; 95% CI: 1.08, 1.57). Results from the sensitivity analyses including overweight definition according to the WHO were comparable to the main results at both ages (Tables S2, S3).

Table 3. Associations between dietary patterns and overweight at 3 years (N=938).

	Overweight at 3 years*					
	Model 1, crude			Model 2, adjusted		
	OR	95% CI	p-value	OR	95% CI	p-value
Dietary pattern						
Pattern 1: 'minimally processed foods'	1.07	0.89, 1.28	0.46	1.10	0.91, 1.33	0.31
Pattern 2: 'ultra-processed foods'	1.02	0.85, 1.23	0.67	0.94	0.77, 1.15	0.54

* defined as BMI-sds >1.310 for boys and >1.244 for girls according to Cole and Lobstein [29]. Both pattern scores were used as determinants simultaneously, in order to adjust for the adherence for the other pattern. Model 2 is adjusted for maternal age, pre-pregnancy BMI, parity, ethnicity, maternal smoking during pregnancy, educational level, birth weight and gestational age.

Table 4. Associations between dietary patterns and overweight at 10 years (N=938).

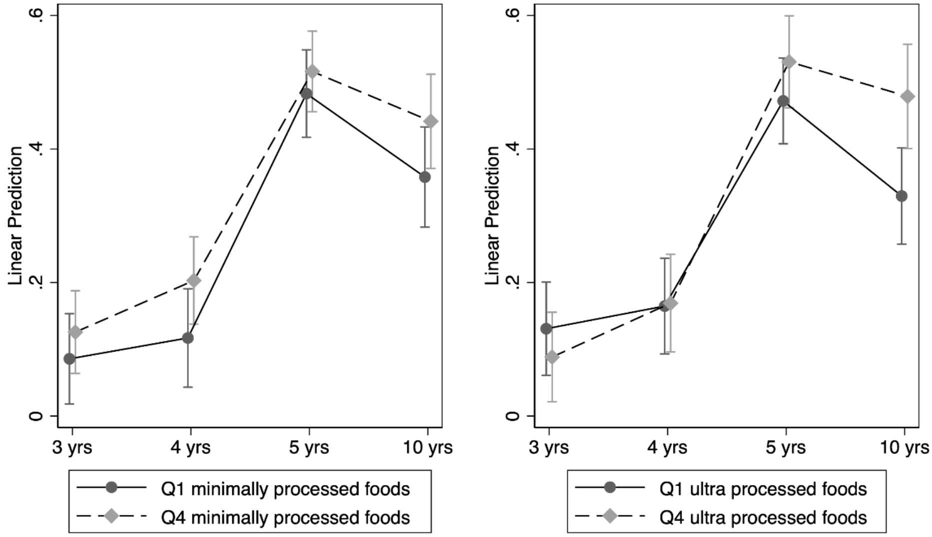
	Overweight at 10 years*					
	Model 1, crude			Model 2, adjusted		
	OR	95% CI	p-value	OR	95% CI	p-value
Dietary pattern						
Pattern 1: ‘minimally processed foods’	0.99	0.84, 1.18	0.94	1.03	0.86, 1.24	0.74
Pattern 2: ‘ultra-processed foods’	1.36	1.14, 1.61	0.001	1.30	1.08, 1.57	0.006

* defined as BMI-sds >1.310 for boys and >1.244 for girls according to Cole and Lobstein [29]. Both pattern scores were used as determinants simultaneously, in order to adjust for the adherence for the other pattern. Model 2 is adjusted for maternal age, pre-pregnancy BMI, parity, ethnicity, maternal smoking during pregnancy, educational level, birth weight and gestational age.

BMI-sds development

Children with a high adherence (quartile 4) to the ‘minimally processed foods’ pattern showed higher BMI-sds development between 3 and 10 years compared to those with a low (quartile 1) adherence (Figure 1, left panel). The differences were significant at 4 and 10 years ($p<0.05$; Table S4). Children with a high adherence (quartile 4) to the ‘ultra-processed foods’ pattern had a BMI development towards a higher BMI-sds from 5 years onwards, than children with a low adherence (quartile 1) to this pattern (Figure 1, right panel). This difference was statistically significant at 10 years ($p<0.001$; Table S4).

Figure 1. Linear predicted values for BMI-sds development between 3 and 10 years of age, adjusted predictions with 95% CIs (N=1233).



Predictions based on mean values for ultra processed foods (left panel graph) and minimally processed foods (right panel graph), respectively, and mean values for all covariates. Both pattern scores were used as determinants simultaneously, in order to adjust for adherence to the other pattern.

Discussion

In this study conducted in Dutch children aged 3 years at baseline, two dietary patterns which we labelled as ‘minimally processed foods’ and ‘ultra-processed foods’, respectively, were identified. We observed that a greater adherence to the ‘ultra-processed foods’ pattern was associated with a statistically significantly increased risk of overweight and development of a significantly higher BMI-sds up to 10 years. No cross-sectional associations of the dietary patterns and overweight at 3 years were observed.

Most previous studies have identified a pattern featuring a mixture of nutrient-poor, low-fibre ultra-processed foods, often labeled either as ‘processed’ or ‘junk food’ pattern [7]. In our study, the ‘ultra-processed foods’ pattern was not cross-sectionally associated with overweight at 3 years, which is in line with some [9, 11, 13] but not all [8, 10, 12] previous cross-sectional studies in young children. However, cross-sectional studies, where dietary intake and weight status are assessed at the same time, do not allow to make conclusions of the causality of the associations.

In contrast to the cross-sectional findings, our prospective findings on ‘ultra-processed foods’ and overweight development up to age 10 were in line with several previous prospective studies in children [14-17]. In these studies, a high adherence to a similar pattern was positively associated with the development of obesity, higher BMI [14] or other adiposity measures [14, 16] during childhood. Previous prospective studies assessing dietary patterns among young children (2 to 5 years), showed in contrast to our results, that a 'processed' or 'junk' pattern was not associated with obesity [18], or that the association with BMI increase was observed only among girls [17]. One possible explanation why we, unlike the other studies, found an association between the 'ultra-processed foods' pattern and the development of overweight and BMI-sds, may be that our study included a longer follow-up. The follow-up time in the other studies (2 to 3 years) might have been too short for obesity to have manifested at such a young age. Furthermore, some studies [16, 37] suggested that a 'junk food' diet at younger age may not lead to weight gain in the long term due to counter regulation of energy intake, since young children may compensate for high energy intakes from junk food at subsequent eating occasions. Our results suggest that this may not be the case as we showed that children as young as 3 years with a high adherence to an ultra-processed dietary pattern are at risk for developing overweight during childhood.

The 'minimally processed foods' pattern identified in our study indicated a high consumption of fruits, vegetables, fish and whole-grain bread, as endorsed by the Dutch dietary guidelines [38]. Nevertheless, this pattern also showed relatively high intakes of foods considered less healthy, but traditionally consumed by Dutch children, such as fried potatoes, meat and savory snacks. The 'minimally processed foods' pattern describes a combination of high factor loadings from two patterns described in previous studies: 'traditional' (meat, vegetables and potatoes) [8, 9, 12] and 'healthy' (fruit, vegetables and fish) [39]. In our study, this dietary pattern was not associated with overweight cross-sectionally or prospectively, which in line with some [9, 10] but not all previous studies [8, 11]. However, we also observed that children with a high adherence to this pattern had a somewhat higher BMI-sds at 4 and 10 years, but not at 5 years. Although we do not have a clear explanation for this finding, one other prospective study [39] found that a 'healthy' dietary pattern at 5 years was positively associated with weight development between 5 and 10 years.

A diet high in ultra-processed foods such as sugary drinks, crisps and savory snacks can comprise healthy growth in different ways. These types of foods are high in added sugars and/or fats, contain low levels of fibre/nutrients and have a high energy density [40]. In addition, such foods and beverages are also highly palatable and tend to be eaten at a fast rate [41]. A high palatability of the foods disrupts the innate appetite control [42], leading to greater energy consumption and weight gain [43]. Additionally, a fast eating rate in combination with a high energy density is suggested as a plausible mechanism by which increased consumption of highly palatable foods promotes higher body weight [44]. Part of the association between the 'ultra-processed foods' pattern and overweight may be also explained by the lack of fruits, vegetables and other nutrient/fibre-rich foods, which was also evident in the ultra-processed pattern observed in our study. Our results suggest that a dietary pattern high in energy-dense, low-fibre ultra-processed foods during toddlerhood seems to be more strongly associated with the development of childhood overweight than a more healthy diet including whole foods [45].

This study has several strengths. The data analyzed come from a large population-based cohort, with a relatively high retainment rate. The study population was representative of the educational level of the general Dutch population. Our study included a follow-up period of 7 years, with BMI measurements available at several timepoints. To the best of our knowledge, our study includes the longest follow-up so far among studies on dietary patterns in young children. For deriving the dietary patterns, we used a validated FFQ, which also assessed information on portion sizes. Additionally, the analyses were adjusted for several known confounders, however information on sedentary- and physical activity was not available. In the GECKO Drenthe cohort, objectively measured moderate-to-vigorous physical activity at 5–6 years of age was not associated with overweight [46].

Some limitations should also be acknowledged. First, compared to the full cohort population (ever active participation), the group of low educated mothers were less represented in the study population (due to missing FFQ data), which may have introduced some bias on educational level. However, the majority of the missing data on FFQ's was due to logistical aspects and can be regarded missing completely at random. Reassuringly, means of important weight-related outcomes and confounders of the included children were very comparable to the full cohort population. Second, since ethnic minorities were slightly underrepresented, our findings may therefore be less representative of the general Dutch population. Third, like in all dietary studies, recall bias and misreporting are potential sources of bias. Especially, food items high in sugar and fat, considered 'unhealthy', may have been underreported by the parent more often compared to 'healthy' foods [47]. This may have attenuated the association between the dietary patterns and the outcomes. Fourth, during the process of the PCA, certain decisions, such as the number of dietary patterns and the food group classification, are prone to subjectivity. Finally, as in all observational studies, we cannot rule out the possibility of residual confounding.

In conclusion, this study in Dutch children indicates that at 3 years of age, a dietary pattern including high intakes of white bread, crisps, savory snacks and sugary drinks, is associated with a higher risk of overweight and a higher BMI-sds later in childhood. In line with the current dietary guidelines, our results suggest that limiting the consumption of energy-dense and nutrient-poor ultra-processed foods during childhood may be important for the prevention of childhood overweight and obesity.

Supplementary information

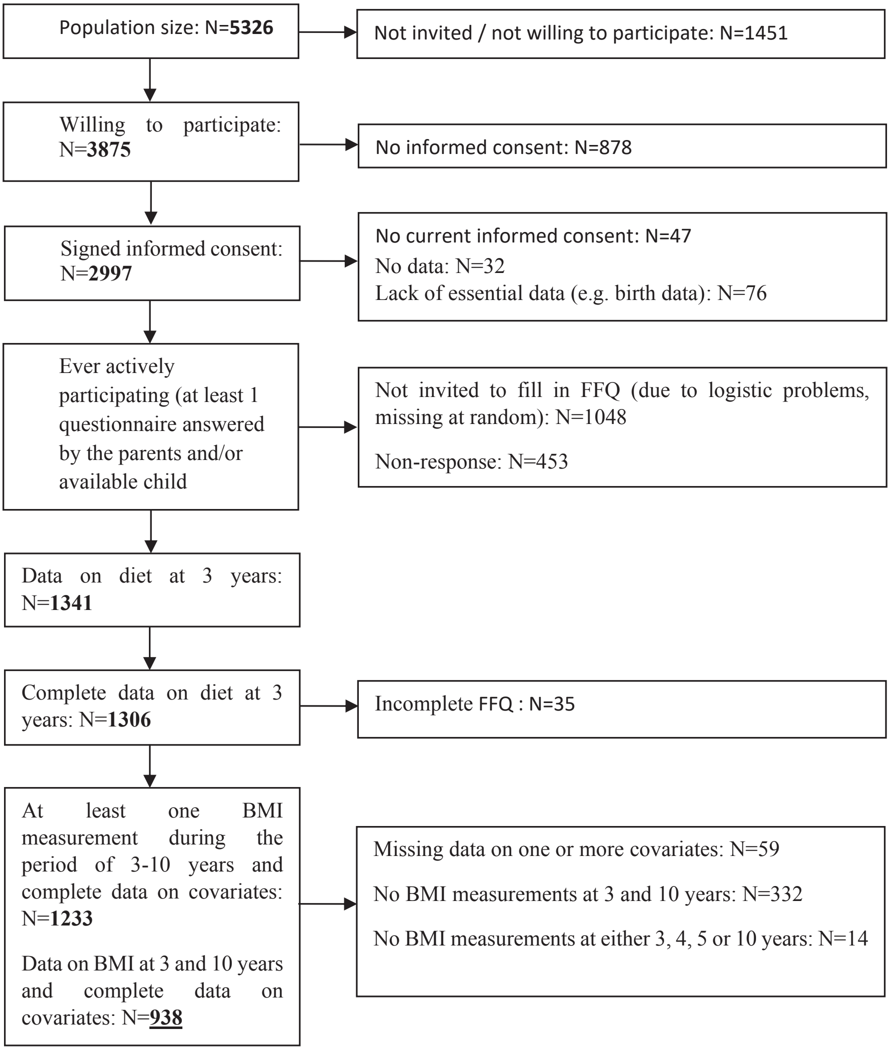


Figure S1. Selection of the study population.

Table S1. Food grouping for the PCA.

Food group	Food items
Water	Water and tea (without sugar)
Vegetables	Raw and cooked vegetables and beans
Fruit	Fruit and fruit compote
Whole-grain bread	Whole-grain bread, rye bread, whole-grain crackers
Fish	Fish, shellfish and fish sticks
Sauces	Ketchup, mayonnaise, brown sauce and other sauces
Potatoes	Plain potatoes (excluding fried or baked potatoes)
Eggs	Fried or baked potatoes and French fries
Fried and baked potatoes	Water and tea (without sugar)
Savory dishes	Composite dishes
Chicken	All processed and non-processed chicken/poultry (except chicken nuggets)
Meat	All processed and non-processed meat (except those included in 'savory snacks' group)
Milk and buttermilk	Plain milk (full-fat, semi-skimmed or skimmed) and plain sour milk
Dairy desserts	Yogurt (full-fat, semi-skimmed or skimmed), custard, pudding and cream
Crisps	Crisps and prawn crackers
Cheese	Cheese and cream cheese
Cakes and confectionery	Cakes, pancakes, wafels, pastry, ice cream, candy and chocolate
Butter and oil	Butter, oil and margarine
White bread	White bread, toast, currant bread, baguette, croissant
Breakfast cereals	Cornflakes, breakfast cereals and muesli
Added sugar	Sugar, honey or syrup added to foods and drinks
Sweet bread toppings	Jam, chocolate spreads, peanut butter, sprinkles
Sugar-sweetened beverages	Soft drinks, fruit drinks and lemonade with sugar
Cookies	Cookies, biscuits and muesli bars
Rice and pasta	Rice and pasta
Vegetarian meat substitutes	Meat substitutes made of soy, quorn or tahoe
Porridge	Oatmeal and wheat porridge

Soya milk products	Soy milk, soy dessert, flavoured soy milk
Nuts and raisins	Peanuts, nuts and raisins
Crackers	Waffles, rusks, crackers and soup sticks
Savory snacks	Pizza, hamburgers, sausage rolls, chicken nuggets, meat croquettes and hot dogs
Dairy drinks with sugar	Yoghurt drinks with sugar and chocolate-flavored milk
Light drinks	Sugar-free, artificially sweetened flavored drinks

Table S2. Associations between dietary patterns and overweight at 3 years, sensitivity analysis using the WHO definition of overweight.

	Overweight at 3 years*					
	Model 1, crude			Model 2, adjusted		
	OR	95% CI	p-value	OR	95% CI	p-value
Dietary pattern						
Pattern 1: 'minimally processed foods'	0.77	0.53, 1.12	0.17	0.78	0.52, 1.15	0.20
Pattern 2: 'ultra-processed foods'	1.47	1.03, 2.10	0.04	1.36	0.92, 2.02	0.12

* defined as BMI-sds according to. Both pattern scores were used as determinants simultaneously, in order to adjust for the adherence for the other pattern. Model 2 is adjusted for maternal age, pre-pregnancy BMI, parity, ethnicity, maternal smoking during pregnancy, educational level, birth weight and gestational age.

Table S3. Associations between dietary patterns and overweight at 10 years, sensitivity analysis using the WHO definition of overweight.

	Overweight at 10 years*					
	Model 1, crude			Model 2, adjusted		
	OR	95% CI	p-value	OR	95% CI	p-value
Dietary pattern						
Pattern 1: 'minimally processed foods'	1.02	0.88, 1.19	0.77	1.06	0.90, 1.25	0.49
Pattern 2: 'ultra-processed foods'	1.28	1.10, 1.50	<0.01	1.21	1.02, 1.44	0.03

* defined as BMI-sds. Both pattern scores were used as determinants simultaneously, in order to adjust for the adherence for the other pattern. Model 2 is adjusted for maternal age, pre-pregnancy BMI, parity, ethnicity, maternal smoking during pregnancy, educational level, birth weight and gestational age.

Table S4. Mean differences in estimated BMI-sds for quartile of adherence (Q1 vs. Q4) to the dietary patterns at each age, derived from the random effects linear regression model (N=1233).

	Pattern 1: 'minimally processed foods'		Pattern 2: 'ultra-processed foods'	
	Mean difference (95% CI)	p-value	Mean difference (95% CI)	p-value
Age (years)				
3	-0.04 (-0.11, 0.03)	0.25	0.04 (-0.04, 0.12)	0.31
4	-0.09 (-0.16, -0.01)	0.02	0.00 (-0.09, 0.08)	0.92
5	-0.03 (-0.10, 0.03)	0.33	-0.06 (-0.14, 0.02)	0.15
10	-0.08 (-0.16, -0.01)	0.03	-0.15 (-0.23, -0.06)	0.001

Both pattern scores were used as determinants simultaneously, in order to adjust for the adherence for the other pattern. Model 2 is adjusted for maternal age, pre-pregnancy BMI, parity, ethnicity, maternal smoking during pregnancy, educational level, birth weight and gestational age.

Table S5. Associations between dietary patterns and BMI-sds development between 3 and 10 years of age (N=1233).

	B	95% CI	p-value
Pattern 1: 'minimally processed foods'	0.03	-0.02, 0.09	0.26
Pattern 2: 'ultra-processed foods'	-0.03	-0.09, 0.03	0.31
Age (years)			
4	0.06	0.02, 0.10	<0.01
5	0.39	0.35, 0.44	<0.001
10	0.30	0.24, 0.36	<0.001
Age x Pattern 1: 'minimally processed foods'			
4	0.04	0.00, 0.08	0.06
5	-0.01	-0.05, 0.03	0.78
10	0.04	-0.02, 0.10	0.22
Age x Pattern 2: 'ultra-processed foods'			
4	0.04	0.00, 0.07	0.07
5	0.08	0.03, 0.12	<0.001
10	0.15	0.08, 0.21	<0.001

Both pattern scores were used as determinants simultaneously, in order to adjust for the adherence for the other pattern. Model is adjusted for maternal age, pre-pregnancy BMI, parity, ethnicity, maternal smoking during pregnancy, educational level, birth weight and gestational age.

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Chapter 6

General discussion

The main aim of this thesis was to investigate associations of early feeding practices with weight-related outcomes, with a focus on overweight and obesity during childhood. Feeding practices related to infant milk feeding, complementary feeding as well as dietary patterns during toddlerhood, were examined. A secondary aim was to understand these associations across different ethnic groups. To this end, data from 3 Dutch population studies in children from 2 different regions of the Netherlands were used; two studies in the urban area of Amsterdam and one study in a northern province and relatively rural area of the Netherlands (Drenthe). This chapter provides a summary and interpretation of the findings, and a discussion related to the findings as well as the methodological considerations. Furthermore, overall conclusion and implications for future research and public health are being provided.

Summary and interpretation of the findings

Main aim: Overall associations of early feeding practices and weight-related growth outcomes during early childhood

Infant feeding

In Chapters 2 and 4, the associations of breastfeeding (BF) duration with BMI-sds and risk of overweight (including obesity) during childhood were studied, using data from two different population studies (ABCD and TIBET). The findings described in **Chapter 2** suggested that in the overall Amsterdam population, exclusive breastfeeding (EBF) for at least for 6 months was associated with lower BMI-sds and decreased risk of overweight at 5-6 years of age compared to EBF less than 6 months. However, when the analyses were stratified by maternal characteristics such as ethnicity, education or BMI, the associations were not consistent across subgroups. This may imply that among certain groups, other risk factors for childhood overweight, such as diet, may counter the beneficial effect of BF. In **Chapter 4**, we did not observe an association between full BF duration and BMI-sds between 2 to 5 years. The different findings from Chapters 2 and 4 may be explained by heterogeneity in several study characteristics, for instance differences in the population (sample size and selection criteria), reference group as well as exposure definition, as EBF or full BF (defined as BF without additional formula feeding). Furthermore, the associations of BF duration and weight outcomes may also differ depending on the different ages at BMI measurement of the children, since the impact of early life exposure on BMI outcomes may become more apparent after the adiposity rebound [1,2]. Inconsistent findings have also been described in the literature; although there is evidence of a small beneficial association between BF duration and childhood overweight [3,4], other studies suggested no association after adjustment for confounding factors [5]. Intervention studies also showed no effect of EBF on weight of children [6]. Overall, the results from this thesis suggest that providing EBF for at least for 6 months is associated with lower BMI and lower risk for childhood overweight, yet the association appears to depend on the population characteristics.

Associations of timing of complementary feeding (CF) with the weight-related growth outcomes during infancy and childhood were investigated in Chapters 2, 3 and 4. In **Chapter 2** we found that CF introduction at or after 5 months was associated with lower BMI-sds at 5–6 years compared with CF introduction before 5 months and the association differed according to subgroups (based on certain characteristics of the mother, e.g. ethnicity, education or BMI). However, in **Chapter 4**, timing of CF was not associated with BMI-sds during 2 to 5 years of age. A potential explanation of finding no association in Chapter 4 could be due to the limited sample size. In addition, the fact that several CF factors were investigated simultaneously may have attenuated potential association between timing of CF and BMI-sds. These findings contribute to the existing inconsistent evidence from the literature on the timing of CF and childhood overweight [7,8]. Furthermore, in addition to investigating timing of CF as a single factor, some studies suggested that the effect of timing of CF on growth outcomes may differ depending on the type of milk feeding [9,10]. In **Chapter 3**, we found that infants who received exclusive formula-feeding and early CF (before 6 months), were more likely to follow a high BMI trajectory during the first year of life (relative to the WHO BMI reference percentiles) compared to infants receiving EBF during the first 3 months of life in combination with late CF introduction (at or after 6 months). Our findings suggest a potential long-term effect on growth since the high BMI trajectory indicated a higher overweight risk at 5 to 6 years of age. It is plausible that the feeding pattern characterized by formula feeding in combination with early CF may lead to higher energy (and protein) intakes and subsequently to excessive weight (BMI) gain compared to infants receiving EBF and late CF [11]. Yet previously reported differences in CF quality between formula- and BF infants could have also explained our findings, however we lacked such data to explore this [12]. It should be noted that the observed associations between infant feeding and growth may also be caused by reverse causality, which will be discussed later in this chapter. Overall, the results from this thesis showed that CF introduction after 6 months was associated with lower BMI and overweight risk during childhood, however the associations were not consistently observed across all populations. Timing of CF has important implications for the BMI trajectory during the first year of life, particularly among formula-fed infants.

Besides the timing of CF and BF duration, associations of other infant feeding factors, such as milk- and CF feeding frequency as well as variety of CF with childhood BMI were investigated in **Chapter 4**. Of all the factors, only high CF variety (defined as 3 food groups or more) at 6 months of age was significantly associated with higher BMI-sds during childhood. The reason why no association between milk feeding frequency and BMI was observed could be due to the fact that we did not separate breast- and formula feeding frequency, which may have a different impact on weight gain, due to the differences both in milk composition as well as the feeding mode. Additionally, several other factors (and their combinations), of which we lacked information on, determine the intake of infant formula within a feeding occasion; these include the duration of feeding occasion as well as the flow of the milk from the feeding bottle [13]. Furthermore, the role of feeding frequency (both milk and CF) may be more important for weight gain during infancy. Although high food variety has been associated with higher energy intake [14 15] and higher BMI [16] among adults and older children, evidence in young children is limited. It is likely that our findings on high CF variety and higher BMI-sds are explained by high variety of specifically energy-dense foods rather than variety in all foods [15]. Since a variety of 'healthy' foods (e.g. vegetables) may be beneficial, but a large variety of palatable high-energy dense foods and drinks may be unfavorable, further investigation into 'healthy' and 'unhealthy' variety is of importance [15]. Although we did not have detailed information on the types of foods provided, there was some indication that children with a high CF variety also seemed to be offered more energy/protein dense foods, such as yogurt and savory snacks, compared to children with a low food variety. Even though most current infant feeding recommendations include advice to increase the variety of healthy foods such as vegetables, as the child grows older, often no detailed guidance is provided. In conclusion, we found that a high food variety during the CF period is associated with higher BMI-sds during childhood. In light of our findings, further research is needed to understand how food variety during the CF period may influence BMI development.

Dietary patterns during toddlerhood

In addition to the infant feeding practices studied in Chapters 2-4, the role of diet during toddlerhood as a potential determinant for later life overweight was investigated using data from the GECKO cohort (**Chapter 5**). Dietary patterns were identified at age 3 and cross-sectional as well as prospective associations with childhood overweight were examined. Two dietary patterns were identified and labelled as 'minimally processed foods' and 'ultra-processed foods'. It was found that higher scores on the 'ultra-processed' pattern, which indicated high intake of foods such as crisps, white bread and sugar-sweetened beverages (SSB), was associated with risk of overweight and higher BMI-sds prospectively up to age 10 years. The other identified pattern 'minimally processed foods', was not consistently associated with these outcomes. This may be since this pattern indicated high intakes of both healthy foods e.g., vegetables, fish and whole-grain bread, as well as less healthy foods such as savory snacks. Although some studies indicated that dietary patterns remain relatively stable as the child becomes older [17-19], we did not have information to assess this. Future studies may provide more insights as to whether the identified dietary patterns track later into childhood. Overall, these findings highlight that in addition to infant feeding practices, diet quality during toddlerhood is an important determinant for the development of BMI and overweight during later in childhood.

Secondary aim: The role of infant feeding in ethnic differences in weight-related outcomes during childhood

Early life feeding has been suggested as an important determinant for ethnic disparities in childhood overweight and obesity. In addition to the primary focus on associations between infant feeding and weight-related growth outcomes, a secondary focus of this thesis was to investigate the associations among different ethnic groups with varying overweight risk (Chapters 2, 3 and 4). As with previous studies in the Netherlands [20,21], we found that children from Turkish and Moroccan descent are at increased risk for having rapid BMI development during infancy (Chapter 3) and childhood overweight (Chapter 2 and 4) compared to children of Dutch descent. In **Chapter 3** it was found that compared to Dutch children, children of Turkish/Moroccan descent were more likely to have a high BMI pattern compared to children of Dutch descent despite of their feeding pattern. Although previous studies suggested that rapid BMI gain during the first year of life among Turkish/Moroccan descent children may be is attributable to mixed feeding [22,23], we did not observe this. However, it should be noted that in this study, mixed feeding was defined based on the duration of EBF and timing of introducing formula feeding, as no detailed information on the amount or the preparation of formula feeding was available. In line with these findings, we found no associations of EBF, full BF duration or CF timing with the weight-related outcomes during childhood among children of Turkish/Moroccan ethnic descent (Chapters 2 and 4). Interestingly, in **Chapter 2**, children of Turkish descent had the longest duration of EBF but also the highest risk for childhood overweight from all risk groups. Studies from other Western countries have reported similar findings among ethnic minority populations [24,25]. A possible explanation for our findings may be that in these populations EBF coincides with less healthy dietary practices. Among children of Turkish descent in the Netherlands a high adherence to 'full-fat' and an unfavorable 'snacking' pattern have been described [26], during childhood, however studies during the CF period among these populations are lacking. In **Chapter 4**, we showed that a large proportion of mothers of Turkish descent seem to already provide higher variety (more than 3 food groups) of foods during the CF period already at 6 months of age, including high-energy/protein foods such as yogurt and savory snacks. However, high CF variety explained a small fraction of the observed ethnic differences in BMI from 2 to 5 years. Moreover, since the group of infants of Dutch descent with a high CF variety was small, this finding should be interpreted with caution. Future studies should investigate the role of dietary quantity/quality during the CF period in explaining the development of overweight among ethnic minority children. It can be concluded that the specific feeding factors investigated in this thesis did not play a major role in explaining the observed ethnic differences in weight-related outcomes. In addition to diet quantity and quality, also other lifestyle-related behaviors of the child as well as the mother (during both pre- and postnatal periods), remains to be further investigated as possible factors that explain ethnic inequalities in childhood overweight [27,21,28].

It is of importance to note that ethnic disparities in overweight and other health outcomes are associated with other inequalities that may coincide with ethnicity [29]. Most importantly, ethnic inequalities seem to be largely explained by complex variables regarding social, cultural, and economic factors [30]. In general, ethnic minority groups have a lower socio-economic status than the more privileged 'majority' population in the host country [31]. Low socioeconomic position may mean low levels of education and low income but can also imply effects of other social determinants of health. These may include complex factors such as health literacy, access to health care, social support, employment, occupation, reduced access to healthier foods and high levels of chronic stress [32]. A combination of such factors is likely to contribute to the higher rates of overweight and obesity among ethnic minority groups. Besides these factors, also specific cultural attitudes to feeding and/or perceptions of optimal body size of babies may, at least in part, explain disparities in overweight between ethnic groups [33,34]. For instance, mothers of Turkish or Moroccan descent frequently underestimate the actual weight status of their child at the age of 5 to 7 years [34]. This emphasizes the importance of creating awareness among parents about the weight and size of their infants and children, particularly in groups at risk for overweight. Other factors such as cultural identity, family composition and lifestyle preferences have also been proposed [35]. Therefore, understanding the broader and complex picture of determinants in ethnic inequalities in childhood overweight is crucial.

Methodological considerations

Certain methodological considerations need to be considered when interpreting the results of the studies described in this thesis. In the following section, considerations related to the assessment of the outcome and exposure as well as the study design are discussed.

Diagnostics and definition of overweight and obesity in children

As outlined in the General Introduction (Chapter 1), several definitions and cut-offs for defining overweight and obesity in children exist. How the choice of outcome (BMI compared to other methods), and the chosen BMI cut-off values to define overweight/obesity applied, may have influenced our findings are discussed in this section.

BMI vs. other methods to define overweight and obesity

Although direct measures of body fatness that can estimate both fat- and fat-free mass are considered the gold standard measures of adiposity [36], they are costly and challenging to use in large epidemiological studies and daily clinical practice. Furthermore, body fatness is difficult to measure in infants and young children because accurate techniques are not often feasible to be used for young children as they require a high degree of subject compliance. In the studies described in this thesis, BMI was used as an outcome measure. Since BMI cannot distinguish between fat- and fat-free mass, misclassification of overweight (and obesity) remains a potential issue in our studies. Although BMI-for-age has a high specificity, it is a less sensitive method to assess adiposity in children, especially young children [37,38]. Therefore, children who truly have a high fat mass but low fat-free mass (and therefore normal BMI), may have been misclassified as non-overweight [39]. Conversely, children with a high fat-free mass (especially short muscular boys) may have been misclassified as having overweight. We expect that such misclassification would be non-differential but may have somewhat attenuated the observed associations. During infancy, weight-for-length is another appropriate measure of weight relative to height in young children, but the disadvantage is that it is not age-adjusted. Furthermore, a high BMI compared to weight-for-length during infancy has been shown to be more strongly associated with childhood obesity [40]. Future studies may benefit from using more accurate measurements of body fatness e.g., a dual-energy X-ray absorptiometry (DEXA) scan in older children.

BMI-based cut-offs to define overweight and obesity in children

In Chapters 2-5 BMI measurements were used to define overweight (and obesity) during childhood. In children, specific age- and sex-standardized BMI cut-off points, albeit somewhat arbitrary, are used to distinguish overweight and obesity [41]. In this thesis, both the BMI cut-offs from the WHO [42] (Chapters 2-5) and the International Obesity Task Force (IOTF) [43] (Chapter 5) were used. These two criteria differ in the reference population from which they were derived and how they define overweight and obesity. The WHO cut-off points were defined based on percentiles in population studies, and thus depend on the BMI distribution of the population [42]. Furthermore, the WHO criteria for children below 5 years of age and above 5 years differs, leading to different estimates around this age [44]. The IOTF cutoff points were based on BMI trajectories and derived from the cut-off points that match the criteria for adult overweight and obesity [45]; these were later extended to match SD scores and centiles [43]. These, in turn, are based on their association between adult BMI and risk of morbidity and all-cause mortality [46,47]. These two criteria lead to different estimates of overweight and obesity in the study population [48,49]. This was also evident in Chapter 5, where the percentage of children with overweight varied substantially depending on the definition used. For instance, at 3 years of age, using the WHO criteria for overweight leads to relatively lower overweight prevalence compared to the IOTF criteria. However, at 10 years the situation is the opposite; more children were considered having overweight with the WHO criteria compared to the IOTF. Despite of these differences, associations between dietary patterns and overweight were fairly similar using the two different BMI cut-offs. An explanation could be that a higher adherence to the 'ultra-processed' dietary pattern is associated with an overall increase in BMI, including also children at the upper end of the normal BMI range. Overall, this suggests that the use of BMI cut-offs warrants careful consideration as it has implications for the number of children classified as overweight/obese and potentially affects the estimations of future disease risks in the population.

Assessment of ethnicity and other maternal characteristics

In the studies described in this thesis, ethnicity was defined as the country of birth of the mother (or maternal grandmother). However, country of birth does not cover all aspects of ethnicity, such as culture and ethnic identity. Ethnic self-identification has been suggested as an alternative indicator [50]. We also did not distinguish between first- or second-generation immigrants. The level of family acculturation in Dutch society may also have been relevant for examining differences in infant feeding practices across ethnic groups but this was not consistently measured in the different studies. In all studies, we used data on maternal education as a proxy of socioeconomic status. However, educational level does not fully capture the material and financial aspects of socioeconomic status [51]. In the ABCD and GECKO cohorts, data on maternal pre-pregnancy BMI (weight and height) were self-reported. As height may have been overestimated and weight underestimated, as a result, BMI may have been underestimated. Since underreporting of weight becomes more exaggerated with increasing BMI [52], potential misclassification of maternal overweight may have been differential. Furthermore, maternal overweight was dichotomized in the analyses based on commonly used international recommendations [53]. Although dichotomizing of covariates can be useful for interpretation purposes, it might also result in underestimation of true associations by loss of information [54].

Assessment of infant feeding and diet during toddlerhood

All studies described in this thesis included prospectively collected data on infant feeding. Therefore, the likelihood of recall bias in these studies is low. In the ABCD cohort, data on infant feeding was obtained prospectively during the youth health care (YHC) evaluations, which parents were routinely invited to complete for their children at around the ages of 1–4, 6, 7.5, 9 and 11 months. However, some (~20%) of the missing information on EBF duration and timing of CF was collected retrospectively at the age of 5 years. These data have been considered reliable by means of intra-class correlation coefficient (>0.75) [22]. Any potential recall bias is unlikely to be related to ethnicity or the specific infant feeding patterns, and, therefore, is not expected to bias our on ethnic-specific results.

In most of our studies, the available infant feeding data were categorical or certain cut-offs were applied. These were mostly based on the current infant feeding guidelines, such as the WHO. Although investigating EBF duration of 6 months would seem ideal considering the recommendations, this is not often practiced in countries such as the Netherlands. Therefore, in Chapter 3, in order to reach sufficient statistical power in the analyses, dichotomization of EBF duration of 3 months was applied. The sensitivity analyses comparing different cut-offs for EBF (3 or 6 months) indicated some differences in the results, which could be explained by the different characteristics of the reference groups. In Chapters 2 and 4, different cut-offs for the timing of CF were used, either at 5 or 6 months. However, sensitivity analyses however indicated similar results regardless of the chosen cut-off. Furthermore, in addition to the choice of cut-off, different perceptions among parents may exist as to what they consider as the start of CF. Even when the same definition of timing of CF was used across the studies, we cannot exclude the possibility that parents may have interpreted the question regarding 'first introduction of CF' differently; either as tasting (or introduction of possible allergens) or a real substitution of a milk feeding.

In Chapter 5, the dietary patterns in toddlerhood were constructed using data obtained by a food frequency questionnaire (FFQ) at age 3 years. FFQs measures habitual intake rather than on specific days, making it suitable to estimate long-term dietary intake [55]. Furthermore, FFQs are suitable for large epidemiological studies due to the low burden to participants and ease of processing. The FFQ used in the GECKO cohort was validated against the gold standard of doubly labelled water in a group of 4 to 6-year-old children [56]. The main limitation of an FFQ is that it relies on subject's memory and is thus prone to recall bias [57]. Additionally, an FFQ can be hampered by an intentional misreporting of the consumption of certain foods; foods that are perceived 'unhealthy' are underreported more often than 'healthy' foods [58]. Underreporting is also more common among individuals with overweight and obesity [59]. Misreporting may also occur when assessing the diet of young children since parents may not be fully aware of their child's diet outside the home. Parents may have also given socially desirable answers, although in the GECKO study the anonymity of the FFQ was assured. These type of measurement errors in the obtained FFQ data could lead to differential misclassification of exposure and potential to over- or underestimate of the associations. Although we expect that any measurement errors are unlikely to bias the prospective associations due to the long follow-up, however, this possibility cannot be ruled out.

Dietary patterns during toddlerhood were investigated in Chapter 5. Analyzing dietary patterns allows to assess the whole diet and takes into account the correlation between foods and nutrients [60]. For example, children who consume SSB typically have a higher consumption of snack foods [61]. Dietary patterns can be obtained using either an 'a priori' or an 'a posteriori' approach [60]. An 'a priori' approach involves a predefined diet, to which the adherence of the studied population is being described. In Chapter 5 the 'a posteriori' approach was used. This approach is data driven and uses methods, such as the principal component analysis (PCA), which allow the identification of common dietary patterns from the data. The main advantage of such method is that it reflects the intakes of the study population, yet, a major disadvantage is that it does not always identify patterns that can be easily identified as 'healthy' or 'unhealthy [62] and it is difficult to compare between studies. Another limitation is that it includes certain decisions that are partly subjective, such as selecting the number of dietary patterns to extract or combining data on single food items into food groups [63]. Despite of the fact that the selected food grouping was performed according to similarities in the nutritional composition of the food items, the chosen approach may have attenuated the observed associations between the dietary patterns and the outcomes.

6

Observational study design

All studies described in this thesis are based on observational cohort studies. In prospective birth cohorts, such as the ABCD or GECKO, studying infant feeding and growth outcomes during childhood are possible among large populations. Prospective studies have several advantages over retrospective or cross-sectional studies. These include data on exposures which are collected prior to the development of the outcome. The prospective birth cohort studies described in this thesis included data on infant feeding which was collected during infancy prior to the development of overweight or obesity. Furthermore, several measurements on weight and length were available during infancy and later in childhood which allowed the identification of BMI trajectories as well as record of several BMI measurements during the follow-up. Across the different studies, information on several maternal and child covariates was available. The main sources of potential bias occurring in observational studies will be addressed in this section as well as the issue of reverse causality.

Confounding

Confounding is one of the main limitations of observational studies [64]. A covariate is considered to be a potential confounder when it is associated with both the determinant and the outcome, and not part of the causal pathway from determinant to the outcome [65]. In our studies, we attempted to control for potential confounding by adjusting for several known confounders from the existing literature, such as maternal BMI, education, birth weight and gestational age [66]. Unfortunately, information on certain known confounders of the mother or the child were not available. For instance, in Chapter 4, maternal BMI was not available from a large group of mothers (>30% data missing). However, results in a sub-sample which included data on maternal BMI showed similar results. In Chapter 5, no information on the child's physical activity or sedentary activity was available. As such factors are also associated with later overweight, any bias may have attenuated the overall estimates as well as the ethnic-specific associations.

The validity of an epidemiologic study may also be threatened by residual confounding, which may be caused by either unmeasured confounders or an imprecise measurement of the confounders for which the analysis was controlled for (such as maternal BMI) [7]. For instance, maternal lifestyle factors such as diet or physical activity, for which we lacked data for, are examples of unmeasured confounders, since mothers who breastfeed and introduce CF later are more health-conscious and promote also other healthy habits in their children; this is likely to reduce the risk of developing overweight and obesity [67,68]. In some previous studies, associations of BF duration with childhood weight-related growth outcomes were largely explained by sociodemographic and lifestyle-related factors [69-71]. Furthermore, studies conducted in low- and middle-income countries, where the confounding structures (such as maternal education) are different compared to high-income countries, suggested no association between BF duration and adult adiposity [72]. Altogether, these findings imply that results from observational studies conducted in high-income countries may be partly explained by (residual) confounding related to maternal education and lifestyle [68,73]. It can therefore be expected that our associations may have been attenuated after adjusting for maternal lifestyle factors. Furthermore, although we adjusted for educational level in our analyses, residual (unmeasured) confounding might play a role in the associations, since occupation and household income were not measured. The extent of residual confounding after adjusting for such factors in our studies is unknown.

Effect modification

Effect modification can be defined as a situation in which the association between a determinant and an outcome varies across strata of a third variable, such as sex, BMI or physical activity level. The aim of Chapter 2 was to assess potential effect modification by maternal characteristics; maternal BMI, education, ethnicity and neighbourhood. Since statistical power to detect interactions in small sample sizes is often undesirably low, a-priori stratification was performed to assess the associations of infant feeding with childhood growth outcomes among certain subgroups in Chapter 2. In Chapter 4, effect modification by ethnicity was also explored by means of statistical tests, however no strong effect modification was observed, which could be explained by the small sample size. Furthermore, in the associations of BF duration and weight gain, the mode of delivery of breastmilk, either direct BF or bottle-feeding expressed breastmilk, may be a potential effect modifier since the impact on weight gain may differ [74]. It is suggested that infants fed at the breast are better able to actively suckle and self-regulate compared to bottle-fed infants (regardless of its contents) who are more passive and may not learn to appropriately balance energy intake [75,76]. However, we lacked data on the mode of feeding of the breastmilk. Mode of feeding should thus be taken into account in future studies assessing BF duration and weight-related outcomes.

Causality

A potential problem in observational studies on infant feeding and growth is reverse causation [77]. Causality assumes the temporal precedence of exposure to the outcome (i.e., that changes in infant feeding occur before subsequent infant growth). It is possible that our results on infant feeding patterns and BMI trajectories may be attributed to reverse causality since infant feeding and growth are dynamic processes in which feeding may affect growth, but preceding growth (and body size) may also influence subsequent feeding decisions [78]. For instance, infants who are thinner or grow more slowly (for genetic or other constitutional reasons) may demand less (frequent) feedings and be “satisfied” with their mothers’ breastmilk production which leads to continued BF [77]. It is also possible that parents may perceive their infant’s growth insufficient and, consequently, introduce (additional) formula feeding in order to increase the growth of their baby [78]. Furthermore, an infant’s large size or faster growth has been shown to prompt mothers to introduce CF early [79,80] and, in certain studies, the inverse associations between timing of CF and infant growth were (partially) explained by infant weight gain before CF introduction [81,82]. Therefore, adjusting for growth prior to the feeding exposure is warranted in infant growth studies. Although we adjusted for birth weight in Chapter 3, it is possible that weight gain after birth may still affect the choice of parents to change feeding practices. However, when investigating BMI trajectories during infancy, adjustment for weight (or BMI) during this time period may be undesirable since it is part of the causal pathway and may lead to overadjustment. The impact of reverse causality to our findings is unknown and may have introduced bias to any direction.

Generalizability

As in all epidemiological studies, the generalizability of the results to specific populations should be considered. Often in cohort studies groups with ethnic minority status or low educational level are underrepresented [83] and this should be considered in the light of the studies included in this thesis. In the ABCD study, mothers who initially participated in the study were older, more often nulliparous and more often of Western ethnic descent than eligible women who did not participate [84]. A non-response analysis determining the degree of selective response and selection bias between pregnancy and birth outcomes indicated that selective non-response was present in the study, but selection bias was acceptably low and did not influence the studied birth outcomes. Regarding ethnicity, it can be expected that the results described in Chapters 2, 3 and 4 can be generalized to the Dutch, Turkish and Moroccan descent children within urban regions in the Netherlands. However, due to the small numbers of the participants from other main ethnic groups in the Netherlands, e.g., of Surinamese and African descent, it was not possible to analyze these populations and further research among these populations is warranted. In the GECKO cohort (Chapter 5), the study population consisted mainly of mothers of Dutch ethnic descent which limits the generalizability of the results to other ethnic groups in the Netherlands.

In the ABCD study, the attrition of study participants over the years was towards a more highly educated population [84]. Due to the fact that children from mothers with a lower educational level are more often formula-fed and experience rapid growth in infancy, it may have led to underestimation of the overall associations in Chapter 3. However, we expect that this is unrelated to ethnicity and thus unlikely to bias the ethnic-specific associations. In Chapter 2 we performed stratified analyses by maternal educational level and therefore, these results can be generalized for these population groups as well. In the GECKO cohort, mothers with a low educational level were slightly underrepresented, however, since no differences in any of the weight-related outcomes and confounders compared to the full cohort were observed, this selection is not expected to bias our results. Overall, this cohort provides a good representation of the study area with regard to educational level and overall bias may still be low in comparison with other birth cohorts.

In the TIBET study (Chapter 4), certain exclusion criteria were applied in the participant selection beforehand; premature, non-singleton and small for gestational age infants were excluded. Infants with maternal and/or fetal medical problems described during pregnancy or neonatal medical problems after birth were also excluded. This selection towards a 'healthier' population may limit the generalizability of our results to the general population.

Implications for future research and public health

Implications for future research

Although the findings from this thesis suggest that infant feeding practices related to milk feeding and CF are associated with weight-related outcomes during childhood, well-designed future research is still recommended for certain topics.

First, more detailed information regarding infant milk feeding is required to understand the underlying mechanisms in the associations of specific feeding patterns and infant growth patterns. For this, detailed information on the quantity and preparation of infant formula as well as the feeding method of BF (direct BF or bottled breastmilk) and intakes of formula milk are needed. Furthermore, the role of mixed feeding on infant weight-related outcomes remains controversial [85]. Mixed feeding can be provided in different ways, for instance, either concurrent (providing both breast- and formula milk during one feeding), or subsequent (replacing one BF occasion by formula feeding). It is also possible that formula milk is added to bottled breastmilk. More detailed information on the different feeding practices in addition to formula intake would allow to study the associations of different mixed-feeding practices with infant growth.

Additional research is also required regarding different aspects of CF. First, further clarity of the role of diet quality rather than, or in addition to, the timing of CF in the observed associations is required. As diet gradually changes during the CF period, describing the pattern in transitioning from a milks-only diet to various types of foods, may be important for infant growth patterns. For instance, the timing of introduction of different types of foods, including high-energy, low fibre, ultra-processed foods, should be investigated. Furthermore, since the current evidence on infant feeding and growth is mostly observational, randomized controlled trials focusing on promotion of infant feeding guidelines could be a possible approach. These future directions are essential to optimize infant feeding guidelines and develop effective early-life interventions for prevention of childhood overweight and obesity.

The large ethnic differences in childhood BMI and overweight prevalence found in this thesis, as well as in other studies in the Netherlands [22,86], remain largely unexplained and require further investigation. First, as discussed above, it can be speculated that the diet quality (and quantity) during early childhood may be more important in explaining the high rates of overweight and obesity than the factors studied in this thesis. Future studies should therefore investigate the role of diet quality during the CF period as well as in toddlerhood on the development of BMI and overweight in children across different ethnic groups. Until now, few studies have collected detailed data on dietary intakes during the CF period among different ethnic groups in the Netherlands. Although few such studies included information on diet, the methodology applied (FFQ) has been validated only in children of Dutch descent. Recently, a new study, the Sarphati Diaries, was set up with the aim to obtain data on dietary intakes during the CF period in a multi-ethnic population cohort in Amsterdam. The design of this study is described more in more detail in Text Box 1 and discussed further in this chapter.

In addition to the feeding practices studied in this thesis, several other aspects of feeding, such as feeding styles, beliefs and perceptions may contribute to ethnic disparities in childhood overweight and obesity [87]. Previous studies in the U.S. have suggested that some feeding beliefs or perceptions of mothers from certain ethnic minority backgrounds may promote infant overfeeding and explain the high infant overweight rates among specific ethnic groups [88]. However, to date, there is limited information on these aspects among infants and young children from different ethnic populations in the Netherlands [89]. A recent qualitative study indicated that certain beliefs of the caregivers or other family members may be important motivations for introducing certain foods and drinks high in energy and/or protein, such as SSB and yoghurt with added sugar [90]. Preliminary results from an ongoing study among different ethnic groups indicated that for instance, the belief that yoghurt is important for healthy gut development seems to be one motivation for parents to introduce it early in infancy (personal communication). Also, mothers often perceive of having an inadequate supply of breast milk to meet their infant's needs or that the baby doesn’t seem to be satisfied with breastmilk (personal communication). Parenting style is also shown to be important for weight development; among Turkish populations, authoritarian parenting and maternal pressure to eat are important predictors of child's weight status [91]. Furthermore, among mothers of Turkish and Moroccan descent, there seems to be culturally-based misconception of what constitutes a healthy weight gain in infancy, which may lead to overfeeding practices and development of overweight and obesity [92,34]. It is therefore important to gain multidimensional insights into infant feeding, including beliefs and underlying sociocultural factors that mothers have towards feeding their young children. Such aspects of feeding may provide important information for developing interventions tailored to the cultural setting.

Sarphati Diaries study

One of the aims of this PhD project was to collaborate with the Public Health Service Amsterdam to design and set up a new study, the 'Sarphati Diaries' (Text Box 1), to gain more detailed insights into CF practices among different ethnic groups in the city of Amsterdam. The main aspects of the collaboration included the design of the study and the data collection methodology as well as initiating recruitment of participants. Here, the development of the dietary assessment methodology and the implementation of different recruitment strategies are discussed further. Several aspects during the phases of the study were given particular attention to ensure successful recruitment and data collection. It is known that recruiting and involving ethnic minority groups in health research may pose certain challenges [93,94], resulting in low participation rates [95]. Therefore, in the 'Sarphati Diaries' study, recruitment procedures have been carefully considered in order to reach an ethnically diverse study population. First, in addition to the recruitment at the YHC, several other recruitment locations were selected after a careful initial evaluation based on the prevalence of ethnic groups visiting those locations. The recruitment has been extended to various locations such as local sport- and activity centers in order to reach the number of eligible participants. Furthermore, in addition to the face-to-face recruitment, social media channels are being used as an additional recruitment strategy. Recent studies have indicated that digital and social media can provide a powerful method for recruiting participants [96].

Since a language proficiency may pose a challenge for ethnic minority groups for their participation in research [97], the 3-day food diaries were translated in English and Turkish and recruitment materials were translated into Turkish. Although mothers were approached in

Dutch, information leaflets in the Turkish language were available. Also, a Turkish speaking dietician student assisted during the start of the recruitment and data collection phases. Including bilingual and bicultural research staff allows better communication in participant's preferred language and may help to overcome barriers related to culturally sensitive topics [98].

In order to capture sufficient details and ethnic diversity of the diet during the CF period, a 3-day food diary methodology was chosen and developed for the purposes of this study (Appendix). The diary included a detailed description of the foods, including the brand, the amount served and the leftovers. Assessment of the food preparation method and the ingredients used in the composite foods were also captured. For infant formula, the preparation and amount consumed was recorded. All study materials were pilot-tested among participants from different ethnic backgrounds. Based on the feedback, certain items of the diary were modified to increase the interpretability. It has also been ensured that participants receive detailed instructions during a face-to-face or telephone appointment prior to filling out the diary. After filling out the diary, participants are interviewed (face-to-face or by telephone) to check the completeness of the diary. In addition, a semi-structured interview is used to collect qualitative information to understand the motivations behind the feeding practices. The food diary method is supplemented by photos of the meals taken by the participants. These are compared with the recorded food items and any missing items are discussed with the participant. Such images can act as a reference for portion size, to aid interpretation of the record as well as the context surrounding an eating occasion, such as the time of consumption [99].

It is anticipated that the Sarphati Diaries study will provide unique and high-quality information on infant feeding among several ethnic groups in the Netherlands. The key value is the detailed information on the CF period, which is lacking from the current cohort studies. These results will be especially valuable for developing ethnic-specific feeding advice for parents of young children. The setting of the Sarphati Cohort, which includes a systematic monitoring of all children by means of the routine consultations with the YHC will enable further follow-up of the participants to study the role of complementary feeding in long-term growth and the development of overweight. Ultimately, this information will aid in developing new interventions for the prevention of overweight.

Box 1: Sarphati Diaries study

Objective and design

The Sarphati Diaries study, initiated by the Public Health Service Amsterdam, is an ongoing cohort study aimed at obtaining more insights into complementary feeding (CF) practices among different ethnic groups in the city of Amsterdam. Sarphati Diaries is a sub-study within the Sarphati Cohort, which is a dynamic cohort study that collects data relating to exercise, sleeping, nutrition, motor development and children's growth to be used for research within Sarphati Amsterdam. This research can provide valuable insights into the causes of non-communicable diseases including diabetes, obesity and cardiovascular diseases.

The primary objective of the Sarphati Diaries study is to measure dietary intakes during the CF period in a multi-ethnic population, with a special interest in potential ethnic differences. For this study, mothers and their babies of Dutch, Turkish, Moroccan and Surinamese ethnic origin, are being recruited. The study will focus on investigating the types of foods provided, feeding frequency and food preparation (method and ingredients), taking into account culturally specific foods.

Methods

Recruitment

A multi-channel approach is used to recruit participants for the Sarphati Diaries study. From September 2019 till March 2020 recruitment of participants took place in the waiting rooms of Youth Health Care (YHC) centers throughout the city. Supported by recruitment at organized activities for parents with young children and through social media. Mothers with an infant of 3-6 months of age who are visiting the YHC location for the child's regular health check or a location for organized activities, were are approached for participation. The data infrastructure of the Sarphati Cohort makes it possible to approach it's participants for this particular sub-cohort study. This means that, starting from the end of November 2019, all participating parents with a 4 month old receive an email inviting them to take part in Sarphati Diaries. Inclusion criteria are: 1) ethnic background (Dutch, Turkish, Moroccan or Surinamese, based on self-identification of the mother) and 2) the child is 3-6 months of age. Infants with a specific medical condition at birth which may impair their nutritional intake or appetite, are excluded. This study was reviewed by the Medical Ethic s Review Committee of the Academic Medical Center (AMC) and they have confirmed that the Medical Research Involving Human Subjects Act (WMO) does not apply to the study and that an official approval of this study is not required.

Data collection

During the 6-month interview, an online administered questionnaire assesses information relevant to 1) parental and infant demographic data 2) birth outcomes 3) (self-reported) body weight and body height of biological parents and 4) infant milk feeding and (in case already receiving CF) the first types of complementary foods (or drinks) provided. Furthermore, a semi-structured interview is used to collect qualitative information on feeding practices

Dietary intake will be assessed using a 3-day food diary. This method was chosen as it allows a detailed capturing of different types of complementary foods, including ethnic-specific foods. Information on dietary intakes will be collected at two phases:

1) The first diet assessment is done at the beginning of CF, at around 6-7 months of age, shortly after the child is been introduced to CF (if not already started earlier).
2) The second dietary measurement will be completed at 12 months of age. This age was chosen as infants are then typically starting to be introduced to family diet, including more diverse foods/drinks and mixed dishes.

Implications for public health

The results of this thesis may strengthen the advice given by YHC professionals to parents about infant feeding in an ethnically diverse population. Overall, the results from this thesis suggest that a long duration of EBF may reduce the risk of overweight and obesity, although the observed effect sizes were modest. Despite the increase in the EBF rates in the Netherlands [100], the latest estimate (2015) shows that only 39% of the mothers provide EBF until 6 months [101]. The main reason for discontinuing EBF is return to work. Currently, the maternity leave in the Netherlands is 16 weeks, of which 12 weeks are post-birth. The national and local government should promote the initiation and continuation of EBF. Employers also have a key role to facilitate successful continuation of EFB. Both aspects require considerations about the optimal duration of maternity leave as well as providing the opportunity to express breastmilk at the workplace.

Although our results indicate that CF introduction after 6 months may provide a (small) benefit for overweight prevention, the current evidence on the timing of CF is conflicting [8,102] and more research is needed on this topic. Therefore, it is too early to change the current recommendations in the Netherlands, which are in line with the EFSA and the ESPGHAN [103,104], stating that CF can be commenced from 4 months onwards. It should be noted that also evidence regarding other health aspects, such as prevention of allergies or iron deficiency, needs to be taken into account when considering the optimal timing of CF introduction and this was not investigated in this thesis [105,106]. Parental choice about what, when and how to start CF should be discussed during the routine YHC consultations during early infancy. The choice of timing should include consideration of an infant's physiological readiness and close monitoring of growth. In the future, if our results regarding formula feeding and timing of CF are confirmed in other studies and populations, specific recommendations on the timing of CF could ultimately be made based on the type of milk feeding.

One important consideration of our results is that successful interventions aiming to reduce the ethnic inequalities in overweight may require more ethnic-specific approaches taking into account specific cultural beliefs and habits. Our results regarding infant feeding can be applied in developing interventions which are tailored for targeted (ethnic) populations.

Since dietary patterns during toddlerhood have been shown to predict dietary patterns later in life [107], focus on a healthy diet during early childhood is of high importance [108]. In particular, the intake of high-energy, low-fibre ultra-processed foods should be discouraged.

Further efforts to educate parents on food choices at the start of CF period are a priority, since infancy is a critical period for flavor and taste learning as well as for the development of long-lasting food preferences [108,109].

General conclusion

The results from this thesis suggest that certain infant feeding factors, such as the duration of EBF and the timing of CF may be important for the prevention of childhood overweight. As the effects vary across subpopulations according to certain maternal characteristics, targeted interventions should be considered. We observed that the studied infant feeding practices did not play a major role in explaining the observed ethnic inequalities in growth-related outcomes during infancy or early childhood. Our findings suggest that in addition to infant feeding, dietary pattern during toddlerhood is also critical in relation to the development of overweight. A diet low in energy-dense, ultra-processed foods during toddlerhood may be important for the prevention of childhood overweight.

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Appendix

Sarphati Diaries study

3-day food diary (example including 1 day)


3 daags
voedingsdagboekje
uw kindje is 6 maanden
Sarphati diaries
Respondentnummer
Sarphati Cohort
GGD Amsterdam

Instructie voor het invullen van het voedingsdagboekje

Uw kind is nu rond de 6 maanden. Dit betekent dat uw kind al wat hapjes heeft geproefd.
U heeft een voedingsdagboekje gekregen: hierin kunt u alles noteren wat uw kind de hele dag eet en drinkt. We vragen u gedurende 2 'normale' doordeweeksedagen en 1 dag in het weekend alles wat uw kind eet en drinkt zo nauwkeurig mogelijk te noteren. Pas de voeding van uw kind niet aan; geef uw kind te eten en te drinken zoals u dat altijd gewend bent. Lees hieronder hoe u het dagboekje moet invullen.

Instructies en aandachtspunten

- **Vul elke keer het dagboekje in nadat uw kind iets heeft gegeten of gedronken**. Hoe eerder u alles noteert, hoe kleiner de kans is dat u iets vergeet.
- Ons advies: zorg ervoor dat u het dagboekje **gedurende de drie dagen zoveel mogelijk bij u** heeft. Zo kunt u de voeding van uw kind direct noteren en zult u minder vergeten.
- **Oppas of kinderopvang**: Is uw kind niet de hele dag bij u, maar bijvoorbeeld bij een oppas of op een kinderdagverblijf? Dan kunt u het dagboekje aan de verantwoordelijke persoon overdragen met korte uitleg en hem/haar vragen deze in te vullen.
- **Foto's maken:** fotografeer in ieder geval de warme maaltijden van uw kind. Als u het fijn vindt kunt u ook foto's maken tijdens het bereiden van de recepten. Dit kan helpen bij het invullen van de ingrediënten en hoeveelheden. Zorg ervoor dat uw kinderen hierbij niet op de foto's staan.
- Is uw dagboekje vol of heeft u meer bladzijden nodig? U kunt zelf een extra blaadje toevoegen of ons bellen voor een extra dagboekje .
- Wanneer het eetgedrag anders is dan normaal, bijvoorbeeld als uw kind zich ziek voelt, dan kunt u onder het kopje "opmerkingen" een notitie maken.
- **Taal:** vul het voedingsdagboekje in het Nederlands in. Weet u de vertaling van bepaalde producten of recepten niet, dan kunt u het ook in een andere taal opschrijven.

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Uitleg per kolom van het voedingsdagboekje

Op de volgende pagina's ziet u enkele invulvoorbeelden van het voedingsdagboek en de recepten van één dag. Deze zijn bedoeld als voorbeeld hoe u de voeding kunt noteren en niet als voorbeeld hoe uw kind zou moeten eten!

Plaats: kruis aan waar uw kind het voedingsmiddel heeft gegeten of gedronken.

Eten en drinken: vul in wat uw kind precies heeft gegeten en gedronken:

Schrijf elk hapje of slokje dat uw kind heeft gegeten of gedronken op, inclusief water, tussendoortjes of een paar hapjes van het een of het ander.

Omschrijving voedingsmiddel: vul extra informatie in over het voedingsmiddel:

- Noteer zoveel mogelijk gegevens van de verpakking, zoals de:
  - Merknaam *(Liga)*
  - Soortnaam *(baby biscuit)*
  - Smaak van producten *(Vanille)*
  - Vetgehalte *(volle, magere of halfvolle melk, minder vet of light)*
  - Suikergehalte *(ongezoet, gezoet met suiker, gezoet met zoetstoffen of light)*
- Vul bij de voedingsmiddelen ook de eventuele toevoegingen in. *(suiker in de thee of rijstebloem in de flesvoeding)*
- Bij kunstvoeding vult u in welk merk, soort en smaak u aan uw kind heeft gegeven. Noteer hierbij de hoeveelheid water en schepjes die u gebruikt heeft om het te bereiden.

Hoeveelheid eten of drinken: beschrijf hoeveel eten of drinken u aan uw kind heeft gegeven.

1 eetlepel
1 theelepel
1 beker
1 schaaltje
1 flesje

- Vermeld de hoeveelheid bij voorkeur in grammen of milliliters (ml). Het gewicht van kant en klare producten wordt meestal op de verpakking aangegeven. Wanneer het gewicht van een product niet bekend is, kunt u de hoeveelheid aangeven in aantal stuks of in huishoudmaten. Heeft u een keukenweegschaal? Gebruik deze dan om de gegeven hoeveelheid in te vullen.

- Bij borstvoeding vult u het aantal minuten per keer dat uw kindje die dag borstvoeding kreeg in. Hiervan hoeft u dus geen hoeveelheid aan te geven. Als er gekolfde borstvoeding wordt gegeven, dan graag de hoeveelheid (ml) wel vermelden.

- Bij kunstvoeding vult u in hoeveel water (ml) en het aantal schepjes melkpoeder dat u gegeven heeft. Geef aan hoeveel (ml) uw kind ongeveer heeft gedronken.

Heeft u vragen of twijfels, dan kunt u contact opnemen met het onderzoeksteam: info@sarphati.amsterdam of 020 555 5495.

Hoeveelheid overgebleven eten of drinken:

Noteer hoeveel eten of drinken uw kind NIET gegeten of gedronken heeft en op zijn/haar bord of in zijn/haar fles heeft gelaten.

zoals "broccoli gekookt in water", "gebakken in blue band margarine" of "gekookt in water met een theelepeltje zout".

Recepten

- In het laatste deel van het dagboekje is ruimte opgenomen om recepten van zelf bereide gerechten te noteren.
- Noteer het recept, welke en hoeveel ingrediënten er zijn gebruikt.
- **Kookt u altijd op gevoel?** Noteer dan in ieder geval de ingrediënten die u gebruikt heeft en probeer een schatting te maken van de hoeveelheden.
- Noteer de **bereidingswijze** van het recept.
- Het recept kan het beste worden ingevuld door degene die het eten heeft bereid. Wanneer uw kind buitenshuis heeft gegeten, kunt u de recepten vanzelfsprekend niet invullen. Probeer dan wel zo nauwkeurig mogelijk te omschrijven wat en hoeveel uw kind heeft gegeten.

A

VOORBEELD

Dag van de week: ☐ MAANDAG ☐ DINSDAG ☐ WOENSDAG ☒ DONDERDAG

Plaats: thuis	kinderopvang	oppas: ____	Tijd	Eten en drinken Elk hapje en slokje dat uw kind heeft gegeten of gedronken
Ochtend (tussen 6.00 en 12.00 uur)				
☒	☐	☐	6.20 u	Borstvoeding
☐	☒	☐	10.00 u	Fruithapje
☐	☒	☐	10.15 u	Water
Middag (tussen 12.00 en 18.00 uur)				
☐	☒	☐	12.00 u	Boterham met smeerkaas
☐	☒	☐	13.00 u	Opvolgmelk 6 maanden
☐	☒	☐	16.30 u	Soepstengel

Voedingsdagboek

☐ VRIJDAG ☐ ZATERDAG ☐ ZONDAG Datum (20 / 07 / 2019)

	Omschrijving voedingsmiddel Volledige naam (inclusief merk, type en smaak) en samenstelling (vet en suiker, extra vitamines enz.)	**Hoeveelheid eten of drinken** Hoeveel eten of drinken u aan uw kind heeft gegeven	**Hoeveelheid overgebleven eten of drinken** Hoeveel eten of drinken uw kind NIET gegeten of gedronken heeft
		20 min	
	Geprakte banaan	Halve banaan	
		50 ml	
	Bruine boterham besmeerd met een beetje Becel margarine 60% en smeerkaas Slankie 20+	1 snee 15 gram smeerkaas	
	Kruidvat opvolgmelk standaard 2 160 ml water en 6 schepjes poeder	180 ml	
	AH soepstengels naturel	1 soepstengel	1/2 soepstengel

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VOORBEELD

Dag van de week: ☐ MAANDAG ☐ DINSDAG ☐ WOENSDAG ☒ DONDERDAG

Plaats: thuis	Plaats: kinderopvang	Plaats: oppas: ______	Tijd	Eten en drinken Elk hapje en slokje dat uw kind heeft gegeten of gedronken
Avond (tussen 18.00 en 22.00 uur)				
☒	☐	☐	17.45 u	Groentehapje
☒	☐	☐	18.00 u	Papje
☒	☐	☐	19.00 u	Water
Nacht (tussen 22.00 en 6.00 uur)				
☒	☐	☐	22.00 u	Borstvoeding OF Opvolgmelk 6 maanden

Voedingsdagboek

☐ VRIJDAG ☐ ZATERDAG ☐ ZONDAG Datum (20 / 07 / 2019)

	Omschrijving voedingsmiddel Volledige naam (inclusief merk, type en smaak) en samenstelling (vet en suiker, extra vitamines enz.)	**Hoeveelheid eten of drinken** Hoeveel eten of drinken u aan uw kind heeft gegeven	**Hoeveelheid overgebleven eten of drinken** Hoeveel eten of drinken uw kind NIET gegeten of gedronken heeft
	Zie recept groente hapje (broccoli en aardappel)	Schaaltje (75 gram)	1/3 schaaltje
	100 ml borstvoeding 2 el Olvarit Fijne Granen Banaan	120 ml	30 ml
		50 ml	20 ml
	Nutrilon opvolgmelk 2 180 ml water en 6 schepjes poeder	10 min 180 ml	

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VOORBEELD

Recepten

Naam gerecht	Ingrediënten, hoeveelheid en eventueel extra toevoegingen (zout, peper, olie etc.)	Bereidingswijze	Voor hoeveel personen gemaakt?
Groentehapje	50 gram verse broccoli 25 gram aardappel of 1 kleine aardappel olijfolie 1 theelepel	Aardappels en broccoli eerst gaar koken in water. Daarna pureren met staafmixer Olie toevoegen	1
Linzensoep	1 ui, gesneden 1/2 rode peper, fijn gesneden 5 tenen knoflook, fijn gesneden 1 groentebouillonblokje 3 theelepels paprikapoeder 200 gram rode linzen 1 flinke klont roomboter 3 theelepels komijnzaad 2 eetlepels tomatenblokjes uit blik Scheutje olijfolie zout en peper	Ui, knoflook en peper gebakken in olijf-olie. Daarna gekookt water, bouillonblokje, zout, paprikapoeder en linzen toegevoegd en gekookt. Komijnzaad gebakken in roomboter samen met de tomatenblokjes. Tomatenblokjes met komijnzaad toege-voegd aan de soep. Als laatste de soep gepureerd.	4
Pompoenhapje	50 g gekookte pompoen 15 g gekookte rijst Klontje roomboter	Pompoen en rijst pureren met beetje boter.	1

VOORBEELD

Vragen

1. Was het eten en drinken van uw kind vandaag normaal, minder dan normaal of meer dan normaal?

- [ ] Normaal
- [x] Minder dan meestal

  Waarom: Sara was vandaag verkouden
- [ ] Meer dan meestal

  Waarom:

2. Wie heeft het voedingsdagboekje van dag 1 ingevuld?

- [x] Moeder
- [ ] Vader
- [x] Anders

  Details: kinderopvang tussen 8.00-17.00 uur

3. Hoe zag de voorbereiding van de maaltijden van uw kind eruit?

- [ ] Mijn kind at hetzelfde eten als de rest van het gezin
- [x] Voor mijn kind zijn aparte maaltijden voorbereid

4. Wie heeft de warme maaltijden op dag 1 klaargemaakt?

- [x] Moeder
- [ ] Vader
- [ ] Iemand anders
- [ ] Kant en klaar gekocht of ergens anders gegeten

5. Andere opmerkingen

Sara heeft vanmiddag meer gespuugd dan normaal

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Voedingsdagboek

Dag van de week: ☐ MAANDAG ☐ DINSDAG ☐ WOENSDAG ☐ DONDERDAG

Plaats			Tijd	Eten en drinken
thuis	kinderopvang	oppas: ______		Elk hapje en slokje dat uw kind heeft gegeten of gedronken
Ochtend (tussen 6.00 en 12.00 uur)				
☐	☐	☐		
☐	☐	☐		
☐	☐	☐		
☐	☐	☐		

Dag 1

☐ VRIJDAG ☐ ZATERDAG ☐ ZONDAG Datum (/ /)

	Omschrijving voedingsmiddel Volledige naam (inclusief merk, type en smaak) en samenstelling (vet en suiker, extra vitamines enz.)	**Hoeveelheid eten of drinken** Hoeveel eten of drinken u aan uw kind heeft gegeven	**Hoeveelheid overgebleven eten of drinken** Hoeveel eten of drinken uw kind NIET gegeten of gedronken heeft

A

Voedingsdagboek

Dag van de week: ☐ MAANDAG ☐ DINSDAG ☐ WOENSDAG ☐ DONDERDAG

Plaats			Tijd	Eten en drinken
thuis	kinderopvang	oppas: ____		Elk hapje en slokje dat uw kind heeft gegeten of gedronken
Middag (tussen 12.00 en 18.00 uur)				
☐	☐	☐		
☐	☐	☐		
☐	☐	☐		
☐	☐	☐		

Dag 1

☐ VRIJDAG ☐ ZATERDAG ☐ ZONDAG Datum (/ /)

	Omschrijving voedingsmiddel Volledige naam (inclusief merk, type en smaak) en samenstelling (vet en suiker, extra vitamines enz.)	**Hoeveelheid eten of drinken** Hoeveel eten of drinken u aan uw kind heeft gegeven	**Hoeveelheid overgebleven eten of drinken** Hoeveel eten of drinken uw kind NIET gegeten of gedronken heeft

A

Voedingsdagboek

Dag van de week: ☐ MAANDAG ☐ DINSDAG ☐ WOENSDAG ☐ DONDERDAG

Plaats			**Tijd**	**Eten en drinken** Elk hapje en slokje dat uw kind heeft gegeten of gedronken
thuis	kinderopvang	oppas: ______		
Avond (tussen 18.00 en 22.00 uur)				
☐	☐	☐	....	....
☐	☐	☐	....	....
☐	☐	☐	....	....
☐	☐	☐	....	....

Dag 1

☐ VRIJDAG ☐ ZATERDAG ☐ ZONDAG Datum (/ /)

	Omschrijving voedingsmiddel Volledige naam (inclusief merk, type en smaak) en samenstelling (vet en suiker, extra vitamines enz.)	**Hoeveelheid eten of drinken** Hoeveel eten of drinken u aan uw kind heeft gegeven	**Hoeveelheid overgebleven eten of drinken** Hoeveel eten of drinken uw kind NIET gegeten of gedronken heeft

A

Voedingsdagboek

Dag van de week: ☐ MAANDAG ☐ DINSDAG ☐ WOENSDAG ☐ DONDERDAG

Plaats			**Tijd**	**Eten en drinken**
thuis	kinderopvang	oppas: ____		Elk hapje en slokje dat uw kind heeft gegeten of gedronken
			Nacht (tussen 22.00 en 6.00 uur)	
☐	☐	☐		
☐	☐	☐		
☐	☐	☐		
☐	☐	☐		

Dag 1

☐ VRIJDAG ☐ ZATERDAG ☐ ZONDAG Datum (/ /)

	Omschrijving voedingsmiddel Volledige naam (inclusief merk, type en smaak) en samenstelling (vet en suiker, extra vitamines enz.)	**Hoeveelheid eten of drinken** Hoeveel eten of drinken u aan uw kind heeft gegeven	**Hoeveelheid overgebleven eten of drinken** Hoeveel eten of drinken uw kind NIET gegeten of gedronken heeft

A

Recepten

Dag 1

Naam gerecht	Ingrediënten, hoeveelheid en eventueel extra toevoegingen (zout, peper, olie etc.)	Bereidingswijze	Voor hoeveel personen gemaakt?

Vragen

Dag 1

1. **Was het eten en drinken van uw kind vandaag normaal, minder dan normaal of meer dan normaal?**

☐ Normaal
☐ Minder dan meestal
Waarom:
☐ Meer dan meestal
Waarom:

2. **Wie heeft het voedingsdagboekje van dag 1 ingevuld?**

☐ Moeder
☐ Vader
☐ Anders
Details:

3. **Hoe zag de voorbereiding van de maaltijden van uw kind eruit?**

☐ Mijn kind at hetzelfde eten als de rest van het gezin
☐ Voor mijn kind zijn aparte maaltijden voorbereid

4. **Wie heeft de warme maaltijden op dag 1 klaargemaakt?**

☐ Moeder
☐ Vader
☐ Iemand anders
☐ Kant en klaar gekocht of ergens anders gegeten

5. **Andere opmerkingen**

Hartelijk dank voor het invullen!

Summary
Acknowledgements
About the author

Summary

Childhood overweight and obesity are important public health problems. Children with overweight or obesity are at risk of developing (or remaining to have) obesity later in life. Children with obesity also have an increased risk of developing several short- and long-term comorbidities. Due to the fact that obesity is difficult to reverse, early prevention of childhood overweight and obesity is crucial. In the Netherlands 14% of 4-20 year-old's have overweight or obesity. Although a stabilization in the prevalence rates in the Netherlands has been observed during the recent years, large and growing ethnic inequalities exist. Whereas among the children of Dutch descent the prevalence of overweight and obesity has stabilized or slightly decreased, at the same time, the rates for children of Moroccan or Turkish descent have been increasing. These inequalities seem to appear already during the first years of life and remain largely unexplained. Understanding early-life determinants of overweight and obesity among different ethnic groups is crucial for early prevention.

An increasing amount of evidence suggests that the early life period is critical for the development of overweight and obesity. Early growth patterns, i.e. development of weight or body mass index (BMI) during the first years of life are indicative of later risk of overweight and obesity. Particularly, excessive body weight or rapid BMI increase during the first years of life is strongly associated with subsequent overweight and obesity. Feeding during infancy and early childhood is suggested as one of the key determinants of growth with potential long-term health consequences. Most studies have focused on breastfeeding (BF) duration or the timing of start of complementary feeding (CF), however, evidence remains inconclusive. Furthermore, the role of different infant feeding factors and early dietary patterns in the development of childhood overweight and obesity is not fully understood.

The main aim of this thesis was to investigate associations of infant milk feeding and CF practices as well as toddler dietary patterns with weight-related outcomes during early childhood. A secondary aim was to investigate these associations among different ethnic populations in the Netherlands at varying risk for overweight and obesity. For the studies described in this thesis, data from 3 Dutch population studies were used: the Amsterdam Born Children and their Development (ABCD) cohort, the TIBET study and the GECKO Drenthe cohort.

In **Chapter 2**, prospective associations of timing of CF and duration of exclusive breastfeeding (EBF) with childhood BMI-sds and overweight (including obesity) were investigated among children from the ABCD cohort. Maternal characteristics of ethnicity, education, pre-pregnancy BMI and neighbourhood were used to describe groups of children at varying risk for childhood overweight. It was found that in the overall population, CF introduction at or after 5 months was associated with lower BMI-sds at 5–6 years of age compared with CF introduction before 5 months. Furthermore, EBF for at least 6 months was associated with a lower BMI-sds and decreased risk of overweight at age 5-6 years compared with EBF duration for less than 6 months. However, when the analyses were stratified by maternal characteristics, the associations differed across the subgroups. The results suggest that associations between infant feeding practices and childhood BMI may differ between risk groups, implying that overweight prevention strategies should be group-specific.

Then, in **Chapter 3** associations between specific infant feeding patterns and BMI trajectories during the first year of life were investigated (ABCD cohort). Furthermore, potential ethnic differences in these associations were studied. Feeding patterns were defined based on the milk feeding type during 0-3 months (EBF, formula feeding or mixed feeding) combined with the timing of CF: early (before 6 months) or late (at or after 6 months). Four distinct BMI trajectories were identified from the data: low, mid-low, mid-high and high. It was found that infants with a feeding pattern of formula feeding combined with early CF were less likely to be in a low BMI trajectory. Also, ethnic-specific associations were revealed. Among infants of Dutch descent, pattern of formula feeding combined with early CF was associated with lower odds for the 'low' trajectory. However, among Turkish/Moroccan infants almost all feeding patterns were associated with lower odds for the low trajectory. These findings suggest that infant feeding patterns are associated with early BMI trajectories with specific ethnic differences.

Subsequently, **Chapter 4** investigated the role of infant feeding factors at 6 months of age in explaining possible ethnic differences in BMI-sds during 2-5 years of age between children of Dutch and Turkish descent (TIBET study). The following feeding factors were investigated: BF duration, milk feeding frequency as well as the timing, frequency and variety of CF. It was found that relative to Dutch children, Turkish children had higher BMI-sds at 3 and 5 years of age. Of all the feeding factors studied, only CF variety explained a small fraction of the ethnic differences in BMI-sds. Furthermore, CF variety was significantly associated with higher BMI-sds during 2-5 years of age. It is likely that the association between CF variety and BMI are explained by a high variety of specifically energy-dense foods rather than variety in all foods. Therefore, further research is needed to understand how food variety during the CF period may influence BMI development during childhood.

Chapter 5 aimed to identify dietary patterns among three-year-old Dutch children and the associations between overweight and BMI development between 3 and 10 years (GECKO cohort). Both cross-sectional as well as longitudinal associations between the dietary patterns and outcomes were investigated. At 3 years of age, two dietary patterns were identified and labeled. The first pattern 'minimally processed foods' indicated a high intake of vegetables, sauces and savory dishes. The second pattern 'ultra-processed foods' indicated a high intake of crisps, white bread and sugar-sweetened beverages. The two dietary patterns were not cross-sectionally associated with the outcomes. Although a high adherence to both dietary patterns was associated with a higher BMI-sds up to 10 years of age, a stronger association for the 'ultra-processed foods' pattern was observed. These finding suggest that a dietary pattern high in energy-dense and low-fiber ultra-processed foods at 3 years is associated with overweight and a high BMI-sds later in childhood.

Finally, **Chapter 6** provided a summary and an interpretation of the findings and the methodological considerations. Furthermore, implications for future research and public health were discussed.

The most important findings were, firstly, that a longer duration of EBF and a later timing of CF were associated with lower BMI and lower risk for childhood overweight. However, these associations were found to vary across subpopulations according to certain maternal characteristics. Therefore, targeted interventions should be considered for the prevention of childhood overweight and obesity. We did not find evidence that infant feeding practices related to milk feeding and CF practices explain the observed ethnic differences in weight-related outcomes. In addition to diet quantity and quality, also other lifestyle-related behaviors of the child as well as the mother (during both pre- and postnatal periods), remains to be further investigated as possible factors that explain ethnic inequalities in childhood overweight and obesity. The results also showed that a dietary pattern high in energy-dense, low-fibre ultra-processed foods during toddlerhood is associated with the development of childhood overweight and obesity. Since dietary patterns during toddlerhood have been shown to predict dietary patterns later in life, focus on a healthy diet during toddlerhood is of high importance. In particular, since infancy is a critical period for the development of long-lasting food preferences and eating habits, educating parents on food choices at the start of CF period is a priority.

To conclude, the results from this thesis suggest that the duration of EBF and the timing of CF may be important for the prevention of childhood overweight and obesity. The specific infant feeding practices studied in this thesis do not seem to play a major role in explaining the observed ethnic inequalities in growth-related outcomes during infancy or early childhood. In addition to infant feeding, dietary pattern during toddlerhood is also critical in relation to the development of overweight and obesity. A diet low in energy-dense, ultra-processed foods during toddlerhood is important for the prevention of childhood overweight and obesity.