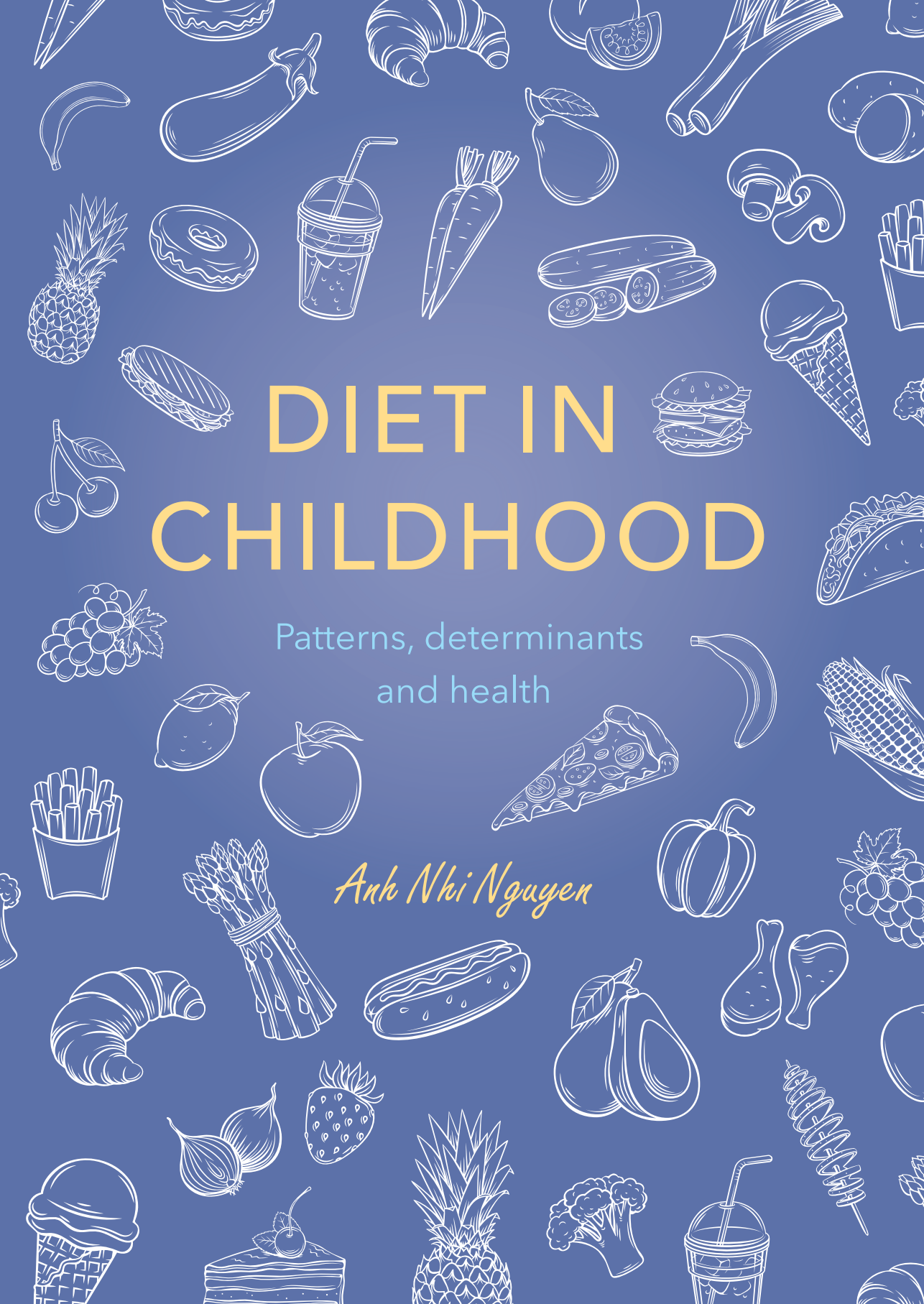

DIET IN CHILDHOOD

Patterns, determinants and health

Anh Nhi Nguyen

Diet in Childhood

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Diet in Childhood

Patterns, determinants, and health

Voeding in de kindertijd

Patronen, determinanten en gezondheid

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof. dr. R.C.M.E. Engels
en volgens besluit van het College voor Promoties.

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Anh Nhi Nguyen

geboren te Hoorn

Erasmus University Rotterdam

"*Doubt is the origin of wisdom*" – René Descartes

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Nguyen AN, Lara M, Gkitakou A, Verhoog S, van Rosmalen B, Boelens M, Bramer WM, Voortman T. Dietary interventions in early childhood and its effects on atopic diseases: a systematic review. *Submitted for publication*.

**Denotes equal contribution*


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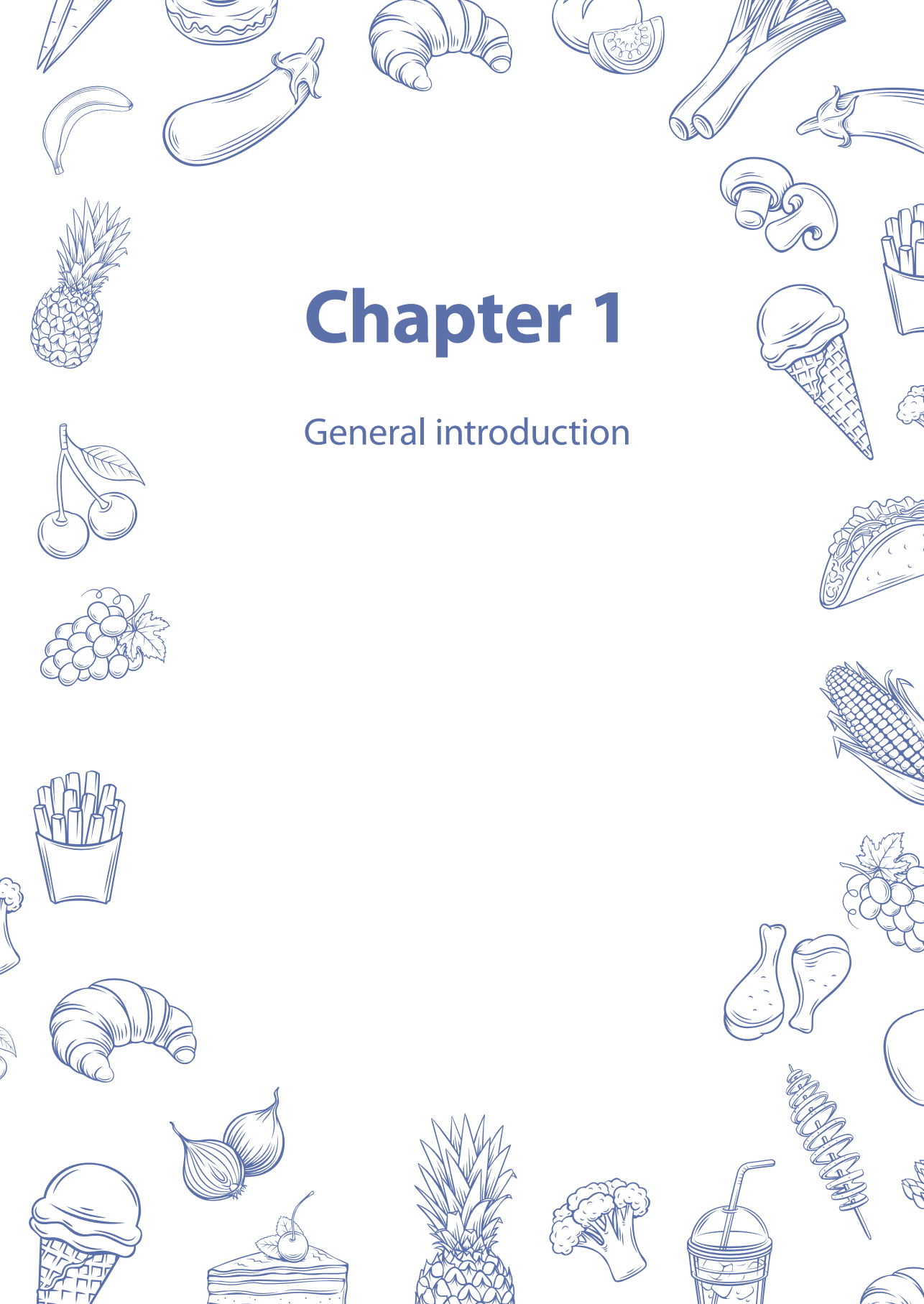

Chapter 1

General introduction

BACKGROUND

Early childhood is a critical period for the development of eating habits, because taste preferences and dietary behaviors are shaped during this period and are suggested to track into adulthood [1,2]. In addition, adequate dietary intake in all phases of childhood is essential for optimal growth, development, and health, not only in childhood, but also in later life [3-5]. It has been shown that the origins of several chronic diseases, including type 2 diabetes and cardiovascular diseases, which are nowadays the leading causes of mortality worldwide, lies in childhood [6,7]. Several studies have shown that potential risk factors for these diseases, including obesity, hyperlipidemia, and high blood pressure, already occur in childhood [6-9], and may track into adulthood [10-12]. Also other diseases with a high burden in the general population, including osteoporosis, and atopic diseases, have been shown to originate in childhood [6,13,14]. Early-life nutrition has been suggested to play an important role in setting the risk of several health outcomes in later life, including coronary heart disease, type 2 diabetes, osteoporosis, and asthma [3-5]. Therefore, nutrition in early life should be a key target in the prevention of chronic diseases and maintenance of health throughout the life course.

This thesis focuses on the relation of diet with health conditions that are highly prevalent already in childhood, including adiposity, other cardiometabolic markers, and atopic diseases. These health conditions are important public health problems, with a large increase in prevalence in recent decades. Also, these problems already occur in childhood and are suggested to track into adulthood. Hence, it is of high importance to identify modifiable risk factors – such as diet – in order to start prevention at an early stage.

DIETARY PATTERNS

Although intake of several single nutrients or foods in childhood has been linked to health, children consume a variety of nutrients and foods combined in meals rather than single nutrients or foods. The combination of nutrients and foods in meals may capture complex synergistic or interaction effects of nutrients and foods, food structure, or preparation methods on health. Over the past few decades, analysis of dietary patterns has emerged as an important research field, complementary to studies focusing on single dietary compounds [15,16]. Well-known dietary patterns include the Mediterranean diet, characterized by high intakes of fruit, vegetables, and fish, and low intakes of red meat; and the Western diet, characterized by high intakes of energy-dense, high-processed foods, and low intakes of fruit and vegetables. Dietary patterns may better capture the

complex interactions between nutrients and foods, which may give better insights on the effects of overall diet on health.

Two main approaches to study dietary patterns can be distinguished, namely data-driven or predefined. Data-driven dietary patterns are identified based on the variation of dietary intake data within a study population, whereas predefined dietary patterns are constructed based on specific dietary guidelines or recommendations [15]. Dietary guidelines are often country specific because of different eating habits [17]. Most dietary guidelines combine recommendations for both foods and individual nutrients. The current dietary guidelines in the Netherlands are unique in the sense that they are completely food-based, which might be easier to link to real-life foods for the general population. Although the Dutch dietary guidelines are based on extensive previous research on nutrients, foods, and dietary patterns in relation to specific diseases, the association of adherence to these overall dietary guidelines with health outcomes has not yet been evaluated. In addition, these dietary guidelines were developed to prevent the most common diseases in the general population, and the effects of adherence to these guidelines on health in childhood has not yet been studied.

BODY COMPOSITION AND CARDIOMETABOLIC HEALTH

Childhood obesity is a rising public health problem worldwide, which causes serious health problems both in childhood as well as later in life [18,19]. Estimates suggest that currently, 15% of children in the Netherlands has overweight or obesity [20]; in South-European countries, estimates of childhood overweight and obesity prevalence even reach 40% [21]. Childhood obesity impacts children's health and quality of life, by causing for example fractures, asthma, and poor self-esteem. In addition, children with obesity are likely to remain obese as adults and are at risk of chronic diseases. Obesity is also strongly related to cardiometabolic health in childhood; e.g., variations in blood lipids, blood pressure, and insulin resistance are already influence by obesity in childhood [19]. These cardiometabolic risk factors have been shown to track from childhood to adulthood [14,22] and thereby increasing the risk of coronary heart diseases, type 2 diabetes, and premature death [7,18,23]. Poor diet in childhood is one of the fundamental causes of childhood obesity and other cardiometabolic markers[24], and should therefore be a key target in the prevention of developing these cardiometabolic risk factors in childhood and later life. Hence, it is essential to gain knowledge about dietary factors that may influence obesity and cardiometabolic health in childhood, which is of high importance for early prevention of chronic diseases. Previous studies that examined the associations of dietary intake with obesity in children mainly focused on body mass index (BMI) as an outcome measure. However, especially in growing children, the use of a general mea-

sure like BMI is not an adequate measure of body fatness, as body mass includes both fat mass as well as lean mass and bone mass [25,26]. Increased BMI may be caused by increased fat mass or increased lean mass, or both [27]. Therefore, it is important to consider both of these as potential obesity-related outcomes.

ATOPIC DISEASES

Another disease that is already highly prevalent in childhood are atopic diseases, such as eczema, asthma, and food allergy. The prevalence of childhood atopic diseases has rapidly increased in recent decades [28-30]. These diseases have a substantial impact on the quality of life of those affected. Genetic background is one of the factors associated with risk of atopic diseases, but given the rapid increase in prevalence, environmental risk factors, including geographic area and lifestyle factors may play a substantial role in the development of allergies and other atopic diseases [30,31]. Early-life nutrition is an important modifiable lifestyle factor that affects the maturation process of a child's immune system, and has therefore often been hypothesized to influence the development of atopic diseases.

There has been great interest in the role of early-life dietary exposures in the development of atopic diseases. Previous studies have examined several nutritional aspects, including the avoidance of several allergenic foods during pregnancy or lactation [32], timing of introduction of highly allergenic foods [33], exclusive and/or longer duration of breastfeeding [34,35], probiotics and prebiotics [36-38], and supplements such as fatty acids [39,40] or vitamin D [41]. However, evidence for an effect of these nutritional interventions remain inconsistent. In addition, these nutritional factors may also represent an overall dietary pattern. Nevertheless, the role of overall diet quality in childhood in the development of atopic diseases remains unclear.

THIS THESIS

Objectives

The aims of this thesis were to evaluate overall diet quality in childhood, to study its determinants, and to examine its associations with body composition, cardiometabolic health, and atopic diseases (**Figure 1.1**).

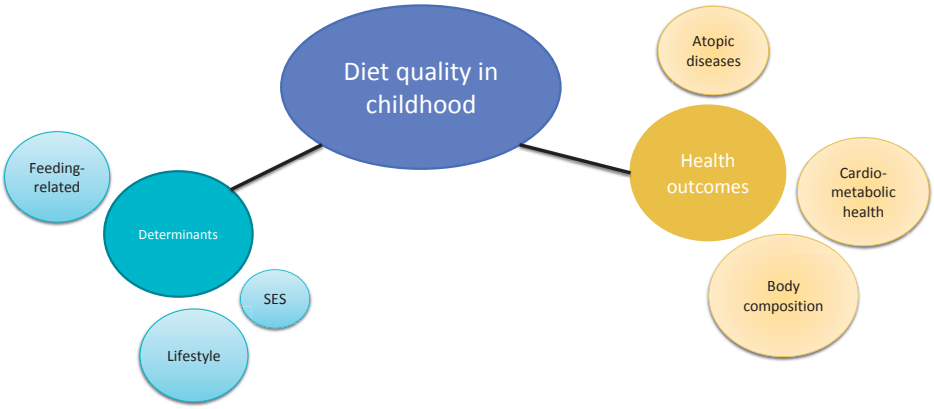

Figure 1.1. Aims of this thesis

Study populations

The studies in this thesis were embedded in three population-based cohort studies: the Generation R Study, the ABCD Study, and the Rhea Study.

Generation R Study

The Generation R Study is an ongoing population-based prospective cohort from fetal life onward in Rotterdam, the Netherlands [42]. Pregnant women with a delivery date between April 2002 and January 2006 were invited to participate in the study. The Generation R Study is designed to identify early environmental and genetic causes of normal and abnormal growth, development, and health from fetal life until young adulthood. In total, 9,778 women were included in the study and 7,893 children were enrolled in early childhood. During pregnancy, physical examinations were performed and questionnaires were used to obtain information on several sociodemographic and lifestyle factors, including diet. From birth onward, we obtained information on health and growth of the children from Child Health Centers and with questionnaires. Child food intake was assessed at two moments in childhood using food-frequency questionnaires (FFQ) which were specifically designed for that age group. At child's ages of 6 and 10 years, they were invited to our dedicated research center at Erasmus University Medical Center for a detailed physical examination. We measured height and weight; and fat mass, fat-

free mass, and bone mass were assessed using dual-energy X-ray absorptiometry (DXA). Additionally, blood pressure and serum concentrations of triacylglycerol, cholesterol, and insulin were measured. At the age of 10 years, skin prick tests were performed to examine sensitization to several inhalant and food allergens.

ABCD Study

The Amsterdam Born Children and their Development (ABCD) Study is an ongoing prospective population-based cohort study in Amsterdam, the Netherlands [43]. Between January 2003 and March 2004, all pregnant women living in Amsterdam were invited to participate. This large prospective population-based cohort study examines the associations between maternal lifestyle, medical, psychosocial and environmental conditions during pregnancy and children's health at birth as well as in later life. Of the 12,373 women approached, 8,266 women were enrolled in the study, and 7,995 children participated at birth. Around the children's age of 6 years, an FFQ was used to assess diet in childhood. In addition, questionnaires were used to obtain information on socioeconomic and lifestyle factors of the participants. Growth of the children were measured at their ages of 6 and 12 years at our research center. In addition, detailed measures of body composition were assessed using bioelectrical impedance analysis (BIA).

Rhea Study

The Rhea Study (The Mother-Child Cohort) is an ongoing prospective population-based cohort on the island of Crete, Greece [44]. This cohort included a representative sample of mother-child pairs from early pregnancy and aims to follow them up to young adulthood. One of the general objectives of the study is to characterize nutritional, environmental, and psychosocial determinants of children's growth and development. A total of 1,610 pregnant women were enrolled in the study between 2007 and 2008 and 1,363 live born children were available for follow-up. Dietary data was collected at child's age of 4 years using an FFQ. Information of sociodemographic and lifestyle factors was obtained using questionnaires. Data on height, weight, and waist circumference were repeatedly collected in early childhood. Blood samples were obtained to determine concentrations of leptin and adiponectin at the age of 4 years and of total, LDL, and HDL-cholesterol, and triglycerides at the ages of 4 and 6 years. Systolic and diastolic blood pressure of the children were measured at both time points. In addition, at the age of 6 years, body composition of the children was measured using BIA.

Outline

Chapter 2 of this thesis focuses on overall diet in early childhood. **Chapters 2.1** and **2.2** describe parental feeding-related determinants of diet quality in early childhood, including maternal history of eating disorders (Chapter 2.1) and feeding practices (Chap-

ter 2.2). **Chapter 2.3** focuses on dietary taste patterns in the diet of young children. In **chapter 2.4**, we evaluated overall diet quality in school-age children in the Generation R Study, its socioeconomic and lifestyle determinants, and its relation with diet quality in early childhood.

Chapter 3 focuses on diet quality in childhood in relation to children's body composition and cardiometabolic health. **Chapters 3.1** and **3.2** describe our research on diet quality in relation to growth and body composition in the Generation R Study (Chapter 3.1) and the ABCD Study (Chapter 3.2). **Chapter 3.3** presents results on the associations of diet quality with bone health in childhood. **Chapters 3.4** and **3.5** describe associations of diet quality with cardiometabolic health in children in the Generation R Study (Chapter 3.4) and the Rhea Study (Chapter 3.5).

Chapter 4 focuses on diet and atopic diseases in childhood. In Chapter 4.1, associations of diet quality at different time points in childhood with allergic sensitization and atopic diseases in the Generation R Study are presented. **Chapter 4.2** provides an overview of the current scientific literature on the effects of dietary interventions in the first 2 years of life on the development of atopic diseases.

Chapter 5 provides on overview of the main findings from all studies described in this thesis. In this chapter, major strengths and limitations as well as implications and recommendations for future studies are discussed.

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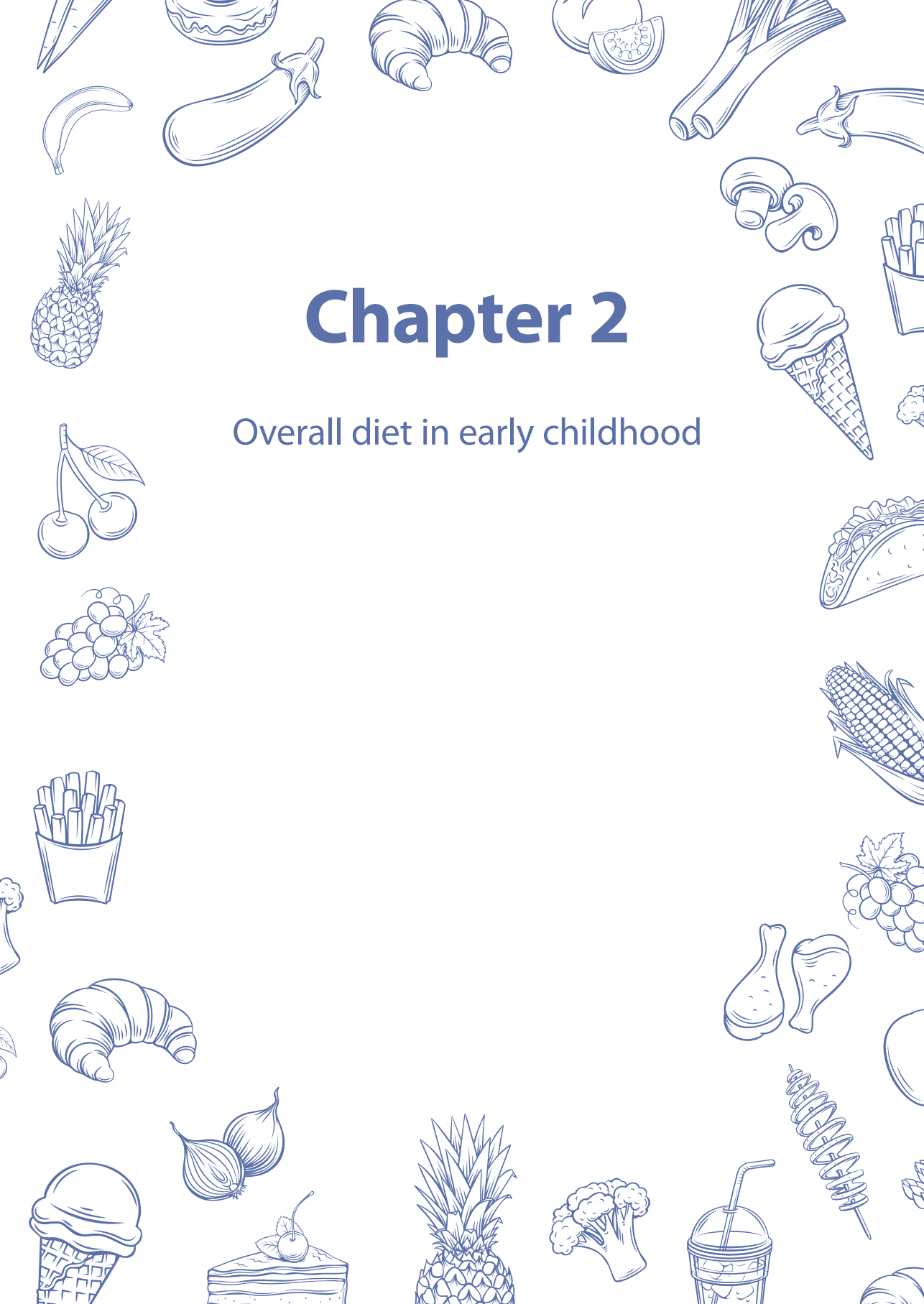

Chapter 2

Overall diet in early childhood


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Chapter 2.1

Maternal history of eating disorders: diet quality during pregnancy and infant feeding

Nguyen AN, de Barse LM, Tiemeier H, Jaddoe VWV, Franco OH, Jansen PW, Voortman T.

Maternal history of eating disorders: Diet quality during pregnancy and infant feeding. *Appetite*. 2017;109:108-114.

ABSTRACT

We studied associations of maternal history of eating disorders (EDs) with diet quality of pregnant women and their infants, and breastfeeding practices. We included 6,196 mother-child pairs from Generation R, a population-based cohort in the Netherlands. Maternal history of lifetime EDs was assessed during pregnancy with a questionnaire. Dietary intake during pregnancy and in infancy was assessed with food-frequency questionnaires and diet quality scores were calculated, reflecting adherence to dietary guidelines. Breastfeeding practices were assessed with questionnaires at 2, 6, and 12 months. We observed that, after adjustment for socioeconomic and lifestyle factors, women with a history of EDs had a higher diet quality than women without a history of EDs (B=0.24SD, 95%CI:0.15;0.33). Mothers with a history of EDs were less likely to breast-feed (unadjusted OR=0.68, 95%CI:0.51;0.93), although no longer statistically significant after adjustment (OR=0.75, 95%CI:0.55;1.03). These findings suggest that mothers with a history of EDs seem slightly less likely to initiate breastfeeding, however, this warrants further investigation. At the age of 1 year, infants of mothers with a history of EDs had a higher diet quality (B=0.15SD, 95%CI:0.02;0.27). We conclude that mothers with a history of EDs and their infants have a relative good diet quality, although follow-up studies are needed to assess the long-term associations with diet in later childhood and adolescence.

INTRODUCTION

Eating disorders (EDs) are mental disorders characterized by disordered eating and distorted body images [1,2]. Anorexia nervosa (AN) is characterized by an extreme restriction of energy intake, a low body weight, an intense fear of gaining weight, and a distorted body image [1,2]. Bulimia nervosa (BN) is characterized by recurrent periods of uncontrolled binge-eating, followed by compensatory behaviors to prevent weight gain [1,2]. Women with an ED have an increased risk of psychiatric co-morbid disorders and medical complications [3,4], including fertility difficulties [5,6], pregnancy complications [7-9], and their offspring might be at increased risk of health issues [6,10]. Women who suffered from an ED in the past may be more aware of what they eat during pregnancy [11] and which foods they provide to their infants [11]. As nutrition during pregnancy and in early childhood may have long-term consequences for growth, development, and health [12-14], it is important to study diet quality during these periods.

Women with a history of EDs may have more nutritional knowledge and therefore provide themselves and their children with healthier diets [15,16]. Indeed, pregnant women with a history of EDs seem more likely to adhere to a dietary pattern characterized by a high intake of meat substitutes, legumes, nuts and herbal teas [17], and to have lower intakes of high-fat meats [18]. Among school-aged children of mothers with a history of EDs, a higher adherence to a data-driven 'health conscious/vegetarian' dietary pattern has also been reported [19]. Likewise, at ages 1-4 years, these children ate less junk food than children of mothers without a history of EDs [20]. Less is known about diet quality in infancy. Moreover, adherence to these data-driven dietary patterns or a low consumption of high-fat foods,does not necessarily imply that the overall diet is actually healthier [21,22]. Therefore, further research examining the overall diet quality beyond specific patterns in women with a history of EDs and their infants is needed.

Although mothers with a history of EDs may provide themselves and their infants with healthier diets, they may face difficulties with breastfeeding [20]. Enduring shape concerns and body awareness in women with a history of EDs could evoke feelings of embarrassment of breastfeeding [6,20]. Alternatively, the common belief that breastfeeding promotes weight loss may increase breastfeeding initiation and duration in women with a history of EDs [23], who may still have the desire to be thin. Contrasting results with regard to breastfeeding have been reported, with a study showing that mothers with a history of EDs were more likely to start breastfeeding and to continue for a longer period [24], whereas other studies found shorter [25,26], or similar durations [27-29]. Thus, associations between maternal EDs and breastfeeding remain unclear.

Therefore, we aimed to explore the associations between maternal history of EDs and overall diet quality of women during pregnancy, as well as their breastfeeding practices and their infants' diet quality during the first year of life.

METHODS

Study design and participants

This study was embedded in the Generation R Study, a multi-ethnic population-based prospective cohort from fetal life onward, conducted in Rotterdam, the Netherlands [30]. Pregnant women living in Rotterdam, with an expected delivery date between April 2002 and January 2006 were invited to participate (baseline response rate: 61%). All participating parents gave written informed consent and medical ethical approval was obtained from the medical ethical committee of the Erasmus Medical Center. Further information is available elsewhere [30].

A total of 6,608 women were enrolled during pregnancy, provided information on their history of EDs and gave full consent for the prenatal and postnatal phase of the study. Those with missing data on all dietary outcome variables were excluded (n= 412), resulting in a total of 6,196 mother-child pairs with eligible data. Because data on diet quality and breastfeeding were not complete for all participants, the population for analysis varied per specific analysis (n between 2,933 and 5,035).

Maternal history of eating disorders

Mothers' history of lifetime EDs was assessed with a self-report questionnaire during pregnancy as described in detail elsewhere [31,32]. The questionnaire included a vignette to clarify what was meant by AN and BN. This vignette was based on diagnostic criteria [1], but was slightly changed to create a clear and understandable description of both AN and BN. The vignette was followed by questions whether the women had suffered from either AN or BN (ever and in the previous year), such as: "Have you ever tried to lose weight to the extent that you may have suffered from anorexia?", "Have you suffered from anorexia in the past year?", and "Have you ever had bouts of compulsive eating as described for bulimia?". Additionally, the questionnaire included items about treatment, medication, and the inability to work as a result of the disorder. Women who answered 'yes' on at least one of these questions, were categorized as having a history of EDs. Due to a low prevalence of EDs in the year before pregnancy [32], women were grouped according to their lifetime history of any ED (i.e., a history of any ED versus no history of EDs).

Given the large sample size, it was not feasible to obtain a clinical diagnosis. However, in a sub-sample (n= 928) of the Generation R Study, our self-reports of EDs were evaluated against clinical diagnoses. Excellent sensitivity (100%) and specificity (96%) were found for self-reported AN, and very good sensitivity (94%) and specificity (81%) were found for self-reported BN [32].

Diet quality during pregnancy

Women's dietary intake in early pregnancy was assessed using a food frequency questionnaire (FFQ) at enrollment (median 13.6 weeks of gestation, interquartile range (IQR) 12.4-16.2). The FFQ included foods that were frequently consumed in the Dutch population and was modified for use during pregnancy [33]. Energy and nutrient intakes were calculated using the Dutch food composition table from 2006 [34]. The FFQ was validated against three 24-hour recalls among 71 pregnant women living in Rotterdam. Intra-class correlation coefficients for macronutrient intakes ranged from 0.5 to 0.7 [35].

National dietary guidelines [36] were used to develop a predefined diet quality score for pregnant women. The following 15 components and cut-offs were included in the diet score: vegetables (≥200 grams/d), fruit (≥200 g/d), whole grains (≥90 g/d), legumes (≥135 g/wk), nuts (≥15 g/d), dairy (≥300 g/d), fish (≥100 g/wk), tea (≥450 g/d), grain quality (ratio whole grains of total grains), soft fats and oils (ratio of total fat), red meat (≤375 g/wk), sugar-containing beverages (≤150 g/d), alcohol (yes/no), salt (≤6 g/d), and folic acid supplements in early pregnancy (periconceptional/first ten weeks/not). For each component, except for alcohol and folic acid supplements, the ratio of the reported intake and the recommended intake was calculated. For example: a woman with a vegetable intake of 120g/d received a score of 0.6 (120g/d divided by 200g/d) for the vegetable component. The maximum score for each component was 1; if a woman exceeded the recommended intake, her score remained 1. For sugar-containing beverages, red meat, and salt, the scores were reversely coded, meaning that higher scores on these food groups reflect lower intakes. Alcohol intake was dichotomously coded, with no intake scored as 1 and any alcohol intake scored as 0. Intake of folic acid supplements was also categorized, with intake periconceptionally scored as 1; in the first ten weeks of gestation scored as 0.5; and no intake in these periods scored as 0. The scores for the individual components were summed, resulting in an overall score ranging from 0 to 15, with a higher score representing a healthier diet.

Breastfeeding

Information on breastfeeding initiation and duration was obtained from delivery reports and postnatal questionnaires at the child's ages of 2 months, 6 months, and 12 months [30]. Mothers were asked whether they had ever breastfed their child (yes/no) and if yes, at what age they stopped breastfeeding their children.

Infant's diet quality

Dietary intake of the child was assessed using a semi-quantitative 211-item FFQ, which was filled out by the mothers when the children were at a median age of 12.9 months (IQR: 12.7-14.0) [37,38].. This FFQ included foods that are frequently consumed by children aged 9-18 months, according to a Dutch national food consumption survey in 2002 [39].

Questions covered the frequency of consumption, serving sizes, type of food items, and food preparation over the last month [37]. This FFQ was validated against three 24-hour recalls in a sample of 32 Dutch children aged 14 months living in Rotterdam. This validation showed reasonable to good intra-class correlation coefficients for nutrient intake of 0.4 to 0.7 [37,38].

The 10 following components were included in the infant diet quality score: vegetables (≥100g/d), fruit (≥150g/d), bread and cereals (≥70g/d), rice, pasta, potatoes and legumes (≥70g/d), dairy (≥350g/d), meat, poultry, eggs and meat substitutes (≥35g/d), fish (≥15g/d), oils and fats (≥25g/d), candy and snacks (≤20g/d), and sugar-sweetened beverages (≤100g/d) [38]. Similar to the maternal diet quality score, ratios of the reported intake and recommended intake were calculated for each component, with reverse coding for the candy and snacks and sugar-sweetened beverage components. Subsequently, these scores were summed, resulting in an overall score ranging from 0 to 10, with higher scores representing a healthier diet. More details on this score are described elsewhere [38].

Covariates

Based on knowledge and previous studies [19,40,41], several covariates that might influence the associations were considered. Potential covariates included maternal age, ethnic background (based on country of birth of the mother and her parents, categorized into Dutch or non-Dutch), educational level (low: ranging from no education up to lower vocational training, or high: higher vocational training and higher academic education), body mass index (BMI), net household income (lower or higher than €2000 per month), and psychiatric symptoms. All variables, except for maternal BMI, were assessed using questionnaires during pregnancy. Maternal psychiatric symptoms were measured with the Brief Symptom Inventory (BSI), a validated 53-item self-report questionnaire. The overall score ranged from 0 to 4, with higher scores representing higher levels of psychiatric symptoms [42]. Maternal height and weight were measured at enrollment in the study to calculate BMI (kg/m^2) [30]. Child sex was examined as a potential effect modifier, because maternal influence on dietary intake might be different for sons and daughters [43,44]. Information on child sex was obtained from birth records.

Statistical analyses

Linear and logistic regression analyses were used where appropriate to assess whether maternal history of any ED was associated with the different dietary measures. In all analyses, maternal history of EDs was coded as 'history of any ED' or 'no history of EDs', with the latter category as the reference. The diet quality scores for pregnant women and infants were standardized for energy intake using the residual method [45]. All associations were analyzed in three models: 1) a crude unadjusted model, 2) a model adjusted for maternal age, ethnic background, educational level, BMI, and household income,

and 3) a model additionally adjusted for maternal psychiatric symptoms. We adjusted separately for psychiatric symptoms because controlling for these symptoms may represent over-adjusting due to the high co-occurrence of EDs with these symptoms [46]. Effect modification by child sex was assessed in the analyses with child diet quality, by including an interaction term in all models.

Sensitivity analyses were performed in participants with a Dutch ethnic background only (n between 1,975 and 2,971) to reduce the risk of residual confounding [47], because the FFQs were developed and validated for a Dutch population [37,48]. Also, analyses with the diet quality score as outcome were repeated, using the original diet quality scores without standardization for energy intake.

To reduce potential bias due to missing values on some of the covariates (ranging from 0% for maternal age to 11.6% for household income), these variables were estimated using multiple imputation techniques (n= 10 imputations) [49]. The results presented are the pooled regression coefficients or odds ratios of the 10 imputed datasets. All statistical analyses were carried out using the statistical software program IBM SPSS statistics, version 21.

Non-response analyses

Of the 6,608 mothers who provided information on their history of EDs, mothers with missing data on all dietary outcome measures (n= 412) were compared to mothers with at least one dietary outcome measure available (n= 6,196). Mothers with missing data on all dietary outcomes were younger ($t(453.5)= -9.7$, $p<0.001$), more often of non-Dutch origin ($x^2(1)= 132.8$, $p<0.001$), lower educated ($x^2(1)= 99.7$, $p<0.001$), and had a higher BMI ($t(450.6)= 2.4$, $p<0.05$), a lower household income ($x^2(1)= 101.6$, $p<0.001$), and higher levels of psychiatric symptoms ($t(414.9)= 6.9$, $p<0.001$).

RESULTS

Population characteristics

Characteristics of the study population are presented in **Table 2.1.1.** In total, 9.5% (n= 591) of the mothers reported to have experienced an ED at any point in their life. Mothers with a history of any ED reported more psychiatric symptoms (median BSI score: 0.29 versus 0.15 for women without a history of EDs, $p <0.001$). Women with and without a history of EDs did not differ significantly on any other characteristics. Most of the women had a Dutch ethnic background (55.8%). Of the non-Dutch group, the largest ethnic groups were women with a Surinamese, Turkish, or Moroccan background. The mean diet quality score of children at age 1 years was 4.3 (standard deviation (SD)= 1.4) on a theoretical range from 0 to 10.

Table 2.1.1. General characteristics of the study population

		N	Percentage, mean (SD), median (IQR)[a]	
Maternal characteristics				
Age at enrollment	mean years (SD)	6,196	30.3	(5.0)
Ethnic background[b]	% Dutch	3,459	55.8	
Educational level[c]	% high	2,914	47.0	
Body mass index at enrollment (kg/m^2)	median (IQR)	6,196	23.7	(21.6-26.6)
Household income	% ≥2000 €/month	3,824	61.7	
Psychiatric symptoms	median (IQR)	6,196	0.15	(0.06-0.35)
History of lifetime eating disorders	% yes	591	9.5	
Diet quality score in pregnancy (before standardization)	mean (SD)	4,824	7.6	(1.6)
Breastfeeding initiation	% yes	4,616	91.7	
Breastfeeding duration	median months (SD)	3,673	3.5	(1.5-8.5)
Child characteristics				
Sex	% girls	3,126	50.5	
Diet quality score at age 1 year (before standardization)	mean (SD)	2,933	4.3	(1.4)

[a]Values are percentages for categorical variables, means (standard deviation) for continuous normally disturbed variables, and medians (interquartile range) for continuous non-normally distributed variables, derived from the imputed dataset (n = 10 imputations).
[b]Large non-Dutch groups included Surinamese (8.2% of all participants), Turkish (6.9%), and Moroccan (4.9%).
[c]Low: ranging from no education up to lower vocational training; high: higher vocational training and higher academic education

Maternal diet quality score

The associations between maternal history of EDs and maternal diet quality score are presented in **Table 2.1.2**. In all models, including model 3, in which associations were independent of maternal psychiatric symptoms, pregnant women with a history of any ED had a higher diet quality score (B= 0.24 SD, 95% confidence interval (CI): 0.15; 0.33) than pregnant women without such a history.

Breastfeeding

In the unadjusted model (model 1), mothers with a history of EDs were less likely to initiate breastfeeding (OR= 0.68, 95%CI: 0.51; 0.93, Table 2.1.2). We observed a similar association after adjustment for covariates, however, the effect estimate slightly attenuated and was no longer statistically significant (model 3: OR= 0.75, 95%CI: 0.55; 1.03). Among mothers who breastfed their infants, we did not find any significant differences in the duration of breastfeeding between mothers with and without a history of EDs (B= 0.15 months, 95%CI: -0.27; 0.57).

Table 2.1.2. Associations of maternal history of eating disorders (EDs) with maternal and infant diet quality and breastfeeding initiation and duration

	Maternal diet quality score (SD)[a] (N= 4,824) B (95%CI)	Breastfeeding initiation (yes/no) (N= 5,035)[a] OR (95%CI)	Breastfeeding duration (months) [a] (N= 3,673) B (95%CI)	Infant diet quality score (SD)[a] (N= 2,933) B (95%CI)
No history of ED	*0 [Reference]*	*1 [Reference]*	*0 [Reference]*	*0 [Reference]*
Lifetime history of any ED[b]				
Model 1	**0.22(0.12; 0.31)**	**0.68 (0.51; 0.93)**	0.01 (-0.42; 0.43)	**0.13 (0.00; 0.25)**
Model 2	**0.23(0.14; 0.32)**	0.74 (0.54; 1.01)	0.11 (-0.31; 0.52)	**0.13 (0.01; 0.26)**
Model 3	**0.24(0.15; 0.33)**	0.75 (0.55; 1.03)	0.15 (-0.27; 0.57)	**0.15 (0.02; 0.27)**

[a]Values are regression coefficients or odds ratios with 95% CIs from linear or logistic regression analyses. Values can be interpreted as the difference between any type of ED and the reference group (no ED). **Bold** values indicate statistically significant effect estimates.

[b]Number of cases with a history of eating disorders; n= 453 for maternal diet quality analyses, n= 478 for breastfeeding initiation analyses, n= 330 for breastfeeding duration analyses, and n= 266 for infant diet quality analyses.

Model 1 is unadjusted.

Model 2 is additionally adjusted for Adjusted for maternal: age, ethnic background, educational level, and BMI, and household income.

Model 3 is additionally adjusted for Additionally adjusted for maternal psychiatric symptoms.

Infant diet quality score

Table 2.1.2 also shows that infants of mothers with a history of EDs had a higher diet quality score (model 3: B= 0.15 SD, 95%CI: 0.02; 0.27) than infants of mothers without such a history. Results did not significantly differ between boys and girls (p for interaction >0.05).

Sensitivity analyses

Analyses restricted to the subsample of participants with a Dutch ethnic background only (n between 1,975 and 2,971) showed similar associations between maternal history of EDs and the dietary outcomes. Only the association between maternal history of EDs and infants diet quality was – although in the same direction – no longer statistically significant (B= 0.12, 95%CI: -0.03; 0.28), probably due to reduced power. Also the analyses with and without standardization for energy intake showed similar results.

DISCUSSION

In this population-based study, we found that maternal history of EDs was associated with a higher diet quality in both pregnant women and their infants. We did not find a statistically significant association of maternal history of EDs with breastfeeding initiation or duration.

Our findings of a higher diet quality during pregnancy are in line with previous studies, reporting that women with a history of EDs consumed less meat, butter, and full-fat milk and more legumes, margarine, vegetable oils, and skimmed milk compared to women without a history of EDs [17]. Congruently, Siega-Riz et al. (2008) reported lower intakes of high-fat meats and sweetened beverages among pregnant women with past or current BN. Although these studies focused on individual food groups, the choices in individual food groups that these women made, are in line with current dietary guidelines. Thus, these results may imply a desire to make healthy food choices, which is confirmed by our findings of a higher overall diet quality among pregnant women with a history of EDs.

Our findings from unadjusted models suggest that mothers with a history of EDs were slightly less likely to initiate breastfeeding. However, after adjustment for covariates, the effect estimate slightly attenuated and was no longer statistically significant. Several explanations, such as socioeconomic factors, might account for this non-significant finding. However, after adjustment for socioeconomic factors, the attenuation in effect size was only minimal, suggesting that limited power after adjustment rather than confounding may explain why statistically significant differences were no longer detected. In a much larger Norwegian cohort (n= 39,355), Torgersen et al. (2010) reported differences in breastfeeding practices between mothers with and without an ED, whereas studies with small sample sizes (ED cases between n= 10 and n= 25) found no differences [27-29]. In contrast to our findings, Torgersen et al. (2010) did not observe differences in breastfeeding *initiation*, but reported shorter *durations* of breastfeeding among mothers with EDs. The same underlying mechanism (i.e. embarrassment and body dissatisfaction [6,20]) could underlie an association of maternal ED history with breastfeeding initiation and duration. Therefore, contrasting findings could be attributed to ED ascertainment. Torgersen et al. defined the presence of an ED in the six months prior to pregnancy and during pregnancy, which may imply that these women had more active and severe psychopathology than the women with a *lifetime* history of EDs in our study. Indeed, they found stronger associations for women with AN than in women with ED not otherwise specified [26], who may have less severe ED psychopathology [50]. Alternatively, since Torgersen et al. did not observe an association between maternal history of BN and breastfeeding, the associations may be ED-specific. In our study, we did not distinguish between AN and BN because the proposed mechanisms, which were body shame, dissatisfaction, embarrassment, and high body awareness, are characteristics of both AN and BN [1,2], and because did not have enough power to distinguish subtypes of EDs.

Although infants of mothers with a history of EDs seemed to be breastfed somewhat less than infants of mothers without a history of EDs, they had a higher diet quality around the age of 1 year. This seems contrary to previous findings, reporting that children who were breastfed, had a higher diet quality [38]. However, this may be different for children of mothers with a history of EDs. These mothers often have a negative self-image [1,2], and

may therefore not feel comfortable about breastfeeding [20]. Previous studies reported that well-functioning breastfeeding requires confidence and belief in the capacity of one's body [51,52]. Moreover, in the general population, women with higher body image concerns were less likely to initiate breastfeeding and more likely to breastfeed for a shorter period [52]. However, because of a higher awareness of food [11], mothers with a history of EDs may have the desire to provide their children with healthy food and limit unhealthy or high-fat foods, which is reflected by the higher overall diet quality score.

Several explanations might account for our findings of the higher diet qualities in pregnant women with a history of EDs and their infants. Some studies suggested that women with EDs may have more nutritional knowledge, especially with regard to the caloric content of food [15,16], or that women who recovered from an ED had a higher preference for foods with health benefits [53]. Thus, mothers with a history of EDs may be more keen and knowledgeable on providing themselves and their children a healthy diet. Alternatively, our findings may be attributed to ongoing or recurrent ED symptoms. Previous studies have reported that ED symptoms tend to improve during pregnancy, but worsen postpartum [54,55]. However, other studies reported that ED symptoms may still be present during pregnancy [56] and that women with an ED tend to worry more about weight gain during pregnancy [57]. To prevent further weight gain, they may therefore choose healthier food products with low calories, thereby scoring higher on our quality score. Since reoccurrence of ED symptoms may be present in the postpartum period [55], concerns about body weight and shape may not only apply to women themselves, but also to their infants. We previously found that children of mothers with a history of EDs or children with a higher diet quality did not have a lower BMI at the age of 6 years [31,58]. However, several studies indicated that mothers with a history of EDs tend to worry about their children's diet [10,44], and weight [59], which may explain the higher infant diet quality.

Strengths and limitations

This study is one of the first that has examined the associations between a mother's history of EDs and diet quality during pregnancy as well as offspring's diet quality in early childhood. The strengths of this study are its population-based, longitudinal design, the repeated measurements of breastfeeding practices, and availability of several covariates, including maternal psychiatric symptoms allowing us to distinguish between EDs and psychiatric problems in general. Another strength is the use of a predefined approach to measure overall diet. An advantage of a predefined approach over a data-driven approach is that predefined diet scores are based on dietary guidelines [21,22], which may therefore better reflect a healthy diet.

Despite these strengths, several limitations should be considered. First, maternal history of EDs was self-reported, which might have resulted in reporter bias. However,

substantial overlap between self-reported lifetime ED and clinical diagnosis in a small subsample of the Generation R Study has been shown previously [32]. Second, a general limitation of FFQs to measure dietary intake is that they rely on memory and reported intakes are subject to measurement errors [60]. Moreover, both exposure and outcomes were reported by the same informant (i.e. the mother), which could have led to common method variance bias [61]. Given the possible preoccupation with diet [29], mothers with a history of EDs may have underreported energy-dense, unhealthy food items, because of embarrassment. If so, the association of maternal history of EDs with a higher diet quality may reflect an overestimation. Alternatively, mothers with a history of EDs may have over-reported unhealthy food items, because of a higher awareness of eating high calorie food, resulting in an underestimation of our findings. Even though Whelan and Cooper [62] provided evidence that women with EDs are capable of reporting reliably on their children's eating behavior, future research should use additional informants of both mothers' and children's food intake. Another limitation is that our FFQs were developed to measure a Dutch diet and that the diet quality scores were partly based on Dutch dietary guidelines, whereas women and children with different ethnic backgrounds, such as Surinamese, Turkish, and Moroccan, were included in our study population. Thus, some caution is needed with regard to the diet quality scores of participants with another ethnic background. However, in our sensitivity analyses restricted to participants with a Dutch ethnic background only, similar results were found, suggesting no large bias due to ethnic background.

Conclusion

Mothers with a history of EDs and their infants had a higher diet quality, independent of psychiatric symptoms, suggesting that our findings are specific for EDs. Although our finding of a lower tendency to initiate breastfeeding among mothers with a history of EDs needs further evaluation, our results suggest that women with a history of EDs and their infants have a relatively good diet quality. However, further research is needed to examine whether these children remain to eat healthier when they start making their own food choices. Further research in which children are followed as they grow older is needed in order to assess long-term associations, preferably with more objectively measured data on EDs as well as on dietary intake.

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Supplemental material for this chapter can be found online:
https://ars.els-cdn.com/content/image/1-s2.0-S0195666316308261-mmc1.pdf


DRINK

Chapter 2.2

Associations of feeding practices with diet quality in childhood

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Associations of feeding practices and family eating routines with children's diet quality: results from the Generation R Study. *Submitted for publication.*


DRINK

Chapter 2.3

Dietary taste patterns in early childhood and its associations with socioeconomic and lifestyle factors

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Dietary taste patterns in early childhood: the Generation R Study.
Submitted for publication.


DRINK

Chapter 2.4

Diet quality in childhood: the Generation R Study

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ABSTRACT

Objective: We aimed to evaluate diet quality of 8-year-old children in the Netherlands, to identify sociodemographic and lifestyle correlates of child diet quality, and to examine tracking of diet quality from early to mid-childhood.

Methods: For 4,733 children participating in a population-based cohort, we assessed dietary intake using a validated food-frequency questionnaire at a median age of 8.1 years (interquartile range:8.0-8.2)(2011-2014). Based on dietary guidelines, we developed and validated a food-based diet quality score for children consisting of ten components (score 0-10): sufficient intake of vegetables; fruit; whole-grains; fish; legumes; nuts; dairy; oils &soft fats; and low intake of sugar-containing-beverages; and high-fat and processed meat.

Results: We observed a mean (±SD) diet quality score of 4.5 (±1.2) out of a maximum of 10. On average, intake of legumes, nuts, and oils or soft fats was below recommendations, whereas intake of sugar-containing beverages and high-fat or processed meat was higher than recommended. The main factors associated with higher diet quality were higher maternal educational level (β=0.29, 95%CI:0.21,0.37 versus low education), higher household income (β=0.15, 95%CI:0.05,0.025), no maternal smoking (β=0.13, 95%CI:0.25,0.02 versus current smoking), and less screen time (β=0.31, 95%CI:-0.38,-0.24)– all independent of each other. For children with available dietary data at age 1 year (n=2,608), we observed weak tracking of diet quality from early to mid-childhood (Pearson's r=0.19,k=0.11 for extreme quartiles).

Conclusion: Overall diet quality of 8-year-old children is not conform dietary guidelines, especially for children having more screen time, children of lower educated and smoking mothers, and from lower-income households.

INTRODUCTION

A healthy diet during childhood is important for healthy growth and development [1], and may contribute to the prevention of obesity and chronic diseases later in life [2,3]. Furthermore, dietary habits in childhood have been shown to track over time and are an important predictor of diet quality in adulthood [4]. Therefore, it is important to examine children's dietary intake, to identify potential gaps between their actual and recommended intake, and to study determinants of diet, in order to develop targeted interventions focusing on groups with a high risk of poor dietary habits early in life.

Given the complexity of the human diet and the strong interactions between intake of different foods and nutrients, measuring overall dietary patterns is recommended as a complementary approach to measuring the intake of only single foods or nutrients [5,6]. One way to study overall diet is by predefined diet quality scores, which are usually based on dietary guidelines [5,7]. Although the use of diet quality indices in children has increased over the past years, Marshall et al. suggested in their systematic review that more prospective cohort studies evaluating diet quality in children and its impact on health are needed [8]. A few studies from different countries including the UK, Brazil, and the US, assessed diet quality among school-age children [9-11]. However, because dietary habits and guidelines may differ between countries and cultures, it is important to use a diet quality score that assesses recommendations specific for the study population [12]. Previously, we developed a food-based diet quality score specifically for preschool children [13]. However, to date, no diet quality score is available for school-age children in the Netherlands, and factors related to diet quality have not been studied in this age category. Furthermore, previous studies reported tracking of diet from mid-childhood or adolescence to adulthood [2,14], but information on changes in diet quality from early childhood to mid-childhood is scarce. This information is needed in order to establish whether dietary interventions could be efficient early in life [2].

Therefore, we aimed to evaluate overall diet quality of 8-year-old children participating in a large population-based cohort in the Netherlands. For this aim we developed a new food-based diet quality score based on current Dutch dietary guidelines [15], and we assessed the construct validity of this new diet quality score. This score can be applied in future studies to evaluate diet quality, to investigate associations between diet quality and health, and to support future dietary advice and interventions. Furthermore, we aimed to identify which parental and child sociodemographic and lifestyle factors, such as educational level, physical activity, and screen time correlate with diet quality of children and we aimed to investigate associations between diet quality at the ages of 1 and 8 years. This information can help to identify the best target groups and time frame for interventions to improve diet quality in children.

METHODS

Study design and study population

This study was embedded in the Generation R Study, a multiethnic population-based prospective cohort from fetal life onward in Rotterdam, the Netherlands. Women living in the city of Rotterdam were enrolled during pregnancy. Children participating in this study were born between April 2002 and January 2006. The study was approved by the Medical Ethics Committee of Erasmus Medical Center and written informed consent was obtained from parents of all participating children [16]. A dietary questionnaire was sent to mothers who provided consent for follow-up when their child was around the age of 8 years (n=7,662). The questionnaire was returned for 4,787 children (62.5%). After exclusion of subjects with invalid dietary data (n=54), defined as a reported energy intake below 650 (n=47) or above 3,700 kcal/d (n=7), valid dietary data were available for 4,733 children (**Figure 2.4.1**). Of all children with dietary data at the age of 8 years, 2,608 children also had dietary data available at their age of 1 year.

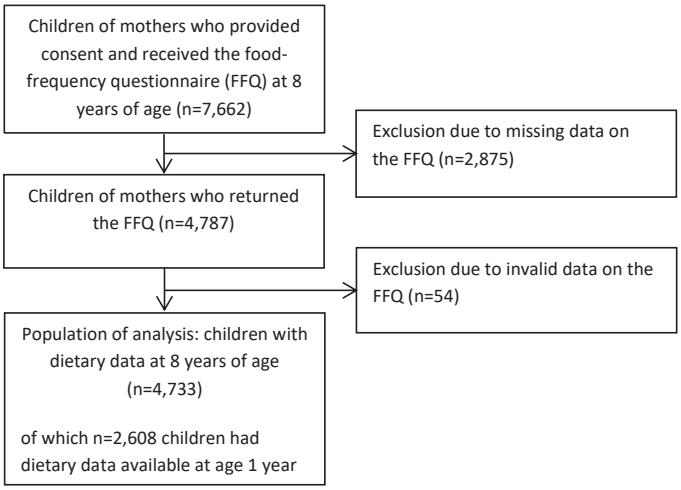

Figure 2.4.1. Flowchart of participants included in the study

Dietary assessment

Dietary intake was assessed at a median age of 8.1 years (interquartile range (IQR): 8.0-8.2) using a validated semi-quantitative food-frequency questionnaire (FFQ) [17]. The FFQ was completed by the parents of the child, using the last four weeks as reference period. As explained in detail previously [17], the FFQ was developed based on results from a national food consumption survey in the Netherlands [18], which resulted in the selection of 71 food items relevant for the energy intake of 2 to 12-year-old children. Questions concerned the frequency of consumption and portion sizes of these foods,

and for 27 food items additional questions were included about specific types or brands and preparation methods. Portion sizes were inquired for in natural units, household units, or grams; and parents were asked to measure the volume of glasses and cups regularly used by their child. Dietary intake data were cleaned and corrected based on detection of missing values, outliers of quantities, and inconsistencies using standardized algorithms developed for the FFQ [17]. Information on frequencies, types, and portion sizes was converted into grams of individual food items per day based on standard Dutch portion sizes, using SAS VoVris (Vovris V2.4, TNO, 1999-2006). Energy and nutrient intakes from foods were calculated using data from the Dutch Food Composition Table (NEVO 2001) with SAS Veves (Veves V2.2, TNO, 1999-2003).

The FFQ has been validated for energy intake among 4 to 6-year-old Dutch children (n=30) using the doubly labelled water method [17]. The Pearson's correlation between energy intake as estimated from the FFQ and energy expenditure measured with doubly labelled water was 0.62, indicating a reasonable capacity to rank subjects with respect to energy intake. Furthermore, no relevant intake-related bias was observed in the Bland-Altman plot. These findings indicate that the FFQ is a valid instrument for the assessment of energy intake in children [17].

Construction of the diet quality score for school-age children

We constructed a food-based diet quality score based on dietary recommendations for children from the Netherlands Nutrition Center [15], thereby also taking into account the Dutch Guidelines for a Healthy Diet of 2015 [19], on which the Nutrition Center recommendations were based. We included ten components (i.e., food groups) in the diet quality score, of which eight were adequacy components (i.e., adequate intake is recommended) and two were moderation components (i.e., low intake is recommended). Only recommended food items were included for the adequacy components, and recommended food items were excluded for the moderation components (**Table 2.4.1**). The components, food items included, and their cut-off values were determined *a priori,* based on the recommendations of the Netherlands Nutrition Center for 8-year-old children [15], and were as follows: fruit (≥150 g/d), vegetables (≥150 g/d), whole-grains (≥90 g/d), fish (≥60 g/w), legumes (≥84 g/w), nuts (≥15 g/d), dairy (≥300 g/d), oils and soft or liquid fats (≥30 g/d), sugar-containing beverages (≤150 g/d) and high-fat and processed meat (≤250 g/w) (Table 2.4.1).

Scoring of diet quality was performed by calculating the ratio of reported and recommended intake for each component [13]. These component scores were truncated at 1. For the adequacy components, this resulted in a minimum score of 0 points when these food items were not consumed and a maximum score of 1 point when the amount of the cut-off value or more was consumed. For example, a fruit intake of 60 g/d resulted in a score of 0.4 (60 divided by 150 g/d) for this component. For the moderation compo-

nents, this scoring system was reversed, with higher scores reflecting lower intakes (e.g., a sugar-containing beverages intake of 75 g/d resulted in a score of 0.5 (1-(75 divided by 150 g/d)). Scores of the individual components were summed, resulting in a total score for diet quality ranging from 0 to 10 on a continuous scale, with a higher score indicating a better overall diet quality.

Table 2.4.1. Components, cut-off values and included and excluded food items of the diet quality score

Component	Cut-off value[a]	Foods included in the diet quality score	Foods not included in the diet quality score
Fruit	≥ 150 g/d	Fresh fruit, frozen fruit, dried fruit (up to 20 g/d[b]), canned fruit without added sugar	Fruit juice, dried fruit (>20 g/d), fruit products with added sugar
Vegetables	≥ 150 g/d	Fresh vegetables, frozen vegetables, canned vegetables[c]	-
Whole-grains	≥ 90 g/d	Brown/ whole grain bread or crackers, whole-grain rice, whole-wheat pasta, whole grain breakfast cereals without added sugar	White bread or crackers, white rice, white pasta, breakfast cereals with added sugar
Fish	≥ 60 g/w	Fish, canned fish, shellfish	Fish products containing <70% fish (e.g. battered fish)
Legumes	≥ 84 g/w	Fresh, dried or canned legumes[c]	-
Nuts	≥ 15 g/d	Nuts, peanuts, peanut butter	Coated nuts
Dairy	≥ 300 g/d	Unsweetened, skimmed and semi-skimmed milk, yoghurt, or quark; dairy products without added sugar; buttermilk; low-fat cheese	Full-fat milk, yoghurt, or quark, dairy products with added sugar, full-fat cheese, whipped cream, ice cream
Oils and soft or liquid margarines	≥ 30 g/d	Vegetable oils, soft margarine (≤ 30% saturated fat of total fat), liquid cooking and frying fats	Hard margarine (>30% saturated fat of total fat), hard cooking and frying fats, butter
Sugar-containing beverages	≤ 150 g/d[d]	Soft drinks, fruit juice, lemonade, fruit juice concentrates	Milk based sugar-containing beverages[e]
High-fat and processed meat	≤ 250 g/w	Processed and/or high fat meat (>5% saturated fat)	Unprocessed low fat meat (≤5% saturated fat)

[a]Based on the recommendations of the Netherlands Nutrition Center and Health Council of the Netherlands [15,19].
[b]According to the guidelines, a maximum of 20 g/d of dried fruit was included in the fruit component.
[c]Canned products with added salt or sugar were not excluded, as no distinction was made in the FFQ.
[d]No quantitative recommendation was available for sugar-containing beverages, we chose a cut-off of 1 glass/d.
[e]As milk-based beverages with added sugar can provide valuable nutrients and have a greater satiating effect compared to sweetened drinks containing sugar only, these were not included in the sugar-containing beverages component.
g/d= gram/ day; g/w= gram/ week.

Diet quality in infancy

To assess tracking of diet quality from infancy to mid-childhood, we used a previously defined diet quality score for infants. As described in detail elsewhere [13], information on dietary intake at the age of 1 year was collected with a semi-quantitative FFQ, which

was developed specifically for this age group. This diet quality score consisted of ten components: vegetables; fruit; bread and cereals; rice, pasta, potatoes, and legumes; dairy; meat; fish; oils and fats; candy and snacks; and sugar sweetened beverages. The scoring system for this diet quality score was similar to that of the diet quality score for 8-year-old children. The score ranged from 0 to 10 on a continuous scale with higher scores reflecting better adherence to dietary guidelines [13].

Assessments of sociodemographic and lifestyle factors

Several sociodemographic and lifestyle factors were assessed for both the children and their parents. Information on date of birth and sex of the child was obtained from medical records and hospital registries. Ethnicity of the child was based on the country of birth of the parents, which was obtained with questionnaires at enrollment. If both parents were born in the Netherlands, the child was considered to have a Dutch ethnic background. If one parent was born outside of the Netherlands, the country of birth of that parent determined the child's ethnicity. If both parents were born abroad, the country of birth of the mother determined the ethnicity of the child [16,20]. Ethnicity was categorized according to the largest ethnic groups in our study population, which were Dutch, Moroccan, Turkish, Surinamese and Antillean, other Western, and other non-Western [13].

During follow-up visits of the participants to our research center at a median ages of 6.0 years (IQR 5.9-6.2) and 9.7 years (IQR 9.6-9.9), we measured several child and maternal factors. As most measurements at these time points were strongly correlated, we used measurements taken at age 9.7 years for the main analyses in the current study, as this age was closest to the age of our dietary assessment at age 8.1 years. Child's height and weight were measured to calculate their body mass index (BMI) (kg/m^2), which was categorized into 'underweight', 'normal weight', or 'overweight' according to the Cole-criteria [21]. Questionnaires were used to assess time spent playing sports (i.e., any organized sports outside school hours), which was categorized into <2, 2 to 4, or ≥4 hours per week, and time spent watching television and/or on the computer (screen time), which was dichotomized into <2 or ≥2 hours per day [22]. At the same visits, we measured mothers' height and weight to calculate BMI, which we categorized into 'underweight' (<18.5), 'normal weight' (≥18.5 to 25), or 'overweight' (≥25) [21]. Information on other parental factors was assessed with questionnaires. Maternal smoking habits were categorized into: 'never smoker', 'past smoker', or 'current smoker'. Maternal educational level was dichotomized into 'no higher education' or 'higher education', with higher education defined as completed higher vocational training or more. Net household income was dichotomized into <2800 or ≥2800 euros per month [23].

Statistical analysis

Child and parental characteristics were described as median (IQR) for continuous variables or percentage for categorical variables. Total diet quality score was described as mean with standard deviation (SD) and as percentage of children with a maximum score. Component scores and intake per component were described as median (IQR) and as percentage of children with a maximum score. Pearson's correlations were used to assess correlations between the individual components of the diet quality score.

Linear regression models were used to identify sociodemographic and lifestyle correlates of diet quality. In these models, we examined children's age, sex, ethnicity, BMI, physical activity, and screen time; and maternal age, BMI, marital status, educational level, and smoking habits; and household income. The basic model was adjusted for total energy intake only; the multivariable model was additionally adjusted for all other sociodemographic and lifestyle variables that were examined in order to assess whether they were independent of each other. Associations of the diet quality score with intake of nutrients associated with a healthy diet were examined in order to assess the construct validity of the diet score (i.e., the degree to which the diet quality score measures a healthy diet) [24]. These associations were evaluated using Pearson's correlations and partial Pearson's correlations, controlling for energy intake.

Pearson's correlations were also used to assess the association between diet quality at age 1 year and 8 years. Tracking of diet quality score from age 1 year to age 8 years was assessed by determining to which extent children maintained their rank in the categories 'lowest 25%', 'middle 50%', or 'highest 25%'. For this, a 3x3 matrix was constructed and a linear weighted Kappa statistic (k) was computed [25], with k <0 indicating poor agreement, and k 0.81-1.0 indicating almost perfect agreement [26].

Because the FFQ was developed and validated for a Dutch population, sensitivity analyses were performed among children with a Dutch ethnic background only (n=3,143). As non-response analysis, descriptive characteristics of children with valid dietary data (n=4,733) were compared to children with missing dietary data but who were eligible for dietary assessment (i.e., those who still participated in the study at the age of 8 years and who received the FFQ) (n=2,929). To reduce potential bias associated with missing data in our study, multiple imputation of missing data on sociodemographic and lifestyle factors was performed and 10 independent datasets were created. Because similar effect estimates were found in analyses with imputed and unimputed data, pooled results after the multiple imputation were presented. All statistical analyses were performed using SPSS version 21.0 (IBM Corp., 2012, Armonk, NY). A two-sided P-value of 0.05 was considered statistically significant.

RESULTS

Subject characteristics

Characteristics of the children and their parents are described in **Table 2.4.2**. The majority of children had a Dutch ethnic background (66.4%). At the 9-year visit, median BMI of the children was 16.9 (IQR 15.7-18.4), with 80.7% of children having a normal weight, 7.2% underweight, and 12.1% overweight. More than half (51.6%) of the children had a screen time of ≥2 hours per day. Median BMI of the mothers was 24.5 (IQR 22.3-27.5), with 55.1% of mothers having a normal weight and 44.1% being overweight. The majority of mothers was highly educated (62.8%) and had never smoked (52.9%).

Characteristics were similar before and after multiple imputation. Of the 7,662 children whose parents received the FFQ, children with missing dietary data (n=2,929) more often had a non-Dutch ethnic background and their mothers were on average younger, lower educated, had a higher BMI, and a lower household income.

Diet quality

Our diet quality score approximated a normal distribution with a mean (SD) of 4.5 (1.2). None of the children reached the maximum possible diet quality score of 10. Median scores on most diet quality score components were around or below 0.5 out of a possible maximum of 1 (**Table 2.4.3**). For the adequacy components, median intakes of vegetables, legumes, nuts, dairy, and oils or soft or liquid fats were well below the cut-off values in our study population. For example, median daily vegetable intake was 79 g (IQR 49-123), whereas 150 g is recommended, resulting in a median component score of 0.53 (IQR 0.32-0.82) out of 1 for vegetables. Intakes of the two moderation components (sugar-containing beverages and high-fat and processed meat) exceeded the recommended intake in most children, with corresponding low scores. Median sugar-containing beverages intake, for example, was 323 g/d (IQR 180-524), with a median score of 0.0 (IQR 0.0-0.0) and only 12.8% of the children having a score above zero. Components with the highest median scores were whole-grains (1.0 (IQR 0.72-1.0)), fruit (0.74 (IQR 0.51-1.0)), and fish (0.63 (IQR 0.0-1.0)). Correlations between the diet score components ranged from -0.13 to 0.08. The scores were comparable between boys and girls (**Supplemental table 2.4.1**).

Associations between the diet quality score and several nutrients was assessed to examine construct validity. We observed a positive correlation between the diet quality score and the intake of protein, mainly plant protein (r=0.41), dietary fiber (r=0.58), and *n*-3 fatty acids (r=0.24), and inversely correlated with intake of saturated fat, and monosaccharides and disaccharides (r=-0.11) (energy-adjusted, all p <0.01). The score was also positively correlated with intake of all of the examined micronutrients (energy-adjusted, r =0.16 to 0.55, all p <0.01) (**Supplemental table 2.4.2)**.

Table 2.4.2. Characteristics of study participants and their parents (n=4,733)

Child characteristics	Median (IQR), Percentage
Boy (%)	49.9
Ethnicity (%)	
Dutch	66.4
Other Western	9.4
Moroccan	3.6
Turkish	5.1
Surinamese and Antillean	7.2
Other non-Western	8.4
Age at FFQ (y)	8.1 (8.0-8.2)
BMI (kg/m^2)	16.9 (15.7-18.4)
Underweight (%)	7.2
Normal weight (%)	80.7
Overweight (%)	12.1
Playing sports (h/w)	
<2	31.9
2-4	40.7
≥4	27.4
Screen time (h/d)	
≥2	51.6
Parental characteristics	
Age mother at 9-year visit (y)	42.0 (39.0-44.6)
BMI mother	24.5 (22.3-27.5)
Underweight (%)	0.8
Normal weight (%)	55.1
Overweight (%)	44.1
Marital status mother (%)	
Married/ partner	88.1
Educational level mother (%)	
Higher education	62.8
Smoking mother (%)	
Never smoker	52.9
Past smoker	33.7
Current smoker	13.4
Household income per month (%)	
≥2800 €	67.6

Values are medians (IQR) for continuous variables, and percentages for categorical variables, on the basis of imputed data (n=10 imputations).
IQR= Interquartile range; FFQ=Food-frequency questionnaire; y= year; BMI=Body mass index; kg/m2= kilogram/ meter^2; h/w= hours/ week; h/d= hours/ day.

Table 2.4.3. Cut-offs values, actual intakes, and scores of the different diet quality score components

Component	Cut-off values	Unit	Intake (n=4,733)	Score (n=4,733)	% with a maximum score
Fruit	≥ 150	g/d	111 (77-167)	0.74 (0.51-1.00)	29.4
Vegetables	≥ 150	g/d	79 (48-123)	0.53 (0.32-0.82)	16.3
Whole-grains	≥ 90	g/d	98 (65-131)	1.0 (0.72-1.00)	57.4
Fish[a]	≥ 60	g/w	38 (0-83)	0.63 (0.00-1.00)	36.0
Legumes[a]	≥ 84	g/w	18 (0-70)	0.21 (0.00-0.83)	21.1
Nuts[a]	≥ 15	g/d	3 (0-10)	0.20 (0.00-0.64)	10.6
Dairy	≥ 300	g/d	164 (54-298)	0.55 (0.18-0.99)	24.9
Oils and soft or liquid fats	≥ 30	g/d	11 (2-17)	0.37 (0.071-0.57)	2.7
Sugar-containing beverages[a]	≤ 150	g/d	323 (180-524)	0.00 (0.00-0.00)	2.1
High-fat and processed meat [a]	≤ 250	g/w	323 (218-453)	0.00 (0.00-0.13)	0.2

Values are median (IQR) Maximum score per component: 1.
Collinearity between the diet score components: r -0.13 to 0.077.
[a]A score of 0 was obtained by 27% of the participants for the fish component, 46.5% for the legumes component, 27.3% for the nuts component, 87.8% for the sugar-containing beverages component, and 68.2% for the meat component.
g/d= gram/ day; g/w= gram/ week; IQR= Interquartile range.

Sociodemographic and lifestyle factors and the diet quality score

Associations between sociodemographic and lifestyle factors and the diet quality score are shown in **Table 2.4.4**. In the multivariable model, children with underweight had a lower diet quality score than children with a normal weight. Children with a screen time of ≥2 hours per week had a 0.31 points lower diet quality score (95%CI -0.38; -0.24) than children with a screen time <2 hours per week, and children who played sports for 2 to 4 hours per week had a 0.10 points higher diet quality (95%CI 0.02; 0.19) than those who played sports <2 hours per week, although no significant difference was found between playing sports for <2 hours per week versus ≥4 hours per week. In the multivariable model, Moroccan children had a 0.29 points higher diet quality score (95%CI 0.10; 0.48) than children with a Dutch ethnicity, whereas in the basic model, without adjustment for the other factors, Turkish as well as Surinamese and Antillean children had a lower diet quality score than children with a Dutch ethnicity. Children's sex or age at dietary assessment was not associated with the diet quality score in the basic and multivariable model.

Parental socioeconomic status was also associated with children's diet quality: children of higher educated mothers or from households with a higher income had a higher diet quality score (Table 2.4.4). Independent of these socioeconomic factors, children of overweight mothers and children of mothers who were current smokers had a lower diet quality score than children of normal-weight or never-smoking mothers, respectively. Sensitivity analyses among Dutch children only showed similar effect estimates.

Table 2.4.4. Associations between sociodemographic and lifestyle factors and the diet quality score

	Basic model[a]		Multivariable model[b]	
	β (95 % CI)	p-value	β (95 % CI)	p-value
Child characteristics				
Sex				
Boy	*Reference*			
Girl	-0.01 (-0.04; 0.03)	0.78	-0.03 (-0.10; 0.04)	0.41
Ethnicity				
Dutch	*Reference*			
Other Western	0.01 (-0.10; 0.13)	0.83	0.03 (-0.08; 0.14)	0.61
Moroccan	0.001 (-0.18; 0.18)	1.00	0.29 (0.10; 0.48)	0.002
Turkish	-0.43 (-0.59; -0.28)	< 0.001	-0.11 (-0.28; 0.06)	0.21
Surinamese and Antillean	-0.21 (-0.34; -0.08)	0.002	0.05 (-0.08; 0.19)	0.47
Other non-Western	-0.11 (-0.23; 0.01)	0.08	0.08 (-0.04; 0.21)	0.19
Age at FFQ (y)	-0.02 (-0.16; 0.12)	0.77	0.06 (-0.08; 0.20)	0.37
Energy intake (100 kcal/ d)	0.10 (0.09; 0.10)	<0.001	0.10 (0.09; 0.11)	<0.001
BMI				
Normal weight	*Reference*			
Underweight	-0.13 (-0.26; 0.003)	0.06	-0.16 (-0.29; -0.03)	0.014
Overweight	-0.17 (-0.27; -0.06)	0.003	0.01 (-0.11; 0.12)	0.92
Playing sports (h/w)				
<2	*Reference*			
2-4	0.17 (0.07; 0.26)	<0.001	0.10 (0.02; 0.19)	0.017
≥4	0.09 (-0.02; 0.20)	0.11	0.04 (-0.06; 0.15)	0.43
Screen time (h/d)				
<2	*Reference*			
≥2	-0.39 (-0.46; -0.32)	<0.001	-0.31 (-0.38; -0.24)	<0.001
Parental characteristics				
Age mother at 9-year visit (y)	0.01 (0.01; 0.02)	<0.001	0.001 (-0.01; 0.01)	0.71
BMI mother				
Normal weight	*Reference*			
Underweight	0.35(-0.04; 0.75)	0.08	0.30 (-0.08; 0.68)	0.12
Overweight	-0.22 (-0.29; -0.14)	<0.001	-0.10 (-0.17; -0.02)	0.01
Marital status mother				
Married/ partner	*Reference*			
No partner	-0.23 (-0.34; -0.12)	<0.001	-0.03 (-0.15; 0.09)	0.61
Educational level mother				
No higher education	*Reference*			
Higher education	0.44 (0.37; 0.51)	<0.001	0.29 (0.21; 0.37)	<0.001
Smoking mother				
Never smoker	*Reference*			

Table 2.4.4. Associations between sociodemographic and lifestyle factors and the diet quality score (continued)

	Basic model[a]		Multivariable model[b]	
	β (95 % CI)	p-value	β (95 % CI)	p-value
Past smoker	0.05 (-0.03; 0.14)	0.23	0.05 (-0.03; 0.13)	0.26
Current smoker	-0.26 (-0.38; -0.14)	<0.001	-0.13 (-0.25; -0.02)	0.027
Household income per month				
<2800 €	*Reference*			
≥2800 €	0.32 (0.23; 0.40)	<0.001	0.15 (0.05; 0.25)	0.004

[a]Values are regression coefficients with 95% confidence intervals from linear regression analyses adjusted for total energy intake.
[b]Values are regression coefficients with 95% confidence intervals from multivariable linear regression analyses including all variables presented in the table.
IQR= Interquartile range; FFQ=Food-frequency questionnaire; y= year; BMI=Body mass index; kcal/ d= kilocalorie/ day; h/w= hours/ week; h/d= hours/ day.

Tracking of diet quality from early to mid-childhood

For children with dietary data at both the ages of 1 year and 8 years (n=2,608), we observed a Pearson's correlation of r=0.19 for the diet quality score between both ages (p<0.01). Significant correlations were also found between the seven individual diet quality score components that were examined at both time points (r=0.11 to 0.23, all p <0.01) **(Supplemental table 2.4.3)**. A linear weighted kappa showed slight agreement between the diet quality scores at both ages (k=0.11 (95%CI: 0.08; 0.14) for their rank in the lowest 25%, middle 50%, or highest 25% of the scores (Supplemental table 2.4.4)**.**

DISCUSSION

We developed a food-based diet quality score based on Dutch dietary guidelines to estimate overall diet quality of children. Using this score, we evaluated diet quality of over 4,700 children at the age of 8 years in a population-based cohort in the Netherlands. We observed that diet quality in this population was suboptimal and none fully adhered to the guidelines. Factors that correlated with a higher diet quality in this group were, amongst others, a higher socioeconomic status and no maternal smoking. We observed only weak tracking of diet quality between the ages of 1 year and 8 years.

Interpretation of findings and comparison with previous research

Diet quality was suboptimal in our study population of 8-year-old children. This is consistent with studies in the US, Brazil, and the UK that showed less than optimal diet quality in similarly aged children [9-11]. Compared to the American population aged 7-9 years [9], level of adherence was similar for the fruit and vegetable components, however, for the dairy component adherence was lower in our study population. This might be

explained by the difference in scoring, as we only included recommended food items in the dairy component, whereas in the US-based study all dairy items were included [9].

As expected from previous studies [27], socioeconomic status was positively associated with diet quality. A strong association was observed particularly for maternal educational level, independent of household income and other factors. Previous studies indicated that individuals with a higher educational level could have more nutritional knowledge [4,27,28]; our study suggests that this also translates to the diet provided to their children. Furthermore, families with a higher income may be more able to buy healthy, more expensive, food products [29,30], explaining our association of household income with child diet quality, independent of educational level. A previous study among households in Canada showed that access to dairy, fruit and vegetables, which are food groups that positively contribute to our diet score, may be constrained by low income irrespective of educational level [31]. Unfortunately we did not assess food security in our study, which may partly explain the association between socioeconomic status and diet quality found in our study.

The negative association of maternal smoking with diet quality score is consistent with previous research among 515 children aged 2 to 17 years in the U.S., which showed that children from low-income families with parents who smoked, had a poorer diet quality than children from low-income families with nonsmoking parents [32]. We also observed a negative association between maternal overweight and child's diet quality score, which is in line with a previous study among 1,640 children aged 3 years in the UK [33]. These findings for maternal smoking and overweight suggest that an unhealthy lifestyle of the mother negatively influences their child's diet quality, independent of socioeconomic status.

Independent of these maternal factors, we also found an association between children's lifestyle and their diet quality. Being more physically active and having less screen time were associated with a higher diet quality in children, although for physical activity this association was not observed for the group with the highest levels of physical activity. These findings are consistent with previous research, which showed that sedentary behavior is associated with a less healthy diet [27,33]. Finally, in our fully adjusted models, we observed that children with a Moroccan ethnic background had a higher diet quality score than those with a Dutch ethnicity. Children with a Moroccan ethnicity had a higher intake of fish, legumes, and nuts and a lower high-fat and processed meat intake, suggesting a more Mediterranean-style diet [34].

In our study population, we found only weak tracking of the diet quality score and its individual components between the ages of 1 year and 8 years. Studies on tracking of diet from early life to later childhood are limited [35]. One previous study found moderate to fair tracking of the intake of fruit, vegetables, and sugar-sweetened beverages from the age of 18 months to 7 years [35]. A review by Nicklaus & Remy (2013), showed moder-

ate tracking of eating habits after the first year of life [36]. Combined, these results suggest that tracking of diet may start after the age of 1 year.

Methodological considerations of the diet quality score

The diet quality score was positively associated with intake of micronutrients, indicating adequate construct validity, since dietary recommendations are, amongst others, developed to provide a sufficient supply of nutrients [24]. We included both healthy and unhealthy components in the score, which may better capture overall diet quality than including healthy or unhealthy components only, as eating healthy foods is not necessarily inversely related to eating unhealthy foods [37]. Further research is needed to examine whether this combined score is indeed associated with child health. Another strength of our diet score is the use of cut-off values based on current dietary recommendations instead of using a population-specific cut-off value such as a population-specific median intake, which may not be related to an actual healthy intake level [24]. Finally, a strength of our diet quality scoring system is that we used a continuous scale, which provides more detail and is more accurate in ranking children with respect to diet quality than a dichotomous scoring system [24].

Constructing an overall diet quality index involves many choices [24]. Although it may have been preferred to ascribe greater weights to components that have a greater effect on health, not enough information on the overall health effects of individual components was available, so we chose not to apply any weighting. In addition to the number and weights of components, another aspect to consider is the type of components included in the diet index. Most diet indices are based on intake of nutrients or food groups, or a combination of these, and some indices also include measures of dietary variety [24,38]. We chose to construct our diet quality score on the basis of intake of food groups only, in line with the Dutch dietary guidelines, but we also observed positive associations of the diet score with intake of micronutrients, suggesting it represent on overall healthy diet. When diet quality score components are similar to each other or when they are strongly correlated, they contribute more heavily to the score [24]. However, in our diet quality score, we observed low correlation between the diet score components (r -0.13 to 0.08). Finally, because our diet quality score is based on Dutch recommendations, important food groups may be absent for children with another ethnic background. However, the Dutch recommendations are comparable to recommendations in other countries [39]. Furthermore, a systematic review conducted by Gilbert & Khokhar (2008) showed that after moving to a Western country, the majority of ethnic groups change their eating habits to a more Western diet [40]. Also, we did not find major differences in diet score between the different ethnic groups in our population, suggesting that the Dutch recommendations and our diet score were also suitable for the study participants with another ethnicity.

Strengths and limitations

Major strengths of the Generation R study, in which we applied our diet quality score, are the population-based prospective cohort design and the large number of subjects. Also, we had information available on many parental and child sociodemographic and lifestyle factors for which we could examine their correlation with diet quality. However, there may be other correlates of diet quality that were not assessed in our study. Unfortunately, we had no detailed information on physical activity of the children. We used the amount of time participating in organized sports as a proxy for physical activity, which may not be an optimal measure, because it does not take into account other sources of physical activity. In addition, not all correlates were assessed at the same moment as dietary assessment, which may have influenced the associations. However, there was a high correlation of most variables throughout childhood, and we expect that any changes in these correlates are only limited. Therefore, we chose the time point that was the closest to our moment of dietary assessment. Furthermore, non-response analyses showed that non-responders to the FFQ more often had characteristics associated with a lower diet quality score, such as a lower educational level, suggesting that diet quality might be even lower in the children in Rotterdam than observed in the study population for which we had data available.

Another limitation of the study was the assessment of dietary intake with an FFQ. Limitations of FFQs in general are that they contain a limited amount of food items, and recollection of the consumed foods and portion sizes can be sources of error [41]. The FFQ used in our study was validated against the doubly labelled water method, regarded as the golden standard for the determination of total energy expenditure in free-living subjects, and this validation showed a reasonable capacity of the FFQ to rank subjects with respect to energy intake [17]. However, the FFQ was not validated for the intake of specific foods or food groups. Finally, for our analyses on tracking of diet quality, a limitation was that diet quality was not scored in exactly the same manner at the ages of 1 and 8 years and that no data on dietary intake were available for the period in between these two age categories.

Implications

The results of our study suggest that overall diet quality among 8-year-old children in our study population in an urban multi-ethnic setting in the Netherlands is suboptimal and that none of the children fully adhered to the dietary guidelines. This is undesirable as a healthy diet is important for healthy growth and development of the child [1]. However, future research is needed to assess whether a higher overall adherence to the dietary guidelines is indeed associated with a better health and evaluate diet quality in other populations of children. Although the observed effect estimates for the correlates of diet quality were relatively small on an individual level, these may be relevant for

public health strategies. We observed for example that children from higher educated mothers had a 0.3 higher diet quality score (scale 0 to 10) than children whose mothers had not completed higher education. Most of the observed correlates of diet quality in our study are in line with previous research. Consistent with other studies, we found low socioeconomic status to be a strong predictor of a lower diet quality [27], emphasizing the need to target child dietary interventions especially to families with a lower socioeconomic status. Interventions should focus on promotion of healthy food products and increase the accessibility of these foods for these groups. Additionally, interventions should also discourage the consumption of unhealthy food products. Adherence to the recommendations was particularly low for the moderation components in our study population, underlining the importance of discouraging the intake of sugar-containing beverages and high-fat and processed meat. As previous evidence showed tracking of diet between mid-childhood and adulthood [14], dietary interventions targeted at children are expected to not only improve diet quality during childhood, but also their diet quality into adulthood. However, we observed only weak tracking of diet quality from early to mid-childhood. Therefore, further research is needed to establish the optimal age and also the best target groups (e.g., children, parents, and/or schools) for dietary interventions in order to improve long-term diet quality.

Conclusion

To conclude, in this large population-based cohort in the Netherlands, we observed that diet quality of 8-year-old children was suboptimal, which indicates that they do not meet the current dietary guidelines. Particularly the intake of legumes, nuts, and oils or soft or liquid fats was too low, whereas the intake of sugar-containing beverages and high-fat and processed meat was too high. Main sociodemographic and lifestyle factors that correlated with a higher diet quality were a higher maternal education, a higher household income, no maternal smoking, and less time spent on watching television or using a computer of the child. Tracking of diet quality from the age of 1 year to 8 years was weak.

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Supplemental table 2.4.1. Median intake per diet quality score component and median score per diet quality score component (maximum score is 1) for boys (n=2364) and girls (n=2369) separately

Component	Unit	Cut-off values	Intake		Score	
			Boys	Girls	Boys	Girls
Fruit	g/d	≥ 150	111 (77-165)	111 (77-167)	0.74 (0.51-1.00)	0.74 (0.51-1.00)
Vegetables	g/d	≥ 150	77 (47-122)	80 (51-123)	0.51 (0.31-0.82)	0.53 (0.34-0.82)
Whole-grains	g/d	≥ 90	101 (65-135)	98 (65-130)	1.00 (0.72-1.00)	1.00 (0.72-1.00)
Fish	g/w	≥ 60	38 (0-95)	38 (0-79)	0.63 (0.00-1.00)	0.63 (0.00-1.00)
Legumes	g/w	≥ 84	35 (0-70)	18 (0-70)	0.42 (0.00-0.83)	0.21 (0.00-0.83)
Nuts	g/d	≥ 15	4 (0-11)	2 (0-8)	0.29 (0.00-0.70)	0.14 (0.00-0.53)
Dairy	g/d	≥ 300	182 (56-319)	152 (54-284)	0.61 (0.19-1.00)	0.51 (0.18-0.95)
Oils and soft or liquid fats	g/d	≥ 30	11 (2-22)	11 (2-17)	0.37 (0.07-0.74)	0.37 (0.07-0.56)
Sugar-containing beverages	g/d	≤ 150	335 (193-557)	311 (169-506)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
High-fat and processed meat	g/w	≤ 250	340 (232-482)	306 (203-430)	0.00 (0.00-0.07)	0.00 (0.00-0.19)

Values are median (IQR).
Energy intake (kcal/d) was 1531 (IQR 1299-1763) among boys and 1391 (IQR 1184-1606) among girls.
g/d= gram/ day; g/w= gram/ week; IQR= Interquartile range; kcal/d= kilocalorie/ day.

Supplemental table 2.4.2. Associations between the diet quality score and intake of nutrients

	Pearson correlation (r) Unadjusted	Pearson correlation (r) Adjusted for energy intake
Macronutrients:		
Fat (g)	0.26	-0.02
Saturated fat (g)	0.20	-0.11
N-3 fatty acids (mg)	0.26	0.24
Protein (g)	0.40	0.29
Animal protein (g)	0.24	0.05
Plant protein (g)	0.49	0.41
Carbohydrates (g)	0.24	-0.11
Monosaccharides and disaccharides (g)	0.15	-0.11
Dietary fiber (g)	0.62	0.58
Micronutrients:		
Vitamin B 1 (mg)	0.46	0.36
Vitamin B 2 (mg)	0.38	0.25
Vitamin B 3 (niacin) (mg)	0.42	0.31
Vitamin B 6 (mg)	0.43	0.32
Vitamin B 12 (µg)	0.30	0.18
Vitamin C (mg)	0.29	0.16
Vitamin D (µg)	0.40	0.30
Calcium (mg)	0.39	0.27
Copper (mg)	0.54	0.52
Iron (mg)	0.45	0.36
Magnesium (mg)	0.55	0.55
Phosphorus (mg)	0.48	0.44
Selenium (µg)	0.37	0.24
Zinc (mg)	0.41	0.31

All r-values were statistically significant at the 0.05 level, except for total fat (adjusted for energy intake): p=0.16.
g= gram; mg= milligram; µg= microgram.

Supplemental table 2.4.3. Associations between the diet quality score and its components at the age of 1 y and at the age of 8 y (n=2,608)

Component	Pearson correlation (r)
Fruit	0.20
Vegetables	0.11
Whole-grains	0.19
Fish	0.23
Dairy	0.14
Oils and unsaturated fats	0.19
Sugar-containing beverages	0.12
Total	0.19

All significant at 0.01 level

The components 'legumes' and 'nuts' were not incorporated in the diet quality score at age 1 year, and the 'meat' component was an adequacy component (low-fat unprocessed meat) in the preschool score and a moderation component (high-fat and processed meat) in the childhood score, therefore no tracking was assessed for these components

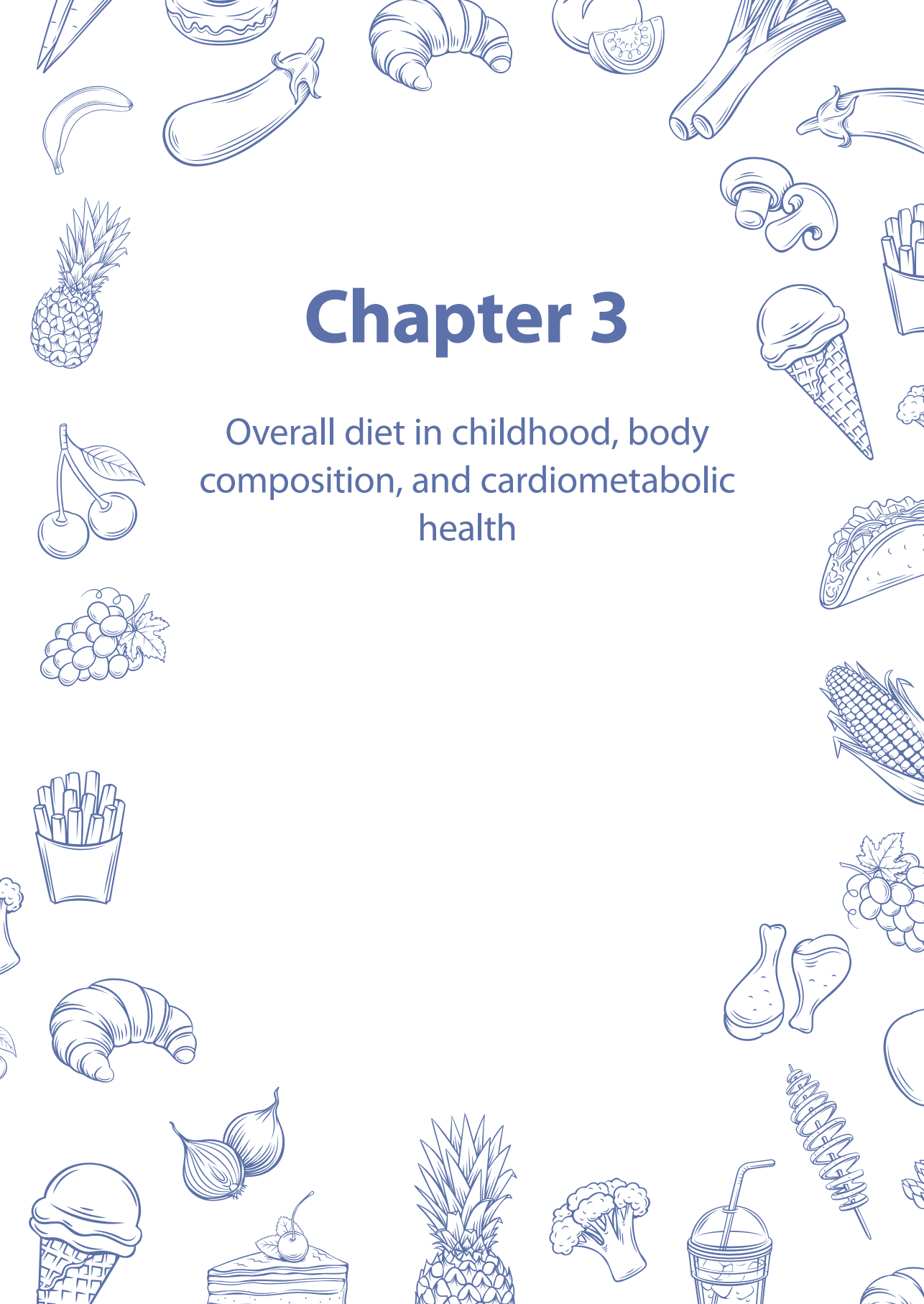
Supplemental table 2.4.4. Tracking matrix constructed for the calculation of weighted Kappa statistic for diet quality score at age 1 y and age 8 y among children with dietary data at both time points (n=2,607)

	Lowest 25% at 8 y	Middle 50% at 8 y	Highest 25% at 8 y
Lowest 25% at 1 y	201	339	112
Middle 50% at 1 y	302	653	348
Highest 25% at 1 y	104	317	231

The entry in a specific cell indicates the number of subjects belonging to the corresponding classes at age 1 y and age 8 y

Additional supplemental material for this chapter can be found online: https://static-content.springer.com/esm/art%3A10.1007%2Fs00394-018-1651-z/MediaObjects/394_2018_1651_MOESM1_ESM.docx


DRINK



Chapter 3

Overall diet in childhood, body composition, and cardiometabolic health


DRINK

Chapter 3.1

Diet quality in early and mid-childhood in relation to growth and body composition

Nguyen AN, Jen V, Jaddoe VWV, Rivadeneira F, Jansen PW, Ikram MA, Voortman T.

Diet quality in early and mid-childhood in relation to trajectories of growth and body composition. *Clinical Nutrition*. doi: 10.1016/j.clnu.2019.03.017.2019.

ABSTRACT

Background: A balanced diet in childhood is important for growth and development. We aimed to examine the associations of overall diet quality in both early and mid-childhood with trajectories of growth and body composition until age 10 years.

Methods: We included 3,991 children from the Generation R Study, a population-based, prospective cohort in Rotterdam, the Netherlands. At child's ages of 1 and 8 years, dietary intake was assessed using food-frequency questionnaires to calculate diet quality scores (0-10), which measures adherence to age-specific dietary guidelines. Height and weight were measured repeatedly between ages 1 and 10 years. Body composition was assessed using dual-energy X-ray absorptiometry at ages 6 and 10 years. We calculated sex- and age-specific SD-scores for body mass index (BMI), fat mass index (FMI), fat-free mass index (FFMI), and body fat percentage (BF%).

Results: After adjustment for socioeconomic and lifestyle factors, results from linear mixed models showed that higher diet quality at 1 year was associated with higher height, weight, and BMI up to 10 years. Using linear regression analyses, similar associations were observed for diet quality at 8 years. For diet quality at both time points, these positive associations with BMI were fully driven by a higher FFMI (β= 0.07 SDS, 95%CI: 0.05,0.10 for diet quality at 8 years), and not FMI or BF%. Most of the observed associations were independent of diet quality at the other time point.

Conclusion: We observed that better diet quality in both early and mid-childhood was associated with higher height, weight, and FFMI, but not FMI or BF% up to 10 years. This was independent of diet quality at an earlier or later time point. Our findings suggest that dietary intake according to dietary guidelines may have a beneficial impact on growth and body composition in childhood.

INTRODUCTION

Nutrition in childhood is important for growth and development of the child, and for health later in life [1]. Previous studies reported that dietary intake of certain nutrients or foods, such as protein, dietary fat, or sugar-sweetened beverages, are associated with children's obesity risk and body composition [2-6]. Childhood obesity may cause serious health complications, and may increase the risk of obesity in adulthood [7] and thereby the risk of coronary heart diseases, diabetes, and premature death [8].

Children consume a variety of foods rather than single nutrients and foods, and these different nutrients and foods interact [9]. Studying overall dietary patterns takes these interactions into account and may be more applicable in public health practices. Dietary patterns can either be data-driven (i.e., based on the variation of dietary intake data within a study population) or predefined (e.g., based on specific dietary guidelines or recommendations) [9]. A review including seven studies among children showed positive associations of data-driven dietary patterns characterized by intakes of energy-dense, high-fat, and low-fiber foods with later obesity risk [10]. However, most studies only used body mass index (BMI) as a measure of obesity, and only one of the cohorts included in this review used dual-energy X-ray absorptiometry (DXA) to assess body fat mass, but not fat-free mass [11]. In addition, a Canadian study observed that children aged 8-10 years with a higher score on a predefined diet quality index gained less body fat over a 2-year period [12]. In contrast to these studies in school-age children, we previously observed in the Generation R Study that a higher predefined diet quality score at age 1 year was not associated with fat mass at age 6 years, but rather with a higher fat-free mass [13]. However, whether these associations track into later childhood and whether diet in early and mid-childhood differently affects body composition remains unclear.

Therefore, we aimed to first extend our previous analyses on diet quality at age 1 year in relation to body composition at age 6 years [13] with data on growth and detailed measures of body composition up to age 10 years, taking into account diet quality in mid-childhood. As a second aim, we explored associations of overall diet quality at age 8 years with anthropometrics and body composition at age 10 years. For both aims, we examined whether associations are independent of diet quality at the other time point.

METHODS

Study design and population

This study was embedded within the Generation R Study, an ongoing population-based prospective cohort from fetal life onward in the Netherlands [14]. Pregnant women were enrolled between April 2002 and January and a total of 9,749 live-born children were

available for follow-up. Parents of all participating children provided written informed consent and approval was obtained from the medical ethical committee of Erasmus University Medical Center, Rotterdam [14].

At the child's age of 1 year, a food-frequency questionnaire (FFQ) to assess diet in early childhood was sent to parents of 5,088 children. Dietary data was available for 3,629 of the children [15]. Of these children, 3,573 had data on anthropometrics and 3,122 on body composition available at one or more time points up to age 10 years. At the age of 8 years, an FFQ was sent to parents of 7,662 children to assess mid-childhood diet. Data on dietary intake was available for 4,733 of these children [16]. Around the age of 10 years, we had data available on anthropometrics for 3,991 children and on body composition for 3,950 children (**Figure 3.1.1)**.

Diet quality in early childhood

As previously described in detail [15,17], dietary intake in early childhood was assessed at a median age of 12.9 months (interquartile range (IQR) 12.7–14.0) with a semi-quantitative FFQ covering the past month. Energy and nutrient intakes were calculated using the Dutch Food Composition Table. The FFQ was validated against three 24-h recalls in 32 Dutch children, which showed reasonable to good intraclass correlation coefficients for nutrient intake ranging from 0.4 to 0.7 [15]. We applied a previously defined diet quality score for pre-school children, which was constructed based on age-specific dietary guidelines [15]. The ten following components were included: intake of vegetables (≥100g/d); fruit (≥150g/d); bread and cereals (≥70g/d); rice, pasta, potatoes, and legumes (≥70g/d); dairy (≥350g/d); meat, poultry, eggs, and meat substitutes (≥35g/d); fish (≥15g/d); oils and fats (≥25g/d); candy and snacks (≤20g/d); and sugar-sweetened beverages (≤100g/d) [15]. For each component, ratios of reported intakes and recommended intakes were calculated, capped at 1. For example; a vegetable intake of 60g/d resulted in a score of 0.6 (60 divided by 100) for the vegetable component. The scores were reversely coded for the 'candy and snacks' and 'sugar-sweetened beverages' components, meaning that higher scores reflected lower intakes. Scores for the individual component (ranging from 0 to 1) were summed, resulting in an overall score between 0 and 10, with higher scores representing a healthier diet [15]. Previous evaluation of this diet score in the Generation R cohort showed adequate construct validity; it was positively associated with intake of nutrients considered healthy and inversely associated with intake of unhealthy nutrients [15].

Diet quality in mid-childhood

Dietary intake in mid-childhood was assessed at a median age of 8.1 years (IQR 8.0–8.2) with a semi-quantitative FFQ covering the past month, as described in detail elsewhere [16,18]. Energy and nutrient intakes were calculated using the Dutch Food Composition Table. The FFQ was validated for energy intake against energy expenditure

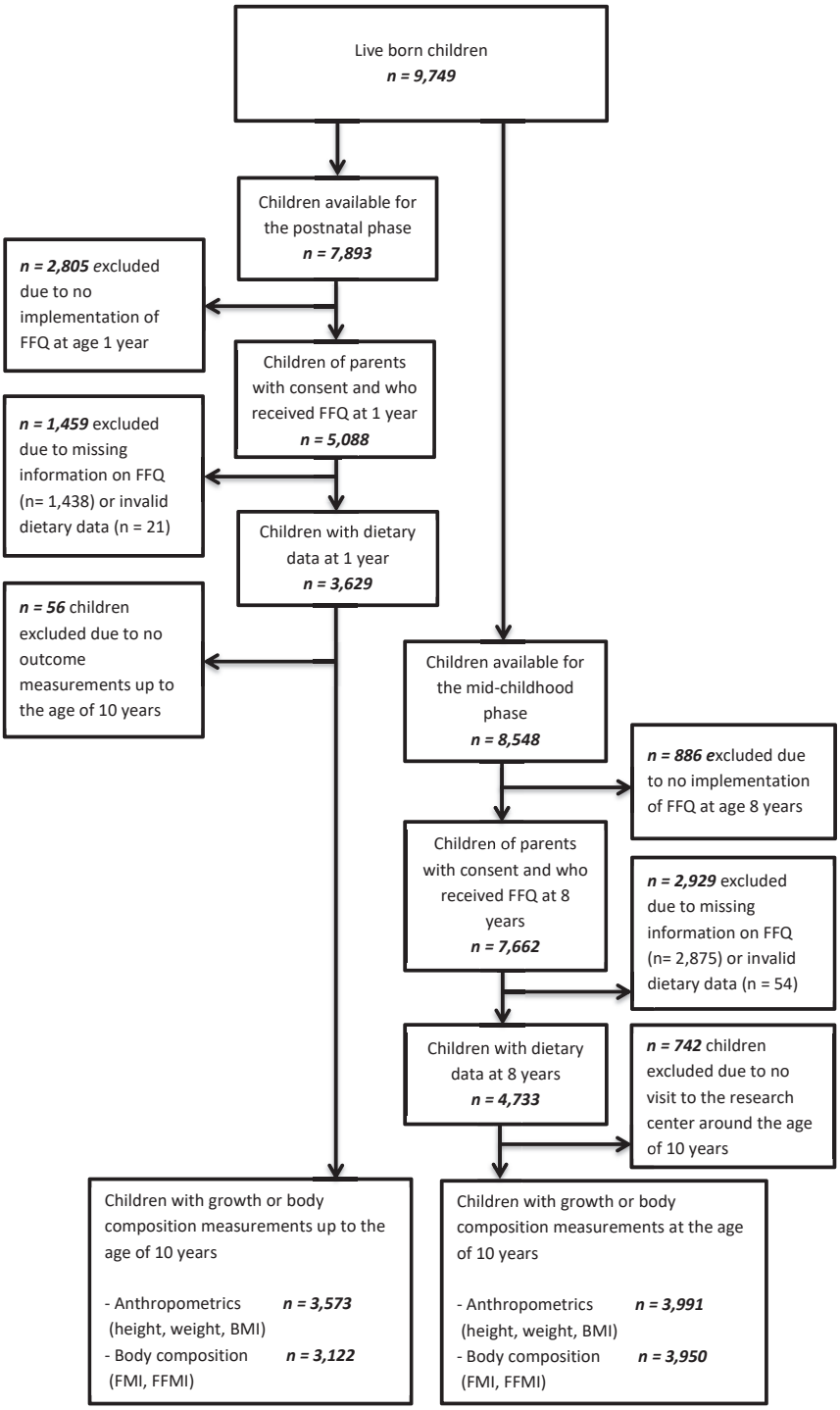


Figure 3.1.1. Flowchart of population for analysis

measured with the doubly labeled water method. This validation showed good correlation (Pearson's r=0.6) and Bland-Altman mean-difference plots showed no relevant systematic bias [18]. We applied a previously defined diet quality score for school-age children reflecting adherence to age-specific dietary guidelines [16]. This score included the following ten components: intake of fruit (≥150g/d); vegetables (≥150g/d); whole grains (≥90g/d); fish (≥60g/w); legumes (≥84g/w); nuts (≥15g/d); dairy (≥300g/d); oils and fats (≥30g/d); sugar-containing beverages (≤150g/d); and meat (≤250g/w). Similar to the approach used for the diet score for preschool children, ratios of reported intakes and recommended intakes were calculated for each component, with reverse coding for the 'sugar-containing beverages' and 'meat' components. The component scores were summed into an overall diet quality score (0-10). Further details on the diet score and its construct validity are reported elsewhere [16].

Anthropometrics and body composition

Children's anthropometrics were measured at eight different time points between ages 1 year and 10 years. All measurements were performed without shoes and heavy clothing. Up to age 4 years, measurements were taken during routine visits at the Child Health Centers at median ages of 14.3 (IQR 14.1–14.6), 18.3 (IQR 18.1–18.9), 24.7 (IQR 24.2–25.6), 30.5 (IQR 30.1–31.3), 36.6 (IQR 36.2–37.4), and 45.8 (IQR 45.3–46.6) months. At the ages of 6.0 (IQR 5.8–6.2) and 9.7 (IQR 9.6–9.8) years, measurements were performed during visits to our research center at Erasmus Medical Center. Weight was measured with a mechanical personal scale (SECA, Almere, the Netherlands), and height was measured with a Harpenden stadiometer (Holtain Limited, DYFED, U.K.). During these visits, we also measured body composition (fat and lean mass) with a DXA scanner (iDXA, Ge-Lunar, 2008, Madison, WI, USA) using enCORE software version 13.6. We calculated BMI (weight(kg)/height(m)^2), fat mass index (FMI) (fat mass(kg)/height(m)^2), fat-free mass index (FFMI) (fat-free mass(kg)/height(m)^2), and body fat percentage (BF%) (fat mass as percentage of total body weight). Overweight status was defined based according to Cole's criteria [19]. Subsequently, we calculated age- and sex-specific standard deviation scores (SDS) for all outcomes based on available data from participants in the Generation R Study [14].

Covariates

We assessed several socioeconomic and lifestyle factors at study enrollment, in infancy, in childhood. Information on maternal age, maternal educational level (low; high), parity (nulliparous; multiparous), folic acid supplement use in early pregnancy (no; started in first ten weeks; started periconceptional), and household income (<2,200; ≥2,200 Euros/month) was obtained using questionnaires at enrollment in the study. During each trimester, questionnaires were used to assess whether mothers drank alcohol (never; until pregnancy was known; continued drinking occasionally; continued drinking frequently) and smoked

(never; until pregnancy was known; continued smoking during pregnancy). Maternal height and weight were measured at our research center at enrollment, and BMI was calculated.

Information on child's date of birth and sex was obtained from medical records. Child's ethnicity (Dutch; non-Dutch) was defined based on the country of birth of the parents, on which information was obtained with questionnaires. Information on breastfeeding was obtained for the first 4 months of life (never; partially; exclusively) via questionnaires.

Around age 10 years, we used questionnaires to obtain information on child's participation in sport activities (<2; ≥2 hours/week) and screen time, defined as time watching television and/or using computers (<2; ≥2 hours/day). Questionnaires were also used to update information on maternal smoking status (never; former; current) and household income (<2,800; ≥2,800 Euros/month). In addition, mother's height and weight were measured to update their BMI.

Statistical analyses

For our first aim, linear mixed models were used to examine associations of diet quality at age 1 year with trajectories of growth between ages 1 and 10 years and body composition between ages 6 and 10 years. This method incorporates all available repeated measurements of the outcomes simultaneously and takes into account that these measurements are correlated within participants. We used likelihood ratio tests to determine a suitable fixed-effect structure and a random effect structure, which we used in each of the longitudinal models. The fixed effect structure was specified using three multivariable models and the random effects structure included a random intercept for the body composition outcomes and a random intercept and slope for time of repeated outcome measures for the growth outcomes. Covariates were selected based on previous literature or a change of ≥10% in effect estimates when they were entered stepwise in model 1. Model 1 included child's sex, ethnicity, age at dietary assessment, and total energy intake. The second model was additionally adjusted for several socioeconomic and lifestyle factors: maternal age, maternal educational level, parity, folic acid supplement use, household income, alcohol intake during pregnancy, smoking during pregnancy, breastfeeding, sports, and screen time. To examine whether associations of diet quality in early childhood with trajectories of growth and body composition were independent of diet in mid-childhood, model 3 was additionally adjusted for diet quality at the age of 8 years. To examine whether diet quality modified trajectories of growth and body composition, we included interactions between diet quality and age of outcome measurements in the fixed effects structure. To examine whether associations of diet quality with growth and body composition differed by child's sex, an interaction term was included in the models.

For our second aim, we used linear regression models to analyze associations of diet quality at age 8 years with child's anthropometrics and body composition at age 10

years. These associations were analyzed using the previously mentioned models 1, 2, and 3, with some adaptations in models 2 and 3. In model 2, the early-life factors were replaced by factors that were more relevant in later childhood (e.g., smoking during pregnancy was replaced by maternal smoking status at the 10-year visit). To examine whether associations were independent of early-childhood dietary factors, model 3 was additionally adjusted for diet quality in early childhood and breastfeeding.

Because the FFQs were originally developed for Dutch populations, we performed sensitivity analyses restricted to participants with a Dutch ethnic background. To verify that associations of the diet scores were not driven by one specific component of the score, we repeated the analyses excluding each component at a time (i.e., diet score including nine components instead of ten). To reduce the possibility of reverse causation, analyses were repeated excluding children with overweight or obesity at baseline. For the linear mixed models, we also performed sensitivity analyses in which we excluded outcome measurements that were taken during the first year following dietary assessment to examine if these measurements drive or attenuate the associations. To reduce potential bias due to missing values on covariates (ranging from 0% to 28.1%), these variables were multiple imputed (n=10 imputations) [20]. Exposures and outcomes were not imputed. When the diet quality score was included as a confounder in the analyses, the multiple-imputed variable was used; when it was used as the main exposure, the unimputed values were used. We present pooled regression coefficients of the 10 imputed datasets. Results were considered statistically significant at $P<0.05$, two-sided alpha error. The statistical analyses were carried out using SPSS statistics version 21.0 (IBM Inc., Armonk, NY, USA) and R version 3.4.1 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Population characteristics

Because we observed significant interactions of diet quality with sex in some of the analyses, **Table 3.1.1** presents characteristics of the total study population and stratified by sex. The majority of the children had a Dutch ethnic background (67.4%), came from households with a higher income (69.5%), or played sports for more than two hours/week (66.4%). Mean (±SD) diet quality of the children was 4.3 (±1.3) out of a maximum score of 10 at age 1 year and 4.6 (±1.2) at age 8 years, indicating that adherence to dietary guidelines at both time points was suboptimal [15,16]. Although boys had a slightly higher diet quality score than girls at both ages, there was no difference after adjustment for total energy intake [15,16]. Diet quality at the two time points was positively but weakly correlated ($r=0.2$, $p<0.01$)[16].

Table 3.1.1. Characteristics of the population for analysis

	Mean ± SD, median (IQR), or %		
	Total population (*n = 3,991*)	**Girls (*n = 2,022*)**	**Boys (*n = 1,969*)**
Child characteristics			
Sex			
Girls	50.7%	-	-
Ethnicity			
Dutch	67.4%	67.5%	67.3%
Child dietary assessments at 1 year			
Age at dietary intake (y)	1.1 (1.1 – 1.2)	1.1 (1.1 – 1.2)	1.1 (1.1 – 1.2)
Total energy intake (kcal/d)	1,261 (1060 – 1,491)	1,210 (1,031 – 1,438)	1,320 (1,095 – 1,547)
Diet quality at 1 year (score range 0-10)	4.3 ± 1.3	4.2 ± 1.3	4.4 ± 1.3
Breastfeeding in the first 4 months			
Never	9.3%	8.9%	9.8%
Partially	63.9%	64.1%	63.9%
Exclusively	26.7%	27.0%	26.4%
Child dietary assessments at 8 years			
Age at dietary intake (y)	8.1 (8.0 – 8.2)	8.1 (8.0 – 8.2)	8.1 (8.0 – 8.2)
Total energy intake (kcal/d)	1,461 (1,239 – 1,703)	1,398 (1,191 – 1,613)	1,537 (1,301 – 1,770)
Diet quality at 8 years (score range 0-10)	4.6 ± 1.2	4.5 ± 1.2	4.6 ± 1.2
Child growth measurements at 10 years			
Age (y)	9.7 (9.6 – 9.8)	9.7 (9.6 – 9.8)	9.7 (9.6 – 9.8)
Height (cm)	141.4 (137.2 – 145.8)	141.2 (136.8 – 145.8)	141.5 (137.4 – 145.8)
Weight (kg)	33.6 (30.2 – 38.0)	33.6 (30.0 – 38.2)	33.6 (30.4 – 37.8)
Body mass index (kg/m^2)	16.8 (15.6 – 18.3)	16.8 (15.5 – 18.5)	16.7 (15.7 – 18.2)
Fat mass index (kg/m^2)	4.1 (3.3 – 5.5)	4.5 (3.7 – 5.9)	3.7 (3.0 – 4.9)
Fat-free mass index (kg/m^2)	12.5 (11.8 – 13.2)	12.1 (11.6 – 12.8)	12.8 (12.2 – 13.5)
Body fat percentage (%)	25.2 (21.1 – 30.6)	27.4 (23.7 – 32.5)	22.6 (19.0 – 27.7)
Overweight or obese*	14.5%	16.0%	12.9%
Screen time			
≥ 2 hours/day	51.3%	46.2%	56.5%
Sports			
≥ 2 hours/week	66.4%	59.2%	73.9%
Parental characteristics during 10-year visit			
Maternal age (y)	42.1 (39.1 – 44.7)	42.0 (39.0 – 44.4)	42.1 (39.2 – 44.8)
Maternal BMI (kg/m^2)	24.4 (22.2 – 27.6)	24.3 (22.2 – 27.8)	24.5 (22.2 – 27.6)
Maternal education			
Higher	63.1%	63.4%	62.9%
Maternal smoking			
Never	53.8%	53.7%	54.0%

Table 3.1.1. Characteristics of the population for analysis (continued)

	Mean ± SD, median (IQR), or %		
	Total population (*n = 3,991*)	**Girls (*n = 2,022*)**	**Boys (*n = 1,969*)**
Former	32.9%	32.7%	33.0%
Current	13.3%	13.6%	13.0%
Household income			
≥ 2,800 Euros/month	69.5%	70.5%	68.4%

Values are means ± SD for continuous variables with a normal distribution, medians (interquartile range) for continuous variables with a skewed distribution, and valid percentages for categorical variables. Missing data of covariates (ranging from 0% to 28.1%) were imputed with multiple imputation (n=10 imputations).
*According to international age- and sex-specific cut-offs for BMI [19].

Diet quality in early childhood

One point higher diet quality score at the age of 1 year was associated with a 0.05 SDS greater height (95%CI:0.02,0.08) and a 0.06 SDS higher weight (95%CI:0.04,0.09) up to the age of 10 years (model 2, **Table 3.1.2**). Additional adjustment for diet quality in mid-childhood hardly affected these associations (model 3, Table 3.1.2). Also, we observed a positive association between diet quality at age 1 year and BMI up to age 10 years (β=0.05 SDS, 95%CI:0.02,0.08), which was completely driven by a higher FFMI (β=0.04, 95%CI:0.004,0.07), and not FMI or BF% (model 2, Table 3.1.2). The direction of the associations remained similar after additional adjustment for diet quality at age 8 years, but the association with FFMI was no longer statistically significant (β=0.03, 95%CI:-0.01,0.06)(model 3, Table 3.1.2). These associations did not differ between boys and girls (p-for-interaction >0.05 for all outcomes).

Diet quality in mid-childhood

For our analyses on diet in mid-childhood, we observed that also higher diet quality score at the age of 8 years was associated with greater height (β=0.06 SDS per one point higher diet score, 95%CI:0.03,0.08) and higher weight (β=0.04, 95%CI:0.02,0.07) at the age of 10 years (model 2, **Table 3.1.3**). These associations attenuated slightly, but remained statistically significant after additional adjustment for early-childhood diet (model 3, Table 3.1.3). We also observed a positive association with BMI at age 10 years (β=0.03, 95%CI:0.003,0.05)(model 2, Table 3.1.3), but this association was no longer statistically significant after additionally adjustment for diet in early childhood (β=0.02, 95%CI:-0.003,0.04)(model 3, Table 3.1.3). When we further examined fat mass and fat-free mass, we observed an association between a higher diet quality at 8 years and a higher FFMI (β=0.07, 95%CI:0.05,0.10), but not FMI or BF% (model 2, Table 3.1.3). This association with FFMI remained similar after additional adjustment for infant diet quality (β=0.06, 95%CI:0.04,0.09) (model 3, Table 3.1.3).

Table 3.1.2. Associations of diet quality at age 1 year with child's trajectories of growth and body composition up to the age of 10 years

	Height (SDS) *n = 3,573*	Weight (SDS) *n = 3,573*	Body mass index (SDS) *n = 3,573*	Fat mass index (SDS) *n = 3,112*	Fat-free mass index (SDS) *n = 3,112*	Percentage body fat (SDS) *n = 3,112*
Diet quality score 1 year						
Model 1 (basic)	**0.05 (0.02, 0.08)**	**0.05 (0.02, 0.08)**	**0.04 (0.01, 0.06)**	-0.01 (-0.04, 0.02)	**0.03 (0.002, 0.06)**	-0.02 (-0.05, 0.01)
Model 2 (confounder)	**0.05 (0.02, 0.08)**	**0.06 (0.04, 0.09)**	**0.05 (0.02, 0.08)**	0.02 (-0.01, 0.05)	**0.04 (0.004, 0.07)**	0.01 (-0.02, 0.04)
Model 3 (DQ 8 y)	**0.04 (0.01, 0.07)**	**0.06 (0.03, 0.09)**	**0.05 (0.02, 0.07)**	0.02 (-0.01, 0.05)	0.03 (-0.01, 0.06)	0.01 (-0.02, 0.04)

Values are regression coefficients and 95% confidence intervals based on linear mixed models and reflect differences in growth or body composition per 1 point higher diet quality score. **Bold** values indicate statistically significant effect estimates.
Model 1 is adjusted for gender, ethnicity, age dietary assessment, and total energy intake.
Model 2 isadditionally adjusted for maternal age, maternal educational level, parity, folic acid supplement use, household income, alcohol intake during pregnancy, smoking during pregnancy, breastfeeding, playing sports, and screen time.
Model 3 is additionally adjusted for diet quality at the age of 8 years.

Table 3.1.3. Associations of diet quality at age 8 years with child's growth and body composition at the age of 10 years

	Height (SDS) *n = 3,991*	Weight (SDS) *n = 3,991*	Body mass index (SDS) *n = 3,991*	Fat mass index (SDS) *n = 3,950*	Fat-free mass index (SDS) *n = 3,950*	Percentage body fat (SDS) *n = 3,950*
Diet quality score 8 years						
Model 1 (basic)	**0.06 (0.04, 0.09)**	0.01 (-0.01, 0.03)	-0.02 (-0.04, 0.004)	**-0.05 (-0.07, -0.03)**	**0.06 (0.03, 0.08)**	**-0.07 (-0.09, -0.04)**
Model 2 (confounder)	**0.06 (0.03, 0.08)**	**0.04 (0.02, 0.07)**	**0.03 (0.003, 0.05)**	0.001 (-0.02, 0.02)	**0.07 (0.05, 0.10)**	-0.01 (-0.04, 0.01)
Model 3 (DQ 1 y)	**0.05 (0.02, 0.08)**	**0.04 (0.01, 0.06)**	0.02 (-0.003, 0.04)	-0.001 (-0.03, 0.02)	**0.06 (0.04, 0.09)**	-0.02 (-0.04, 0.01)

Values are regression coefficients and 95% confidence intervals (CIs) from linear regression analyses and reflect differences in growth or body composition per 1 point higher diet quality score. **Bold** values indicate statistically significant effect estimates.
Model 1 is adjusted for gender, ethnicity, age dietary assessment, and total energy intake.
Model 2 is additionally adjusted for maternal educational level, playing sports, screen time, maternal smoking, household income, and maternal BMI.
Model 3 is additionally adjusted for diet quality at age 1 year and breastfeeding.

Table 3.1.4. Associations of diet quality score at 8 years with child's growth and body composition around 10 years stratified for sex

	Height (SDS)	Weight (SDS)	Body mass index (SDS)	Fat mass index (SDS)	Fat-free mass index (SDS)	Percentage body fat (SDS)
Girls	*n = 2,022*	*n = 2,022*	*n = 2,022*	*n = 2,004*	*n = 2,004*	*n = 2,004*
Diet quality score 8 years						
Model 1 (basic)	**0.09 (0.06, 0.13)**	**0.04 (0.01, 0.08)**	0.01 (-0.03, 0.04)	-0.03 (-0.06, 0.001)	**0.08 (0.04, 0.11)**	**-0.06 (-0.09, -0.02)**
Model 2 (confounder)	**0.09 (0.05, 0.12)**	**0.07 (0.04, 0.10)**	**0.05 (0.01, 0.08)**	0.01 (-0.02, 0.04)	**0.10 (0.06, 0.13)**	-0.01 (-0.05, 0.02)
Model 3 (DQ 1 y)	**0.07 (0.03, 0.11)**	**0.06 (0.02, 0.09)**	**0.04 (0.004, 0.07)**	0.004 (-0.03, 0.04)	**0.09 (0.05, 0.12)**	-0.02 (-0.05, 0.02)
Boys	*n = 1,969*	*n = 1,969*	*n = 1,969*	*n = 1,946*	*n = 1,946*	*n = 1,946*
Diet quality score 8 years						
Model 1 (basic)	0.03 (-0.003, 0.07)	-0.02 (-0.06, 0.01)	**-0.04 (-0.08, -0.01)**	**-0.07 (-0.10, -0.03)**	0.03 (-0.003, 0.07)	**-0.08 (-0.11, -0.04)**
Model 2 (confounder)	0.03 (-0.01, 0.07)	0.02 (-0.02, 0.05)	0.01 (-0.03, 0.04)	-0.01 (-0.04, 0.03)	**0.04 (0.01, 0.08)**	-0.01 (-0.05, 0.02)
Model 3 (DQ 1 y)	0.03 (-0.01, 0.06)	0.01 (-0.02, 0.05)	0.002 (-0.03, 0.04)	-0.01 (-0.04, 0.03)	**0.04 (0.000, 0.07)**	-0.01 (-0.05, 0.02)

Values are regression coefficients and 95% confidence intervals (CIs) from linear regression analyses and reflect differences in growth or body composition (age- and sex-specific SD scores) per 1 point higher diet quality score. **Bold** values indicate statistically significant effect estimates. P-for-interaction gender x diet quality score ranged from 0.01 to 0.04 for growth and from 0.14 to 0.58 for body composition.

Model 1 is adjusted for ethnicity, age dietary assessment, and total energy intake.

Model 2 is additionally adjusted for maternal educational level, playing sports, screen time, maternal smoking, household income, and maternal BMI.

Model 3 is additionally adjusted for diet quality at age 1 year and breastfeeding.

After stratification by sex (p-for-interaction <0.05 for height, weight, and BMI), associations for diet quality at 8 years with anthropometrics only remained in girls, but not in boys (**Table 3.1.4**). The positive association of diet quality at age 8 years with FFMI at age 10 years was observed for both boys and girls, but the effect estimate was larger in girls than in boys (β=0.09 SDS, 95%CI:0.05,0.12 in girls versus β=0.04, 95%CI:0.000,0.07 in boys) (model 3, Table 3.1.4).

Sensitivity analyses

Interactions of diet quality with age at outcome measurements were not statistically significant. This suggests that diet quality does not affect the velocity of growth or body composition. Analyses restricted to children with a Dutch ethnic background (n between 2,145 and 2,691) yielded similar effect estimates as compared to the whole group. In this subgroup, associations of diet quality at age 1 year with FFMI up to age 10 years remained statistically significant also in model 3. Analyses in which we excluded outcomes measurements that were taken during the first year following dietary assessment showed similar associations as in the main models, suggesting that body size around the time of food intake assessment does not seem to drive our findings. Sensitivity analyses with diet quality scores excluding one component stepwise at a time and analyses excluding children with overweight or obesity at baseline also showed similar effect estimates.

DISCUSSION

In this population-based cohort study, we observed that better diet quality, both in early and mid-childhood, was associated with higher height and weight up to the age of 10 years, independent of diet quality at the other time point. The association of diet quality with higher weight was explained by a higher fat-free mass, and not fat mass or BF%. For diet quality in mid-childhood, effect estimates were generally higher in girls compared to boys.

Interpretation and comparison with previous studies

In line with our previous findings that higher diet quality in early childhood in is associated with higher height, weight, BMI, and FFMI at age 6 years in the Generation R Study [13], our current findings show that these associations remain up to age 10 years. In addition, we observed that most of these associations were independent of diet quality in later childhood, which emphasizes the importance of early-childhood diet on growth and body composition. Also for mid-childhood diet, these associations were independent of diet in early childhood, suggesting that not only early-childhood diet is of high importance, but that dietary intake in later childhood is important as well. Overall diet

quality in our population was suboptimal and not confirm age-specific dietary guidelines [15,16], but in line with other studies on diet quality of children in Western countries [21,22]. Although previous studies suggested that diet quality may track throughout childhood [23], diet quality at the young age of 1 year and 8 years in our study population was only weakly correlated [16]. Although the two diet quality scores that we used were not exactly the same (e.g., a few differences in food groups and different cut off values), these differences reflect differences in age-specific dietary guidelines. Both scores thus reflect level of adherence to dietary guidelines for that age. Our findings that both diet quality in early and mid-childhood are important emphasize that children should have a healthy diet in early childhood, but should also maintain this healthy diet throughout childhood for optimal growth and to prevent the development of obesity.

For diet quality at age 8 years, associations were stronger in girls than boys. Diet quality did not differ between boys and girls at either time point [15,16]. Given the age of our study population of 10 years at the final body composition assessment, children may be at different peri-pubertal stages. As puberty starts at an earlier age in girls than boys, developmental changes associated with puberty, such as the growth spurt and hormonal changes, may explain the stronger associations of diet quality with growth and body composition among girls. The analyses of diet quality in mid-childhood may support this as only body composition measurements at age 10 years were included in these analyses. As suggested by Wells *et al.,* height should be taken into account in measurements of body composition, especially during this stage of child's development in which rapid growth occurs [24]. The importance of height in associations of diet with body composition in children is also supported by findings from a Canadian study, which showed that better diet quality was associated with lower BF% in children aged 8-10 years, but not with BMI or FMI, in which height is taken into account [12]. Unfortunately, sex differences in these associations were not examined. In addition to the difference in timing of growth spurt between boys and girls, hormonal changes that occur during puberty can also influence body composition differently; from onset of puberty onwards, the percentage of body fat is generally higher in girls than boys [25]. Indeed, also in our study population, girls had a higher FMI and a lower FFMI than boys. Further study is needed to examine sex differences in the associations of diet in childhood with growth and body composition at different ages and to study whether these differences track into adolescence and adulthood.

Previously, researchers from the ALSPAC Study in the UK used reduced rank regression to identify a data-driven energy-dense, high-fat, low-fiber dietary pattern at children's ages of 7, 10, and 13 years. This pattern was associated with a higher FMI at the ages of 11, 13, and 15 years [11]. Other studies reported a lower weight, BMI, or BF% among children with a healthier dietary pattern [12,13,22]. Given this previous evidence, we had expected that children with a higher diet quality would have a lower weight and FMI,

but instead we observed associations with a higher weight and FFMI. These partly contrasting findings could be explained by the use of different dietary patterns. One of the previously described studies in British children used a diet quality index [22]. This diet quality index included intakes of both food groups and nutrients (including fruit, vegetables, bread and cereals, but also total fat, saturated fat, cholesterol, protein, sodium, and calcium). Contrary, our diet quality score included only intake of food groups, which may make associations difficult to compare. Also, in our diet quality score, healthier and less healthy choices were taken into account within the components. For example, we included healthy fats (i.e., vegetable oils and soft margarine) rather than total fat, and we included whole-grain products rather than total grains. Indeed, for both the early and mid-childhood diet scores in our study, good construct validity for nutrient intakes was observed [15,16]. In addition, the diet quality index used a categorical scoring system; for each component of the diet quality index, participants could score a 0, 1, or 2, whereas our scoring system was continuous, thereby providing better discrimination [26]. Since their diet quality index and our diet quality score were constructed in differently, these scores could represent different dietary patterns, which may explain why the British study observed a lower weight and BMI in children with a higher diet quality, whereas we observed a higher weight and BMI in those with a healthier diet. However, the overall health effect may be similar, as our associations with higher BMI were fully driven by a higher FFMI, and not FMI. Therefore, evidence from both this previous study and our current study suggests that a healthy dietary pattern may prevent the development of adiposity in children, through a lower fat mass and/or a higher fat-free mass.

Strengths and limitations

Strengths of this study include its large sample size, the population-based, longitudinal design, and the availability of data on several potential confounders. Another important strength is that measurements of body composition were assessed with DXA-scans, allowing us to distinguish between fat mass and fat-free mass, since BMI only is not an adequate measure of adiposity [27,28]. A few previous studies used skinfold thickness to estimate adiposity, but this method has been shown to underestimate body fat in children [29]. Therefore, especially among growing children, it is important to study the role of diet in obesity using accurate and detailed measures of body composition, assessed with for example DXA-scans. Furthermore, we evaluated overall dietary intake instead of one single nutrient or food product. Following this approach, we were able to take into account the high interactions between nutrients and foods within a diet [9]. In addition, we had data on dietary intake available at two different moments during childhood, one as a measure for early-childhood diet and one for mid-childhood diet, and both diet quality scores have previously been shown to have good construct validity [15,16]. This allowed us to study whether associations of diet with anthropometrics and

body composition were independent of diet at earlier or later time points in childhood. However, dietary intake data at more time points throughout childhood would have been better to perform longitudinal analyses.

Several limitations should be taken into account as well. Dietary intake was assessed with FFQs, which may be subject to measurement errors [30]. However, FFQs have shown to be able to accurately rank participants according to their dietary intake [30]. In addition, results from validation studies using the doubly labeled water method [18] or against repeated 24h recalls [15] showed moderate to good validity of the FFQs used in our study. Although both FFQs used in our study were originally developed for and validated in Dutch children and our study population has a multi-ethnic background, sensitivity analyses restricted to children with a Dutch ethnic background showed similar results, suggesting no large bias due to ethnicity. Although we were able to control for several socioeconomic and lifestyle factors, some of these factors may not have been measured perfectly and we could have missed some important factors. For example, we did not have information on pubertal status and no detailed information on physical activity. For the latter, we used amount of time playing sports as a proxy, which could have led to residual confounding. Finally, most of the participants included in our study had a Dutch ethnic background, were highly educated, and had a high household income, which may limit the generalizability of our findings to other populations.

Conclusion

In conclusion, we observed that a higher diet quality, both in early and mid-childhood, was associated with a higher height, weight, and FFMI up to the age of 10 years, independent of diet at the other time point. Our findings suggest that a healthy diet according to dietary guidelines, during several stages of childhood, has a beneficial effect on growth and may decrease the risk of adiposity.

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https://ars.els-cdn.com/content/image/1-s2.0-S026156141930130X-mmc1.docx


DRINK

Chapter 3.2

Diet quality and body composition in childhood: the ABCD Study

Nguyen AN, Rashid V, Vrijkotte T, Nicolaou M, Voortman T.

Longitudinal associations of diet quality with body composition in childhood: the ABCD Study. *Manuscript.*


DRINK

Chapter 3.3

Diet quality and bone health in childhood

Nguyen AN, Minnaard L, Medina-Gomez C, Trajanoska K, Rivadeneira F, Voortman T.

Diet quality and bone health in childhood: a population-based cohort study.
Manuscript.


DRINK

Chapter 3.4

Diet quality in childhood and cardiometabolic health: the Generation R Study

Siddiqui N, **Nguyen AN**, Santos S, Jaddoe VWV, Ikram MA, Voortman T.

Diet quality and cardiometabolic health in children: the Generation R Study.
Submitted for publication.


DRINK

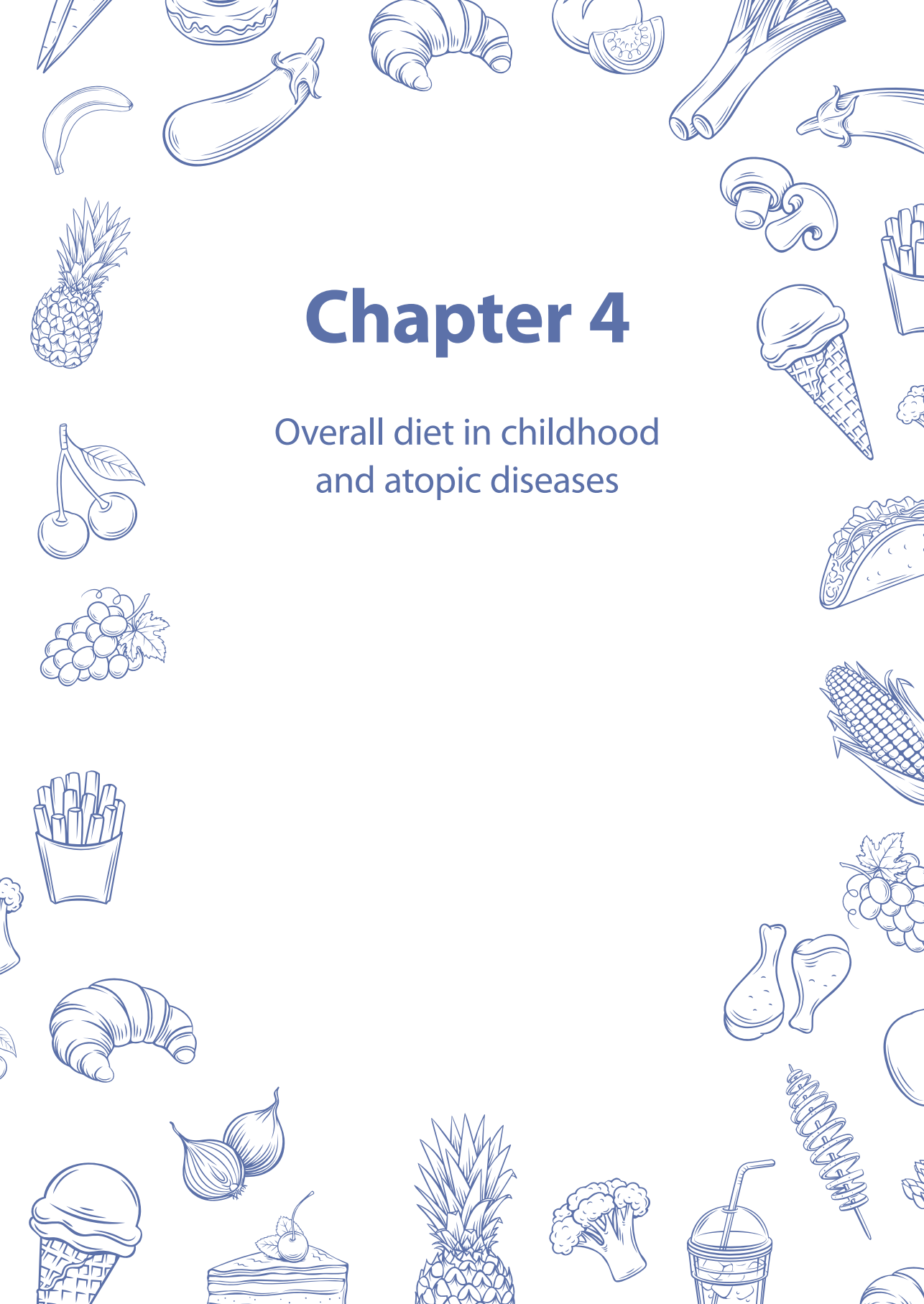
Chapter 3.5

Diet quality in early childhood and cardiometabolic health: the Rhea Study

Nguyen AN, Stratakis N, Ikram MA, Chatzi L, Voortman T.

Longitudinal analyses of diet quality with cardiometabolic factors in young children participating in the Rhea Study. *Manuscript*.


DRINK



Chapter 4

Overall diet in childhood and atopic diseases


DRINK

Chapter 4.1

Diet quality in early life and allergic sensitization and atopic diseases

Nguyen AN, Elbert NJ, Pasmans SGMA, Kiefte-de Jong JC, de Jong NW, Moll HA, Jaddoe VWV, de Jongste JC, Franco OH, Duijts L, Voortman T.

Diet quality throughout early life in relation to allergic sensitization and atopic diseases in childhood. *Nutrients.* 2018;*9*(8):841.

ABSTRACT

Early-life nutrition is an important modifiable determinant in the development of a child's immune system, and may thereby influence the risk of allergic sensitization and atopic diseases. However, associations between overall dietary patterns and atopic diseases in childhood remain unclear. We examined associations of diet quality in early life with allergic sensitization, self-reported physician-diagnosed inhalant and food allergies, eczema, and asthma among 5,225 children participating in a population-based cohort in the Netherlands. Diet was assessed during pregnancy, infancy, and childhood using validated food-frequency questionnaires. We calculated food-based diet quality scores (0-10 or 0-15), reflecting adherence to dietary guidelines. At age 10 years, allergic sensitization was assessed with skin prick tests. Information on physician-diagnosed inhalant and food allergies, eczema, and asthma was obtained with questionnaires. We observed no associations between diet quality during pregnancy and allergic sensitization (OR=1.05 per point in the diet score, 95%CI:0.99,1.13), allergies (0.96, 95%CI:0.88,1.04), eczema (0.99, 95%CI:0.93,1.06), or asthma (0.93, 95%CI:0.85,1.03) in childhood. Also diet quality in infancy or childhood were not associated with atopic outcomes in childhood. Our findings do not support our hypothesis that a healthy dietary pattern in early life is associated with a lower risk of allergic sensitization or atopic diseases in childhood.

INTRODUCTION

The prevalence of childhood atopic diseases, such as eczema and food allergy, has increased in the past decades [1]. These diseases have a substantial impact on the quality of life of those affected [2]. Genetic background is one of the factors associated with atopic diseases, but given the rapid increase in the prevalence, environmental risk factors, including geographic area and lifestyle factors may play a substantial role in the development of allergies and other atopic diseases [3-5]. Early-life nutrition is an important modifiable lifestyle factor that influences the development of a child's immune system [6]. Suboptimal nutrition during pregnancy, infancy, or childhood may interrupt the maturation process of the immune system from fetal life until childhood [6,7], which may increase sensitization and thereby the risk of atopic diseases in childhood. There has been great interest in early-life dietary exposures in relation to atopic diseases, with studies focusing on breastfeeding [8], timing of solid food introduction [9,10], food allergen avoidance [11,12], or intake or blood levels of specific nutrients during pregnancy or in infancy [13-16]. Although these specific nutritional factors may indeed be relevant for atopic health, these factors may also represent an overall dietary pattern. Individuals do not consume one specific nutrient or food at a time, but a variety of nutrients combined in foods and meals that may interact. Studying overall dietary patterns takes these potential interactions into account [17] and may be more applicable in clinical practice.

A few previous studies examined dietary patterns in relation to atopic diseases. So far, most studies mainly focused on a Mediterranean diet in pregnant women or children in relation to atopic diseases [18-20]. However, findings are inconsistent and most of these studies only examined self-reported atopic diseases, such as asthma or allergic rhinitis [18-20]. Assessing atopy using skin prick tests may be more sensitive and less affected by measurement error, but only a few studies examined associations between dietary patterns and objectively measured atopy. A study in Spain observed an inverse association between a Mediterranean diet during pregnancy and atopy in childhood [21], whereas other studies did not observe associations of either data-driven dietary patterns [22,23] or predefined dietary patterns (i.e., Mediterranean diet score and Alternate Healthy Eating Index) [23] during pregnancy with atopy in children. A few other studies focused on early childhood dietary patterns in relation to atopic outcomes. For example, a nested case-control study in the United Kingdom found better adherence to a dietary pattern including high intakes of fruits, vegetables, and home-prepared foods in 2-year-old children without food allergy than children who did have a diagnosis of food allergy [24]. Recently, a population-based cohort in Singapore reported an inverse association of a dietary pattern high in noodles and seafood at the age of 1 year with allergic sensitization to house dust mite at the ages of 18 months and 5 years, but not with self-reported eczema or rhinitis [25]. Finally, results from other population-based cohorts,

including previous analyses in our cohort, showed positive associations of a Western dietary pattern with self-reported asthma symptoms in children aged 3-4 years [26] and 8-11 years [27], but not with allergic sensitization measured by skin prick tests [27]. These previous studies examined diet at different time points in early life, focused on different types of dietary patterns, and did not adjust for diet at other time points in childhood. In addition, previous studies mainly focused on a traditional Mediterranean diet or examined data-driven dietary patterns, which may not represent actual healthy diets and which cannot be extrapolated to other populations because these patterns are population-specific.

Therefore, we aimed to examine the associations between predefined dietary patterns based on Dutch dietary guidelines (i.e., diet quality) during pregnancy, infancy, and childhood with allergic sensitization, inhalant and food allergy, eczema, and asthma in mid-childhood. In addition, we examined whether associations of early-life diet were independent of diet at other time points, including current child diet, and whether associations differed between boys and girls, by maternal history of atopic diseases, and between those who received breastfeeding for at least 4 months exclusively, partially, or not at all.

METHODS

Study design and population

This study was embedded in the Generation R Study, an ongoing population-based prospective cohort from fetal life onward in Rotterdam, the Netherlands [28]. Pregnant women with an expected delivery date between April 2002 and January 2006 were invited to participate. Parents of all participating children provided written informed consent and medical ethical approval was obtained from the medical ethical committee of Erasmus University Medical Center, Rotterdam (MEC 198.782/2001/31, 2001). Further information on the design of the Generation R Study is available elsewhere [28].

In total, parents of 5,225 children provided consent, had dietary data for at least one time point (i.e., during pregnancy, infancy, or childhood) and had valid data for at least one of the outcome variables (i.e., sensitization, allergy, eczema, or asthma). Because data on dietary intake at the different time points and the atopic outcomes were not complete for all participants, the population for analysis varied per specific analysis (n between 2,519 and 3,776).

Dietary intake during pregnancy

Dietary intake in early pregnancy (median 13.6 weeks of gestation (IQR 12.4 – 16.2)) was assessed using a semi-quantitative food-frequency questionnaire (FFQ). The FFQ included foods that were frequently consumed in the Dutch population and was modified

for use in pregnant women. Energy intakes were calculated using data from the Dutch Food Composition Table. The FFQ was validated against three 24-h recalls among 71 pregnant women living in Rotterdam. Intra-class correlation coefficients for macronutrient intakes ranged from 0.5 to 0.7.

We applied a previously developed predefined food-based diet quality score for pregnant women, reflecting adherence to dietary guidelines, as described in detail elsewhere [29]. Briefly, this diet quality score included continuous scores on 15 components: high intake of vegetables, fruit, whole grains, legumes, nuts, dairy, fish, tea; ratio whole grains of total grains, and ratio soft fats (i.e., soft margarines) and oils of total fat; low intake of red meat, sugar-containing beverages, alcohol, salt; and folic acid supplement use in early pregnancy. The maximum score for each component was 1, resulting in an overall sum-score ranging from 0 to 15. A higher score represented a better diet quality [29]. More details on the included components and cut-offs are described elsewhere [29].

Dietary intake in infancy

Dietary intake of the children at a median age of 12.9 months (IQR 12.7-14.0) was assessed using a semi-quantitative FFQ, which was developed specifically for Dutch 1-year-old children and filled out by the parents [30,31]. Energy and nutrient intakes of the children were calculated using the Dutch Food Composition Table. The FFQ was validated against three 24-h recalls among 32 children and reasonable to good intra-class correlation coefficients for nutrient intake of 0.4 to 0.7 were found [30,31].

We applied a previously constructed predefined diet quality score for preschool children [30]. As described in detail elsewhere [30], this continuous score reflected adherence to dietary guidelines for preschool children and included ten components, resulting in an overall sum-score ranging from 0 to 10, with a higher score representing a healthier diet [30]. More details on the included components and cut-offs are described elsewhere [30].

Diet quality in childhood

Dietary intake in childhood at a median age of 8.1 years (IQR 8.0-8.2) was assessed with a semi-quantitative FFQ, as described in detail elsewhere [32,33]. The FFQ developed for Dutch children this age group and was filled out by the parents. Energy intakes were calculated using data from the Dutch Food Composition Table. The FFQ was validated for energy intake using the doubly labelled water method (Pearson's r=0.62) [33].

We applied a previously developed diet quality score for school age children [32], with a similar scoring system as used for the pregnant women and infants. This child diet quality score included ten components, resulting in an overall diet quality sum score ranging from 0 to10. More details on this diet quality score and the included components are described elsewhere [32].

Allergic sensitization and atopic diseases

Children visited our research center at a median age of 9.7 years (IQR 9.6-9.9). Sensitization to inhalant (including house dust mite, 5-grass mixture, birch, cat, and dog) and food (including peanut, cashew nut, hazelnut, and peach) allergens was assessed by skin prick tests using the scanned area method [34]. Histamine dihydrochloride (10 mg/mL) was used as a positive control in duplicate and a saline solution (NaCl 0.9%) as a negative control. Skin responses were measured 15 min after applying allergens to the skin by measuring the area of the wheal (mm^2). An area that was ≥40% of the histamine response was considered as positive [35]. Children with a positive skin response to any of the allergens were categorized as 'any allergic sensitization'. We further categorized children into inhalant allergic sensitization and food allergic sensitization. In addition, questionnaires including questions adapted from the International Study of Asthma and Allergies in Childhood core questionnaire [36] were used to obtain information on physician-diagnosed inhalant ('Was your child ever diagnosed by a physician with an allergy to pollen (hay fever)/house dust mite/cat/dog?') (no; yes) and food allergies ('Was your child ever diagnosed by a physician with an allergy to cashew nut/peanut?') (no; yes). Based on this questions, we dichotomized children into 'any allergy' (no; yes). Finally, we further categorized children into 'sensitization to any allergen and any allergic symptom' versus 'no sensitization and no symptoms'. Information on ever eczema and asthma at the age of 10 years was obtained with the same questionnaire ('Was your child ever diagnosed by a physician with eczema/asthma?') (no; yes).

Covariates

At enrollment in the study, maternal height and weight were measured and body mass index (BMI) was calculated (kg/m^2). Questionnaires were used to obtain information on educational level of the mother (low; high), net household income (<2,200 or ≥2,200 Euros/month), parity (nulliparous; multiparous), prenatal pet exposure (yes; no), and whether mothers drank alcohol (never; until pregnancy was known; continued drinking occasionally; continued drinking frequently), smoked (never; until pregnancy was known; continued smoking during pregnancy), and used folic acid supplements (no; started in first ten weeks; started periconceptional) during pregnancy. We used questionnaires to obtain information on maternal history of atopic disease, including allergy (hay fever/house dust mite/food), eczema, or asthma. If a mother reported to have any of these outcomes, we categorized her as having a history of atopic disease.

Information on child's date of birth and sex was obtained from medical records. Child's ethnic background (Dutch; non-Dutch) was defined based on the country of birth of the parents, which was obtained with questionnaires at enrollment. Information on breastfeeding during the first 4 months (never; partial; exclusive) was obtained via postnatal questionnaires. Exclusive breastfeeding was defined as receiving breastmilk only for

at least 4 months. Timing of solid food introduction in the first year of life (<3; 3-6; ≥6 months) was obtained from the FFQ administered in infancy. Questionnaires were used to obtain information on day care attendance in the first year of life (≤24 or >24 h/wk).

Statistical analyses

Non-linearity of associations of diet quality during pregnancy, infancy, or childhood with all atopic outcomes was explored using natural cubic splines (df=3). As no indications for non-linear associations for the main models were found, all analyses were performed using models assuming linearity. Multivariable logistic regression analyses were used to analyze the associations of either diet quality during pregnancy, infancy, or childhood with allergic sensitization and atopic diseases around the age of 10 years. All associations were analyzed in three models with stepwise adjustment for potential confounders based on previous evidence. The first model was adjusted for child's ethnic background, sex, age at outcome assessment, and total energy intake. The second model was additionally adjusted for several socioeconomic and lifestyle factors, including maternal BMI at enrollment, maternal educational level, household income, parity, prenatal pet exposure, alcohol intake during pregnancy, smoking during pregnancy, folic acid supplements during pregnancy, and maternal history of atopic disease. In the final model, we examined whether associations of diet quality in pregnancy, infancy, or childhood with allergic sensitization and atopic diseases were independent of diet at the other two time points by additionally adjusting them for each other. Breastfeeding, child's sex, child's ethnic background, and maternal history of atopic diseases were separately examined as potential effect modifiers by including interaction terms in the models.

As sensitivity analyses, we repeated our analyses restricted to participants with a Dutch ethnic background only to reduce the risk of residual confounding by ethnicity, since the FFQs were developed for a Dutch population. Also, we repeated our analyses excluding children with any allergic disease in the first year of life for the analyses on infant and child diet quality. In addition, we examined associations of diet quality with the combination of sensitization and allergic symptoms versus no sensitization or symptoms as outcome. Furthermore, we examined whether associations of early-life diet quality with allergic sensitization and atopic diseases were independent of the other outcomes by adjusting associations with atopic diseases for allergic sensitization and vice versa. Finally, to verify that any associations of the overall diet quality scores were not driven by any specific component of the score, we repeated the main analyses excluding one component from the diet score at a time.

To reduce potential bias due to missing values on some of the covariates (ranging from 0% to 30.1%), these variables were multiple imputed (n=10 imputations). Diet quality scores at different time points were treated as either exposure or confounders in

the different models. When diet quality was included as a confounder, multiple imputed values of diet quality scores were used and when diet quality was the exposure of interest, the non-imputed variable was used. The results presented are the pooled regression coefficients of the 10 imputed datasets. All statistical analyses were carried out using the statistical software program SPSS Statistics version 21.0 (IBM Inc., Armonk, NY, USA).

RESULTS

Population characteristics

Characteristics of the study population are presented in **Table 4.1.1**. The majority of the children had a Dutch ethnic background (63.7%), and half of the children were girls (50.8%). Mean (±SD) diet quality score during pregnancy was 7.7 (±1.6) out of theoretical range of 0 to 15, mean diet quality score in infants was 4.3 (±1.4) out of 10, and mean diet quality in 8-year-old children was 4.5 (±1.2) out of 10. None of the participants (either pregnant women or their children) reached the maximum diet quality score. In total, 26.0% of the children were sensitized to one or more allergens, with 25.6% of all children being sensitized to an inhalant allergen and 5.7% to a food allergen. A physician diagnosed allergy was reported for 11.1% of the children, with a total of 10.6% of the children diagnosed with an inhalant allergy and 1.9% with a food allergy. Eczema was present in 20.0% of the children, and 8.3% of the children had asthma.

Table 4.1.1. Characteristics of the study population (n=5,225)

	N (%), median (IQR), or mean (SD)
Maternal characteristics	
Age at enrollment, years	31.7 (28.4-34.4)
Total energy intake, kcal/d (n=4,069)	2,047 (1,670-2,439)
Diet quality score (n=4,069)	7.7 (1.6)
Educational level, higher	2,751 (52.7%)
Household income, ≥2200 Euros per month	3,234 (61.2%)
Parity, nulliparous	3,027 (57.9%)
Prenatal pet exposure, yes	1,800 (34.4)
Alcohol intake during pregnancy	
Never	2,040 (39.0%)
Until pregnancy was known	722 (13.8%)
Occasionally during pregnancy	1,949 (37.3%)
Frequently during pregnancy	514 (9.8%)

Table 4.1.1. Characteristics of the study population (n=5,225) (continued)

	N (%), median (IQR), or mean (SD)
Smoking during pregnancy	
Never	3,978 (76.1%)
Until pregnancy was known	484 (9.3%)
Continued during pregnancy	763 (14.6%)
Folic acid supplement use	
No	1,084 (20.8%)
Started in the first 10 weeks of pregnancy	1,745 (33.4%)
Started periconceptional	2,395 (45.8%)
History of atopic disease, yes	2,116(40.5%)
Infant characteristics	
Sex, female	2,652 (50.8%)
Ethnic background, Dutch	3,331 (63.7%)
Age at dietary assessment, months (n=2,796)	12.9 (12.7-13.9)
Total energy intake, kcal/d (n=2,796)	1,261 (1058-1505)
Diet quality score (n=2,796)	4.3 (1.4)
Breastfeeding	
Never	508 (9.7%)
Four months partially	3,401 (65.1%)
Four months exclusively	1,315 (25.2%)
Child characteristics	
Age at dietary assessment, years	8.1 (8.0-8.2)
Total energy intake, kcal/d (n=4,066)	1,461 (1,240-1,702)
Diet quality score (n=4,066)	4.5 (1.2)
Age at outcome assessment, years	9.7 (9.6-9.9)
Any allergic sensitization (n=3,911)	1,357 (26.0%)
Inhalant allergic sensitization	1,335 (25.6%)
Food allergic sensitization	298 (5.7%)
Any allergy (n=4,577)	579 (11.1%)
Inhalant allergy	554 (10.6%)
Food allergy	97 (1.9%)
Ever eczema (n=4,598)	1,046 (20.0%)
Ever asthma (n=4,616)	432 (8.3%)

Values are means (± standard deviation (SD)) for continuous variables with a normal distribution, or medians (interquartile range (IQR)) for continuous variables with a skewed distribution, and absolute numbers (percentages) for categorical variables and are based on imputed data. Missing values for educational level (5.0%), household income (18.9%), parity (2.8%), prenatal pet exposure (20.6%), alcohol intake (during pregnancy (14.2%), smoking during pregnancy (17.1%), folic acid supplement use (28.2%), history of atopic disease (17.2%), child ethnic background (0.2%), and breastfeeding (30.1%) were multiple imputed (n=10 imputations).

Diet quality during pregnancy

Associations of diet quality during pregnancy and allergic sensitization in children are presented in **Table 4.1.2**. In model 1, we observed a statistically significant association for inhalant allergic sensitization (OR=1.06, 95%CI: 1.01, 1.12) (model 1, Table 4.1.2). However, this association was no longer statistically significant after adjustment for socioeconomic and lifestyle factors. In model 3, which was our main model, we observed no associations between diet quality during pregnancy and food allergic sensitization (OR=1.04, 95%CI 0.92, 1.17) in children at the age of 10 years (model 3, Table 4.1.2). In line with our findings for allergic sensitization, we observed no statistically significant associations with self-reported physician-diagnosed inhalant (OR=0.94, 95%CI: 0.88, 1.00) or food allergies (OR=1.11, 95%CI: 0.91, 1.35), eczema (OR=0.99, 95%CI: 0.93, 1.06), or asthma (OR=0.93, 95%CI: 0.85, 1.03) in 10-year-old children (model 3, Table 4.1.2).

Table 4.1.2. Associations of diet quality in pregnancy with allergic sensitization and allergic diseases in childhood at the age of 10 years

	OR (95%CI) per 1 point higher diet quality score		
	Model 1	*Model 2*	*Model 3*
Any allergic sensitization (n=1,019/2,960)	1.06 (1.00, 1.11)	1.06 (0.99, 1.13)	1.05 (0.99, 1.13)
Inhalant allergic sensitization (n=1,002/2,960)	**1.06 (1.01, 1.12)**	1.06 (0.99, 1.13)	1.06 (0.99, 1.13)
Food allergic sensitization (n=224/2,960)	1.04 (0.93, 1.14)	1.04 (0.93, 1.16)	1.04 (0.92, 1.17)
Any allergy (n=449/3,588)	0.96 (0.90, 1.03)	0.96 (0.88, 1.04)	0.96 (0.88, 1.04)
Inhalant allergy (n=427/3,588)	0.95 (0.89, 1.00)	0.94 (0.88, 1.00)	0.94 (0.88, 1.00)
Food allergy (n=69/3,588)	1.06 (0.91, 1.24)	1.04 (0.86, 1.25)	1.11 (0.91, 1.35)
Ever eczema (n=840/3,600)	1.03 (0.98, 1.08)	1.00 (0.94, 1.06)	0.99 (0.93, 1.06)
Ever asthma (n=319/3,610)	0.91 (0.84, 0.98)	0.94 (0.86, 1.03)	0.93 (0.85, 1.03)

Values are odds ratios with 95% confidence intervals (CIs) from logistic regression analyses, for allergic sensitization or atopic disease per 1 point higher diet quality score. Numbers (n) represent cases/total population with valid data included in the analyses. **Bold** values indicate statistically significant effect estimates.
Model 1 is adjusted for sex, ethnic background, age at outcome assessment, and total energy intake.
Model 2 is additionally adjusted for maternal BMI at enrollment, maternal educational level, household income, parity, prenatal pet exposure, alcohol intake during pregnancy, smoking during pregnancy, folic acid supplements during pregnancy, maternal history of atopic disease, and breastfeeding.
Model 3 is additionally adjusted for diet quality in infancy and childhood.

Diet quality in infancy

Associations of diet quality in infancy and allergic sensitization and atopic diseases in children are presented in **Table 4.1.3**. For diet quality in infancy, similar null findings were observed for inhalant allergic sensitization (OR=0.99, 95%CI: 0.92, 1.06) and for food allergic sensitization (OR=0.98, 95%CI: 0.86, 1.12) in model 3). Also, no associations were observed with inhalant (OR=0.96, 95%CI: 0.87, 1.05) or food allergies (OR=0.84, 95%CI: 0.70, 1.05) or with eczema or asthma in children around the age of 10 years (Table 4.1.3).

Table 4.1.3. Associations of diet quality in infancy with allergic sensitization and allergic diseases in childhood at the age of 10 years

	OR (95%CI) per 1 point higher diet quality score		
	Model 1	*Model 2*	*Model 3*
Any allergic sensitization (n=823/2,456)	1.00 (0.94, 1.06)	1.00 (0.94, 1.07)	0.99 (0.92, 1.06)
Inhalant allergic sensitization (n=808/2,456)	1.00 (0.94, 1.07)	1.00 (0.94, 1.07)	0.99 (0.92, 1.06)
Food allergic sensitization (n=173/2,456)	0.99 (0.93, 1.05)	0.99 (0.87, 1.12)	0.98 (0.86, 1.12)
Any allergy (n=316/2,519)	0.94 (0.86, 1.02)	0.94 (0.86, 1.03)	0.94 (0.86, 1.04)
Inhalant allergy (n=302/2519)	0.95 (0.88, 1.04)	0.96 (0.87, 1.05)	0.96 (0.87, 1.05)
Food allergy (n=58/2,519)	0.84 (0.68, 1.03)	0.82 (0.67, 1.01)	0.84 (0.70, 1.05)
Ever eczema (n=586/2543)	1.00 (0.97, 1.04)	1.00 (0.93, 1.07)	1.00 (0.93, 1.08)
Ever asthma (n=236/2542)	0.95 (0.86, 1.05)	0.96 (0.86, 1.06)	0.96 (0.86, 1.07)

Values are odds ratios with 95% confidence intervals (CIs) from logistic regression analyses, for allergic sensitization or atopic disease per 1 point higher diet quality score. Numbers (n) represent cases/total population with valid data included in the analyses.
Model 1 is adjusted for sex, ethnic background, age at outcome assessment, and total energy intake.
Model 2 is additionally adjusted for maternal BMI at enrollment, maternal educational level, household income, parity, prenatal pet exposure, alcohol intake during pregnancy, smoking during pregnancy, folic acid supplements during pregnancy, maternal history of atopic disease, and breastfeeding.
Model 3 is additionally adjusted for diet quality in pregnancy and childhood.

Diet quality in childhood

Table 4.1.4 presents associations of diet quality in childhood with the allergic outcomes. We observed no associations of diet quality in childhood with inhalant allergic sensitization (OR=1.03, 95%CI: 0.96, 1.11) or food allergic sensitization (OR=1.00, 95%CI: 0.88, 1.15) in childhood (model 3, Table 4.1.4). Similar null findings were observed for inhalant allergy (OR=1.05, 95%CI: 0.95, 1.15), food allergy (OR=0.86, 95%CI: 0.69, 1.05), eczema (OR=1.02, 95%CI: 0.95, 1.10), and asthma (OR=1.03, 95%CI: 0.93, 1.15) (Table 4.1.4).

Additional analyses

Associations were not statistically significantly different between Dutch and non-Dutch children for any of the outcomes (p-for-interaction >0.1). In line with this, sensitivity analyses restricted to children with a Dutch ethnic background only resulted in similar effect estimates as observed in the whole population. An exception was that among children with a Dutch ethnic background only, a higher diet quality during pregnancy was associated with a higher odds of inhalant allergic sensitization. However, we interpret this as a chance finding, since there was no association with any of the other outcomes; the interaction with ethnicity was not statistically significant; and because this finding would not remain if we would take into account multiple testing (P=0.02). Also, analyses excluding children with any allergic disease in the first year of life resulted in similar findings , except for an inverse association of diet quality in infancy with food allergy (OR=0.64, 95%CI: 0.43, 0.95, P=0.03), but not with any of the other outcomes. Analyses

Table 4.1.4. Associations of diet quality in childhood with allergic sensitization and allergic diseases in childhood at the age of 10 years

	OR (95%CI) per 1 point higher diet quality score		
	Model 1	*Model 2*	*Model 3*
Any allergic sensitization (n=1012/3,017)	1.03 (0.97, 1.10)	1.04 (0.97, 1.11)	1.03 (0.96, 1.11)
Inhalant allergic sensitization (n=994/3,017)	1.04 (0.97, 1.11)	1.04 (0.97, 1.12)	1.03 (0.96, 1.11)
Food allergic sensitization (n=218/3,017)	0.99 (0.93, 1.06)	0.99 (0.87, 1.13)	1.00 (0.88, 1.15)
Any allergy (n=463/3,750)	1.00 (0.92, 1.09)	1.02 (0.94, 1.12)	1.04 (0.95, 1.14)
Inhalant allergy (n=445/3,750)	1.00 (0.92, 1.08)	1.03 (0.94, 1.12)	1.05 (0.95, 1.15)
Food allergy (n=79/3,750)	0.88 (0.72, 1.06)	0.85 (0.69, 1.04)	0.86 (0.69, 1.05)
Ever eczema (n=850/3,766)	1.02 (0.98, 1.05)	1.01 (0.95, 1.09)	1.02 (0.95, 1.10)
Ever asthma (n=335/3,776)	0.97 (0.92, 1.02)	1.01 (0.91, 1.12)	1.03 (0.93, 1.15)

Values are odds ratios with 95% confidence intervals (CIs) from logistic regression analyses, for allergic sensitization or atopic disease per 1 point higher diet quality score. Numbers (n) represent cases/total population with valid data included in the analyses.

Model 1 is adjusted for sex, ethnic background, age at outcome assessment, total energy intake.

Model 2 is additionally adjusted for Maternal BMI at enrollment, maternal educational level, household income, parity, prenatal pet exposure, alcohol intake during pregnancy, smoking during pregnancy, folic acid supplements during pregnancy, maternal history of atopic disease, breastfeeding.

Model 3 is additionally adjusted for diet quality in pregnancy and infancy.

with a combination of allergic sensitization and allergic symptoms as the outcome (n=642) versus no sensitization and symptoms (n=1,699) resulted in similar null findings. Additional adjustment for the other outcome variables did not affect the results. Also, excluding one component from the diet scores at a time, or additional adjustment for introduction of solid foods and day care attendance in the first year of life did not affect the results (data not shown). We observed a significant interaction (p=0.03) of infant diet quality with sex on food sensitization, and of infant diet quality with breastfeeding on eczema (P=0.03), but not on any of the other outcomes (p-for-interaction ranging from 0.1 to 0.9). For none of the associations, we observed a significant interaction for maternal history of atopic diseases or child's ethnic background (p-for-interaction >0.1). Stratification by sex suggested effect estimates in different directions (boys: OR=0.88, 95%CI: 0.73, 1.06, model 3, girls: OR=1.10, 95%CI: 0.91, 1.32, model 3), but none statistically significant. Similarly, after stratification by breastfeeding, no significant associations were observed in the different groups.

DISCUSSION

In this large population-based study, we aimed to examine the associations between diet quality during pregnancy, infancy, and childhood with allergic sensitization, physician-diagnosed inhalant and food allergy, eczema, and asthma in mid-childhood.

Overall, we observed no associations of overall diet quality during either pregnancy, infancy, or childhood with allergic sensitization or atopic diseases in children around the age of 10 years.

Interpretation and comparison with previous studies

Although we observed a few associations of diet quality with atopic outcomes in our sensitivity analyses, these were not consistent and do not remain if multiple testing would be taken into account. In addition, the effect estimates were similar as observed in the main analyses. Our finding of a higher diet quality in infancy with lower odds of food allergy in additional analyses warrants caution and needs further study, as the prevalence of food allergy in these analyses is low (n=18).

Previous studies mainly reported on associations of one particular time point in childhood (e.g., either pregnancy, infancy, or childhood) with different atopic outcomes. In this study, we examined diet at three different time points in early life. Although some previous studies observed an inverse association of overall diet during either pregnancy or infancy with atopic outcomes in childhood [21,25], we did not observe such associations. This is in line with a previous study in the United Kingdom that also observed no associations of data-driven dietary patterns in pregnancy with asthma or atopy in children around the age of 7 years [22]. A recent systematic review suggested that a Mediterranean diet during pregnancy may only have an inverse association with asthma in the offspring in their first year of life, but not afterwards [19]. The longer time window between exposure and outcomes, and the measurement of atopic outcomes at the age of 10 years may therefore explain the absence of an association in our study, as children may outgrow some atopic diseases as they become older [37] and diet may have no long-term effects. Indeed, previous analyses in our cohort showed a positive association of adherence to a 'Western-like' dietary pattern in early life with asthma-related symptoms such as wheezing at the ages of 3 and 4 years [26], whereas we did not observe associations of diet quality with asthma at the age of 10 years in the current study. This suggests that any potential association between early-life diet and atopic outcomes may take place within a short term and may not persist into later childhood.

However, studies with shorter time windows between exposure and outcome also report inconsistent findings. Several cross-sectional studies examined associations of a predefined Mediterranean dietary pattern in childhood with allergic outcomes [18,19]. Inverse associations were reported in some of these studies, for example for diet in children aged 6 to 7 years [38] and 10 to 12 years [39]. A study in the United Kingdom observed a positive association of a Western dietary pattern, which was high in processed foods, at the age of 8 years with asthma, but no associations with allergic sensitization at the ages of 8 and 11 years [27]. Finally, another study observed no associations of children's adherence to a Mediterranean diet at the age of 6.5 years with atopy at the same age [21].

In addition to the time window of measurements, geographic area and cultural differences may play a role in the inconsistent associations observed in the different studies. A meta-analysis suggested, for example, that a Mediterranean diet may only be protective for atopic symptoms among children in the Mediterranean area [18]. A possible explanation for this may be the use of different Mediterranean diet indices, which may reflect slightly different food products. Also, a recent study in Singapore reported that a dietary pattern which was particularly high in fish and other seafood such as shellfish, at the age of 1 year was associated with less allergic sensitization to house dust mite at the ages of 18 months, but also at the age of5 years [25]. The high fish intake may have driven the observed association. However, children and also adults In the Netherlands have a relatively low fish and shellfish intake [40] and low variability. Therefore, these food groups do not drive large variations in our diet quality scores [30]. In addition, our diet quality scores were based on dietary guidelines, whereas most previous studies examined indices based on a traditional Mediterranean diet or data-driven dietary patterns and did not take into account dietary guidelines. However, these dietary patterns are population-specific and may not represent actual healthy diets. The absence of an association in our study may suggest that specific foods or nutrients, such as fish or fatty acids, rather than overall dietary patterns may be more relevant for the prevention of atopic outcomes in children. Further studies in specific populations are needed to confirm this.

Strengths and limitations

The strengths of this study are its population-based, prospective design, the inclusion of a large number of participants, and the availability of numerous covariates. Also, we had detailed information on allergic sensitization to several common allergens relevant for school-age children, measured with skin prick tests. For these tests, we used the scanned area method to determine the wheal area, which is considered to be more accurate than measuring the average wheal diameter, and is recommended for use in academic research [34]. Furthermore, we analyzed overall dietary patterns, and not just single nutrients, which takes into account the interactions between different nutrients [17], and we had dietary data available at several time points throughout early life.

Several limitations of this study should also be considered. First, dietary intake during pregnancy, infancy, and childhood were assessed with FFQs, which are prone to measurements errors [41]. However, FFQs are commonly used in large epidemiological studies and have been shown to rank participants accurately according to their dietary intake [41]. In addition, in our study, we used validated, extensive, population-specific FFQs [30,31,33]. Although allergic sensitization was measured objectively using skin-prick tests, our other atopic outcomes were assessed with questionnaires filled out by the parents, which may have resulted in some misclassification. These questionnaires included questions on physician-diagnosed inhalant or food allergies, eczema, and asthma by

any physician, but with no further details. However, we expect any misclassification to be unrelated to the exposure and therefore only resulting in random information bias. Furthermore, results for the associations of diet quality with objectively assessed allergic sensitization with skin prick tests and the self-reported atopic diseases were consistent. Despite that we were able to adjust the analyses for several confounders, some may not have been measured perfectly and there may be other possible confounding factors that we did not have available. Finally, most of the participants included in our study had a Dutch ethnic background, were, on average, highly educated, and had a high household income, which may limit the generalizability of our findings to other populations. However, in our sensitivity analyses restricted to participants with a Dutch ethnic background only similar results were obtained, suggesting no large bias due to ethnic background.

Conclusion

In conclusion, our findings suggest that overall diet quality in early life, either during pregnancy, infancy, or childhood, is not associated with the risk of allergic sensitization or atopic diseases in later childhood. Specific nutrients rather than overall dietary patterns may be more relevant for atopic outcomes in children and require further study.

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Chapter 4.2

Dietary interventions in early childhood and its effects on atopic diseases: a systematic review

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Dietary interventions in early childhood and its effects on atopic diseases: a systematic review. *Submitted for publication.*


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Chapter 5

General discussion

AIMS

The aims of this thesis were to evaluate overall diet quality in childhood, to study its determinants, and to study its associations with several health outcomes. We evaluated diet quality of children participating in three different population-based cohorts. Main determinants of interest were feeding-related factors and socioeconomic and lifestyle factors. Main outcomes of interest were body composition, cardiometabolic health, and atopic diseases.

MAIN FINDINGS

Diet quality in childhood

To assess overall diet quality of children, we developed a novel food-based diet quality score for school-age children, based on age-specific dietary guidelines. Subsequently, we used this score to evaluate diet quality of children participating in the Generation R, ABCD, and Rhea cohorts. In the first cohort, the Generation R Study, we first assessed the construct validity of the diet quality score, i.e. whether this score actually measures what it is supposed to measure, namely a healthy diet. To do this, we assessed associations of the diet quality score with intake of several nutrients. The score was positively correlated with intake of macronutrients considered to be healthy, including protein, mainly plant protein, dietary fiber, and $n-3$ fatty acids, and inversely correlated with intakes of more unhealthy nutrients, including saturated fat, monosaccharides and disaccharides. The score was also positively correlated with intakes of essential micronutrients, such as vitamins, calcium, and magnesium. These results indicate that the diet quality score has adequate construct validity and that the score may be used as an indicator of a healthy diet. We applied this diet quality score in three different populations of children of different ages, living in different environments, and we observed similar diet qualities among these children. These results add to the validity of our diet quality score and suggest that it could indeed be used as an indicator of healthy diet in children.

Using this diet quality score, we observed that diet quality of children at the ages of 4, 6, and 8 years, living on Crete (Greece), in Amsterdam (the Netherlands), and Rotterdam (the Netherlands), was suboptimal, with median scores in the different populations ranging from 4 to 6 on a continuous scale from 0 to 10, indicating that their dietary intake was not conform current age-specific dietary guidelines. In general, children scored relatively high for their intakes of whole-grains, fruits, and fish, whereas low scores were observed for sugar-containing beverages and red- and processed meat **(Figure 5.1)**. These findings are in line with results from the Dutch National Food Consumption Survey [1] and other studies on diet quality in children [2,3]. Given this low diet quality in

children and its potential effects on later health, dietary intake in children needs to be improved. In order to do this, it is essential to study potential determinants of diet quality to identify children at high risk of poor diet quality.

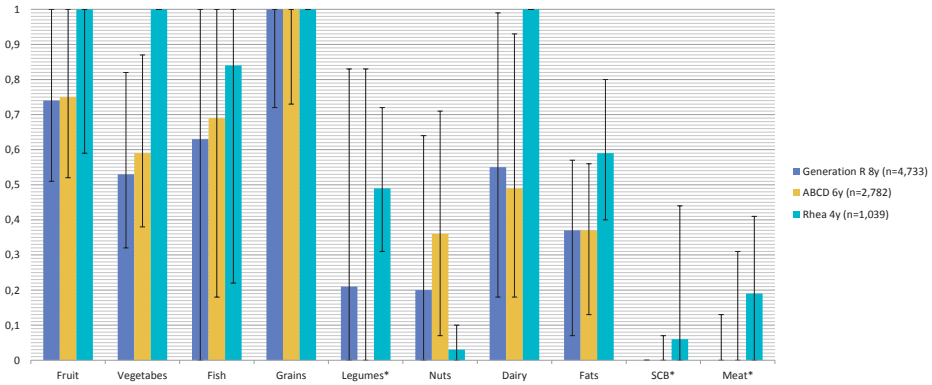

Figure 5.1. Median scores for the individual components of the diet quality score in three cohorts of children

Values are medians and interquartile ranges. Maximum score per component: 1. *median score of 0.

In Chapters 2.1 to 2.4, we studied several potential determinants of diet quality in early and mid-childhood. We observed that children with more screen time, children from lower educated mothers, or from lower-income households have a lower diet quality – all independent of each other. In addition, we observed that women with a history of eating disorders have a relatively good diet quality during pregnancy, which was also observed in their infants. These findings could provide directions for public health interventions to specifically target children at risk of poor diet quality. Other important determinants of dietary intake are eating environment and taste preferences. It has been suggested that taste preferences and eating habits are shaped in early childhood and that they tend to track into adulthood, thereby influencing food choices [4,5]. In Chapter 2.2 we examined associations of parental feeding practices and family eating routines with diet quality in school-age children. Findings of this study suggested that parental monitoring and restrictive feeding is associated with higher diet quality, while pressure to eat and less frequent family meals were associated with lower child diet quality. This suggests that targeting parental feeding strategies could improve diet quality of children. In Chapter 2.3 we evaluated dietary taste patterns in early childhood and its determinants. Children at the age of 1 year obtained most of their energy intake from foods within a neutral cluster, which are low in all basic taste intensities. Once they reach the age of 2 years, their dietary intake becomes more intense in taste, i.e., they have a higher consumption of food products that taste more sweet, sour, or salty. Similar determinants of dietary taste patterns have been identified as for diet quality.

In addition, we observed positive correlations of several taste patterns with diet quality score in infancy, suggesting that intervening in the food products given at an early age could affect taste preferences and thereby diet quality. Still, more research is needed to explore overall dietary taste patterns in early childhood, how these track over time, and how it is related to dietary habits and actual dietary intake in later life.

Diet quality, body composition, and cardiometabolic health

Using this diet quality score, not only adherence to guidelines and its determinants can be studied, but also associations of overall diet with health outcomes, in order to identify important modifiable risk factors of (common) diseases. In this thesis, I examined the associations of diet quality with highly prevalent and important public health problems in childhood: childhood obesity, cardiometabolic risk factors, and atopic diseases. Concerning obesity, we used repeated measures of children's growth and detailed measures of body composition (Chapters 3.1 to 3.3). We observed that a higher diet quality score at different ages throughout childhood was associated with better growth and a higher BMI up to age 12 years. However, we observed that this association may be explained by higher fat-free mass rather than fat mass. These findings therefore suggest that BMI is not an adequate measure to examine associations of dietary intake with adiposity in children. Furthermore, we observed that higher diet quality in childhood was associated with better bone health at the age of 10 years, independent of child BMI. Our findings therefore suggest that dietary intake according to dietary guidelines may have a beneficial impact on growth and body composition throughout childhood. In Chapters 3.4 and 3.5, we examined associations of diet quality with cardiometabolic health in children. Our findings from chapter 3.4 suggest that better diet quality is associated with overall lower cardiometabolic risk in school-age children, which was mainly driven by a lower blood pressure. It has been shown that obesity and other cardiometabolic risk factors tend to track from childhood to adulthood and increase the risk of chronic diseases [6-10]. Hence, targeting these factors during childhood could be a good strategy to prevent later chronic diseases. Certain cardiometabolic risk factors may only become apparent at a later age. Studies with longer follow-up and repeated measurements are crucial to examine associations of diet in childhood with cardiometabolic health over a longer time period.

Overall diet and atopic diseases

Another common health problem in childhood are atopic diseases, including asthma, eczema, and food allergy. We examined associations of overall diet quality in early life, i.e., during pregnancy, infancy, and in childhood, with allergic sensitization or atopic diseases in children around the age of 10 years. Overall, we did not observe associations of diet quality at one of these time points with atopic outcomes at age 10 years. It

has been suggested that children may outgrow some atopic diseases as they become older [11-13]. The long time-window between exposure and outcome in our study and the measurement of atopic outcomes at the age of 10 years may explain the absence of an association in our study. Any potential associations between early-life diet and atopic outcomes may take place within a short time window and may not persist into later childhood. In addition, specific foods or nutrients, such as fish or fatty acids, rather than overall dietary patterns may be more relevant for the prevention of atopic outcomes in children.

In addition to this observational study, we also conducted a systematic review of RCTs on dietary interventions in early childhood. Most interventions yielded inconsistent findings for the development of atopic diseases. However, interventions on allergen avoidance in early life seemed promising for preventing atopic diseases. More high-quality research with proper control groups are needed to confirm these findings.

METHODOLOGICAL CONSIDERATIONS

Study design and populations

The studies in this thesis were embedded in three cohort studies of children and we conducted a systematic review of randomized controlled trials. Most of the studies in this thesis were performed in the Generation R Study, based in Rotterdam, the Netherlands. In addition, data from the ABCD Study (Amsterdam, the Netherlands) and the Rhea Study (Island of Crete, Greece), were analyzed. All three studies are large ongoing population-based prospective cohort studies. Major strengths of population-based studies are the ability to identify potential risk factors of common diseases, and the availability of a wide range of potential covariates. In addition, cohort studies could indicate temporal associations between exposures and outcomes, because participants in a cohort study are known to be disease-free at the timing of exposure assessment. However, all studies in this thesis were of observational nature, which does not allow to directly infer causality of the associations [14]. In addition, prospective cohort studies may require long follow-up periods, which could be accompanied with high rates of loss to follow-up. This loss to follow up during a study as well as the selection of subjects into a study could lead to selection bias. Participants included the Generation R Study tended towards a more healthy population, with participants in general having more healthy habits and were more highly educated than the total population. This selective participation at baseline might influence prevalence rates and thereby affect the external validity of the study, i.e. the generalizability of our results to other populations [15]. Nevertheless, selective loss to follow-up could introduce selection bias, which also threatens internal validity of the study. Selection bias occurs when associations of dietary intake with our outcomes

of interest are different for the children included in our study compared to those who were not included, but would have been eligible [16]. In Chapter 2.4, we reported that non-responders to the FFQ more often had characteristics associated with a lower diet quality score, such as lower educational level. Diet quality may therefore even be lower in children not included in the analysis. This would have consequences for the external validity, as observed results may not be directly generalizable to the general population. However, it could also result in selection bias if the associations of diet quality with health outcomes are different between children who were included in the analysis and children who were not. Other important sources of error in cohort studies are information bias and confounding, which will be discussed later in this chapter.

Some of these limitations of cohort studies could be tackled in RCTs, which are generally considered to provide the best level of evidence [17]. However, RCTs might face other limitations, as we also observed in Chapter 4.2 where we conducted a systematic review of RCTs. Especially in nutritional research, it is challenging to find a proper placebo or control group. For example, dietary interventions of foods can typically not be blinded, leading to the possibility that the observed effect is due to knowledge of intervention assignment. Hence, RCTs of dietary interventions often examine the effects of nutrients by comparing supplements to a placebo. However, the effects of supplements might not be the same as real foods, as nutrients are not consumed in insolation and diets are complex, with interactions and synergistic effects across different nutrients and dietary components. Therefore, cohort study designs remain useful and necessary to study associations of actual dietary intake with health outcomes. Consistent observations of an association between dietary intake and health in different populations and with different study designs and approaches of dietary analysis may also lend support to a real effect.

Dietary assessment

The dietary data from all cohorts used in this thesis were measured using FFQs. An FFQ measures habitual intake rather than intake on one or a few specific days, making them suitable to estimate long-term dietary intake. In addition, FFQs are commonly used in population-based evaluations of dietary patterns in childhood and adulthood and are favored in large-scale studies because they are less burdensome to participants than e.g. food diaries and are relatively easy to process [18]. However, FFQs are self-reported and are therefore prone to measurement errors [19-21]. This measurement error is an important source of information bias in studies on dietary intake, as it may result in misclassification of the exposure [21]. Misclassification can be non-differential or differential. In the case of non-differential misclassification of the exposure, the measurement error is random and not related to the outcome of interest, leading to attenuation of the association. However, in the case of differential misclassification, the measurement error is related to the outcome of interest. It has been suggested that overweight adults tend to

underreport their dietary intake compared to adults with normal weight [22]. Since young children have a limited ability to self-report their food intake, the ability of parents to accurately recall their children's food intake is vital. Although a few studies suggested that parents are capable of accurately reporting dietary intake of their child [23,24], not much is known about potential differential-misclassification of parent-reported dietary intake of children. In our studies, estimated energy intakes from our FFQs were similar to the recommended energy intakes for the specific age groups, suggesting no large under- or over reporting. Also, validation of our FFQ showed reasonable capacity of the FFQ to rank children according to their energy intake [25]. Although exact amounts of nutrients intakes are difficult to estimate with the use of an FFQ due to these measurement errors, it has been shown that FFQs are appropriate for ranking participants according to their dietary intake, making it a suitable method to assess dietary intake in large populations. In addition, in our studies, we used validated, extensive, population-specific FFQs.

A big challenge of FFQs is that they should be tailored to the specific study population. Food items in the FFQ should be chosen in such a way that it covers a large part of the habitual intake in the study population. An FFQ for young children should therefore be different than for older children, as several specific food items are more frequently consumed in particular age groups, e.g. baby formula are only consumed by infants and not by older children. In addition, an extensive FFQ including many food items provides more detail and contributes to a more accurate estimation of dietary intake. In our studies, we used FFQs that were validated using other dietary assessment methods and that showed good results for this validation. For example, the FFQ that was used for school-age children in both the Generation R and ABCD studies was validated against the doubly labeled water method, which is regarded as the golden standard for the determinations of total energy expenditure in individuals. This validation showed a Pearon's correlation of 0.62 for energy intake as estimated from the FFQ and energy expenditure measured with the doubly labeled water method, indicating a reasonable capacity of the FFQ to rank children with regard to their energy intake [25]. However, the FFQ was not validated for intake of specific foods or food groups.

A main limitation of an FFQ is that it is self-reported and it relies on the memory of the respondents. However, all self-report methods to asses dietary intake, including not only FFQs, but also e.g., 24h recalls and food diaries, are challenging [21]. In general, individuals do not remember everything that they or their children consumed, do not know the contents of the foods eaten, and have difficulties to estimate portion sizes accurately. In addition, in parent-reported dietary intakes, parents might not be aware of everything that their child eats outside of the house, for example at school or the day care. Another method to assess dietary intake are the use of biomarkers [26]. These biological indicators of intakes are not limited by errors in self-reporting, but they have other limitations,

including that they often reflect status rather than intake, are highly specific, and are generally expensive and invasive.

In the studies included in this thesis, FFQs were sent to the participants in hard copy. This might have resulted in incompleteness of responses. Technology could offer a wide range of feasible options for dietary assessment, which are easy to incorporate into daily routines. For example, an online FFQ could enhance the completeness of responses, as it is able to prevent unanswered questions or implausible answers. Also, in recent years, the use of image-based dietary assessment has been used to assist traditional dietary assessment methods such as dietary records [27,28]. Images can be taken with handheld devices or wearable cameras, and have been used to assist traditional methods for among others the estimation of portion sizes. These images could further reduce self-report errors by taking and storing food images before and after consumption. Previous studies have suggested that the use of image-based approach complementary to traditional self-report assessments could improve accuracy of dietary assessment and that underreporting is reduced compared to traditional assessment methods only. However, at this moment, this image-based approach cannot yet be used as a dietary assessment method on its own, but can only be used to assist certain traditional, prospective assessment methods such as food diaries, but not for retrospective assessment methods such as 24h recalls or FFQs.

Dietary indices

Over the past few decades, analysis of dietary patterns has emerged as an important research field, complementary to studies focusing on single dietary compounds. An advantage of examining dietary patterns is that the complex correlations between intakes of foods and nutrients are taken into account [29]. Dietary patterns can either be data-driven (i.e., based on the variation of dietary intake data within a study population) or predefined (i.e., based on specific dietary guidelines or recommendations)[30]. The data-driven approach identifies similarities of dietary habits or food groups consumed within a study population, based on their intercorrelations. However, because these dietary patterns are identified on the basis of actual dietary intake from a study population rather than guidelines or existing knowledge, these patterns represent common diets in a population but do not necessarily represent a healthy diet. Predefined dietary patterns are usually based on dietary guidelines or recommendations, and therefore better reflect a desirable dietary pattern [31,32]. In addition, dietary patterns of different populations can be more easily compared. However, disadvantages of such dietary patterns are that the variations between individuals within a population might be small.

For the studies in this thesis, we used predefined diet quality scores to quantify diet quality of pregnant women, infants, and children at different ages, reflecting adherence to age-specific food-based dietary guidelines in the Netherlands. These Dutch dietary

guidelines are unique in the regard that they are completely food-based, since dietary guidelines from other countries often combine recommendations for both foods and individual nutrients. However, the predefined dietary index approach is limited by current scientific evidence and understanding of diet-disease relationships. The Dutch dietary guidelines were based on extensive previous research on nutrients, foods, and dietary patterns in relation to specific diseases that are common in the general Dutch population [33,34], but mostly evident in adults. Although Dutch dietary recommendations from the Netherlands Nutrition Center, based on guidelines form the Health Council, are available for children from age 1 year onwards, these are extrapolated based on evidence of the diet-disease relation in adult populations. An optimal diet for children might be different from an optimal diet in adulthood and may also be different in different phases of childhood. For example, exclusive breastfeeding is the most optimal diet for infants [35]. After this, there is a weaning period in which young children get introduced to foods other than milk, which is also an important period for the development of taste preferences and eating habits. Gradually, children will reach the point where they consume more regular table foods around the age of 1 year. Because children are likely to have different needs than adults, it might not be sufficient to extrapolate evidence from adults to guidelines for children. In addition, the association of adherence to these overall dietary guidelines with health outcomes in childhood has not yet been thoroughly evaluated and it remains unclear whether these associations in adulthood also applies to children. In future development of dietary guidelines, more studies in children are needed, and should be taken into account to develop guidelines that are truly age specific rather than just extrapolation of evidence from adult-based studies.

Constructing an overall diet quality index involves many choices. First, individual components of the score should be selected, and cut-off points have to be defined. Most diet indices are based on intake of nutrients, food groups, or a combination of these, and some indices also include measures of dietary variety [36]. We chose to construct our diet quality score on the basis of intake of food groups only, in line with current Dutch dietary guidelines. As we observed positive associations of the diet score with intake of essential micronutrients, the diet quality score may indeed represent an overall healthy diet. However, these nutrients have been estimated using the same FFQ as used for the development of the diet quality score. Ideally, one would like to validate the score against nutrients assessed with another method or with the use of biomarkers. In addition, our diet quality scores were continuous, which provide more detail and is more accurate in ranking children with respect to dietary quality than a dichotomous scoring system. We included both healthy and unhealthy components in the scores, which may better capture overall diet quality than including healthy or unhealthy components only, as eating healthy foods is not necessarily inversely related to eating unhealthy foods [37]. Although it may have been preferred to ascribe greater weights to components that

have a greater effect on health, not enough information on the overall health effects of individual components was available, so we chose not to apply any weighting.

Studying dietary patterns in relation to health in childhood could provide directions to improve future dietary guidelines specifically targeted at children of different ages. In addition, this diet quality score provides an overall estimation of a healthy diet, which can be used to control for diet quality in epidemiological studies on associations of other dietary or lifestyle factors with health. Dietary pattern analysis will not replace nutrient or food analysis in nutrition research, but instead, it serves as a complementary approach. Evidence for a real effect of dietary intake is supported when the results from multiple approaches (i.e. analysis of nutrients, foods, and dietary patterns) are consistent.

Outcome assessments

The primary outcomes in the studies presented in this thesis were body composition, cardiometabolic health, and atopic diseases. Children participating in the Generation R Study visited our research center at their ages of 6 and 10 years for a detailed physical examination. We measured their height and weight to calculate BMI. The use of BMI as measure of adiposity is practical and low in costs, making it ideal for large-scale studies. However, it has some limitations as BMI includes both fat mass as well as lean mass and bone mass [38-40], and its interpretation among children and adolescents is further complicated by the changes that occur in body composition during growth and development. BMI might therefore be misleading when examining associations of dietary intake with adiposity in children. In the studies included in this thesis, we therefore also examined fat, lean, and bone mass, measured using DXA-scans and BIA. We observed that children with higher diet quality in childhood have higher BMI, but that this higher BMI was fully explained by higher fat-free mass rather than fat mass. Thus, confirming that BMI only is not an adequate measure of adiposity. Reliable and valid body composition assessment is important in both clinical and research settings. Several methods and techniques for the measurement of body composition in children exist, including skinfold thicknesses, BIA, and DXA [41,42]. Skinfold thicknesses are relatively simple measurements to estimate adiposity, however, it has been shown to underestimate body fat in children. BIA is commonly used to assess body composition in research settings. It is a simple, non-invasive, and low-cost method to measure body composition. However, it has been suggested that BIA might be less accurate and underestimates body fatness as compared to DXA-scans, which is considered to be the gold standard for measuring body composition. DXA is also a rapid and non-invasive method to assess body composition. However, DXA requires specialized radiology equipment and is more expensive, and participants as well as researchers are exposed to some radiation.

For cardiometabolic factors, we measured blood pressure and blood concentrations of several metabolic markers, including triacylglycerol, cholesterol and, insulin. The

blood samples were collected in a non-fasting state. If the fasting time of the children before the measurement was randomly distributed and not related to diet in early childhood, this measurement error would only have led to non-differential misclassification of these outcomes. This measurement error of the outcome may therefore have resulted in an underestimation of the associations of diet quality with cardiometabolic factors.

For the atopic outcomes, we examined both sensitization to allergens and physician-diagnosed atopic diseases. Although allergic sensitization was measured objectively using skin-prick tests using the scanned area method, other atopic outcomes were assessed with parents-reported questionnaires, which may have resulted in misclassification. These questionnaires was adapted from the International Study of Asthma and Allergies in Childhood core questionnaire[43] and included questions on physician-diagnosed inhalant or food allergies, eczema, and asthma by any physician, but with no further details. However, for the studies in this thesis, we expect any misclassification to be unrelated to the exposure, i.e. diet quality at earlier time points, and therefore only resulting in random information bias, potentially leading to an underestimation of true associations. Furthermore, results for the associations of diet quality with objectively assessed allergic sensitization with skin prick tests and the parent-reported atopic diseases were consistent.

Confounding

As described earlier in this chapter, all studies included in this thesis are of observational nature, except for one. A major limitation of observational studies is the risk of confounding bias [44], because observational studies are not randomized to ensure equivalent groups for comparison. This is especially important for studies examining lifestyle factors such as dietary intake. It has been suggested that healthy habits tend to cluster. For example, children who have a more healthy diet also tend to have more physical activity and less screen time, as we also reported in Chapter 2.4. These other lifestyle factors may also be associated with health, and could therefore be potential confounders in the association of dietary intake with health outcomes such as body composition and atopic diseases.

Although information on a wide range of potential confounders was available and controlled for in our studies, residual confounding may still be present. These could be caused by unmeasured confounders, but also by measurement errors in the data on confounders that were available. For example, in the associations of diet with body composition in growing children, developmental stage of the children may be a confounder. As the children in the Generation R Study were 10 years at the final body composition measurement, some of the children might have already reached puberty. Unfortunately, we were not able to correct for puberty status in the Generation R Study. However, for

associations of diet with body composition up to age 12 years in children participating in the ABCD study, puberty status did not affect the associations.

Another important aspect when examining associations of a specific component of dietary intake with health, is confounding by other dietary factors. Intakes of foods and nutrients are often highly correlated and could therefore confound each other in diet–disease relationships. Because of these correlations within the diet, it is often difficult to examine the effect of one specific nutrient or food and to draw conclusions for that particular nutrient or food only. Dietary pattern analysis takes these correlations between nutrients and foods into account, and could therefore reduce confounding by other dietary factors.

PUBLIC HEALTH IMPLICATIONS AND FUTURE RESEARCH

Overall, our results suggest that diet quality of children is suboptimal. We observed that especially children with more screen time, children of lower-educated mothers, or from lower-income households had lower diet quality. In general, intakes of sugar-containing beverages and meat were much higher than recommended, whereas intakes of nuts and legumes were much lower than recommended. These findings provide directions for public health interventions to improve dietary intake in children at risk of having poor diet quality. Our results in Chapter 2.4 suggest that these interventions should particularly be targeted at children with more screen time, and children whose mothers have a lower socio-economic background, or who smokes. In addition, we observed that most of the associations were independent of diet quality at another time point in childhood, which emphasizes the importance of adequate dietary intake throughout childhood, not only at specific time windows, for optimal growth and development. Previous studies have shown that dietary intake tends to track from childhood to adulthood [45-48]. In Chapter 2.4 we also observed positive tracking of diet quality throughout childhood, i.e., children with higher diet quality in early childhood tend to have higher diet quality in mid-childhood. Hence, interventions to promote healthy diet should start early in childhood to achieve long-term benefits.

The results of the studies presented in this thesis add to the existing literature on the effects of dietary intake in childhood on body composition, cardiometabolic factors, and atopic diseases. Combined with results from previous studies on specific foods and nutrients, they can provide directions for future studies and public health interventions. For example, previous studies reported that in general, foods and foods groups that are considered to be healthy, e.g., fruit, vegetables, and whole grains, are associated with decreased risk obesity in children [49], whereas unhealthy foods such as sugar-containing beverages and energy-dense, low-fiber foods are associated with childhood obesity [50].

Our findings add to this evidence that these associations also hold when examining overall dietary patterns, and that associations are not driven by specific food groups. Our findings suggest that dietary intake according to current Dutch dietary guidelines may be associated with better body composition and cardiometabolic health in childhood. More research is needed to examine whether these associations persist to adolescence and adulthood, and whether a healthy diet in childhood can thereby indeed help prevent the development of adoposity and cardiometabolic diseases later in life.

Given that children of different ages have low diet quality, which may have adverse effects on health both in childhood and adulthood, it is important to improve diet quality of children. However, it is well known that changing behavior is very challenging. Individuals make many food choices on a daily basis, most of them even unconsciously. These food choices are influenced by many factors, including taste preferences, peers, costs, and availability. Especially in young children, parents have a high degree of control over their food intake, for example through feeding practices [51]. Given that dietary habits are established in early childhood and tend to track over time [52], it might be most effective to intervene already as young as possible. Many intervention programs to improve dietary intake in children have been studied. For young children, parents are the main source of food, but also schools, kindergartens, and day cares are important. Therefore, it is necessary to involve all of them in intervention programs. School gardening programs are considered to be a promising intervention to improve children's dietary intake, in particular intake of vegetables [53]. Previous studies have suggested that school gardening programs improve children's vegetable knowledge and preferences, increase their willingness to try vegetables, and even increase their intake [53,54]. Other school-based interventions seem promising as well, including the healthy school canteen and school policies to decrease sweet treats and to promote drinking water rather than sugar-containing beverages [55-57]. Using school-based interventions, all children could be reached and by making the healthy choice the default at schools, the problem of individual, unhealthy choices will decrease. Another strategy to modify intake of specific nutrients in the population is by food reformulation, which will result in making healthier food choices easier for consumers without them actively choosing for it. However, modifying food products might influence food acceptance, as the taste of food products could change. Studies have suggested that gradually lowering the salt content in bread – a commonly consumed product in the Netherlands – did not lead to lower bread consumption or compensation behaviors [58,59], indicating that food reformulation could be an effective approach to decrease intake of specific nutrients in the general population. In addition to population-wide strategies, it might be effective to specifically target children at high risk of having a poor diet quality, such as children from lower socioeconomic households, as described in Chapter 2.4. Intervention strategies could include education programs to increase knowledge on healthy diets in both

parents and their children. As food choices are influenced by many factors, it is important to involve different stakeholders in intervention programs in order to create a healthy environment for children.

Conclusion

Findings from the studies presented in this thesis suggest that diet quality in childhood is suboptimal and that this may affect body composition and cardiometabolic health. More specifically, we observed that, on average, children only adhered to half of the age-specific dietary guidelines. Especially children of lower socioeconomic households and with more screen time are at higher risk of having lower diet quality. Furthermore, we observed that a higher diet quality may be beneficial for body composition and for certain cardiometabolic markers. In this thesis we observed no associations of overall diet quality with atopic diseases, but our systematic review of RCTs suggested that the avoidance of a combination of allergens in early childhood seems promising for the prevention of atopic diseases. Our findings may be important for public health interventions to improve diet quality in children and for early prevention of chronic diseases such as obesity and cardiometabolic diseases. More studies are needed on diet in different phases of childhood, using repeated dietary and health measurements to examine optimal diet for different age groups for long-term health.

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DRINK

Chapter 6

Appendices

Summary
Nederlandse samenvatting

SUMMARY

Adequate dietary intake in childhood is essential for optimal growth, development, and health of children, but also for health later in life. Nutrition in early life has been suggested to play an important role in setting the risk of several health outcomes in later life, including obesity, type 2 diabetes, cardiovascular diseases, osteoporosis, and asthma. It has been suggested that risk factors for these diseases already occur in childhood and that they tend to track into adulthood. Therefore, it is essential to identify important modifiable determinants for early prevention. **Chapter 1** provides a general introduction on diet in childhood, some important and highly prevalent health problems, and a description of the studies on which this thesis is based.

In **Chapter 2** we examined overall diet of children. We developed a food-based diet quality score for children on the basis of dietary guidelines. Using this score, we observed that diet quality of children at the ages of 4, 6, and 8 years, living on Crete (Greece), in Amsterdam (the Netherlands), and Rotterdam (the Netherlands), was suboptimal. Median diet quality scores in the different populations ranged from 4 to 6 on a continuous scale from 0 to 10, indicating that their dietary intake was not conform current age-specific dietary guidelines. In general, children scored relatively high for their intakes of whole-grains, fruits, and fish, whereas low scores were observed for sugar-containing beverages and red and processed meat. Especially children with more screen time, children from lower educated mothers, or from lower-income households have a lower diet quality. In addition, parents may influence their child's diet quality through feeding practices and eating environment. We observed that monitoring and restrictive feeding were associated with a higher diet quality, whereas pressure to eat and less frequent family meals were associated with a lower diet quality in school-age children.

Chapter 3 describes our research on diet quality in childhood in relation to children's body composition and cardiometabolic health. We observed that a higher diet quality score at different ages throughout childhood was associated with higher weight and greater height and a higher BMI. However, in one of the studies, the association with higher BMI was explained by higher fat-free mass rather than fat mass. In addition, we observed that higher diet quality was also associated with better bone health in children. These findings suggest that higher diet quality in childhood may be beneficial for body composition. Furthermore, our findings also suggest that higher diet quality may be associated with certain cardiometabolic markers in childhood. We also examined associations of diet quality with a combined cardiometabolic risk factor score, which consists of several cardiometabolic risk factors and reflects overall cardiometabolic health. Results suggest that higher diet quality is associated with lower cardiometabolic risk in childhood.

Chapter 4 focuses on dietary intake and atopic diseases in childhood. We examined the association of overall diet quality in early life i.e., during pregnancy, infancy, and childhood with allergic sensitization and atopic diseases in the Generation R Study. No associations of overall diet quality at different time points in early life with atopic diseases at the age of 10 years has been found. Additionally, Chapter 4.2 provides an overview of the current scientific evidence on the effects of dietary interventions in the first two years of life on the development of atopic diseases. In this systematic review, we identified 3,375 references, of which 54 studies met all our selection criteria. Most common dietary interventions were fortified infant formulas, probiotic or prebiotic supplementation, or timing of exposure to specific food allergens. Although most dietary interventions yielded inconsistent effects on the development of atopic diseases, interventions in which several allergens were avoided seemed promising for prevention of asthma and eczema.

Lastly, **Chapter 5** provides a general discussion of the studies described in this thesis. Overall, findings from this thesis suggest that diet quality in childhood is suboptimal. We identified several determinants of diet quality that could be tackled to improve dietary intake in children. In addition, we observed that higher diet quality may be beneficial for body composition and certain cardiometabolic markers in childhood. In Chapter 5 we also discuss methodological considerations of our studies as well as implications and recommendations for future research.

NEDERLANDSE SAMENVATTING

Goede voeding in de kindertijd is essentieel voor optimale groei, ontwikkeling en gezondheid van kinderen, maar ook voor de gezondheid in het latere leven. Voeding in het vroege leven kan van invloed zijn op het ontwikkelen van risicofactoren voor verschillende gezondheidsuitkomsten in het latere leven, waaronder obesitas, diabetes type 2, hart- en vaatziekten, osteoporose en astma. Risicofactoren voor deze ziekten kunnen al op jonge leeftijd aanwezig zijn en kunnen aanhouden tot in de volwassenheid. Voor een vroege preventie van deze ziekten is het daarom van belang om belangrijke en veranderbare determinanten te onderzoeken. **Hoofdstuk 1** van dit proefschrift biedt een algemene introductie van voeding in de kindertijd, enkele belangrijke en veelvoorkomende gezondheidsproblemen en een beschrijving van die studies waarop dit proefschrift is gebaseerd.

In **hoofdstuk 2** hebben we het gehele voedingspatroon van kinderen bestudeerd. We hebben een score ontwikkeld om de kwaliteit van het eetpatroon van kinderen volgens de huidige richtlijnen te meten. Met behulp van deze score zagen we dat de voedingskwaliteit van kinderen op de leeftijden van 4, 6 en 8 jaar die op Kreta (Griekenland), in Amsterdam (Nederland) of Rotterdam (Nederland) wonen niet optimaal was. De gemiddelde score varieerde tussen de 4 en 6 op een continue schaal van 0 tot 10, wat aangeeft dat de voedingsinname van deze kinderen niet in overeenstemming was met de huidige voedingsrichtlijnen. Over het algemeen scoorden kinderen relatief hoog voor hun inname van volkoren granen, fruit en vis, terwijl lage scores werden waargenomen voor suikerhoudende dranken en rood en bewerkt vlees. Vooral kinderen die meer tijd doorbrachten voor een beeldscherm, kinderen van lager opgeleide moeders of kinderen van huishoudens met een lager inkomen hebben een lagere voedingskwaliteit. Ouders kunnen bovendien de voedingskwaliteit van hun kind beïnvloeden met behulp van voedingsmethoden en de eetomgeving waarin kinderen opgroeien. We hebben geconstateerd dat kinderen van ouders die de voeding van hun kinderen bijhouden en beperken, een hogere voedingskwaliteit hadden, terwijl druk zetten om te eten en minder frequente gezinsmaaltijden geassocieerd waren met een lagere voedingskwaliteit bij kinderen.

Hoofdstuk 3 beschrijft ons onderzoek naar voedingskwaliteit in de kindertijd in relatie tot lichaamssamenstelling en cardiometabole gezondheid van kinderen. We stelden vast dat een hogere voedingskwaliteit op verschillende leeftijden gedurende de kindertijd geassocieerd is met een hoger gewicht, lengte en BMI. In één van de studies werd de associatie met hogere BMI verklaard door hogere vetvrije massa in plaats van vetmassa. Bovendien zagen we dat een hogere voedingskwaliteit geassocieerd is met gezondere botten bij kinderen. Deze bevindingen suggereren dat een hogere voedingskwaliteit in de kindertijd gunstig kan zijn voor de lichaamssamenstelling. Bovendien

vonden we dat hogere voedingskwaliteit geassocieerd is met bepaalde cardiometabole factoren in de kindertijd. We onderzochten ook associaties van voedingskwaliteit met een gecombineerde cardiometabole risicofactorscore, die bestaat uit verschillende cardiometabole risicofactoren en de algehele cardiometabole gezondheid weerspiegelt. Onze resultaten suggereren dat een hogere voedingskwaliteit geassocieerd is met een lager cardiometabole risicoprofiel in de kindertijd.

Hoofdstuk 4 richt zich op voeding en atopische ziekten in de kindertijd. We hebben bestudeerd hoe voedingskwaliteit in het vroege leven, d.w.z. tijdens de zwangerschap, de peutertijd en de kindertijd, samenhangt met allergische sensibilisatie en atopische aandoeningen in de Generation R Studie. Er zijn geen associaties gevonden tussen voedingskwaliteit op verschillende momenten in het vroege leven met atopische aandoeningen op de leeftijd van 10 jaar. Hoofdstuk 4.2 geeft een overzicht van de huidige wetenschappelijke literatuur over de effecten van voedingsinterventies in de eerste twee levensjaren op de ontwikkeling van atopische aandoeningen. In deze systematische review hebben we 3.375 referenties geïdentificeerd, waarvan 54 studies aan al onze selectiecriteria voldeden. De meest voorkomende voedingsinterventies waren verrijkte flesvoeding, probiotische of prebiotische suppletie of blootstelling aan specifieke voedselallergenen. Hoewel de meeste voedingsinterventies inconsistente effecten op de ontwikkeling van atopische ziekten rapporteerden, leken interventies waarbij verschillende allergenen werden vermeden veelbelovend te zijn voor de preventie van astma en eczeem.

Tot slot biedt **hoofdstuk 5** een algemene bespreking van de studies die in dit proefschrift zijn beschreven. Over het geheel genomen suggereren bevindingen uit dit proefschrift dat de voedingskwaliteit van kinderen niet optimaal is. We hebben verschillende determinanten van voedingskwaliteit geïdentificeerd die aangepakt kunnen worden om de voedselinname bij kinderen te verbeteren. Bovendien zagen we dat een hogere voedingskwaliteit gunstig kan zijn voor de lichaamssamenstelling en bepaalde cardiometabole factoren in de kindertijd. In hoofdstuk 5 bespreken we ook methodologische overwegingen van onze studies, evenals implicaties en aanbevelingen voor toekomstig onderzoek.