BEHAVIORAL DETERMINANTS AND CONSEQUENCES OF CHILDHOOD ADIPOSITY

Epidemiological studies in high-income populations

Ivonne P.M. Derks

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Behavioral Determinants and Consequences of Childhood Adiposity
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Epidemiologische studies in populaties met een hoog inkomen

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General introduction

INTRODUCTION

The childhood obesity epidemic

The obesity epidemic is commonly discussed in the media including topics on its adverse consequences, new dieting methods and advice for healthy lifestyles and exercise. Regardless of all this attention, overweight and obesity rates are still rising, with currently 39% of the adults worldwide being overweight and 13% being obese according to the World Health Organization.[1] Parallel to the rising prevalence of obesity in adults, the prevalence of childhood overweight and obesity also increased dramatically over the last four decades. The global age-standardized prevalence of obesity in children and adolescents increased from 0.7% in 1975 to 5.6% in 2016 in girls, and from 0.9% in 1975 to 7.8% in 2016 in boys. Region-specific results showed that the prevalence of obesity in children and adolescents now plateaued in most high-income countries, but rates in Latin-America and parts of Asia are still increasing.[2] Compared with the global prevalence of childhood obesity, the prevalence of childhood obesity in the Netherlands is slightly lower, estimated at 2.8%, and another 13.5% of the children being overweight in 2017.[3]

Children with overweight or obesity are likely to maintain this high weight status throughout adolescence and adulthood,[4,5] and this tracking of adiposity starts already early in life. Being small at birth and early postnatal "catch-up growth" predicts more adiposity later in childhood.[6] Furthermore, in a large British population-based cohort, 63% of the children who were overweight at 7 years, were still overweight at 11 years, and 75% of the children with obesity also continued to be obese.[7] Body Mass Index (BMI), calculated as weight (kg)/ height $(m)^2$, is the widely used measure to indicate relative weight status in children by using sex- and age-adjusted standardized scores.[8,9] While it is generally assumed that a high BMI is explained by a high adiposity level, it only serves as a proxy for the level of body fat because it cannot distinguish between fat mass and fat free mass. Therefore, the amount and distribution of body fat and fat free mass (i.e. body composition) are now recognized to be important health outcomes in children,[10] though much less frequently studied in children as compared to BMI.

A high weight status in childhood poses a risk for developing related adverse health consequences later in life, such as the metabolic syndrome, type 2 diabetes, cardiovascular disease and cancer. Moreover, psychiatric disorders, such as depression, are also more commonly reported in overweight or obese individuals.[11-18] First signs of these adverse consequences can already be observed in children with a high weight status, as shown by increased lipid and insulin concentrations and higher blood pressure.[19,20] Moreover, lower self-esteem and more emotional problems are commonly found in children with overweight.[21-23] Social problems also occur since these children are more often victims of bullying due to their weight.[24-26] Accordingly, the elevated risk of maintaining a high weight status through the life course, as well as the physical and psychological burden

of high adiposity, highlight the need for effective prevention and intervention strategies. However, prevention and intervention programs in children have only been mildly effective so far.[27,28] Moreover, obesity prevention starting early in life is essential for maintaining a healthy weight throughout the life course and ultimately reversing the obesity epidemic.

The obesogenic environment

In order to develop effective prevention and intervention strategies, the complex etiology of childhood obesity needs to be well-understood. This has been a major challenge for researchers given the many underlying factors involving genetic, physiological, environmental and behavioral factors, each accountable for a small proportion of obesity development. However, the global increasing trend in childhood obesity is likely largely due to changes in the environment.[29,30] The 'obesogenic environment' was defined by Swinburn et al. in 1999 as "The sum of influences that the surroundings, opportunities or conditions of life have on promoting obesity in individuals or populations".[31] In the past decades, our environment markedly changed from an environment characterized by food scarcity and traditional work towards an environment with a tremendous availability of low-priced palatable, high-calorie food, increasing sedentary behaviors due to screen-based entertainments, and reduced physical activity through changes in mechanization and transportation.[32] However, despite the fact that every child is exposed to this obesogenic environment, not every child becomes overweight or obese. Individual variability in body weight can be explained by the level of genetic predisposition, consisting of multiple, independent genes, which are all responsible for a small part of genetic susceptibility for obesity.[33] The interaction of this genetic predisposition with the obesogenic environment may result in excess weight gain,[32] for which the obesogenic environment influences weight gain of children indirectly, partially dependent on parental- and child behaviors.

Behavioral correlates of childhood adiposity

Parental and child behaviors related to a healthy lifestyle are of key interest in preventing childhood obesity, because behaviors are considered to be directly modifiable risk factors while genetics and the obesogenic environment are more difficult, if not impossible, to change. One of the child behaviors of interest in preventing obesity are eating behaviors. Eating behaviors can influence energy intake through choices about when and where to eat and the amount and type of food consumed.[34,35] The development of children's eating behaviors depends on many factors such as genetic predisposition, the development of appetite regulation, early food experiences and the family environment.[33,36,37] In early life, children are predisposed to preferences for salty and sweet tastes, the tendency to reject new flavors, and learn to eat what is available in their environment. Therefore, children's dietary intake largely depends on food choices and preferences of the parents, feeding

strategies and the availability of foods.[38] Next to this, parents also serve as role models: children are likely to copy eating habits and can therefore learn healthy or unhealthy eating behaviors.[38] Many cross-sectional studies have reported on the relationship between eating behaviors and weight status in childhood[39] and suggested that children with overweight or obesity show more emotional overeating, food responsiveness and enjoyment of food, and show less satiety responsiveness. However, there is a lack of prospective studies reporting on eating behaviors develop across childhood and its association with body composition.

Another child behavior of interest is sleep. At the moment, there is a lot of debate on sleep deprivation in children and its consequences on child health. Guidelines on sleep duration in children recommend that infants until one year of age should sleep 12 to16 hours per 24 hours, which decreases with age towards a recommended 8 to 10 hours of sleep in adolescence.[40] Variation in child sleep duration can be due to individual differences in sleep need but can also be due to increasing screen time or parents influencing the sleep-wake cycle. Numerous studies have focused on the relationship between sleep duration and child weight and showed that shorter sleep was associated with a higher weight status.[41-44] Yet, the influence of sleep duration very early in life (i.e. infancy) on body composition and cardiometabolic health later in childhood and early adolescence remains unclear.

The need for prospective studies examining bi-directionality

The evidence for behavioral determinants of child adiposity mainly derives from cross-sectional studies (i.e. performed at a single time point). These studies described associations between behavioral factors and BMI and assumed that behavior affects weight gain, while no evidence for causal inference can be provided by these studies and information on reversed causality is lacking. Prospective studies, preferably with repeated measurements, can improve our understanding on the direction of associations by examining whether child behaviors can predict changes in weight status and cardiometabolic health. Relationships in the opposite direction – a higher weight status early in life might predict subsequent unhealthy child behavior – are also reasonable but are rarely examined. For instance, children with a higher weight status might be hindered in their physical activity due to decreased mobility or might eat more in response to negative feelings raised by their weight concern. Examining whether behaviors are determinants or consequences of child adiposity is essential for developing effective prevention or intervention strategies, and therefore more insight in the direction of the association between behavioral traits and weight status in children is needed.[27]

THIS THESIS

Aim

The aim of this thesis was to examine the relationship of parental- and child behaviors with adiposity development and cardiometabolic health in childhood and to provide more insight in the direction of the associations by using data of prospective population-based studies in high-income populations. Specifically, the objectives of this thesis were:

1. To provide insight in the development of eating behaviors in children.
2. To examine the association of different child behaviors with body composition and cardiometabolic health, and to determine the direction of associations.
3. To examine the role of maternal feeding practices on children's eating behaviors and body composition.

Setting

The studies presented in this thesis were all embedded in prospective population-based cohort studies in high-income countries, including the Netherlands, the United States, Australia, and Sweden.

Most studies were embedded in The Generation R Study, a population-based cohort from fetal life onward, situated in Rotterdam, the Netherlands.[45] The Generation R Study was designed to investigate genetic and early determinants of children's development, health and disease. All pregnant women living in Rotterdam, the Netherlands, with an expected delivery date between April 2002 and January 2006 were invited to participate (participation rate of 61%). Written informed consent was obtained from all participants at each wave. The Generation R Study was conducted in accordance with the Declaration of Helsinki and was approved by The Medical Ethical Committee of the Erasmus Medical Center. After birth, parents reported repeatedly on different aspects of child development by postal questionnaire and when children were aged 6 and 10 years, mothers and children visited the research center where a range of behavioral and physical examinations took place.

One study was embedded in Project Viva, a pre-birth longitudinal cohort study situated in Eastern-Massachusetts, USA, which originally included 2128 mother-child dyads.[46] Another study was performed using data of the PEAS Kids Growth Study (Parent Education And Support), which started as a prospective quasi-experimental study and was followed-up as an prospective community-based study focused on growth and cardiovascular health in children born in Melbourne and surrounding areas in Australia.[47] Finally, one study was performed with data of three population-based cohorts, namely The Generation R Study and two twin cohorts: the Nederlands Tweelingen Register and The Swedish Twin Study of Child and Adolescent Development.

Outline

In **Part I** the development of eating behaviors across childhood and potential predictors of obesogenic eating behaviors are described. In **Part II** prospective associations of different child behaviors with body composition and cardiometabolic health are studied, including an examination of potential bi-directionality. In **Part III**, we examined the role of different types of maternal feeding practices on child eating behaviors and body composition.

Part I. The development of eating behaviors in children

In **Chapter 2**, patterns of food approaching and food avoidant eating behaviors from 4 to 10 years are examined using a person-centered approach. Potential parental and early life predictors of these patterns were subsequently examined in order to identify targets for the prevention of developing obesogenic eating behaviors. In **Chapter 3**, the extend to which exposure to impaired maternal gestational glucose tolerance might affect eating in the absence of hunger was studied in 13-year-old children.

Part II. Child behavior, body composition and cardiometabolic health

In **chapter 4**, bi-directional associations between eating behaviors, BMI and body composition were investigated. In **chapter 5 and 6**, the relationship of infant sleep duration with body composition, metabolic- and cardiovascular health later in childhood and adolescence was studied in two populations. Finally, bi-directional associations between child aggressive behavior and BMI are examined **chapter 7**, in three population-based cohort studies.

Part III. Maternal feeding practices and child body composition

In **chapter 8**, the direction of effects between parental restrictive feeding practices and child body composition across childhood was investigated. In **chapter 9**, the longitudinal relationship of maternal emotional feeding during infancy with body composition across childhood and the role of child emotional overeating in this relationship was studied.

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PART I

THE DEVELOPMENT OF EATING BEHAVIORS IN CHILDREN

2

Predictors and patterns of eating behaviors across childhood: Results from The Generation R Study

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ABSTRACT

Introduction: Only a few studies have prospectively examined stability of eating behaviors in childhood. These argue that eating behaviors are fairly stable from early childhood onwards, but knowledge on individual patterns across childhood is lacking. Here, we examined patterns of eating behaviors from ages 4 to 10 years in a population-based sample and aimed to identify parental and early-life predictors of these patterns.

Methods: Participants were 3514 children from The Generation R Study with repeated assessments of the Child Eating Behavior Questionnaire at ages 4 and 10 years. Patterns of emotional overeating, food responsiveness, enjoyment of food and satiety responsiveness were studied with person-centered Latent Class Growth Analysis with the aim to identify sub-groups of children with distinct eating behavior patterns. Using univariate multinomial logistic and linear regression, parental and early life predictors of eating behavior patterns were examined.

Results: We identified three patterns of emotional overeating (stable low (n=2240); moderately increasing (n=1028); strongly increasing (n=246)) and five patterns of food responsiveness (stable low (n=2343); high decreasing (n=238); moderately increasing (n= 679); strongly increasing (n=141); stable high (n=113)) from 4 to 10 years. For enjoyment of food and satiety responsiveness a similar pattern was identified for all children. Obesogenic eating behavior patterns were associated with a higher birth weight and BMI, emotional and behavioral problems, maternal overweight/obesity and controlling feeding strategies.

Discussion: This study suggests that children develop distinct patterns of emotional overeating and food responsiveness across childhood. Parental and early life predictors, particularly a higher weight status and psychiatric problems, are potential correlates of the development and maintenance of unhealthy eating behavior patterns across childhood. This knowledge might help identifying children at risk of developing obesogenic eating behaviors.

INTRODUCTION

Appetite-related eating behaviors influence food preferences, patterns of energy intake and are closely linked to weight status.[1,2] Several factors are likely to contribute to the development of eating behaviors, including genetic predisposition, in utero programming of appetite, first food experiences and the family environment.[3-9]

Previous studies suggest that eating behavior traits are already established in the first years of life and remain stable thereafter. A study among young children indicated that eating behaviors, such as food responsiveness, emotional overeating, satiety responsiveness and enjoyment of food were already stable (i.e. individual ratings of this behavior were consistent over time) and continuous (i.e. group ratings were consistent and similar over time) from 2 to 5 years of age.[10] Recently, a weak correlation for emotional overeating (r=0.25) was reported in a twin study within the same age span.[11] Further, the level of eating in the absence of hunger, loss of control in eating and overeating remained comparable after 6 months, 1 and 2 years of follow-up.[12-14] Yet, these studies included small sample sizes[10,12-14] - except for the twin study comprising 3784 children[11] -, had follow-up periods of maximum 3.5 years,[11] and one was performed in girls only.[12] Only one study with a follow-up period of seven years was performed: Ashcroft et al. examined stability and continuity of eating behaviors in 322 children aged 4 to 11 years and reported moderate correlations between the two ages on different obesogenic eating behaviors, ranging from r=0.44 for food responsiveness to r=0.46 for satiety responsiveness.[15] These moderate to low correlations across childhood suggest that there is also potential individual variation in eating behaviors over time. Identifying patterns of eating behaviors across childhood and its early life predictors might help detect potential targets for prevention and intervention in developing unhealthy eating behavior.

The aim of the present study was to examine patterns of obesogenic eating behaviors in a large, population-based sample of children aged 4 to 10 years, by using Latent Class Growth Analysis. This is a person-centered and data-driven approach to identify and cluster subgroups of children with homogenous response patterns. This is a different methodology than previously used, as studies generally examined the correlation between variables at different time points, without consideration of individual differences.[16] Exploratory analyses were conducted to identify potential early life and parental predictors of eating behavior patterns across childhood.

METHODS

Study design and population

This study was embedded in the Generation R Study, a population-based prospective birth cohort from fetal life onward, described previously in detail.[17] In brief, all pregnant women living in Rotterdam, the Netherlands, with an expected delivery date between April 2002 and January 2006 were invited (participation rate of 61%). Written informed consent was obtained from all participants and The Medical Ethical Committee of the Erasmus Medical Center approved the study. Full consent for the postnatal phase was obtained for 7294 children and their parents (74% of those originally enrolled). Children were included in the current sample for analyses when they had information available on eating behavior at the age of 4 years and again 10 years, resulting in a study sample of 3514 children (Supplementary Figure 2.1).

We compared children who were lost to follow-up (n=966 with missing eating behavior at the age of 10 years) with children included in the sample for analyses (n=3514). Those who were lost to follow-up were more often boys (52.7% versus 49.1%, p=0.046) and of non-western ethnic background (34.0% versus 19.4%, p<0.001) but were similar in their weight status at 3.5 years of age (9.0% overweight/obese versus 7.8% overweight/obese, p=0.261). Mothers of children who were lost to follow-up were more often low educated (23.3% versus 10.3%, p<0.001) and overweight/obese than mothers of children included in the study sample (38.4% versus 32.5%, p=0.001).

Measures

Child eating behaviors

Child eating behavior was assessed twice using the same measure, when children were 4 and 10 years old. At both time points, mothers reported on their child's eating behavior with the Child Eating Behavior Questionnaire (CEBQ). The CEBQ is a 35-item instrument developed by Wardle et al. in 2001 and assesses variation in eating behaviors among children using seven subscales.[18] In this study, four subscales were included, namely: Food responsiveness, enjoyment of food, emotional overeating and satiety responsiveness. Food responsiveness is a 5- item subscale reflecting the child's sensitivity to external food cues (e.g. "Given the choice, my child would eat most of the time"), enjoyment of food is a 4-item subscale (e.g. "My child loves food"), emotional overeating consists of 4 items (e.g. "My child eats more when he/she is upset"), and lastly, satiety responsiveness is a combined subscale of 9 items covering satiety responsiveness and slowness in eating. The satiety responsiveness and slowness in eating scales are sometimes examined as separate constructs, and sometimes combined. Here, we used the combined scale, because slower eating speed has been considered as a response to internal satiety cues during

food intake. We and others used this combined scale before, which has been validated against observed behavioral assessments of food intake [2,3,19,20] (e.g. "My child gets full up easily"). Answering options ranged from 1. "never" to 5. "always", and mean item-scores per subscale were calculated, allowing for 25% missing answers per subscale. The CEBQ has well-established psychometric properties, including good test-retest reliability, internal consistency and concurrent validity with actual/observed eating behavior.[19,21,22] At both time points, the subscales showed high reliability in the study sample: At 4 years Cronbach's α for emotional overeating= 0.85, food responsiveness= 0.84, enjoyment of food= 0.89 and satiety responsiveness= 0.81. At the age of 10 years, Cronbach's α for emotional overeating= 0.92, food responsiveness= 0.86, enjoyment of food =0.87 and satiety responsiveness= 0.85.

Parental and child early life predictors

Several child early life- and parental characteristics were considered as potential predictors of eating behavior patterns across childhood, since they have been linked with eating behavior before.[4,6,23] Information about child date of birth, sex and birth weight were obtained from midwife- or hospital registries. Birth weight SD scores were calculated adjusted for gestational age, according to Niklasson et al.[24] Child ethnicity was based on country of birth of both parents, as assessed with a prenatal questionnaire. In postnatal questionnaires, mothers reported at 2 months, 6 months and 12 months on whether they breastfed their infant. If mothers reported that they had stopped breastfeeding, they were asked how old their infant was when they stopped breastfeeding. At the age of 3 years, mothers and fathers separately completed the Child Behavior Checklist (CBCL/1.5-5), a 99-item questionnaire including a range of child emotional and behavioral problems rated on a three-point Likert scale (0. "Not true", 1. "Somewhat true, sometimes true", 2. "Very true, often true").[25] We included the two broadband scales in our study: Emotional problems (i.e. internalizing behavior), consisting of the subscales Emotionally reactive, Anxious/Depressed, Withdrawn and Somatic Complaints (36 items); and behavioral problems (i.e. externalizing behavior) consisting of the subscales Attention Problems and Aggressive Behavior (24 items). Sex and age adjusted T-scores were calculated based on a normative sample using the program ASEBA PC. The derived T-scores were subsequently standardized (presented in SD scores). The Dutch translation of the CBCL has shown to be valid and reliable.[26] The two broadband scales showed good reliability within our sample (Cronbach's α emotional problems= 0.81, behavioral problems= 0.89). At 3.5 years of age, children visited the Municipal Health Centers where their height and weight were measured without shoes or heavy clothing by staff assistants, from which sex- and age adjusted BMI scores were calculated and weight status was determined according to the cut-off points of Cole et al.[27]

Mothers reported on their educational level in a prenatal postal questionnaire. During their visit in the first trimester of pregnancy, mother's and father's height and weight were measured at the Generation R research center by trained research assistants. BMI was calculated and categorized into underweight-normal weight (BMI<25.00) or overweight/obesity (BMI≥25.00). Maternal glucose and insulin levels were derived from non-fasting serum blood samples collected during the first trimester of pregnancy, with an average of 13 weeks gestation. When children were 3 years old, mothers and fathers each reported on their psychopathology symptoms using a shortened version of the Brief Symptom Inventory (BSI). The BSI is a validated self-report questionnaire originally including 53 items with 8 subscales, and response options ranging from 0. "Not at all" to 4. "Extremely".[28] The Dutch translation of the BSI showed high validity and good reliability.[29] With the shortened version, 4 subscales were assessed: Depression, Anxiety, Hostility and Interpersonal Sensitivity. The standardized mean score of all items was calculated and showed good reliability for both mothers and fathers (Cronbach's α mother= 0.89, father= 0.88). Finally, when children were 4 years old, mothers reported on their own feeding practices using the validated Child Feeding Questionnaire including the subscales Monitoring (3 items), Restriction (8 items) and Pressure to eat (4 items).[30] Answering options ranged from 1. "Never" to 5. "Always", and mean item scores were calculated per subscale. The reliability of these subscales in our sample were moderate to high (Cronbach's α for monitoring = 0.91, restriction= 0.72 and pressure to eat=0.65).

Statistical analysis

First, sample characteristics and correlations between eating behavior subscales at ages 4 and 10 years were examined. Then, patterns of eating behavior were determined for each subscale separately by Latent Class Growth Analysis (LCGA) in Mplus 7.0.[31] With LCGA, distinct groups of children can be identified based on response patterns at ages 4 and 10 years. This is a person-centered, data-driven approach that can be used with repeatedly measured outcomes where the latent classes reflect groups of children with similar response patterns over time. This way, heterogeneity in developmental patterns of eating behaviors can be determined, while the within-class variation is constrained to zero. This method was considered suitable for this study, because the goal was to identify differences between classes and not variation within classes.[32]

First, we identified a single class growth curve model including all children. From there, we increased the number of classes by one each time until we found the best-fitted model with x number of classes for each eating behavior subscale. Optimal model fit was determined by the following criteria: the lowest Bayesian Information Criterion (BIC), the highest Entropy (measurement of accuracy for the classification of each individual into a latent class, with >0.80 indicating adequate classification), at least 5% of all individuals in one class, high posterior probabilities for each class and a significant Bootstrapped

Likelihood Ratio Test (BLRT), comparing the current model with the model with one class less. For each class, an intercept (reflecting the baseline level at age 4 years) and a slope was obtained.[16,33]

After patterns of eating behavior were determined, we examined associations between predictors and eating behavior patterns in SPSS 21.0 (IBM statistics). Given that we aimed to characterize the groups of children with specific eating behavior patterns and were not examining any causal relations, we only present univariate analyses. For food responsiveness and emotional overeating (with 5 and 3 identified classes, respectively) we used univariate multinomial logistic regression analyses to examine associations between early-life predictors and subsequent eating behavior patterns (in both subscales, "stable low" was chosen as the reference group). For enjoyment of food and satiety responsiveness a single pattern was observed, and therefore, we used univariate linear regression analyses to examine the association between early life predictors and the slope (similar to the delta) between the two time points. We used the Benjamini and Hochberg False Discovery Rate (FDR) procedure to correct for multiple comparisons. We listed the values of $d \times i/n$ in which d is the significance threshold of 0.05, n is the number of tests and i is the test number along with the obtained and sorted p-value. When the p-value is smaller than $d \times i/n$, it is declared significant.[34] Finally, we repeated our analyses with parental and early-life predictors after excluding siblings (19.6%) to check whether results were not driven clustering within families. Associations for siblings might be similar for factors such as sociodemographic and parental conditions, and could potentially create an overestimation of the observed associations when siblings had a similar eating behavior pattern.

RESULTS

Descriptive characteristics of the study sample are reported in Table 2.1. Of all included children, 19.4% had a non-western background and 7.8% of the children were overweight or obese at the Municipal Health Center visit (mean age=3.5 years). During the first trimester of pregnancy, 32.5% of the mothers and 46.5% of the fathers were overweight or obese. Mean item scores on each eating behavior subscale per time point are presented in Supplementary Table 2.1.

Patterns of eating behavior from 4 to 10 years

Patterns of eating behavior from 4 years to 10 years are presented for each eating behavior subscale separately in 3514 participants (Figure 2.1). The number of patterns (latent classes) depended on model fit, which can be found in Supplementary Table 2.2.

Table 2.1. Descriptive characteristics of the study sample

Child characteristics	**Total n**	**Percentage, mean (SD) or median [IQR][a]**
Age at 4 years questionnaire, mean (SD)	3514	4.05 (0.09)
Age at 10 years questionnaire, mean (SD)	3514	9.70 (0.28)
Sex, % girls	3514	50.9%
Child ethnicity, %	3507	
Dutch	2504	71.4%
Other Western	322	9.2%
Non-Western	681	19.4%
Birth weight in grams, mean (SD)	3499	3449 (562)
Weight status category at last CB visit, % overweight/obese	3251	7.8%
Emotional problems t-score at 3 years, median [IQR][b]	3246	43.00 [12.00]
Behavioral problems t-score at 3 years, median [IQR][b]	3246	43.00 [11.50]
Duration of breastfeeding in months, mean (SD)	2870	4.73 (3.90)
Parental characteristics		
Maternal education level, %	3392	
Low (No education - high school)	350	10.3%
Medium (Lower vocational education)	923	27.2%
High (Higher vocational education and university)	2119	62.5%
Maternal pre-pregnancy BMI, % overweight/obese	3128	32.5%
Paternal BMI, % overweight/obese	2681	46.5%
Maternal glucose level during first trimester of pregnancy, mmol/L, mean (SD)	2435	4.38 (0.86)
Maternal insulin level during first trimester of pregnancy, pmol/L, median [IQR]	2433	106.80 [152.02]
Maternal psychopathology symptoms SD score, median [IQR][c]	3231	0.10 [0.19]
Paternal psychopathology symptoms SD score, median [IQR][c]	2821	0.05 [0.14]
Maternal feeding practices, mean item score[d]		
Monitoring	3499	4.47 (0.74)
Restriction	3507	2.97 (0.77)
Pressure to eat	3513	3.09 (0.97)

[a] Values are percentages for categorical variables, means (standard deviations) for continuous normally distributed variables and medians (interquartile ranges) for continuous, non-normally distributed variables. [b] Mother-reported with the Child Behavior Checklist. [c] Psychopathology symptoms were assessed with the Brief Symptom Inventory. [d] Maternal feeding practices were assessed with the Child Feeding Questionnaire, mean item scores range from 1 to 5.

Three patterns of emotional overeating were identified according to optimal model fit criteria. We identified a "stable low" pattern of emotional overeating, including 2240 children (intercept=1.36, slope=−0.31). Further, 1028 children increased by 0.49 points

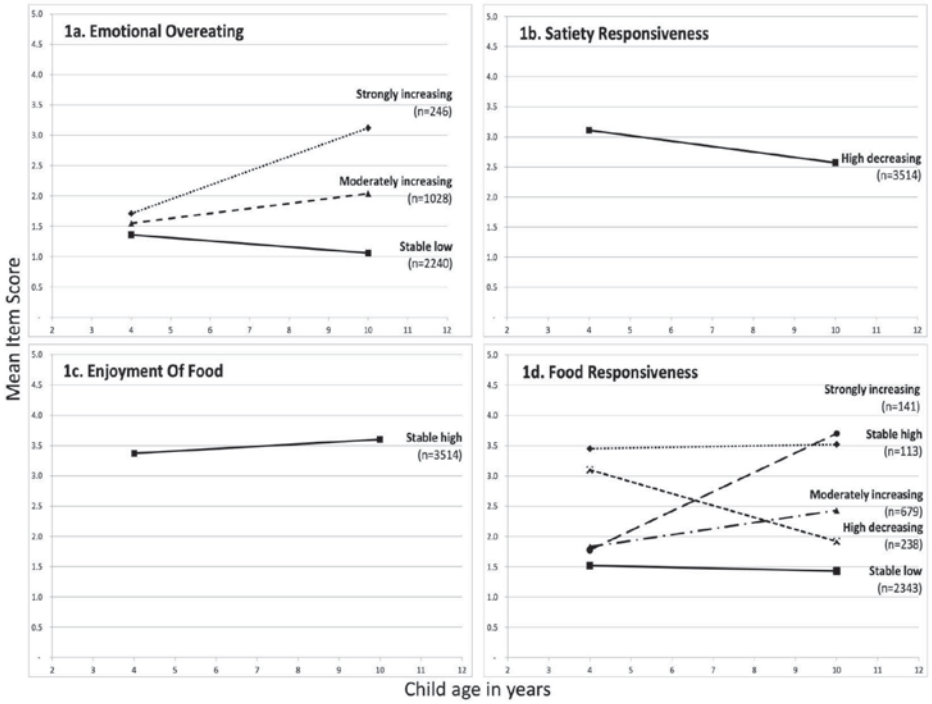

Figure 2.1. Latent Class Growth Trajectories of eating behavior subscales in children aged 4 to 10 years

on mean item score from 4 to 10 years (intercept=1.55) and were classified as "moderately increasing". Lastly, 246 children increased by 1.41 points on mean item score (intercept=1.71), showing a "strongly increasing" response pattern for emotional overeating.

For food responsiveness, we found five distinct patterns among children. Most children (n= 2343) had a stable low pattern of food responsiveness, from a mean score of 1.52 at 4 years to a mean item score of 1.43 at 10 years ("stable low"). Further, 238 children had a high mean item score at age 4 years and a lower score at 10 years (intercept=3.10, slope=−1.19, "high decreasing"). Next, 679 children increased by 0.60 points on mean item score (intercept=1.83) from 4 to 10 years ("moderately increasing"), while 141 children increased in food responsiveness by 1.92 points on mean item score (intercept=1.72; "strongly increasing"). For 113 children, we observed a "stable high" food responsiveness pattern across childhood (intercept=3.45, slope=0.07).

For enjoyment of food and satiety responsiveness, BIC and BLRT indicated the possibility of more than one class, while entropy in both cases suggested that a one class-solution should be preferred. Inspection of the two- and three class solutions for enjoyment of food and satiety responsiveness showed that patterns were added parallel to the one class pattern, which suggested that there was no clear distinction in the developmental course of these behaviors. Moreover, the entropy did not meet the threshold of 0.80. Therefore,

Table 2.2. Univariate multinomial logistic regressions between predictors and patterns of emotional overeating

Early life predictors	Total n	Patterns of Emotional overeating		
		Stable low OR (95% CI)	Moderately increasing OR (95% CI)	Strongly increasing OR (95% CI)
Child characteristics				
Sex – girls	3514	*Reference*	1.24 (1.07, 1.44)*	0.99 (0.76, 1.29)
Ethnicity[a]	3507			
Other western		*Reference*	1.14 (0.88, 1.47)	0.85 (0.51, 1.41)
Non-western		*Reference*	1.21 (1.00, 1.46)	1.33 (0.97, 1.84)
Birth weight SD score	3499	*Reference*	0.94 (0.87, 1.01)	1.13 (0.99, 1.29)
BMI at age 3.5 years – Overweight/obese[b]	3251	*Reference*	1.62 (1.23, 2.13)*	2.11 (1.37, 3.23)*
Emotional problems t-score at 3 years, SD score[c]	3246	*Reference*	1.15 (1.06, 1.24)*	1.40 (1.22, 1.61)*
Behavioral problems t-score at 3 years, SD score[c]	3246	*Reference*	1.17 (1.08, 1.26)*	1.28 (1.12, 1.47)*
Duration of breastfeeding, per month	2870	*Reference*	1.01 (0.99, 1.03)	0.99 (0.95, 1.02)
Parental characteristics				
Educational level[d]	3392			
Medium		*Reference*	0.96 (0.81, 1.14)	0.97 (0.71, 1.33)
Low		*Reference*	1.06 (0.82, 1.36)	1.19 (0.77, 1.83)
Maternal pre-pregnancy BMI – Overweight/obese	3128	*Reference*	1.18 (1.00, 1.39)	1.38 (1.04, 1.84)
Paternal BMI – Overweight/obese	2681	*Reference*	0.98 (0.83, 1.16)	1.24 (0.91, 1.70)
Maternal prenatal glucose level, mmol/L[e]	2435	*Reference*	1.01 (0.91, 1.12)	1.10 (0.91, 1.31)
Maternal prenatal insulin level, log pmol/L[e]	2433	*Reference*	1.03 (0.94, 1.14)	1.10 (0.92, 1.30)
Maternal total psychopathology symptoms SD score	3231	*Reference*	1.07 (0.99, 1.17)	1.17 (1.03, 1.33)*
Paternal total psychopathology symptoms SD score	2821	*Reference*	1.08 (0.98, 1.18)	1.14 (0.98, 1.32)
Maternal feeding practices, mean item score				
Monitoring	3499	*Reference*	0.82 (0.75, 0.91)*	0.74 (0.63, 0.86)*
Restriction	3507	*Reference*	1.37 (1.24, 1.51)*	1.33 (1.12, 1.59)*
Pressure to eat	3513	*Reference*	1.02 (0.95, 1.10)	1.11 (0.97, 1.28)

[a] Reference group for ethnicity = Dutch. [b] Child BMI was assessed at the Municipal Child Health Center visit, mean age 3.5 years (SD= 0.5). [c] Mother –reported, results were comparable with father–reported sum scores of emotional and behavioral symptoms. [d] Reference group for maternal educational level= High. [e] Maternal glucose and insulin levels were assessed during the first trimester of pregnancy and adjusted for the number of weeks of gestation. * Significant after FDR procedure.

we preferred the one-class pattern for both subscales. For all participants, scores of enjoyment of food increased slightly over time (intercept=3.37, slope=0.23) while for satiety responsiveness, mean item scores decreased by 0.55 points (intercept=3.11).

Parental and early life predictors

Table 2.2 shows the relationship between predictors and patterns of emotional overeating (stable low = reference group). Girls had 1.24 times higher odds of having a moderately increasing emotional overeating pattern compared to boys (95% CI= 1.07, 1.44). Furthermore, children with overweight or obesity at the age of 3.5 years were two times more likely to be classified in the moderately increasing or a strongly increasing emotional overeating pattern compared to underweight/healthy weight children (e.g. $OR_{\text{strongly increasing}}$ = 2.11, 95% CI= 1.37, 3.23). Emotional and behavioral problems at 3 years of age were associated with moderately increasing or strongly increasing emotional overeating patterns across childhood (e.g. for behavioral problems: $OR_{\text{strongly increasing}}$ = 1.28, 95% CI=1.12, 1.47). Parental predictors of offspring emotional overeating patterns were also identified: offspring of mothers with more psychopathology symptoms were more likely to have a strongly increasing emotional overeating pattern (OR= 1.17, 95% CI =1.03, 1.33). More maternal monitoring of food intake was associated with less emotional overeating, while restrictive feeding was associated with higher odds of developing a moderately or strongly increasing emotional overeating pattern ($OR_{\text{high increasing}}$ = 1.33, 95% CI =1.12, 1.59).

In Table 2.3, associations of predictors with patterns of food responsiveness are presented ("stable low" = reference group). Children with a higher birth weight and a higher weight status at 3.5 years had higher odds of a high decreasing, increasing or stable high food responsiveness pattern. For instance, overweight or obese children had 9.53 higher odds of having a stable high food responsiveness pattern compared to underweight/normal weight children (95% CI= 6.03, 15.07). Additionally, more behavioral problems were associated with more food responsiveness across childhood ($OR_{\text{strong increasing}}$ = 1.58, 95% CI= 1.30, 1.91). Offspring of mothers with a high BMI had higher odds of developing unhealthy food responsiveness patterns, as well as offspring of mothers who practiced more restriction and less pressure to eat in their feeding strategies. Paternal BMI was not consistently associated with more food responsiveness, nor were maternal and paternal psychopathology symptoms.

Associations of parental and early life predictors with the change in enjoyment of food and satiety responsiveness from 4 to 10 years are shown in Table 2.4. A higher birth weight, being overweight or obese and more maternal monitoring were associated less change in enjoyment of food (e.g. for overweight/obese at 3.5 years, B= −0.13, 95% CI = −0.23, −0.04) than a lower birth weight, underweight/normal weight and less maternal monitoring. Relatively high levels of emotional problems of the child and of maternal restriction were associated with more change in enjoyment of food from 4 to 10 years. For

Table 2.3. Univariate multinomial logistic regressions between predictors and patterns of food responsiveness

Early life predictors	Total n	Patterns of Food responsiveness				
		Stable low OR (95% CI)	High decreasing OR (95% CI)	Moderately increasing OR (95% CI)	Strongly increasing OR (95% CI)	Stable high OR (95% CI)
Child characteristics						
Sex – girls	3514	*Reference*	1.08 (0.82, 1.41)	1.02 (0.86, 1.21)	1.03 (0.74, 1.45)	1.67 (1.13, 2.47)*
Ethnicity[a]	3507					
Other western		*Reference*	0.78 (0.46, 1.33)	1.18 (0.88, 1.57)	0.97 (0.53, 1.80)	0.78 (0.37, 1.63)
Non-western		*Reference*	1.35 (0.98, 1.85)	0.90 (0.72, 1.13)	1.23 (0.82, 1.86)	1.11 (0.69, 1.77)
Birth weight SD score	3499	*Reference*	1.21 (1.06, 1.39)*	1.15 (1.05, 1.25)*	1.28 (1.08, 1.52)*	1.43 (1.18, 1.72)*
BMI at age 3.5 years – Overweight/obese[b]	3251	*Reference*	5.62 (3.83, 8.24)*	2.03 (1.44, 2.87)*	5.09 (3.14, 8.23)*	9.53 (6.03, 15.07)*
Emotional problems t-score at 3 years, SD score[c]	3246	*Reference*	1.10 (0.95, 1.27)	1.12 (1.02, 1.23)	1.09 (0.91, 1.32)	1.13 (0.92, 1.38)
Behavioral problems t-score at 3 years, SD score[c]	3246	*Reference*	1.38 (1.20, 1.59)*	1.32 (1.21, 1.45)*	1.58 (1.30, 1.91)*	1.53 (1.24,1.88)*
Duration of breastfeeding, per month	2870	*Reference*	1.03 (0.99, 1.07)	1.00 (0.98, 1.02)	0.96 (0.92, 1.01)	1.02 (0.96, 1.07)

Table 2.3. Univariate multinomial logistic regressions between predictors and patterns of food responsiveness (*continued*)

Early life predictors	Total n	Patterns of Food responsiveness				
		Stable low OR (95% CI)	High decreasing OR (95% CI)	Moderately increasing OR (95% CI)	Strongly increasing OR (95% CI)	Stable high OR (95% CI)
Parental characteristics						
Educational level[d]	3392					
Medium		*Reference*	1.00 (0.73, 1.37)	0.92 (0.75, 1.13)	0.97 (0.65, 1.45)	0.78 (0.49, 1.25)
Low		*Reference*	1.49 (0.98, 2.26)	1.21 (0.91, 1.61)	1.29 (0.74, 2.24)	1.55 (0.88, 2.72)
Maternal pre-pregnancy BMI – Overweight/obese	3128	*Reference*	0.88 (0.64, 1.20)	1.29 (1.06, 1.56)*	1.96 (1.37, 2.79)*	1.86 (1.24, 2.80)*
Paternal BMI – Overweight/obese	2681	*Reference*	1.03 (0.76, 1.39)	1.37 (1.12, 1.67)*	1.48 (1.01, 2.18)	1.54 (0.98, 2.41)
Maternal prenatal glucose level, mmol/L[e]	2435	*Reference*	0.86 (0.71, 1.04)	1.05 (0.93, 1.18)	1.07 (0.85, 1.35)	0.91 (0.68, 1.20)
Maternal prenatal insulin level, log pmol/L[e]	2433	*Reference*	1.18 (0.99, 1.40)	1.02 (0.91, 1.14)	1.02 (0.97, 1.50)	1.01 (0.77, 1.31)
Maternal total psychopathology symptoms SD score	3231	*Reference*	1.05 (0.90, 1.22)	1.17 (1.07, 1.28)*	0.95 (0.76, 1.20)	1.19 (1.00, 1.42)
Paternal total psychopathology symptoms SD score	2821	*Reference*	1.03 (0.88, 1.21)	1.04 (0.94, 1.16)	0.93 (0.73, 1.19)	1.12 (0.91, 1.37)
Maternal feeding practices, mean item score						
Monitoring	3499	*Reference*	1.00 (0.83, 1.20)	0.96 (0.85, 1.07)	0.88 (0.71, 1.09)	1.01 (0.79, 1.32)
Restriction	3507	*Reference*	2.53 (2.08, 3.08)*	1.39 (1.23, 1.56)*	1.44 (1.14, 1.81)*	2.63 (2.00, 3.47)*
Pressure to eat	3513	*Reference*	0.68 (0.59, 0.78)*	0.84 (0.77, 0.92)*	0.74 (0.62, 0.88)*	0.44 (0.36, 0.53)*

[a] Reference group for ethnicity = Dutch. [b] Child BMI was assessed at the Municipal Child Health Center visit, mean age 3.5 years (SD= 0.5). [c] Mother –reported, results were comparable with father–reported sum scores of emotional and behavioral symptoms. [d] Reference group for maternal educational level= High. [e] Maternal glucose and insulin levels were assessed during the first trimester of pregnancy and adjusted for the number of weeks of gestation. * Significant after FDR procedure.

Table 2.4. Univariate associations of early life predictors with the change in enjoyment of food and satiety responsiveness from 4 to 10 years

Early life predictors	Total n	Δ Enjoyment of food B (95% CI)	Δ Satiety responsiveness B (95% CI)
Child characteristics			
Sex – girls	3514	0.04 (−0.01, 0.08)	0.02 (−0.02, 0.06)
Ethnicity[a]	3507		
Other western		−0.02 (−0.10, 0.07)	0.03 (−0.04, 0.11)
Non-western		0.04 (−0.02, 0.10)	0.03 (−0.03, 0.08)
Birth weight SD score	3499	−0.04 (−0.06, −0.01)*	0.03 (0.01, 0.05)*
BMI at age 3.5 years – Overweight/obese[b]	3251	−0.13 (−0.23, −0.04)*	0.07 (−0.01, 0.15)
Emotional problems t-score at 3 years, SD score[c]	3246	0.04 (0.02, 0.07)*	−0.04 (−0.06, −0.02)*
Emotional problems t-score at 3 years, SD score[c]	3247	0.03 (0.00, 0.05)	−0.03 (−0.05, −0.01)*
Duration of breastfeeding, per month	2870	−0.00 (−0.01, 0.00)	0.00 (−0.01, 0.01)
Parental characteristics			
Educational level[d]	3392		
Medium		−0.02 (−0.08, 0.04)	0.05 (−0.00, 0.10)
Low		−0.09 (−0.17, −0.01)	0.11 (0.04, 0.19)*
Maternal pre-pregnancy BMI – Overweight/obese	3128	0.02 (−0.04, 0.07)	0.03 (−0.02, 0.08)
Paternal BMI – Overweight/obese	2681	−0.01 (−0.07, 0.04)	0.02 (−0.03, 0.06)
Maternal prenatal glucose level, mmol/L[e]	2435	0.03 (−0.01, 0.06)	−0.01 (−0.04, 0.02)
Maternal prenatal insulin level, log pmol/L[e]	2433	0.03 (−0.00, 0.06)	−0.01 (−0.04, 0.02)
Maternal total psychopathology symptoms SD score	3231	0.01 (−0.02, 0.04)	−0.00 (−0.03, 0.02)
Paternal total psychopathology symptoms SD score	2821	−0.01 (−0.04, 0.02)	−0.02 (−0.05, 0.01)
Maternal feeding practices, mean item score			
Monitoring	3499	−0.07 (−0.10, −0.04)*	−0.01 (−0.04, 0.02)
Restriction	3507	−0.01 (−0.04, 0.02)	−0.01 (−0.04, 0.02)
Pressure to eat	3513	0.12 (0.09, 0.14)*	−0.08 (−0.12, −0.06)*

[a] Reference group for ethnicity = Dutch. [b] Child BMI was assessed at the Municipal Child Health Center visit, mean age 3.5 years (SD= 0.5). [c] Mother –reported, results were comparable with father–reported sum scores of emotional and behavioral symptoms. [d] Reference group for maternal educational level= High. [e] Maternal glucose and insulin levels were assessed during the first trimester of pregnancy and adjusted for the number of weeks of gestation.* Significant after FDR procedure.

satiety responsiveness we observed an overall decrease over time (slope=−0.55). Children of mothers with a low education level showed more change in their satiety responsiveness over time than children of mothers with high education (B= 0.11, 95% CI= 0.01, 0.05), while children with higher levels of emotional or behavior problems as well as those exposed to more maternal pressure to eat decreased more in their satiety responsiveness ($B_{\text{maternal pressure to eat}}$ = −0.08, 95% CI = −0.12, −0.06). Lastly, we found comparable results after excluding siblings from our study sample.

DISCUSSION

In this prospective cohort study with repeated measurements of eating behaviors, we showed individual differences in development of emotional overeating and food responsiveness from age 4 years to 10 years. With regards to enjoyment of food and satiety responsiveness, no distinct patterns were identified with all children showing a similar pattern of increasing and decreasing patterns for food enjoyment and satiety responsiveness, respectively. These findings suggest that emotional overeating and food responsiveness are dynamic behaviors in the first years of life and can change after pre-school age. Children's overweight and emotional and behavioral problems early in life were likely to temporally precede the development of more unhealthy eating behaviors, along with maternal feeding practices. Socio-demographic factors were not associated with eating behavior patterns.

Strengths and limitations

Strengths of this study comprised its prospective population-based design including repeated measurements of eating behaviors, the comprehensive assessment of various important parental and child early life predictors, and a large sample size. There are, however, also limitations that should be discussed. First, both assessments of eating behavior were mother-reported. Maternal ratings of child eating behavior might be affected by her own beliefs about eating and weight status of the child. Having multiple informants, such as father- and child self-report, would be preferential. Yet, during this age period one might assume that the mother is the most accurate reporter and high correlations between observed food intake of the child and parental reported CEBQ scores were previously found.[19] Likewise, maternal mental well-being might also influence her ratings of her child's behaviors, and associations might therefore be the result of a divergent perception of the mother. However, associations of father-reported emotional and behavioral problems with (mother-reported) eating behaviors yielded similar results. Further, eating behavior was assessed only twice, while preferably, more time points were used to determine patterns of eating behavior. This way, also potential non-linearity of

the eating behavior patterns can be determined. Moreover, due to the observational and descriptive nature of this study, causal effects of the predictors cannot be proven. Finally, as non-Dutch children with lower socioeconomic backgrounds and a higher maternal BMI were relatively often lost to follow-up, generalizability of the results may be limited.

Patterns of eating behavior

A few previous studies reported on stability and continuity of eating behavior across childhood.[10-15] Ashcroft et al. (2008) concluded from the TEDS cohort that eating behaviors showed striking continuity throughout childhood with only obesogenic eating behaviors, such as emotional overeating and food responsiveness, increasing slightly over time.[15] We observed comparable correlations for each eating behavior subscale in The Generation R Study, except for emotional overeating (r=0.21 in Generation R versus r=0.45 in TEDS). Yet, we further explored individual stability by identifying groups of children based on a person-centered empirical approach, which to our knowledge, has not been done before. Importantly, we found distinct patterns of food responsiveness and emotional overeating throughout childhood, suggesting that – despite continuity and stability in most children – the developmental patterns may not be uniform.

Emotional overeating has been previously described as a learned behavior influenced by environmental factors and that develops over time, with shared environmental factors explaining 71% of the variance in 4-year old twins.[11,35] This fits our observation of relatively low scores with little variability between classes on emotional overeating at 4 years, which became more variable at the age of 10 years. Identified patterns revealed that, although the majority of children remained low in their emotional overeating, some children developed a tendency towards more eating in response to emotions across childhood.

Children developed distinct patterns in their sensitivity to external food cues. Seven percent of the children already scored relatively high on food responsiveness at pre-school age, suggesting that, unlike emotional overeating, some children already developed high levels of food responsiveness early in life. A part of these children (44%) decreased in their sensitivity to external food cues by the age of 10 years. Opposed to this, 23% of the children increased in their food responsiveness after the age of 4 years, probably in line with a gradual increase in exposure to food quantities. For both emotional eating and food responsiveness, future research is warranted to further monitor the developmental patterns of these eating behaviors, as preferably, the increasing trends stabilize.

We did not observe distinct patterns of enjoyment of food and satiety responsiveness from 4 to 10 years of age. Children's scores on enjoyment of food remained quite stable over time with mean item scores at 4 and 10 years being comparable to those of Ashcroft et al.[15] However, Farrow et al.[10] reported no significant correlation of enjoyment of food in children at ages 2 and 5 years. Given the age difference with our and Ashcroft's study,

perhaps children are still developing their food enjoyment very early in childhood, a period where picky eating is most prevalent and presumably affecting the pleasure of eating.[36]

Our results showed that, generally, children became slightly less sensitive to internal satiation cues over time. This rather small change fits the observation that heritability for satiety responsiveness appeared to be higher than other eating behavior dimensions, estimated at 63-72%.[37,38] Apparently, genes strongly influenced the internal regulation of satiety responsiveness and if expressed early in life, this results in a rather stable pattern over time which is only minimally influenced by environmental factors.

Parental and early life predictors

Although there is a strong genetic influence on appetite traits in children, this varies between the different eating behaviors, with 53% for enjoyment of food to 72% for satiety responsiveness. These heritability estimates suggest that a considerable amount of variability can be explained by environmental factors.[37] First of all, our results foremost suggest that children who are already overweight or obese by the age of 3.5 years have strikingly higher odds of developing more and more emotional overeating and food responsiveness over the next years, although not corrected for potential confounding. This indicates that children who are already on a high weight trajectory from early life onwards are prone to develop unhealthy eating behaviors. Only a few recent studies also have suggested that a higher weight status might precede subsequent unhealthy eating behaviors in childhood,[20,23,39,40] which was mainly due to an increase in fat rather than muscle mass.[41] Yet, a higher weight status early in life was associated with less increasing food enjoyment and less decreasing satiety responsiveness over time. Maternal overweight/obesity was correlated with patterns of increasing food responsiveness only. Previous studies showed that parental obesity was associated with a preference for high-fat food, and tendencies towards external eating, overeating and eating in the absence of hunger among offspring.[6,42-44] The latter is an appetitive trait comparable to food responsiveness and external eating in which children ignore their internal satiety feelings in response to the presence of food. Here, parental obesity was not associated with other eating behaviors across childhood than food responsiveness.

This is one of the first studies showing that emotional and behavioral problems might be important predictors of the development of obesogenic eating behaviors. As suggested here, children might react differently to their emotional and behavioral problems, by either more food approaching or more food avoidant behavior. As a 'natural' response, stress and anxiety can suppress appetite,[45] explaining higher scores of satiety responsiveness. Indeed, emotional problems have been previously associated with food avoidant behavior.[46] However, overeating has also been shown as a reaction to emotional and behavioral problems. A previous study observed that children aged 3.5-4 years with

emotional problems, conduct problems and peer problems, also showed more obesogenic eating behaviors.[47] Moreover, overweight children reporting loss of control over eating experienced more psychological distress.[48] Due to deficits in emotion-regulation and inhibition, some children possibly respond more to external food cues or emotional triggers, which can activate the brain-reward system, resulting in overeating.[4] Decreased self-regulation has been linked with childhood obesity.[49,50] Besides children's emotional and behavioral problems, maternal – but not paternal – psychopathology symptoms were associated with more emotional overeating and food responsiveness, which was also previously reported.[6] Maternal psychiatric problems were shown to affect controlling and emotional feeding practices,[51,52] a potential pathway towards overeating. Further, psychiatric problems and eating behavior traits might share genetic vulnerabilities, as it was previously reported that the phenotypic associations between depressive symptoms and disordered eating were due to common genetic factors.[53]

Exposure to controlling feeding practices, such as restricting the child's access to palatable foods and pressuring the child to eat more are suggested to negatively influence children's appetite-related eating behaviors: such parenting behaviors may encourage children to eat in response to external food cues rather than to their internal satiety cues.[3,54,55] This study adds to this hypothesis by showing that restricting the child to certain types of sugary or palatable foods is associated with patterns of increasing responsiveness to food as well as increasing emotional overeating from 4 to 10 years. However, monitoring food intake of the child was associated with a lower risk of emotional overeating, while no associations for monitoring were found with other eating behaviors. As shown in previous literature, pressuring the child to eat more has a counterproductive effect of more food avoidant and less food approaching behavior,[56-58] which is reflected in our findings with food responsiveness. However, pressure also increased enjoyment of food and decreased satiety responsiveness. Although we and previous studies suggest that maternal feeding strategies might negatively affect children's eating behaviors,[59,60] current observational research also suggests a more bi-directional nature,[61] with mothers increasing their controlling feeding strategies as a response to unhealthy eating behaviors and weight status of her children.[61-63] However, a recent review of experimental studies still concluded adverse effects in eating behaviors as a result of controlling feeding practices. Lastly, of the studied predictors, we found no associations for sociodemographic factors, breastfeeding duration, and diabetes indicators with eating behavior development, which is largely consistent with other studies.[6,23]

Conclusion

In conclusion, this study suggests that children may develop distinct patterns of emotional overeating and food responsiveness across childhood, while for enjoyment of food and satiety responsiveness a single pattern was observed for all children. Child early life pre-

dictors related to a higher weight status and emotional and behavioral problems, as well as maternal feeding practices are likely correlates of the development and maintenance of unhealthy eating behavior patterns across childhood. Our findings therefore help to identify children with a higher risk to develop unhealthy eating behaviors for whom targeted intervention strategies may be effective. Such interventions may, for instance, teach children alternative coping strategies to deal with stress and negative mood, which can replace the emotional eating strategy.

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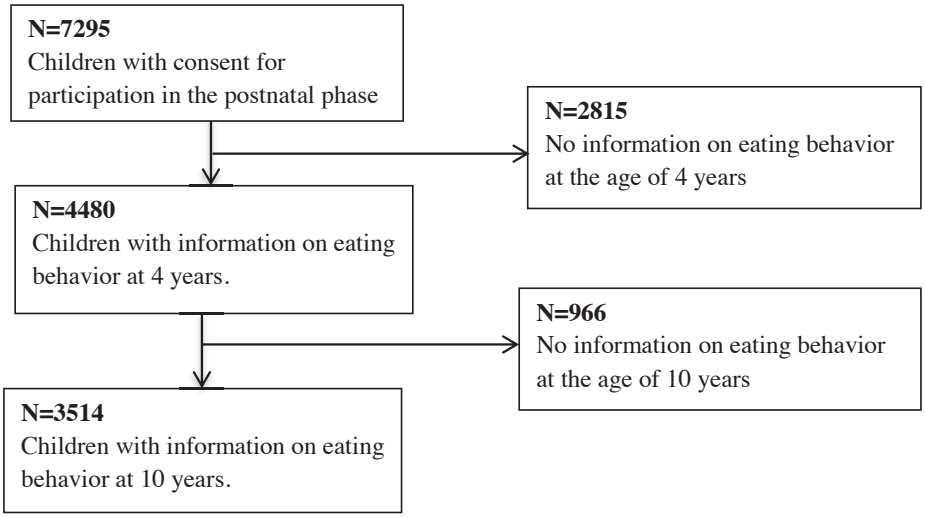
SUPPLEMENT



Supplementary Figure 2.1. Flowchart of the study sample

Supplementary Table 2.1. Difference in eating behavior between the age of 4 years and 10 years, n=3514

CEBQ subscale	Age 4 years Mean item score (SD)	Age 10 years Mean item score (SD)	r	*p* value
Emotional overeating	1.44 (0.60)	1.49 (0.66)	0.21	<0.001
Food responsiveness	1.77 (0.67)	1.83 (0.76)	0.37	<0.001
Enjoyment of food	3.37 (0.72)	3.60 (0.66)	0.46	<0.001
Satiety responsiveness	3.11 (0.62)	2.57 (0.65)	0.48	<0.001

*Spearman correlations for Emotional overeating and Food responsiveness, and Pearson correlation coefficients for Enjoyment of food and Satiety Responsiveness.

Supplementary Table 2.2. Fit indices of the LCGA procedure for each eating behavior subscale, n=3514

	BIC	Entropy	Lowest n in class	Lowest latent class posterior probability	BLRT[a] p-value
Food responsiveness					
1 class	15182.892	-	3514	-	-
2 classes	13826.470	0.900	425	0.906	0.0000
3 classes	13345.153	0.889	272	0.844	0.0000
4 classes	12981.769	0.885	101	0.848	0.0000
5 classes	12789.752	0.852	113	0.790	0.0000
6 classes	12642.179	0.859	47	0.818	0.0000
Enjoyment of food					
1 class	14802.462	-	3514	-	-
2 classes	14044.049	0.645	854	0.838	0.0000
3 classes	13893.865	0.687	137	0.803	0.0000
4 classes	13535.148	0.885	133	0.913	0.0000
Emotional overeating					
1 class	13352.870	-	3514	-	-
2 classes	12284.095	0.874	1101	0.938	0.0001
3 classes	10340.375	0.977	246	0.989	0.0000
4 classes	10364.869	0.982	0	0.000	1.0000
Satiety responsiveness					
1 class	13620.014	-	3514	-	-
2 classes	12806.113	0.619	1155	0.842	0.0000
3 classes	12631.093	0.571	586	0.737	0.0000
4 classes	12623.140	0.604	88	0.744	0.0000

[a] Bootstrapped Likelihood Ratio Test

3

Associations of prenatal exposure to impaired glucose tolerance with eating in the absence of hunger in early adolescence

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ABSTRACT

Objective: Exposure to impaired gestational glucose tolerance has been shown to have sex-specific associations with offspring obesity risk, perhaps by affecting the development of appetite regulation. We examined the extent to which prenatal exposure to impaired glucose tolerance was associated with eating in the absence of hunger (EAH) in early adolescent offspring, and in turn, whether EAH was cross-sectionally associated with body composition.

Methods: We included data from 1097 adolescents participating in Project Viva, a pre-birth longitudinal cohort. We obtained results of 2-stage prenatal glycemic screening (50g glucose challenge test, followed if abnormal by 100g oral glucose tolerance test) at 26-28 weeks gestation, and categorized mothers as having normal glucose tolerance, isolated hyperglycemia (IH, n=92, 8.4%), impaired glucose tolerance (IGT, n=36, 3.3%), or gestational diabetes mellitus (GDM, n=52, 4.7%). At a median age of 13 years, offspring reported on two modified items of the Eating in the Absence of Hunger in Children and Adolescents questionnaire, we measured height and weight, and performed dual X-ray absorptiometry scans to assess fat- and fat free mass. We used multivariable linear regression analyses adjusted for sociodemographic and prenatal covariates, including maternal pre-pregnancy BMI.

Results: On a 10-point scale, mean (SD) EAH score was 4.4 points (SD=1.5) in boys and 4.4 (SD=1.4) in girls. In girls, prenatal exposure to both IH and IGT was associated with more EAH compared with normal glucose tolerance (e.g. for IH: 0.56 points, 95%CI: 0.17, 0.96), whereas in boys, prenatal exposure to IGT was associated with less EAH (−0.81 points, 95%CI: −1.41, −0.21). We did not observe an association between exposure to GDM and EAH, nor did we observe associations between EAH and body composition in early adolescence.

Conclusions: These findings suggest sex-specific associations of exposure to impaired gestational glucose tolerance with offspring EAH in early adolescence.

INTRODUCTION

In the United States (US), the prevalence of maternal gestational diabetes mellitus (GDM) increased during the past 20 years and ranged between 5.8% and 9.2% of all pregnancies in 2010.[1-3] Longitudinal studies demonstrate that offspring exposed to impaired gestational glucose tolerance (defined as all abnormal prenatal glucose tolerance screening outcomes, ranging from isolated hyperglycemia to GDM) have an increased risk of obesity and impaired glucose tolerance during childhood and adolescence.[4-9] A possible mechanism by which impaired gestational glucose tolerance could affect body composition in childhood and adolescence is via appetite regulation.

Exposure to impaired gestational glucose tolerance might affect the intrauterine programming of appetite regulation. Neuroendocrine feedback systems between the gut, brain and adipose tissue regulate appetite. Balanced levels of insulin, leptin and ghrelin signal the hypothalamus to maintain energy homeostasis, but resistance to these hormones disturbs satiety signaling and may lead to increased food intake in response to external food cues rather than hunger.[10,11] Disturbances in this mechanism in offspring caused by maternal diet, parental obesity and GDM have been previously reported in animal studies.[12-16] Resistance to satiety signaling in the hypothalamus might also result in an increase in food intake in humans. Fisher and Birch conceptualized "eating in the absence of hunger (EAH)" in 1999, which can be described as eating past satiety in response to external food cues and indicating disinhibition in eating.[17] A recent systematic review including cross-sectional and prospective studies showed that children or adolescents with a higher weight status often showed more EAH, and results were often sex-specific.[18]

Parental obesity has also been associated with more EAH in the offspring. Francis et al.[19] showed that having overweight parents was associated with more EAH in girls, whereas Faith et al.[20] showed that high maternal pre-pregnancy BMI was associated with more EAH in boys. Furthermore, children from obese parents have been found to have a higher preference for high-fat food and a tendency towards overeating.[21] We are aware of only one study that examined the association between exposure to maternal gestational glucose tolerance and offspring EAH. Shapiro et al.[22] showed among 268 US adolescents that GDM exposure *in utero* was associated with more EAH in females, but not in males. In turn, more EAH was associated with a higher overall energy intake, but whether GDM exposure was associated with energy intake or adiposity was not examined. Thus, more studies are needed to examine whether offspring exposed to impaired gestational glucose tolerance show more EAH.

The aim of this study was to examine the extent to which prenatal exposure to impaired gestational glucose tolerance is associated with EAH in early adolescent offspring. Early adolescence may be a sensitive period for the development of eating problems as EAH appears to peak during this life stage.[23] Additionally, we examined the extent to which

exposure to impaired gestational glucose tolerance was associated with self-reported sugar-sweetened beverage (SSB) intake and consumption of energy-dense, low nutritive foods as indicators of diet quality. Lastly, we examined the cross-sectional relationship between EAH and body composition in early adolescence.

METHODS

Study population

This study was embedded in Project Viva, a prospective pre-birth cohort situated in Eastern Massachusetts, US. Between April 1999 and July 2002, pregnant women were recruited at their initial prenatal visit from Atrius Harvard Vanguard Medical Associates. Informed consent was given by all mothers, and the Institutional Review Boards of participating institutions approved the study. All procedures were in accordance with the ethical standards established by the declaration of Helsinki.[24] All Project Viva questionnaires are available at https://www.hms.harvard.edu/viva/data-collection-by-visit.html.

In total, 2128 mothers had a live singleton birth in Project Viva. We excluded 16 mothers with a previous diagnosis of type 1 or type 2 diabetes and 45 mothers without prenatal glycemic screening data. From the remaining 2067 mothers, 1161 adolescents had any early teen data available. We excluded 64 adolescents with missing EAH data, resulting in a final study sample of 1097 mother-child pairs for analysis. We measured height and weight in 1000 of these adolescents, and of those, 715 adolescents had body composition measures.

Compared to excluded participants (n=1031), mothers of the 1097 included adolescents were older at enrollment (32.3 years vs. 31.3 years), were more likely to be white (66.2% vs. 60.8%) and had a higher annual household income (>$70,000 per year, 61.8% vs. 53.5%). Mothers of included vs. excluded participants had similar mean maternal pre-pregnancy BMI (24.7 vs. 25.1 kg/m^2) and gestational weight gain before glycemic screening (9.2 kg vs. 9.3 kg).

Procedures

At the age of 13 years, Project Viva staff invited adolescents to participate in the early teen wave. At an in-person visit, or via mail or online, adolescents completed the early teen questionnaire, including the assessment of EAH, SSB intake and consumption of energy-dense, low nutritive foods. During the early teen visit, trained research assistants collected objective physical health measures.

Measures

Maternal gestational glucose tolerance

Obstetric clinicians assessed maternal gestational glucose tolerance status by routine 2-stage prenatal glycemic screening at 26-28 weeks of pregnancy. All mothers completed a non-fasting 50g oral Glucose Challenge Test (GCT). If serum blood glucose exceeded 140 mg/dL after one hour, mothers were referred for a fasting three-hour 100g Oral Glucose Tolerance test (OGTT). OGTT results were considered abnormal when blood glucose was >95 mg/dL at baseline, >180 mg/dL after one hour, >155 mg/dL after two hours or >140 mg/dL after three hours. Mothers were diagnosed with GDM if they had two or more abnormal values on the OGTT. We categorized mothers with one abnormal result on the OGTT as having Impaired Glucose Tolerance (IGT), and mothers with an abnormal GCT but normal OGTT as having isolated hyperglycemia (IH). Clinicians typically instructed mothers diagnosed with GDM to check their fasting blood glucose levels daily, arranged follow-up with a nutritionist, provided advice about management with diet and physical activity, or prescribed insulin.[25] In our sample, 10 mothers with GDM and 1 mother with IGT were treated with insulin. In general, clinicians managed mothers with IGT or IH similar to normal glycemic mothers and therefore they typically did not receive further screening or treatment. As secondary exposures, we considered other indicators of maternal glycemic status during pregnancy including the serum blood glucose levels in mg/dL from the GCT, and fructosamine levels (μmol/l) measured in blood collected in the second trimester of pregnancy, reflecting mean blood sugar levels over the past 2-3 weeks. We transformed glucose and fructosamine levels into z-scores for comparison purposes.

Eating in the absence of hunger

We assessed self-reported EAH using two modified items derived from the Eating in the Absence of Hunger in Children and Adolescence questionnaire (EAH-C).[26] The questions were: 1. "Imagine you are eating a meal or snack at home or in a restaurant. Imagine that you have eaten enough so you are not hungry anymore. How often would you keep eating?" and 2. "Imagine you ate a meal or snack a little while ago and are not hungry anymore. How often would you start eating again?" Response options were on a five-point scale ranging from 1- never to 5- always. Internal consistency between both items was considered acceptable, with a Cronbach's α of 0.67. Only when adolescents completed both items, we calculated sum scores (ranging from 2 to 10 points).

Sugar Sweetened Beverage intake

Adolescents reported on beverage intake with 10 questions about intake of soda, diet soda, sports drinks, low-calorie sports drinks, energy drinks, juice, fruit and flavored

drinks, milk, flavored milk, and water. Five response options ranged from less than once per week to twice or more per day. We combined questions on sugary soda, sport- and energy drinks, fruit- and flavored drinks and flavored milk to generate an estimate of total daily intake of SSB in servings per day.

Consumption of energy-dense, low nutritive foods

Adolescents reported on two items taken from PrimeScreen, a validated semi-quantitative food frequency questionnaire:[27] 1. How often have you eaten baked products (such as donuts, cookies, muffins, crackers, pastries, cakes or sweet rolls) during the past month? and 2. How often have you eaten deep-fried foods (such as deep-fried chicken, fish or seafood, French fries, onion rings) during the past month? Five response options ranged from less than once per week to twice or more per day. We added both questions to generate an estimate of total consumption of energy-dense, low nutritive foods in servings per day.

BMI and body composition

Trained research assistants measured adolescent's height and weight without shoes and heavy clothing. We calculated BMI in kg/m^2 and determined sex and age specific BMI z-scores from US national reference data.[28] Further, whole-body DXA scans (Hologic model Discovery A, Hologic, Bedford, MA) were conducted, using Hologic software version 12.6 for scan analysis. Scans were checked for positioning, movement and artifacts. We calculated fat mass index (FMI) as total fat mass (kg)/ height $(m)^2$, fat free mass index (FFMI) as total fat free mass (kg)/ height $(m)^2$ and percentage body fat as total fat mass (kg)/ total weight (kg).

Covariates

Based on previous literature and theory,[8,18] we considered several possible confounders. During the first prenatal visit, mothers reported on their age, educational level, marital status, household income and parity, pre-pregnancy- and paternal weight and height. In the first trimester, mothers completed a validated semi-quantitative Food Frequency Questionnaire (FFQ) adapted for pregnancy, from which we calculated western and prudent dietary pattern scores using principal components analysis (PCA).[29-31] We obtained serial prenatal weights from medical records and calculated gestational weight gain only up to 26 weeks of gestation since subsequent weight gain can be influenced by diagnosis and treatment of GDM. We obtained child sex, birthweight and birth date from medical records and calculated sex-specific birthweight for gestational age z-scores using US reference data.[32] In early childhood, mothers reported on their child's race/ethnicity.

Statistical analyses

We calculated means and frequencies of each covariate according to maternal gestational glucose tolerance status. We included covariates in the main analyses when they were associated with EAH, SSB intake, or consumption of energy-dense, low-nutritive foods, by bivariate analyses. In general, we did not include intermediate covariates in our models in order to prevent collider bias (for instance, the association between impaired gestational glucose tolerance and EAH was not adjusted for birthweight, and was only adjusted for gestational weight gain until the time of GDM screening but not later weight gain).[33]

We used multivariable linear regression analyses to examine associations of impaired gestational glucose tolerance with EAH sum scores. Three models are presented: the basic model, adjusted for child sex and age. Model 2 was additionally adjusted for pre-pregnancy and prenatal covariates (maternal age, education, marital status, parity, pre-pregnancy BMI, gestational weight gain, and prudent diet and western diet scores during pregnancy; household income and paternal BMI; and child race/ethnicity). Model 3 was additionally adjusted for child BMI z-score in early adolescence, as this could be a proxy for unmeasured confounders. We repeated these analyses with the outcomes of SSB intake and consumption of energy-dense, low-nutritive foods, and BMI z-score in early adolescence (model 2 only).

Next, we studied cross-sectional associations of EAH with body composition using multivariable linear regression analyses. Two models were created: the basic model, adjusted for sex and age; second, additionally adjusted for maternal age, education, marital status, parity, pre-pregnancy BMI, gestational weight gain, prudent diet and western diet scores during pregnancy; household income and paternal BMI; and child race/ethnicity and birth weight for gestational age z-score.

In sensitivity analyses, we repeated our analyses of maternal gestational glucose tolerance with EAH excluding those mothers who were treated with insulin during pregnancy. We also studied associations of child BMI z-score with adolescent EAH, again using multiple linear regression analyses. We calculated the change in BMI (Δ BMI) from the mid-childhood to the early teen visit.

We tested interactions with sex in confounder-adjusted models, given previous studies showing sex differences in child anthropometrics by impaired gestational glucose tolerance within Project Viva,[8] as well as sex-specific findings in previous literature.[18,22] We presented stratified analyses when a significant interaction effect ($p<0.05$) by sex was found.

We checked diagnostics for linear regression analyses and confirmed concordance with model assumptions. Multiple imputation was used to estimate missing data on covariates. All study variables were included in the imputation model and results are based on pooled results of 50 imputed datasets. Multiple imputation was performed with SAS version 9.4 (Cary, NC) and analyses in SPSS version 24.0 (IBM corp.).

RESULTS

Sample characteristics according to maternal gestational glucose tolerance status are provided in Table 3.1. Of the 1097 adolescents, 917 (83.6%) were prenatally exposed to normal glucose tolerance, 92 to IH (8.4%), 36 to IGT (3.3%), and 52 to GDM (4.7%). Adolescents exposed to IGT reported slightly lower scores of EAH (mean=4.2 points, SD=1.6), while adolescents exposed to IH or GDM reported slightly higher scores of EAH (IH, mean= 4.6 points, SD=1.4 or GDM, mean= 4.6 points, SD=1.4) compared to normal glucose tolerance (mean= 4.4, SD= 1.4). Mothers with GDM had a higher pre-pregnancy BMI but lower early pregnancy gestational weight gain, compared to normal glycemic mothers. Adolescents prenatally exposed to impaired gestational glucose tolerance were less often white and had a higher fat mass in early adolescence.

Table 3.1. Characteristics of 1097 adolescents in Project Viva according to maternal gestational glucose tolerance status

	Overall n=1097	**Maternal gestational glucose tolerance status**			
		Normal n=917	**IH n=92**	**IGT n=36**	**GDM n=52**
Prenatal characteristics					
Maternal educational level, n (%)					
< College graduate	307 (28)	254 (28)	19 (21)	12 (33)	22 (42)
≥ College graduate	790 (72)	663 (72)	73 (79)	24 (67)	30 (58)
Mother married or cohabitating, n (%)					
No	81 (7)	70 (8)	4 (4)	4 (11)	3 (6)
Yes	1016 (93)	847 (92)	88 (96)	32 (89)	49 (94)
Annual household income, n (%)					
≤ $ 70 000	419 (38)	348 (38)	33 (36)	14 (38)	25 (48)
> $ 70 000	678 (62)	569 (62)	59 (64)	22 (62)	27 (52)
Nulliparous, n (%)					
No	563 (51)	470 (51)	48 (52)	21 (58)	24 (46)
Yes	534 (49)	447 (49)	44 (48)	15 (42)	28 (54)
Maternal age at enrollment, years	32.3 (5.0)	32.0 (5.1)	34.0 (4.3)	33.4 (3.9)	32.9 (3.8)
Maternal pre-pregnancy BMI, kg/m^2	24.7 (5.1)	24.4 (5.0)	25.2 (5.0)	25.4 (4.2)	28.1 (6.4)
Gestational weight gain up to 26 weeks gestation, kg	9.2 (3.8)	9.3 (3.7)	8.7 (3.7)	10.0 (4.1)	8.3 (4.8)
Maternal prudent dietary pattern 1st trimester z-score	0.01 (0.99)	−0.00 (0.99)	0.09 (0.94)	−0.10 (0.85)	0.14 (1.07)
Maternal western dietary pattern 1st trimester z-score	−0.03 (0.95)	−0.04 (0.96)	−0.04 (0.87)	−0.19 (0.89)	0.22 (1.02)
Paternal BMI, kg/m^2	26.4 (4.0)	26.3 (4.0)	27.2 (4.2)	26.2 (2.9)	26.7 (3.6)

Table 3.1. Characteristics of 1097 adolescents in Project Viva according to maternal gestational glucose tolerance status (*continued*)

	Overall n=1097	Maternal gestational glucose tolerance status			
		Normal n=917	IH n=92	IGT n=36	GDM n=52
Child characteristics					
Sex, n (%)					
Boys	552 (50)	459 (50)	40 (43)	25 (69)	28 (54)
Girls	545 (50)	458 (50)	52 (57)	11 (31)	24 (46)
Race/ethnicity, n (%)					
Black	160 (15)	135 (15)	9 (10)	6 (17)	10 (19)
Hispanic	49 (4)	39 (4)	6 (7)	1 (3)	3 (6)
Asian	35 (3)	29 (3)	2 (2)	2 (6)	2 (4)
White	726 (66)	605 (66)	68 (74)	22 (61)	31 (60)
Other	126 (11)	108 (12)	7 (8)	5 (14)	6 (12)
Gestational age at birth, weeks	39.6 (1.6)	39.6 (1.6)	39.9 (1.1)	39.9 (1.0)	38.9 (1.7)
Birth weight, kg	3.49 (0.53)	3.47 (0.54)	3.62 (0.47)	3.75 (0.45)	3.52 (0.49)
Birth weight for gestational age z-score	0.19 (0.95)	0.14 (0.95)	0.37 (0.94)	0.55 (0.90)	0.35 (0.88)
Early adolescence					
Age at visit, years	13.3 (1.0)	13.3 (1.0)	13.1 (0.8)	13.2 (0.9)	13.5 (1.0)
BMI z-score	0.36 (1.06)	0.33 (1.07)	0.53 (1.05)	0.34 (0.95)	0.70 (0.92)
BMI category, n (%)					
Normal weight (<85th percentile)	731 (73)	625 (75)	50 (58)	25 (81)	31 (65)
Overweight (85th-<95th percentile)	148 (15)	114 (14)	23 (27)	2 (6)	9 (19)
Obese (≥85th percentile)	121 (12)	96 (11)	13 (15)	4 (13)	8 (17)
Fat Mass Index, kg/m^2	6.3 (3.1)	6.2 (3.0)	6.9 (2.9)	6.3 (3.0)	7.4 (3.6)
Fat Free Mass Index, kg/m^2	14.9 (2.1)	14.9 (2.1)	14.7 (1.9)	14.5 (1.6)	15.9 (2.1)
% Body fat	28.5 (7.5)	28.1 (7.5)	30.9 (7.0)	29.0 (8.5)	30.2 (7.6)
Eating in the absence of hunger sum score[a]	4.4 (1.4)	4.4 (1.4)	4.6 (1.4)	4.2 (1.6)	4.6 (1.4)
Sugar sweetened beverages, servings/day	0.8 (0.9)	0.8 (0.9)	0.7 (0.9)	0.9 (0.8)	0.8 (0.8)
Energy-dense, low nutritive foods, servings/day	0.5 (0.4)	0.5 (0.4)	0.5 (0.3)	0.5 (0.4)	0.5 (0.4)

Values are means (SD) or frequencies (%). [a] Range: 2-10 points.

Table 3.2. Associations of maternal gestational glucose tolerance status with offspring eating in the absence of hunger in early adolescence among 1097 adolescents in Project Viva

	Prenatal exposure to glucose tolerance status	N	Frequency (%)/mean (SD)	Eating in the absence of hunger score in early adolescence		
				Model 1 Basic model β (95%CI)	Model 2 Confounder adjusted β (95%CI)	Model 3 BMI adjusted β (95%CI)
Boys	Maternal glucose tolerance status					
	Normal glycemic	459	83.2	*Reference*	*Reference*	*Reference*
	Isolated hyperglycemia	40	7.2	−0.22 (−0.70, 0.26)	−0.13 (−0.61, 0.35)	−0.14 (−0.62, 0.34)
	Impaired glucose tolerance	25	4.5	−0.77 (−1.37, −0.17)	−0.81 (−1.41, −0.21)	−0.79 (−1.39, −0.19)
	GDM	28	5.1	0.32 (−0.25, 0.89)	0.33 (−0.24, 0.91)	0.33 (−0.24, 0.90)
	Maternal serum glucose level after GCT, mg/dL	548	115.0 (27.9)	−0.06 (−0.18, 0.07)	−0.03 (−015, 0.10)	−0.03 (−0.15, 0.10)
	Second trimester fructosamine level, µmol/l	438	233.7 (49.6)	0.04 (−0.09, 0.17)	0.03 (−0.11, 0.16)	0.03 (−0.11, 0.16)
Girls	Maternal glucose tolerance status					
	Normal glycemic	458	84.0	*Reference*	*Reference*	*Reference*
	Isolated hyperglycemia	52	9.5	0.50 (0.12, 0.89)	0.56 (0.17, 0.96)	0.55 (0.16, 0.94)
	Impaired glucose tolerance	11	2.0	0.89 (0.08, 1.70)	0.76 (−0.05, 1.57)	0.75 (−0.06, 1.56)
	GDM	24	4.4	0.03 (−0.52, 0.59)	0.01 (−0.56, 0.57)	−0.01 (−0.58, 0.56)
	Maternal serum glucose level after GCT, mg/dL	545	111.6 (26.4)	0.10 (−0.02, 0.22)	0.12 (−0.01, 0.24)	0.12 (−0.01, 0.24)
	Second trimester fructosamine level, µmol/l	433	233.4 (45.5)	0.02 (−0.11, 0.16)	0.06 (−0.08, 0.19)	0.06 (−0.08, 0.19)

Maternal serum glucose level after GCT and first trimester fructosamine level are modeled as z-scores. Model 1 is adjusted for child age at outcome, Model 2 is additionally adjusted for maternal age at enrollment, parity, educational level, marital status, pre-pregnancy BMI, gestational weight gain up to 26 weeks of gestation, and prudent and western dietary pattern scores; household income and paternal BMI; and child race/ethnicity. Model 3 is additionally adjusted for BMI z-score in early adolescence.

Sex differences were present in the association between IH and EAH and between IGT and EAH (both p<0.03, overall F(df1, df2) =4.78 (3, 1074), p= 0.003). Boys prenatally exposed to IGT reported less EAH compared to boys exposed to normal gestational glucose tolerance (model 2, confounder adjusted β=−0.81 points, 95%CI: −1.41, −0.21, Table 3.2 and Figure 3.1). No evidence of an association was found for EAH scores in boys exposed to other categories or for maternal glucose levels after the GCT and fructosamine levels. For girls, prenatal exposure to IH was associated with more EAH compared to exposure to normal gestational glucose tolerance (model 2, β= 0.56 points, 95%CI: 0.17, 0.96, Table 3.2 and Figure 3.1). Further, girls prenatally exposed to IGT also reported more EAH, (model 2, β= 0.76 points, 95%CI: −0.05, 1.57), although the confidence interval included zero. EAH scores were similar for GDM compared to normal glucose tolerance exposure. We further observed a positive association between maternal glucose levels after GCT with EAH in girls, but confidence intervals contained zero. For both sexes, additional adjustment for BMI z-score at 13 years did not attenuate the associations between im-

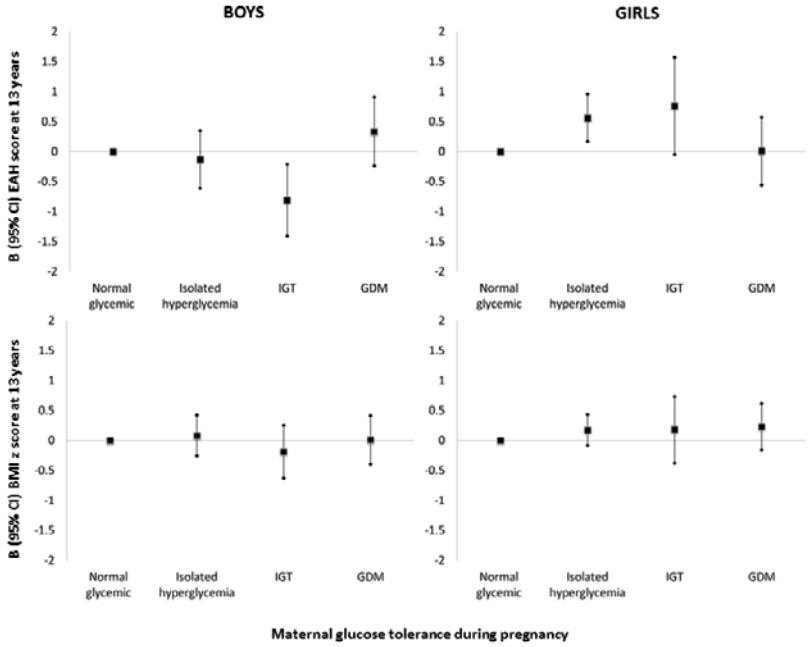

Figure 3.1. Adjusted linear regression coefficients and their associated 95% confidence intervals for eating in the absence of hunger (EAH) and BMI z-score in early adolescence (median age= 13 years), according to maternal glucose tolerance status during pregnancy and stratified by child sex (N=552 boys and N= 545 girls for EAH; N=496 boys and N=504 girls for BMI z-score). Effect estimates were adjusted for maternal age at enrollment, parity, educational level, marital status, pre-pregnancy BMI, gestational weight gain up to 26 weeks of gestation, and prudent and western dietary pattern scores; household income and paternal BMI; and child race/ethnicity and age at outcome assessment.

paired gestational glucose tolerance and EAH (Table 3.2, model 3). Figure 3.1 displays the associations between categories of gestational glucose tolerance and EAH scores as given in Table 3.2 (model 2), as well as associations between categories of gestational glucose tolerance with BMI z-score in early adolescence. Although patterns of associations of maternal glucose tolerance with BMI z-score were comparable to findings with EAH, no evidence for an association was found for BMI z-score in boys or girls prenatally exposed to impaired glucose tolerance (e.g. for IGT in girls: β= 0.18, 95%CI= −0.38, 0.73).

In Table 3.3 we show associations of exposure to impaired gestational glucose tolerance with SSB intake and consumption of energy-dense, low-nutritive foods. We observed a sex-interaction between exposure to GDM for SSB intake (p=0.03), overall F(df1, df2)= 1.70 (3, 1074), p=0.17. In boys, prenatal exposure to GDM was associated with less SSB intake (β= −0.29 servings/day, 95%CI: −0.65, 0.06), whereas in girls, exposure to GDM was associated with more SSB intake (β= 0.18 servings/day, 95%CI: −0.13,

Table 3.3. Associations of maternal prenatal gestational glucose tolerance status with offspring self-reported SSB intake and consumption of energy-dense, low nutritive foods in early adolescence

		SSB intake in early adolescence (servings/day)	**Consumption of energy-dense, low nutritive foods in early adolescence (servings/day)**
	Prenatal exposure to glucose tolerance status	**β (95% CI)**	**β (95% CI)**
Boys	Maternal glucose tolerance status		
	Normal glycemic	*Reference*	*Reference*
	Isolated hyperglycemia	−0.03 (−0.33, 0.27)	−0.09 (−0.24, 0.07)
	Impaired glucose tolerance	0.01 (−0.36, 0.37)	−0.08 (−0.27, 0.11)
	GDM	−0.29 (−0.65, 0.06)	0.03 (−0.16, 0.21)
	Maternal serum glucose level after GCT, mg/dL	−0.07 (−0.15, 0.00)	−0.02 (−0.06, 0.02)
	Second trimester fructosamine level, μmol/l	−0.02 (−0.11, 0.06)	0.02 (−0.02, 0.06)
Girls	Maternal glucose tolerance status		
	Normal glycemic	*Reference*	*Reference*
	Isolated hyperglycemia	−0.02 (−0.23, 0.19)	0.00 (−0.11, 0.11)
	Impaired glucose tolerance	0.18 (−0.27, 0.62)	0.22 (−0.01, 0.45)
	GDM	0.18 (−0.13, 0.49)	−0.04 (−0.20, 0.12)
	Maternal serum glucose level after GCT, mg/dL	0.02 (−0.05, 0.09)	0.01 (−0.03, 0.04)
	Second trimester fructosamine level, μmol/l	0.00 (−0.07, 0.07)	0.02 (−0.02, 0.06)

Serum glucose level after GCT and second trimester fructosamine level are modeled as z-scores. Effect estimates were adjusted for maternal age at enrollment, parity, educational level, marital status, pre-pregnancy BMI, gestational weight gain up to 26 weeks of gestation, and prudent and western dietary pattern scores; household income and paternal BMI; child race/ethnicity and age at outcome.

0.49), although confidence intervals contained zero. We did not observe a sex-interaction effect with consumption of energy-dense, low-nutritive foods (overall F(df1, df2)= 0.62 (3, 1066), p=0.60). Only in girls, exposure to IGT was associated with more consumption of energy-dense, low-nutritive foods (β= 0.22 servings/day, 95% CI: −0.01, 0.45), while no associations were observed in boys.

Cross-sectional associations between EAH and body composition are shown in Table 3.4. We did not observe a sex-interaction effect with EAH on body composition (e.g. BMI: F(df) =0.69 (980), p=0.41). Basic models showed that more EAH was positively associated with body composition measures (e.g. for FMI β= 0.20, 95% CI:0.05, 0.36) (model 1). All associations attenuated after additional adjustment for sociodemographic and prenatal factors (model 2). Maternal pre-pregnancy BMI, gestational weight gain and paternal BMI were important contributors to this attenuation of effect for all body composition outcomes.

Table 3.4. Cross-sectional associations between eating in the absence of hunger and body composition in early adolescence

Predictor		**Body composition**			
		BMI z-score β (95%CI)	**FMI β (95%CI)**	**FFMI β (95%CI)**	**% Body fat β (95%CI)**
Eating in the absence of	n	1000	715	715	715
hunger, per point	Model 1 Basic model	0.07 (0.03, 0.12)	0.20 (0.05, 0.36)	0.14 (0.03, 0.24)	0.37 (0.00, 0.75)
	Model 2 Confounder adjusted	0.04 (0.00, 0.08)	0.12 (−0.02, 0.26)	0.03 (−0.06, 0.12)	0.29 (−0.06, 0.64)

Model 1 was adjusted for sex and age at outcome. Model 2 was additionally adjusted for maternal age at enrollment, parity, educational level, marital status, pre-pregnancy BMI, gestational weight gain up to 26 weeks of gestation, and prudent and western dietary pattern scores; household income and paternal BMI; child race/ethnicity, birth weight for gestational age z-score.

We found no associations between BMI z-score in mid-childhood and EAH in early adolescence, nor did we observe an association of BMI z-score change from mid childhood to early adolescence with EAH in early adolescence (Supplementary Table 3.1). Finally, we observed similar results after excluding mothers who were treated with insulin during pregnancy (not tabulated).

DISCUSSION

In this pre-birth cohort, we found sex-specific associations for prenatal exposure to impaired glucose tolerance with EAH in early adolescence. Girls prenatally exposed to IH or IGT reported more EAH, while boys exposed to IGT reported less EAH compared to adolescents exposed to normal glucose tolerance. Comparable sex-specific patterns of associations were found for impaired gestational glucose tolerance with BMI z-score, self-reported SSB intake and consumption of energy-dense, low nutritive foods in early adolescence, although the associations were weaker. We did not observe cross-sectional associations between EAH and body composition in early adolescence.

The observed sex differences in prenatal exposure to impaired glucose tolerance on EAH might reflect differential sensitivity to the intrauterine environment with a long-lasting effect on appetite regulation. Our finding that girls were especially sensitive to adverse effects from exposure to gestational glucose intolerance was consistent with the only previous study, to our knowledge, that examined the same relationship. Shapiro et al.[22] studied exposure to GDM versus no GDM and its association with EAH, whereas we extended this investigation by examining two intermediate categories of gestational glucose intolerance, namely IH and IGT. Remarkably, these two intermediate categories were associated with more EAH in girls, whereas exposure to GDM was not. This pattern may have resulted from treatment that mothers diagnosed with GDM received, while mothers with IH or IGT during pregnancy were generally treated the same way as mothers with normal glucose tolerance, thus presumably having higher levels of glycemia throughout the third trimester than normoglycemic women. The results were unchanged when we excluded women who received insulin treatment, although we had no information on degree of adherence to GDM treatment, suggesting that this pattern may still have resulted from treatment that mothers with GDM received, typically including glucose level monitoring, lifestyle changes and weight control. Although it can be assumed that mothers with GDM also received treatment in Shapiro et al., this was not reported. Our result that prenatal exposure to IGT was associated with less EAH in boys was partially in line with Shapiro et al., who reported a non-significant negative association in boys.[22]

An increasing number of studies have recently reported differential sensitivity to impaired gestational glucose tolerance by sex in relation to offspring health outcomes. Prior results in Project Viva showed that in female offspring, exposure to IGT during pregnancy had greater adiposity levels in mid-childhood, which is in line with our findings in girls. However, the same study showed that GDM exposure was associated with higher adiposity in boys, while we observed less EAH in boys exposed to GDM,[8] although relationships attenuated in early adolescence.[34] Other studies showed sex differential associations in growth and adiposity by maternal and cord blood C-peptide concentrations.[35,36] Moreover, Landon et al. showed that treatment of maternal hyperglycemia during pregnancy

resulted in lower glucose levels in female offspring aged 5-10 only.[37] Our findings add to these studies by suggesting that sex differences *in utero* might also affect the development of long-term appetite regulation.

Prenatal exposure to impaired glucose tolerance might influence release of or sensitivity to leptin, resulting in more EAH in the offspring. A few studies reported higher (cord) blood leptin concentrations in offspring exposed to GDM,[38,39] or in boys exposed to IGT and GDM,[40] but also in girls of non-diabetic mothers compared to boys.[39] Furthermore, a Mendelian randomization study provided causal support for the premise that maternal hyperglycemia influences offspring leptin regulation.[41] Reduced leptin signaling in the hypothalamus might be a potential mechanism as this was shown in offspring of diabetic mothers in animal studies,[13] and fMRI studies in humans showed that the hypothalamus is connected with brain centers that process food reward.[42] Yet, whether prenatal exposure to impaired glucose tolerance affects long-term appetite regulation through disturbed leptin signaling in humans needs to be explored further.

The association between EAH and weight status has been extensively studied, and most cross-sectional studies showed that children with EAH have a higher weight status.[18] Most studies were, however, conducted during childhood, while studies suggest that EAH is increasing with age, with a peak in early adolescence.[23,43] Sex-specific associations have also been reported. In a series of prospective studies among 197 girls, EAH was associated with weight gain up to 13 years.[44-46] Two cross-sectional studies, however, examined associations in both sexes and only found associations for overweight boys.[47,48] Butte et al.[49] studied 879 children aged between 4-19 years old and found that EAH was not associated with weight gain over one-year follow-up, and similar findings were reported by Kelly et al.[50] We did not find an association with body composition in early adolescence after adjustment for confounders, nor did we find sex differences. These discrepancies in findings might be due to the lack of uniformity in the assessment of EAH and different settings where social desirability of limiting food intake might play a role, especially in girls.[18,48] Finally, our findings were in line with another study examining measures of adiposity other than BMI.[50] More studies are needed to examine whether EAH might prospectively influence adiposity levels later in adolescence.

Strengths and limitations

Strengths of this population-based study were its large sample size, the prospective data collection starting in the first trimester of pregnancy with several prenatal glycemic indicators, and DXA-derived body composition measures in addition to BMI. This study includes also some limitations. First, EAH was measured with two modified items of the EAH-C questionnaire. Usually, EAH is measured by observation in a lab setting,[17] but this is not always feasible in large cohorts. In treatment-seeking overweight children, total scores on EAH-C questionnaire were positively associated with total dietary intake.[51]

Yet, validity against observational EAH in a population-based cohort, including healthy weight children, has not been reported. Compared to the original items, only the stimulus for EAH was left out in our items. For instance: "How often do you keep eating because you are feeling depressed?" was changed into "How often do you keep eating?". Nevertheless, EAH was correlated with SSB intake (r = 0.22), but not with consumption of energy-dense low-nutritive foods in this sample (r = 0.09). Second, the sex-specific results might be a result of chance given small number of adolescents in each stratum. However, these sex-differential effects by gestational glucose tolerance were also previously reported for other outcomes in the present cohort, such as cord-blood hormone levels and child adiposity.[8,40] Loss to follow-up might have introduced selection bias and limits the generalizability, since included participants reported better socioeconomic conditions. The cross-sectional nature of associations between EAH and body composition limits causal interpretation even with adjustment for confounders. In all cases unmeasured confounding and measurement error may also bias our effect estimates.

Conclusions

These findings suggest sex-specific associations of exposure to impaired gestational glucose tolerance in offspring appetite regulation. Girls prenatally exposed to IH and IGT showed more EAH in early adolescence, whereas boys prenatally exposed to IGT showed less EAH. In early adolescence, EAH was not associated with body composition. These results suggest that impaired glucose tolerance might affect sex-specific intrauterine programming and long-term appetite dysregulation. More research is needed to further explain the early origins of sex differences in appetite regulation and how it affects adiposity later in life.

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SUPPLEMENT

Supplementary Table 3.1. Associations of change in child BMI z score from mid-childhood to early adolescence with eating in the absence of hunger in early adolescence

Child BMI measures		**Eating in the absence of hunger sum score in early adolescence β (95%CI)**
Mid childhood BMI z score	n	861
	Model 1	0.11 (0.01, 0.21)
	Model 2	0.06 (−0.05, 0.16)
Early adolescence BMI z score	n	1000
	Model 1	0.13 (0.05, 0.21)
	Model 2	0.09 (−0.01, 0.18)
Δ BMI z score	n	861
from mid childhood to early adolescence	Model 1	0.10 (−0.05, 0.26)
	Model 2	0.09 (−0.07, 0.24)

Model 1 was adjusted for sex and age at outcome. Model 2 was additionally adjusted for maternal age at enrollment, parity, educational level, marital status, pre-pregnancy BMI, gestational weight gain up to 26 weeks of gestation, and prudent and western dietary pattern scores; household income and paternal BMI; child race/ethnicity and birth weight for gestational age z-score.

PART II

CHILD BEHAVIOR, BODY COMPOSITION AND CARDIOMETABOLIC HEALTH

4

Eating behavior and body composition across childhood: a prospective cohort study

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ABSTRACT

Background: Although many cross-sectional studies reported that children with overweight or obesity show more food approaching and less food avoidant eating behaviors, there is a lack of replication in longitudinal studies. Therefore, the question remains whether healthcare professionals should target eating behaviors in childhood obesity interventions and prevention. We aimed to examine the longitudinal and possible bi-directional associations between eating behavior and body composition across childhood.
Methods: Data was included from 3331 children participating in the Generation R Study. At 4 and 10 years, mothers reported on the Child Eating Behavior Questionnaire including the subscales Food Responsiveness, Enjoyment of Food, Emotional Overeating and Satiety Responsiveness, and children's BMI was measured. Body composition, consisting of Fat Mass Index and Fat Free Mass Index was measured at 6 and 10 years with Dual-energy-X-ray-Absorptiometry scans.
Results: Cross-lagged models including both directions of the BMI – eating behavior association showed that a higher BMI at the age of 4 years predicted more food responsiveness and enjoyment of food and less satiety responsiveness at 10 years (e.g. satiety responsiveness: $\beta = -0.10$, 95% CI= −0.14, −0.07), but no associations were found in the opposite direction. For emotional overeating, however, a bi-directional association was found with BMI predicting more emotional eating and vice versa. Multivariable linear regression analyses showed that associations were stronger for Fat Mass Index than for Fat Free Mass Index.
Conclusions: Results showed that a higher BMI, and particularly higher fat mass, at pre-school age predicted more food approaching and less food avoidant eating behaviors at the age of 10 years, rather than the hypothesized reverse direction. This suggests that increased adiposity in early childhood might upregulate appetite and related eating behaviors.

INTRODUCTION

Eating behaviors and Body Mass Index (BMI) are closely linked across the lifespan.[1] Numerous cross-sectional studies in childhood reported that children with a higher weight status show more food approaching and less food avoidant eating behaviors. Namely, children with overweight or obesity are more sensitive to external food cues (i.e. food responsiveness), they tend to eat more when they experience negative emotions (i.e. emotional overeating) and show more pleasure and interest in eating (i.e. enjoyment of food) than healthy weight children, which are considered food approaching behaviors. In turn, children with overweight or obesity showed to be less responsive to their internal satiety cues (i.e. satiety responsiveness) than their healthy weight counterparts, where satiety responsiveness is considered a food avoidant behavior.[2-14] Two of these studies showed a gradient relationship of these behaviors across the BMI span, indicating a dose-response relationship between BMI and eating behaviors.[3,7] In contrast to this abundance of evidence, two studies found no cross-sectional assocation between eating behaviors and weight status in children.[15,16] Consequently, scholars and policy makers have advocated that eating behaviors should be targeted in childhood obesity interventions.[17] This implication is, however, hardly supported by prospective research. Only two studies showed that higher food responsiveness and a poor satiety responsiveness at 3 months of age, but not at 12 months, were associated with subsequent BMI until 15 months of age.[18,19] In contrast, Mallan et al. reported a prospective association of poorer satiety responsiveness at 2 years with a higher BMI at 4 years of age, but found no association between food approaching behaviors and BMI.[20] Besides these few studies in early life with a relative short follow-up period, the evidence for the potential effect of eating behavior on subsequent BMI is rather poor. Conversely, a higher BMI might also affect eating behavior through an increase in energy needs and up-regulation of appetite. A recent study conducted among 807 Norwegian community children found evidence for this, as higher fat mass levels at age 6 predicted an increase in food responsiveness by age 10 years, while higher muscle mass predicted a decrease in satiety responsiveness.[21] However, the association in the opposite direction – examining whether eating behavior affects later body composition – was not reported.

Clearly, prospective studies with repeated measurements are needed to ascertain potential (reverse) causality in the eating behavior – BMI association. To date, only two longitudinal studies investigated both directions during one period in separate models and found evidence of bi-directionality in the relationship between food responsiveness and BMI, while results on satiety responsiveness were inconsistent.[22,23] Moreover, other eating behaviors such as emotional overeating and enjoyment of food, as well as fat- and fat free mass were not examined. In order to determine the strongest direction of effect, both directions of the association between eating behavior and BMI must be examined

in a one model. Determining causes and consequences will help identify whether eating behaviors are indeed a right target for obesity interventions aimed at primary prevention, which is of upmost importance for policy makers. Educating parents on the development of eating behaviors and how to change unhealthy eating habits is only effective when eating behaviors indeed have a long-term effect on weight development. If it appears that food approaching and food avoidant eating behaviors are a consequence of a high weight status, these preventive interventions may not be effective in reducing childhood obesity. Therefore, the aim of this study was to prospectively examine both directions of the association between eating behavior and body composition across childhood (from 4 and 6 to 10 years) in a large population-based cohort in the Netherlands. We expect that more food responsiveness, emotional overeating, enjoyment of food and less satiety responsiveness prospectively predict a higher BMI - and particularly a higher fat mass - later in childhood, and that the opposing direction will be weaker.

METHODS

Study design and population

This study was embedded in the Generation R Study, a population-based prospective birth cohort situated in Rotterdam, the Netherlands.[24] All pregnant women living in Rotterdam with an expected delivery date between April 2002 and January 2006 were invited (participation rate: 61%). Written informed consent was obtained from all participants and the Medical Ethical Committee of the Erasmus Medical Center approved the study. Full consent for the postnatal phase was obtained for 7294 children and their parents (73,7% of those originally enrolled). Information on eating behavior at both 4 and 10 years was available for 3514 children. The final study sample consisted of 3331 children, for whom BMI was also assessed at the age of 10 years (Supplementary Figure 4.1). The study sample for analyses with body composition at 6 years was slightly smaller (n=3097), due to missing body composition data. Missing values on BMI at 4 years (n=1136) were handled with missing imputation procedures (see Statistical analyses). Children included in this study were more often girls and had more often a Dutch background (n=3331), compared to children who were excluded due to missing data (n=3963). Further, children included in this study had mothers with a lower median BMI and came from families with a higher household income (all p-values<0.01).

Measures

Child eating behavior

Eating behavior was assessed twice using the same measure, when children were 4 and 10 years old. At both time points, mothers reported on their children's eating behavior with the Child Eating Behavior Questionnaire (CEBQ).[25] The CEBQ is a 35-item instrument that assesses variation in eating behaviors among children. For this study, three subscales were included with high scores reflecting food approaching behavior, namely: emotional overeating, food responsiveness and enjoyment of food, as well as the subscale satiety responsiveness reflecting food avoidant behavior. Emotional overeating consists of 4 items (e.g. "My child eats more when he/she is upset"), food responsiveness is a 5- item subscale which assesses children's sensitivity to external food cues (e.g. "Given the choice, my child would eat most of the time") and enjoyment of food is a 4-item subscale (e.g. "My child loves food"). Satiety responsiveness consists of 9 items combining the subscales satiety responsiveness and slowness in eating - considered as a response to the progressive triggering of internal satiety cues during food intake.[26] This combined scale has been validated against behavioral tests of food intake.[3,27] The CEBQ has well-established psychometric properties, including good test-retest reliability, internal consistency and concurrent validity with actual/observed eating behavior.[4,12,25,27] At both time points, the subscales showed good internal consistency in The Generation R sample, with Cronbach's alpha at the age of 4 years ranging from 0.78 to 0.89, and at 10 years ranging from 0.84 to 0.92.

Child BMI and body composition

At 4 years, children's growth characteristics were obtained as part of routine health care by trained staff of the community Child Health Centers, where growth and health are regularly monitored for all children living in the Netherlands. At 10 years, children visited the dedicated Generation R research center in Rotterdam. At both occasions, child height was measured in standing position using a Harpenden stadiometer and weight was measured without shoes and heavy clothing using a mechanical personal scale (SECA). Sex- and age- adjusted BMI (kg/m^2) SD scores were calculated according to the Dutch reference growth curves (www.growthanalyzer.org).[28]

During the in-person visits at the ages of 6 and 10 years, a detailed assessment of body composition took place by using Dual-energy-X-ray-Absorptiometry (DXA) scan (iDXA, GE-Lunar, 2008, Madison, WI, USA). Body fat mass and fat free mass were measured while children were laying down in horizontal position. Sex- and age adjusted Fat Mass Index (FMI, fat mass (kg)/length $(m)^2$) and Fat Free Mass Index (FFMI, fat free mass (kg)/length$(m)^2$) SD scores were calculated, based on all participating children with body composition available, for each time point separately.

Covariates

Several covariates were considered as potential confounders in the association between eating behavior and body composition. Information on child sex and birth weight were obtained from midwife- and hospital registries. Birth weight was transformed into standardized scores adjusted for gestational age according to the Swedish reference standards.[29] Ethnicity of the child was based on the country of birth of both parents, which was assessed by prenatal questionnaires, as well as maternal highest attained educational level. After birth, mothers reported on the duration of breastfeeding by postal questionnaire when the child was 2 months, 6 months and 12 months old. Mothers were asked whether they ever breastfed their child, and if yes, duration of any breastfeeding was assessed by asking at what age of the infant they stopped breastfeeding (in months). Depression and anxiety symptoms of the mother were assessed with the validated Brief Symptom Inventory (BSI) when children were 3 years old.[30] The BSI consists of 53 items about how the participant felt during the last seven days with answering options on a five-point scale, ranging from "0 = not at all" to "4 = extremely". The Depression and Anxiety scales both consists of six items, for example "Not interested in anything anymore" for depression and "Having fear or panic attacks" for anxiety. Mean scale scores were calculated for both scales separately. At the 6 years visit, maternal BMI was measured at the research center and in the same examination household income was assessed by postal questionnaire.

Statistical analyses

We used multiple imputation (i.e., fully conditional specification) to impute missing data on covariates and child BMI at the age of 4 years. We analyzed 20 imputed datasets of which the results were pooled. All study variables and additional information (i.e. BMI at 12 other time points from birth to 10 years) were included in the imputation model. For the cross-lagged modeling, Full Information Maximum Likelihood estimation was used to deal with missing data.

Sum scores of CEBQ subscales were standardized for comparison purposes. Potential confounders were included in the analyses when they changed one of the unadjusted effect estimates in the eating behavior-BMI association by more than 5% but did not have to be significant predictors of the outcome. As a result, the following confounders were included: child ethnicity, birth weight, maternal educational level, maternal BMI, maternal anxiety symptoms and household income. We examined the association between eating behaviors and body composition with a step-by-step approach including cross-sectional and uni-directional relationships, which enhances the comparability with previous studies. First, cross-sectional associations between child BMI and body composition at 10 years were studied using multivariable linear regression analyses, adjusted for confounders. Next, using multivariable linear regression, we studied the longitudinal relationship between eating behaviors at the age of 4 years with BMI, FMI and FFMI

SD scores at 10 years, adjusted for confounders (model 1), and additionally adjusted for BMI SD score at 4 years to assess the temporal relationship adjusted for baseline (model 2). Associations in the opposing direction were also examined with multivariable linear regression analyses. In model 1, the association of BMI SD score at 4 years, FMI and FFMI SD scores at 6 years with subsequent eating behaviors at the age of 10 years were examined adjusted for confounders. In model 2, we additionally adjusted for the corresponding eating behavior at the age of 4 years for temporal purposes. We previously reported on cross-sectional associations between eating behavior and BMI at 4 years.[5]

Finally, to better account for the complexity of the data, the directionality of the association between child eating behavior and BMI was examined with a cross-lagged modeling approach for each subscale of the CEBQ separately. In this type of analysis, the opposing prospective associations (the lagged effects) between eating behavior and BMI are studied in the same model while accounting for cross-sectional relations and for continuity between BMI assessments and between eating behavior assessments over time. Confounders were regressed on the BMI and eating behavior assessments at age 4 years. Wald tests were used to determine the significance of differences between the lagged coefficients for each model. Multivariable linear regression analyses were performed with SPSS version 24.0 (IBM Corp.), and the cross-lagged analyses were performed with Mplus, version 7.11 (Muthèn & Muthèn).

RESULTS

Non-imputed sample characteristics are presented in Table 4.1. Children had mostly a Dutch background (71.5%), and mothers had a median BMI of 23.9 (IQR= 5.1). At 10 years, emotional overeating, food responsiveness and enjoyment of food were cross-sectionally associated with BMI, FMI and FFMI SD scores (e.g. food responsiveness with FMI SD score: B= 0.31, 95%CI= 0.28, 0.33), whereas satiety responsiveness was negatively associated with these body composition measures (e.g. satiety responsiveness with FFMI: B= −0.27, 95%CI= −0.30, −0.24) (Table 4.2).

Next, longitudinal associations between eating behavior at age 4 years with BMI and body composition at 10 years were examined (Table 4.3). Adjusted for covariates and baseline BMI, emotional overeating at age 4 years was positively associated with a higher BMI and FMI 6 years later (e.g. B= 0.03, 95%CI= 0.00, 0.06). Food responsiveness was not associated with later BMI or body composition measures. Enjoyment of food showed a negative association with FMI (B=−0.03, 95%CI= −0.05, −0.00) and a positive association with FFMI (B=0.05, 95%CI= 0.02, 0.08) at 10 years. Satiety responsiveness predicted lower FFMI SD scores 6 years later (B= −0.08, 95%CI= −0.11, −0.05), but not BMI or FMI SD score.

Table 4.1. Descriptive characteristics of the study sample

Sample characteristics	Total n	No. (%), mean (SD) or median (IQR)[a]
Age at 10 years visit, mean (SD)	3331	9.8 (0.3)
Sex, No. % boys	3331	1622 (48.7)
Child ethnicity, No. %	3324	
Dutch		2377 (71.5)
Other Western		307 (9.2)
Non-Western		640 (19.2)
Birth weight in grams, mean (SD)	3329	3447.7 (566.4)
Birth weight for gestational age, mean (SD)	3317	−0.01 (1.01)
BMI at age 4 years, mean (SD)	2195	15.8 (1.3)
BMI at age 10 years, mean (SD)	3331	17.2 (2.4)
Maternal education level, No. %	3213	
Low (no education - high school)		332 (10.3)
Medium (Lower vocational education)		885 (27.5)
High (Higher vocational education and university)		1996 (62.1)
Maternal BMI, median (IQR)	3142	23.9 (5.1)
Maternal anxiety symptoms, median (IQR)[b]	3040	0.00 (0.17)
Household income, No. %	3037	
Low (<1600 euro per month)		268 (8.8)
Medium (1600-4000 euro per month)		1470 (48.4)
High (>4000 euro per month)		1299 (42.8)

[a] Values are percentages for categorical variables, means (standard deviations) for continuous normally distributed variables and medians (interquartile ranges) for continuous, non-normally distributed variables and all values are based on original data. [b] Maternal psychopathology symptoms were assessed with the Brief Symptom Inventory.
Abbreviations: BMI= Body Mass Index; IQR= Inter Quartile Range; SD= Standard Deviation.

Associations in the opposing direction, from BMI at 4 years and body composition at 6 years to eating behaviors at 10 years, are presented in Table 4.4. A higher BMI predicted more emotional overeating, food responsiveness and enjoyment of food, and less satiety responsiveness 6 years later, adjusted for covariates and baseline eating behavior (e.g. emotional overeating: B=0.09, 95%CI= 0.05, 0.12). The same pattern was also found for body composition measures at the age of 6 years and eating behaviors 4 years later. Adjusted for confounders and corresponding eating behaviors at 4 years (model 2), higher FMI and FFMI at 6 years were associated with more emotional overeating, food responsiveness and enjoyment of food, and less satiety responsiveness at 10 years (e.g. FMI with satiety responsiveness: B= −0.19, 95%CI= −0.23, −0.15). Overall, higher effect estimates

for FMI (i.e. food responsiveness: B=0.37, 95%CI= 0.32, 0.41) than for FFMI (B=0.17, 95%CI= 0.13, 0.20) were observed according to non-overlapping confidence intervals.

Results of the cross-lagged models are shown in Figure 4.1. Although the model fit indices, especially the CFI and TLI, were poor, the parameter estimates were very reasonable, suggesting that the models are consistent with the data.[31] Results indicated that, when accounting for cross-sectional associations and continuity over time, a higher BMI at age 4 predicted more food responsiveness and enjoyment of food and less satiety

Table 4.2. Cross-sectional associations between eating behaviors and body composition at the age of 10 years

CEBQ subscales (z-scores)	Body composition		
	BMI SD score B (95% CI)	FMI SD score B (95% CI)	FFMI SD score B (95% CI)
Emotional overeating	0.13 (0.10, 0.16)	0.12 (0.10, 0.15)	0.07 (0.04, 0.10)
Food responsiveness	0.35 (0.32, 0.38)	0.31 (0.28, 0.33)	0.23 (0.20, 0.26)
Enjoyment of food	0.21 (0.17, 0.24)	0.15 (0.12, 0.17)	0.17 (0.14, 0.20)
Satiety responsiveness	−0.28 (−0.31, −0.25)	−0.16 (−0.19, −0.13)	−0.27 (−0.30, −0.24)

Values are linear regression coefficients, the CEBQ subscales were transformed into z-scores. All values were significant at p <0.001. Analyses were adjusted for child ethnicity, birth weight for gestational age SD score, household income, maternal educational level, maternal BMI and maternal anxiety symptoms. N=3331.

Abbreviations: CEBQ: Child Eating Behavior Questionnaire; BMI: Body Mass Index; FMI: Fat Mass Index; FFMI: Fat Free Mass Index; SD score: Standard Deviation score.

Table 4.3. Longitudinal associations between eating behavior at 4 years and body composition at the age of 10 years

CEBQ subscales at age 4 years (z-scores)		Body composition at age 10 years		
		BMI SD score B (95% CI)	FMI SD score B (95% CI)	FFMI SD score B (95% CI)
Emotional overeating	Model 1	0.03 (0.00, 0.06)	0.03 (0.00, 0.06)*	0.01 (−0.03, 0.04)
	Model 2	0.03 (0.00, 0.06)*	0.03 (0.00, 0.06)*	0.01 (−0.02, 0.03)
Food responsiveness	Model 1	0.14 (0.10, 0.17)**	0.09 (0.06, 0.12)**	0.13 (0.10, 0.16)**
	Model 2	0.02 (−0.01, 0.05)	0.02 (−0.01, 0.04)	0.02 (−0.01, 0.05)
Enjoyment of food	Model 1	0.09 (0.06, 0.12)**	0.03 (0.00, 0.06)*	0.13 (0.10, 0.16)**
	Model 2	0.00 (−0.03, 0.03)	−0.03 (−0.05, −0.00)*	0.05 (0.02, 0.08)*
Satiety responsiveness	Model 1	−0.15 (−0.19, −0.12)**	−0.06 (−0.09, −0.03)**	−0.19 (−0.22, −0.16)**
	Model 2	−0.03 (−0.06, 0.00)	0.02 (−0.01, 0.05)	−0.08 (−0.11, −0.05)**

Values are linear regression coefficients. Model 1 was adjusted for child ethnicity, birth weight for gestational age SD score, household income, maternal educational level, maternal BMI and maternal anxiety symptoms. Model 2 was additionally adjusted for BMI at 4 years. N=3331. * represents p-value <0.05. ** represents p-value <0.001

Abbreviations: CEBQ: Child Eating Behavior Questionnaire; BMI: Body Mass Index; FMI: Fat Mass Index; FFMI: Fat Free Mass Index; SD score: Standard Deviation score.

Table 4.4. Longitudinal associations between body composition at 4 and 6 years and eating behavior at the age of 10 years

Body composition		CEBQ subscales at age 10 years (z-scores)			
		Emotional overeating B (95% CI)	Food responsiveness B (95% CI)	Enjoyment of food B (95% CI)	Satiety responsiveness B (95% CI)
At age 4 years					
BMI SD score	Model 1	0.09 (0.05, 0.12)**	0.23 (0.19, 0.28)**	0.17 (0.13, 0.21)**	−0.24 (−0.28, −0.20)**
	Model 2	0.09 (0.05, 0.12)**	0.15 (0.11, 0.19)**	0.09 (0.06, 0.13)**	−0.12 (−0.16, −0.08)**
At age 6 years (n=3097)					
FMI SD score	Model 1	0.17 (0.12, 0.21)**	0.45 (0.40, 0.49)**	0.23 (0.18, 0.27)**	−0.26 (−0.31, −0.22)**
	Model 2	0.16 (0.11, 0.20)**	0.37 (0.32, 0.41)**	0.17 (0.13, 0.21)**	−0.19 (−0.23, −0.15)**
FFMI SD score	Model 1	0.06 (0.02, 0.10)*	0.22 (0.19, 0.26)**	0.17 (0.13, 0.20)**	−0.28 (−0.32, −0.24)**
	Model 2	0.06 (0.03, 0.10)*	0.17 (0.13, 0.20)**	0.10 (0.06, 0.13)**	−0.17 (−0.21, −0.14)**

Values are linear regression coefficients. Model 1 was adjusted for child ethnicity, birth weight for gestational age SD score, household income, maternal educational level, maternal BMI and maternal anxiety symptoms. Model 2 was additionally adjusted for the corresponding eating behavior subscale at 4 years. N=3331, for the analyses with FMI and FFMI at age 6 years, n=3097. * represents p-value <0.05. ** represents p-value <0.001

Abbreviations: CEBQ: Child Eating Behavior Questionnaire; BMI: Body Mass Index; FMI: Fat Mass Index; FFMI: Fat Free Mass Index; SD score: Standard Deviation score.

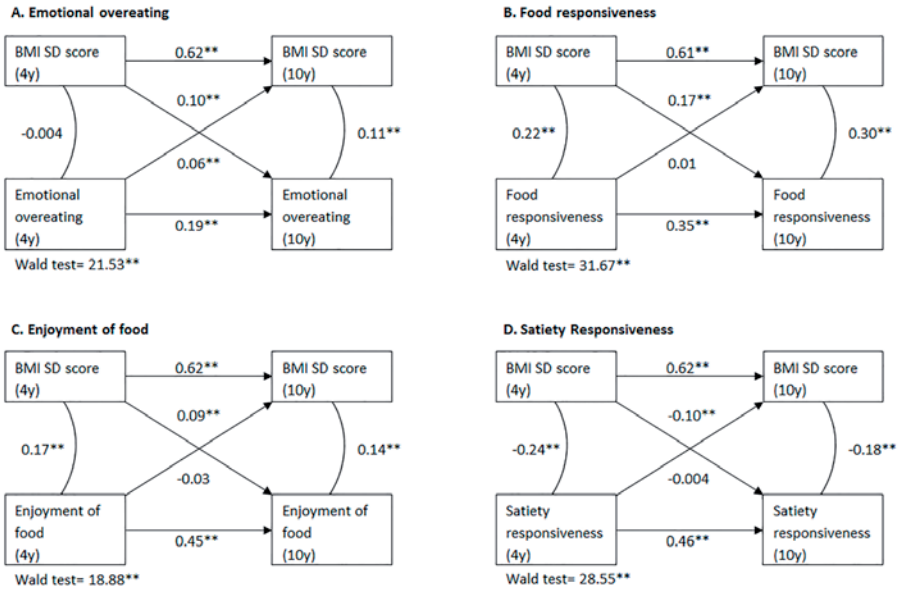

Figure 4.1. Cross-lagged models of BMI with emotional overeating (a), food responsiveness (b), enjoyment of food (c) and satiety responsiveness (d) across childhood, n = 3331. Values represent standardized linear regression coefficients (Betas). Models are adjusted for child ethnicity, birth weight for gestational age SD score, household income, maternal educational level, maternal BMI and maternal anxiety symptoms. Wald tests compare the paths from eating behavior at 4 years to BMI at 10 years versus BMI at 4 years to eating behavior at 10 years, for which a significant Wald test indicates a significantly stronger pathway. Fit indexes for each model were: Comparative Fit Index ≥0.790, Root Mean Square Error Of Approximation ≤0.083.
* represents p-value <0.05. ** represents p-value <0.001

responsiveness at 10 years (e.g. satiety responsiveness: β= −0.10, 95%CI= −0.14, −0.07). We found no associations in the opposite direction, from eating behavior to subsequent BMI. A higher BMI predicted subsequent emotional overeating (β=0.10, 95%CI= 0.06, 0.14) and higher levels of emotional overeating also predicted more weight gain over time (β=0.06, 95%CI= 0.03, 0.09). For all four eating behavior subscales, the pathway from BMI to eating behavior was stronger than the reversed, as indicated by significant Wald tests.

DISCUSSION

To the author's knowledge, this study was the first to test the directionality of the association between eating behavior and BMI across childhood by using a cross-lagged modeling approach. With this method, we showed that more food approaching and less food avoidant eating behaviors were mainly a consequence of a high BMI in childhood, rather than the reverse direction. For emotional overeating, a bi-directional relationship was found, indicating that emotional overeating was both a predictor and a consequence of a relatively high BMI. In line with our findings regarding BMI, we found no clear evidence for eating behaviors at 4 years predicting fat mass or fat free mass six years later, but instead, higher fat mass and fat free mass at the age of 6 years were both associated with subsequent eating behaviors. Although effect sizes were somewhat stronger for fat mass than for fat free mass, we did not observe distinct effects on eating behaviors. The findings of this study contradict our a priori hypothesis that more food approaching and less food avoidant eating behaviors would prospectively predict a higher BMI and fat mass.

Previous studies showed that eating behavior prospectively predicted weight gain (mostly by examining delta weight or BMI, e.g. BMI outcome - BMI baseline),[18-20,22,23] while we found limited evidence of a prospective association after adjusting for baseline BMI. Moreover, in the cross-lagged models, the effect estimates of food responsiveness, enjoyment of food and satiety responsiveness on BMI in later childhood were further attenuated. Our specific type of modelling might explain differences in conclusions between this study and other studies, as previous studies did not examine the bi-directional nature of eating behaviors and BMI in a cross-lagged model. Another possibility for the inconsistency in findings would be that most previous studies were conducted before 4 years of age, which is the baseline age of our study. Possibly, the association between eating behavior and weight gain differs across the childhood years, with infancy and early childhood reflecting a critical period for influences of appetite on weight development. Future studies with repeated measurements of eating behavior and BMI from early infancy to late childhood are needed to examine this hypothesis.

An important finding is that a higher BMI in the pre-school years predicted more food responsiveness and enjoyment of food, and less satiety responsiveness at the age of 10 years. Two previous studies also found an association in this direction, in infancy and mid-childhood.[22,23] Moreover, Steinsbekk et al.[21] showed that fat mass and muscle mass had distinct associations with specific eating behaviors over time: higher fat mass at 6 years and 8 years was only associated with more food responsiveness at 8 and 10 years, respectively, while in turn, higher muscle mass was only associated with less satiety responsiveness. This is partly replicated in our study; although we did not find distinct associations for fat mass and fat free mas, children with higher fat mass were more likely

to eat in response to external food cues, while those with higher fat free mass were more likely to eat even when they were full. Related literature also found evidence for a potentially causal relationship between BMI and other dimensions of eating behavior. A recent Mendelian randomization study showed that a higher BMI in childhood predicted more disordered eating such as binge eating in adolescence.[32] Our study adds to this previous work by showing that a higher BMI at 4 years of age already was associated with eating behaviors a few years later. The reported standardized effect sizes of the cross-lagged models were small, but comparable to those reported in previous studies on the relationship between BMI and subsequent eating behaviors.[22,23]

Biological mechanisms linking a high weight status and subsequent eating behaviors may potentially explain our findings. First, an increased BMI may up-regulate appetite through an increased energy-balanced set point at which the body tries to maintain the current weight status. Obesity can be considered as a condition of body energy regulation at an elevated set point, for which more energy intake is needed.[33,34] Secondly, overeating might be a result of decreased leptin sensitivity. The satiety-hormone leptin has an inhibitory effect on appetite regulation in healthy-weight individuals. However, in obese adults chronically elevated leptin levels are causing impaired leptin-signaling capacity in the hypothalamus, leading to leptin resistance.[35,36] Likewise, a strong positive correlation between leptin concentrations and fat mass has been observed in children with obesity.[37,38] Potentially, subclinical levels of excess weight might already affect children's leptin sensitivity, which consequently decreases satiety levels. Thirdly, dopamine – a neurotransmitter involved in food intake regulation by modulating food-reward sensitivity - might also play a role in unhealthy eating behavior among children with excess weight. In individuals with obesity, availability of dopamine receptors in the brain striatum is decreased, resulting in difficulty to obtain feelings of reward from food. As a result, more food is needed to obtain the same rewarding feeling.[39,40] To date, these hypothetical biological mechanisms have been examined primarily among obese adults, but it is unclear whether these mechanisms operate across the BMI range (from underweight to obesity) and if they play a role in childhood.

In our study, emotional overeating was bi-directionally associated with BMI across childhood. Remarkably, emotional overeating was not cross-sectionally associated with BMI at 4 years, and there was only a low correlation of emotional overeating over time. This suggests that variation in this trait is expressed with increasing age, probably due to more free access to foods, although it might also reflect a later recognition of parents. In line with this, Ashcroft et al.[41] also reported an increase in emotional overeating from age 4 years to 11 years. Furthermore, a British twin study showed that emotional overeating was explained mostly by environmental variance, rather than genetic influences. This suggests that overeating in response to negative emotions is a learned behavior, which might explain the increase in variation over time.[42] These findings suggest that a vicious

cycle may appear with emotional eating resulting in more food intake and weight gain, while in turn, excess weight may lead to overeating, e.g. due to higher body dissatisfaction.[43] This implies that targeting emotional overeating during childhood might be useful for obesity prevention.

Strengths and weaknesses

Strengths of this study were its prospective design including repeated measurements of eating behavior, BMI and body composition, and a large sample size. However, there are also some limitations. First, in-depth body composition measures of fat mass and fat-free mass were not available at the age of 4 years. This limits our conclusions regarding directionality between body composition and eating behavior. Second, no information on eating behavior was available before 4 years of age, while more food approaching and less food avoidant eating behaviors in infancy may precede a higher BMI at 4 years. Thirdly, eating behavior was only assessed using mother-reported questionnaires. Reports on child eating behavior can be sensitive to reporter-bias. However, we tried to minimize this bias by adjusting for several maternal characteristics in our analyses. While these covariates included in our analyses had only a minimal effect on the results, it cannot be completely ruled out that mother's attitudes affected her ratings. On the other hand, a validation study showed that parent-reported food responsiveness, satiety responsiveness and enjoyment of food were associated with a range of behavioral food intake tests, such as total energy intake and eating rates.[27] Emotional overeating was not examined in that study. Finally, generalizability may be limited, because the non-response analyses indicated that participants who were lost to follow-up in the Generation R study were more often from a non-Dutch background, lower household income and higher maternal BMI, which are risk factors for a higher BMI.[44, 45]

Conclusion

Although it is often assumed that unhealthy eating behavior is a risk factor for childhood obesity, our results do not support this. Instead, we found evidence for the reverse direction: a higher BMI –and particularly a higher fat mass - at pre-school age predicted more food approaching and less food avoidant behaviors at the age of 10 years. These findings suggest that children who are already on a high BMI trajectory at a young age develop more excess weight through an up-regulation in appetite. Thus, it may not be possible to prevent childhood obesity by targeting eating behaviors in middle childhood. Future studies covering infancy to adolescence are needed to replicate and explain our novel findings.

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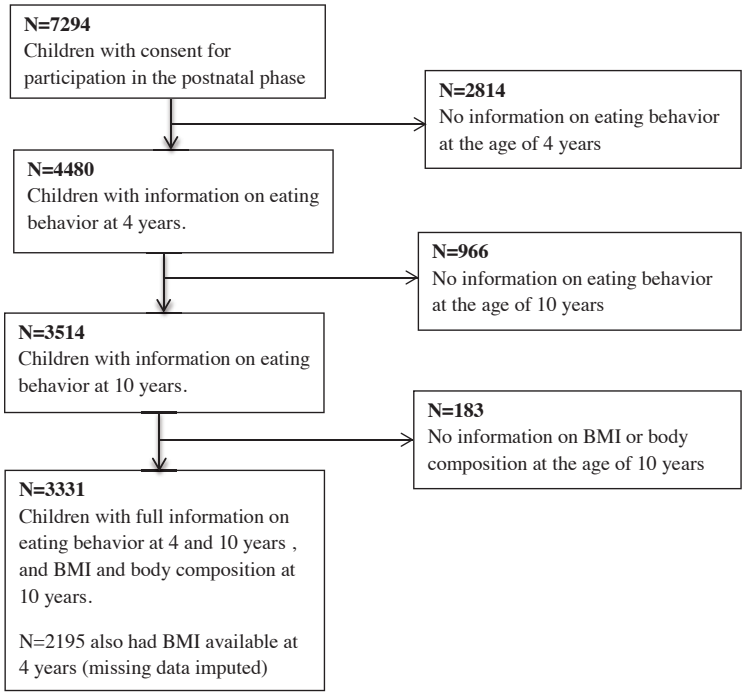
SUPPLEMENT



Supplementary Figure 4.1. Flowchart of the study sample

5

Longitudinal associations of sleep duration in infancy and early childhood with body composition and cardiometabolic health at the age of 6 years: The Generation R Study

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ABSTRACT

Background: A short sleep duration is associated with a higher obesity risk from mid-childhood onwards. However, whether sleep duration in early childhood is associated with body composition and cardiometabolic health remains unclear. This study aims to examine the prospective association of sleep duration in infancy and early childhood with body composition and cardiometabolic health at 6 years of age.

Methods: Data was available for 5161 children from a population-based cohort in the Netherlands. Sleep duration was assessed at ages 2, 6, 24, and 36 months by parental reports. When children were 6 years old, measures of body composition (iDXA), blood pressure, insulin and lipid levels were collected. Longitudinal associations between sleep duration, body composition and cardiometabolic health were studied with multivariable linear regression analyses. Additionally, potential bidirectional associations between sleep duration and BMI were studied by using cross-lagged modeling.

Results: Shorter sleep duration at 2 months predicted higher BMI and fat mass in 6-year-old children, accounting for confounders and BMI at 2 months (e.g. for BMI, per hour sleep, B= −0.018, 95% CI= −0.026; −0.009). No temporal relations between sleep duration at other ages, and later body composition and cardiometabolic outcomes were found. The cross-lagged model indicated a bidirectional associations between sleep duration and BMI in early life (2 to 6 months of age).

Conclusions: Shorter sleep duration at 2 months, but not at later ages, predicted poorer body composition 6 years later. We found no clear evidence for an effect of sleep duration in early life on cardiometabolic health.

INTRODUCTION

Obesity researchers have expanded their focus to a broad spectrum of potentially modifiable factors – including the role of sleep – in order to restrain the obesity epidemic.[1] An association between short sleep duration and overweight in children has been indicated by several reviews, including both cross-sectional studies[2,3] and longitudinal research.[4] However, most of these studies were performed in school-aged children, whereas the role of sleep duration at younger ages remains uncertain. Four longitudinal studies reported an association between shorter sleep duration in early childhood and higher BMI in mid-childhood,[5-8] whereas two studies found no association.[9,10] Furthermore, while it is suggested that sleep affects metabolism, reversed causality cannot be fully ruled-out yet, as it has hardly been examined. Another knowledge gap relates to the assumption that shorter sleep is associated with a higher BMI due to increases in fat mass.[11] However, only a few studies disentangled the different components of body composition. Taveras et al.[12] showed an association between sleep duration at 6 months and BMI and skinfold thickness at 3 years. Moreover, Carter et al.[13] observed a relation of sleep with fat mass but not fat free mass in children aged 3 to 7-years old, while Baird et al.[11] reported an association with both fat mass and fat free mass in children aged 3 to 4 years.

Recently, sleep duration has also been studied in the context of cardiometabolic risk factors other than obesity in children. Research showed an association between short sleep duration and increased glucose concentrations or reduced insulin sensitivity,[14-17] but this was not always replicated.[18] In addition, children who slept less had increased cholesterol concentrations,[18,19] but again, results were inconsistent and associations with triglycerides were not found.[17,20] Moreover, most studies had a cross-sectional design, making it difficult to infer a temporal relation.

Using data from a large population-based prospective study in the Netherlands, we examined the longitudinal association of sleep duration at four time points in infancy and early childhood (i.e. from 2 months until 36 months) with body composition and cardiometabolic health at the age of 6 years. Furthermore, the relation between sleep duration and BMI was studied during early childhood with cross-lagged modeling to determine directionality of the association.

METHODS

Study population

This study was embedded in Generation R, a population-based, prospective cohort from fetal life onwards.[21] All pregnant women with an expected delivery date between April 2002 and January 2006 living in Rotterdam, the Netherlands, were invited to participate

(participation rate: 61%). Written informed consent was obtained from all participants and the study was approved by the Medical Ethical Committee of the Erasmus Medical Center, Rotterdam.

Information on sleep duration at any time point was available for 6565 children (for 2220 children, sleep duration was available at all 4 time points). Of these children, 78,6% (n=5161) participated in the follow-up study at the research center where measurements on body composition and cardiometabolic outcomes were assessed. Blood samples were available in fewer participants reflecting lower consent rates for venous puncture (n=3495). In the analyses, the study population varied due to missing data on determinants or outcomes (Supplementary Figure 5.1).

Of the 6565 children with at least one assessment of sleep duration, 1404 children had missing data on all outcomes. These children (n=1404) were more often of non-Dutch origin ($p<0.001$) and had lower educated mothers ($p<0.001$).There were no differences in birth weight ($p=0.32$) or maternal BMI ($p=0.96$).

Measures

Sleep duration

Sleep duration was assessed by questionnaires filled out by the parents at 4 different time points during infancy and early childhood, i.e. when the children were 2 months, 6 months, 24 months and 36 months of age. Parents were asked to write down the usual bedtimes and wake times of their child at that moment. Daytime sleep was assessed categorically with answering options ranging between <30 minutes to >2.5 hours. For each time point, sleep duration was calculated as hours of sleep per 24 hours by adding nighttime and daytime sleep.

Body composition

At the age of 2, 6, 24, 36 and 48 months, child growth characteristics were obtained at the municipal Child Health Centers where trained staff measured children's height and weight by standard procedures. At the age of 6 years, children were invited to our research center for detailed measurements. Height and weight were measured without shoes and heavy clothing. Height was measured by a stadiometer (Holtain Limited, Crosswell, Crymych, UK) to the nearest 0.1 cm. Weight was measured to the nearest 0.1 kg using an electronic scale (Seca 888, Almere, The Netherlands). Body Mass Index (kg/m^2) standard deviation (SD) scores were calculated by adjusting BMI for age and sex of the child using the Dutch reference growth curves (http://www.growthanalyser.org).[22] Body composition was measured by a dual energy x ray absorptiometry (iDXA, GE-Lunar, 2008, Madison, WI). Children were positioned in horizontal position on the table without shoes, heavy clothing and metal objects. Fat Mass Index (FMI) was calculated as total fat mass/ length

(kg/m^2) and Fat Free Mass Index (FFMI) as total fat free mass/length (kg/m^2). FMI and FFMI were transformed into sex- and age-specific SD scores, calculated by internal standardization with the residual method in all participating children who had measures of body composition available.

Cardiometabolic health

At the age 6 years, systolic- and diastolic blood pressure were measured four times with one-minute intervals at the right brachial artery using the automatic sphygmomanometer Datascope Accutor Plus TM (Paramus, NJ, USA). While measuring blood pressure, children were lying supine. For each child, the mean value of the last three measurements was calculated to determine systolic and diastolic blood pressure. Thirty minute fasting blood samples were collected to measure total cholesterol, high density lipoprotein (HDL)-cholesterol, triglycerides, and insulin concentrations, using Cobas 8000 analyser (Roche, Almere, the Netherlands). Intra- and inter-assay coefficients of variation in quality control samples ranged from 0.77-1.39%, and 0.87-2.40%, respectively.

Covariates

Information on sex and birth weight of the children was obtained from medical records. Children's age at outcome assessment was derived from the date they visited the research center. Child ethnicity was based on country of birth of the parents which was assessed by prenatal questionnaire. In the same questionnaire, information on maternal educational level and maternal psychopathology symptoms were obtained. Maternal psychopathology symptoms were assessed during the first trimester of pregnancy with the Brief Symptom Inventory (BSI). The BSI is a validated 53-item questionnaire assessing a broad spectrum of psychopathology, including depression, somatization, anxiety, and psychotic symptoms.[23] Postnatal parental questionnaires were used to assess duration of breastfeeding (in months) and duration of television watching (in hours, at age 36 months). Height and weight measurements in early pregnancy (<14 weeks of pregnancy) were used to calculate maternal BMI.

Statistical analysis

Correlations between sleep duration and metabolic risk factors were tested using Pearson and Spearman-Rank correlation techniques. Associations between sleep duration at four different time points and body composition and cardiometabolic health at 6 years were examined by multiple linear regressions. Analyses were first adjusted for age and sex, and in a second step for confounders that changed the effect estimates by 5% or more. To examine the temporal relation, analyses with body composition were additionally adjusted for BMI at the age sleep duration was measured when model 2 was significant.

Baseline BMI was used as a proxy for FMI and FFMI, since FMI and FFMI were not measured before 6 years of age.

Finally, a cross-lagged modeling approach was used to examine the possible bidirectional association between sleep duration and BMI from infancy to 6 years of age. To establish this, we included all sleep duration time points (at age 2 months, 6 months, 24 months and 36 months) and BMI measurements at the same time points, as well as at age 48 months and 6 years in one model. First, wave-on-wave associations within each of the two key variables (stability paths) and cross-sectional relations between the sleep assessments and the BMI assessments were included in the model, with confounders regressed on the baseline assessments of sleep duration and BMI at 2 months of age. Next, we included lagged associations from each sleep duration assessment to all following waves of BMI assessments, and in the opposite direction, lagged associations from each BMI assessment to all following waves of sleep duration assessments. This way, the cross-lagged model estimates the relation between sleep duration and BMI in both directions over time, while accounting for the continuity of sleep duration and BMI over time and the cross-sectional associations at each time point.

Insulin and triglycerides were non-normally distributed and therefore square-root transformed. Standardized scores for cardiometabolic outcomes were used to improve comparability between effect estimates. Missing values of covariates ranged between 0.5% for birth weight and 22.8% for maternal psychopathology symptoms and were estimated using multiple imputation techniques. Pooled results of 20 imputed datasets were reported. All statistical analyses were performed using SPSS 21.0, except for the cross-lagged analysis, which was conducted in Mplus version 7.11.

RESULTS

Child and maternal characteristics are shown in Table 5.1. At the age of 2 months, children slept on average 14.7 hours (SD=3.0) per 24 hours. This decreased to a mean sleep duration of 12.6 hours (SD= 1.1) per day at age 36 months. Most children were of Dutch origin (62.4%) and most mothers were high educated, with higher vocational education or university (53.2%). Correlation coefficients between sleep, body composition and cardiometabolic outcomes are shown in Supplementary Table 5.1.

Table 5.2 presents the associations of sleep duration with body composition at 6 years of age. After adjustment for covariates, shorter sleep duration at 2, 24 and 36 months was associated with a higher BMI SD score at age 6 years (per hour sleep at 2 months, B= −0.015, 95% CI= −0.024; −0.007), but there was no association between sleep duration at 6 months and BMI SD score. Adjusted for BMI at the same age as sleep duration, only sleep duration at 2 months of age remained associated with a higher BMI at 6 years of

Table 5.1. Child and maternal characteristics

	N	Mean (SD) or %
Child characteristics		
Gender, boy, %	5161	49.7
Age, mean (SD)	5161	6.1 (0.4)
Ethnicity:		
Dutch, %	3185	62.4
Other Western, %	465	8.9
Non-Western, %	1464	28.7
Birth weight in grams, mean (SD)	5157	3426.2 (567.1)
Duration of breastfeeding in months, median (IQR)	4019	3.5 (5.5)
Hours of TV watching per day at 36 months, median (IQR)	4091	0.8 (0.9)
Average sleep duration in hours per day:		
At age 2 months, mean (SD)	3909	14.7 (3.0)
At age 6 months, mean (SD)	3293	15.0 (2.8)
At age 24 months, mean (SD)	4277	13.4 (1.1)
At age 36 months, mean (SD)	4178	12.6 (1.1)
Child outcomes at the age of 6 years:		
Body Mass Index (kg/m^2), mean (SD)	5161	16.1 (1.7)
Fat Mass Index (kg/m^2), mean (SD)	5004	4.0 (1.3)
Fat Free Mass Index (kg/m^2), mean (SD)	5004	11.9 (0.9)
Total cholesterol, mmol/L, mean (SD)	3482	4.2 (0.6)
HDL-cholesterol, mmol/L, mean (SD)	3483	1.3 (0.3)
Triglycerides, mmol/L, median (IQR)	3471	1.0 (0.6)
Insuline, pmol/L, median (IQR)	3457	112.3 (123.0)
Systolic blood pressure	4756	102.4 (8.1)
Diastolic blood pressure	4756	60.5 (6.8)
Maternal characteristics		
Maternal educational level:		
High (higher vocational education to university), %	2589	53.2
Medium (lower vocational education), %	1429	29.4
Low (no education to secondary school), %	847	17.4
Maternal BMI, median (IQR)	4618	23.7 (4.8)
Maternal psychopathology symptoms, median (IQR)	3982	0.2 (0.3)

Values represent means (Standard Deviations), medians (Interquartile Ranges) or percentage of subjects, derived from the unimputed dataset. FFMI, fat-free mass index; FMI, fat mass index; HDL, high-density lipoprotein; IQR, interquartile range; SD, standard deviation.

age (per hour sleep, B= −0.018, 95% CI= −0.026; −0.009). Adjusted for covariates, short sleep duration at 2 months was associated with higher fat mass at 6 years of age (per hour sleep, B= −0.012, 95% CI= −0.020; −0.003), whereas shorter sleep duration at 24 and 36 months was associated with a higher fat free mass. After including BMI at the same age of sleep duration in the model, shorter sleep duration at 2 months remained associated with higher fat mass at 6 years (per hour sleep, B= −0.013, 95% CI= −0.022; −0.044), but the associations of sleep duration at 24 months and 36 with fat free mass attenuated to non-significance.

Table 5.2. Associations of sleep duration at different time points with body composition at 6 years

Sleep duration (per hour)		**BMI SD score B (95% CI)**	**FMI SD score B (95% CI)**	**FFMI SD score B (95% CI)**
At 2 months	N	3909	3796	3796
	Model 1	−0.024 (−0.033; −0.015)***	−0.026 (−0.035; −0.016)***	−0.006 (−0.016; 0.004)
	Model 2	−0.015 (−0.024; −0.007)***	−0.012 (−0.020; −0.003)**	−0.007 (−0.017; 0.003)
	Model 3	−0.018 (−0.026; −0.009)***	−0.013 (−0.022; −0.004)**	NA
At 6 months	N	3293	3203	3203
	Model 1	−0.021 (−0.031; −0.010)***	−0.022 (−0.033; −0.012)***	−0.011 (−0.023; 0.000)
	Model 2	−0.008 (−0.018; 0.002)	−0.005 (−0.015; 0.005)	−0.010 (−0.022; 0.001)
	Model 3	NA	NA	NA
At 24 months	N	4277	4144	4144
	Model 1	−0.051 (−0.074; −0.027)***	−0.047 (−0.071; −0.023)***	−0.041 (−0.067; −0.014)**
	Model 2	−0.025 (−0.048; −0.002)*	−0.012 (−0.035; 0.011)	−0.036 (−0.062; −0.011)**
	Model 3	−0.008 (−0.027; 0.011)	NA	−0.019 (−0.042; 0.004)
At 36 months	N	4178	4055	4055
	Model 1	−0.043 (−0.066; −0.019)***	−0.012 (−0.035; 0.011)	−0.068 (−0.094; −0.043)***
	Model 2	−0.031 (−0.052; −0.009)**	−0.001 (−0.023; 0.020)	−0.058 (−0.083; −0.033)***
	Model 3	0.014 (−0.002; 0.031)	NA	−0.016 (−0.037; 0.005)

Values are linear regression coefficients (95% confidence intervals). Model 1 is unadjusted and model 2 is adjusted for ethnicity, birth weight, duration of television watching, duration of breastfeeding, maternal educational level, maternal BMI and maternal psychopathology symptoms. Model 3 is additionally adjusted for baseline BMI SD score, when Model 2 showed a significant association. NA= not applicable.
* p<0.05, ** p<0.01, *** p<0.001.
CI, confidence interval; NA, not applicable; FFMI, fat-free mass index; SD, standard deviation.

Figure 5.1 shows the significant pathways from the cross-lagged model. Both sleep duration and BMI showed moderate to high consistency between subsequent assessments. The longitudinal pathways indicated that a shorter sleep duration at age 2 months predicted a higher BMI at ages 6 months and 6 years. Reverse associations were also

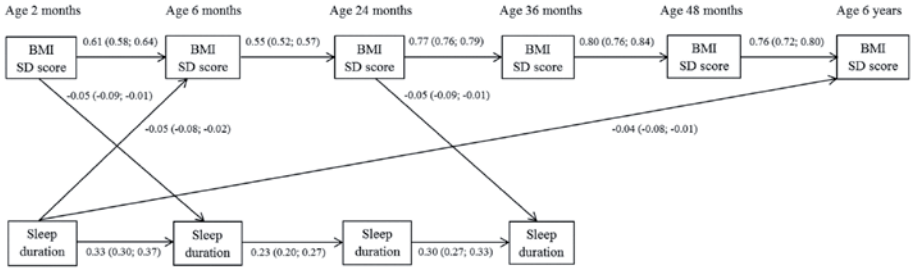

Figure 5.1. Cross-lagged model of associations between sleep duration and BMI (N= 5161). Values represent standardized linear regression coefficients (95% confidence intervals); only significant cross-lagged associations are depicted. Model fit indexes were considered as good (Comparative Fit Index: 0.867, Root Mean Squared Error of Approximation: 0.068). This model was adjusted for ethnicity, maternal education, maternal BMI, maternal psychiatric symptoms, birth weight, duration of breastfeeding, and TV watching.

found: a higher BMI at 2 months predicted shorter sleep duration at 6 months, and a higher BMI at 24 months predicted shorter sleep duration at 36 months.

Table 5.3 presents the associations between sleep duration and the different cardiometabolic health outcomes. Adjusted for covariates, sleep duration at 6 months was associated with higher HDL-cholesterol concentrations, while sleep duration at 2 months was inversely associated with systolic blood pressure (B= −0.013, 95% CI= −0.024; −0.003). This association disappeared after adjustment for BMI at age 6 years (B=−0.010, 95% CI= −0.020; 0.000; not tabulated). There were no significant associations between sleep duration at 24 months and 36 months and cardiometabolic risk factors at the age of 6 years.

DISCUSSION

Findings from this longitudinal population-based study suggest that a shorter sleep duration in infants as young as 2 months of age was associated with a higher BMI and higher fat mass 6 years later, with each hour less sleep predicting a 0.018 higher BMI SD score. Moreover, the cross-lagged model indicates a bidirectional relationship between sleep duration and BMI, starting already at 2 months of age. Sleep duration at later ages was not associated with body composition after adjusting for baseline BMI nor with cardiometabolic health at the age of 6 years.

This study is one of the first studies examining the prospective relation of sleep duration in infancy and early childhood with later body composition. Although our results initially showed that sleep duration at 3 time points was related to body composition, the effects of sleep duration of 24 months and 36 months on BMI and fat free mass attenuated

Table 5.3. Associations of sleep duration at different time points with cardiometabolic health outcomes at 6 years

Sleep duration (per hour)		Systolic blood pressure B (95% CI)	Diastolic blood pressure B (95% CI)	Total cholesterol B (95% CI)	HDL-cholesterol B (95% CI)	Triglycerides B (95% CI)	Insulin B (95% CI)
At 2 months	N	3611	3611	2623	2624	2618	2609
	Model 1	−0.018 (−0.028; −0.008)***	−0.014 (−0.024; −0.003)**	−0.011 (−0.024; 0.002)	0.003 (−0.009; 0.016)	0.005 (−0.008; 0.018)	0.004 (−0.009; 0.016)
	Model 2	−0.013 (−0.024; −0.003)*	−0.009 (−0.020; 0.002)	−0.009 (−0.022; 0.004)	0.008 (−0.005; 0.021)	0.002 (−0.011; 0.015)	0.000 (−0.013; 0.013)
At 6 months	N	3050	3050	2234	2234	2229	2222
	Model 1	−0.011 (−0.023; 0.002)	−0.010 (−0.023; 0.002)	−0.014 (−0.029; 0.001)	−0.021 (−0.036; −0.006)**	0.002 (−0.014; 0.017)	−0.001 (−0.015; 0.014)
	Model 2	−0.005 (−0.018; 0.007)	−0.005 (−0.017; 0.008)	−0.010 (−0.025; 0.005)	−0.016 (−0.031; −0.001)*	0.000 (−0.016; 0.015)	−0.003 (−0.018; 0.013)
At 24 months	N	3945	3945	2894	2896	2885	2874
	Model 1	−0.021 (−0.048; 0.007)	−0.015 (−0.042; 0.013)	−0.004 (−0.037; 0.029)	−0.004 (−0.038; 0.029)	0.004 (−0.029; 0.037)	0.025 (−0.009; 0.058)
	Model 2	−0.010 (−0.038; 0.018)	−0.003 (−0.032; 0.025)	0.003 (−0.031; 0.037)	0.006 (−0.029; 0.040)	−0.002 (−0.036; 0.032)	0.017 (−0.017; 0.052)
At 36 months	N	3845	3845	2821	2825	2812	2803
	Model 1	−0.019 (−0.046; 0.008)	−0.010 (−0.037; 0.018)	0.013 (−0.019; 0.045)	−0.015 (−0.047; 0.017)	0.010 (−0.022; 0.043)	−0.011(−0.043; 0.022)
	Model 2	−0.019 (−0.047; 0.008)	−0.011 (−0.039; 0.016)	0.011 (−0.021; 0.043)	−0.015 (−0.047; 0.017)	0.009 (−0.024; 0.041)	−0.013(−0.045; 0.019)

Values are linear regression coefficients (95% confidence intervals). All metabolic risk factors represent standardized scores. Model 1 is adjusted for sex and age and model 2 is additionally adjusted for ethnicity, birth weight, duration of television watching, duration of breastfeeding, maternal educational level, maternal BMI and maternal psychopathology symptoms. * $p<0.05$, ** $p<0.01$, *** $p<0.001$. CI, confidence interval; HDL, high-density lipoprotein.

after adjustment for BMI at the same age as sleep. This suggests that at these ages, there was no temporal association between sleep duration and body composition. This might be due to the BMI trajectory decline and rebound that occurs between 2 and 7 years of age.[24] However, the cross-lagged model shows that the association between sleep duration and BMI appears at 2 months towards 6 months and 6 years, but not at other ages. This might indicate that this association might continue over time conditionally on the baseline relationship, since BMI and sleep duration are both reasonably stable over time, without an additive effect of sleep duration at later ages. This finding is not consistent with some other studies that reported a relationship between sleep duration in early childhood and later BMI,[5-8] although two studies also found no association.[9,10] None of these studies, however, examined sleep duration as early as 2 months of age. Our study suggests that infant sleep is important, and might indicate a critical period for weight development with possible long-lasting effects. Therefore, this adds new evidence to previous research showing that from middle childhood onwards, sleep duration is a risk factor for obesity.[2-4]

Different pathways could explain the observed association between short sleep duration at 2 months, higher BMI and fat mass at 6 years of age. First, short sleep inevitably leads to having more time to eat, or at this age, to be fed by parents. Indeed, shorter-sleeping children consume more calories during the night.[25] Second, it has been proposed that shorter sleep duration disturbs appetite regulation. Studies found that shorter sleep is associated with reduced leptin and increased ghrelin levels, two crucial hormones in appetite regulation, resulting in increased appetite. Third, a short sleep duration may also influence other hormonal regulations related to metabolic disturbances, like a disturbed secretory profile of growth hormone and cortisol.[26] However, we found no support for this mechanism in children, given the lack of an association between sleep duration and insulin levels. Alternatively, both a relatively high BMI and poor sleep might be indicative of certain households characterized by a lack of regularity and unhealthy lifestyle habits.

Results from the cross-lagged model indicated that there might be a bidirectional relationship between sleep duration and BMI in early childhood, since we found an association in the opposite direction: higher BMI SD scores at the ages of 2 months and 24 months predicted shorter sleep duration at the ages of 6 months and 36 months, respectively. It has previously been reported that obese children sometimes suffer from sleep apnea, and therefore experience poor sleep.[27] However, this is unlikely for our finding given the young age of the children and the low prevalence of obese children in our sample. A more likely explanation is that infants with a higher BMI are perhaps less active, which might result in a decreased need for sleep. As stated above, other covariates characterized by unhealthy lifestyle habits might play a role in this association. However, these explanations are speculative and should be examined in future studies.

In this study, sleep duration in early childhood was not clearly associated with cardiometabolic risk factors in middle childhood. The observed association of shorter sleep

duration at 2 months with higher systolic blood pressure and of shorter sleep duration at 2 months with higher HDL-cholesterol must be interpreted cautiously, since they were not consistent and not reflected in diastolic blood pressure or other cholesterol concentrations. Our findings contrast with other studies reporting a relation between shorter sleep duration and a disturbed glucose homeostasis, insulin insensitivity and higher cholesterol profiles.[14-16,18,19] However, in line with our results, some of these studies reported that the sleep duration- cardiometabolic health association was not independent of child BMI, or was particularly evident in obese children.[14,17] This suggests that the cardiometabolic changes are a consequence of obesity, rather than a direct effect of short sleep duration. For instance, Cespedes et al.[28] found that chronic sleep curtailment in early childhood was related to a higher combined metabolic risk score in mid-childhood, but not after adjustment for BMI. This was also partly reflected in our results, since the association between sleep duration and systolic blood pressure was not independent of BMI.

Strengths of this study were the large number of children, the repeated assessments of sleep duration starting at 2 months after birth and the detailed measurements on cardiometabolic health. There are, however, also limitations that should be discussed. First, sleep duration was not objectively measured, but reported by parents in postal questionnaires. Parents tend to overestimate the sleep duration of their child.[19] Therefore, we tried to minimize this effect by asking parents to report the bedtimes and wake times, which previously showed good agreement with accelerometer-estimated sleep.[29] However, information on nighttime awakenings was lacking and only limited information on infant sleep during the day (categorical data only) was available. This source of imprecision might affect the infant sleep duration estimates, and ideally future studies would include more objective sleep measures in this age group. Moreover, sleep duration was not measured at the age of 6 years, when cross-sectional associations between sleep, body composition and cardiometabolic health at this age might have influenced our findings. Another limitation was the use of 30-minutes fasting blood samples instead of completely fasting blood samples, which might have reduced the accuracy of our measurements. It has previously been shown that non fasting lipid levels may change after food intake, although this change is only minimal.[30] Furthermore, we performed a large number of statistical tests, which may have led to false positive associations. However, applying a Bonferroni correction to our analyses based on 4 determinants and 4 grouped outcomes, namely body composition, blood pressure, lipids and insulin, did not change our conclusions. Finally, due to loss to follow-up, Generation R participants were relatively high educated and more often of Dutch origin, making generalizations more difficult.

Conclusion

Results from this prospective population-based study show that parent-reported shorter sleep duration as early as 2 months after birth may affect the child's body composition at the age of 6 years. Moreover, a bidirectional relationship between sleep duration and BMI was shown in infancy. Whereas effect estimates of these associations were rather small, these might reflect larger individual differences. Sleep duration in infancy is determined by intrinsic, biological factors as well as parental influences, such as bedtime interactions and soothing methods.[31] Therefore, staff members of baby well clinics and general practitioners should inform parents about the importance of healthy sleep routines for their infant. Future research should incorporate studies with repeated assessments of sleep duration, body composition and cardiometabolic health from birth until adulthood to monitor possible long-term effects.

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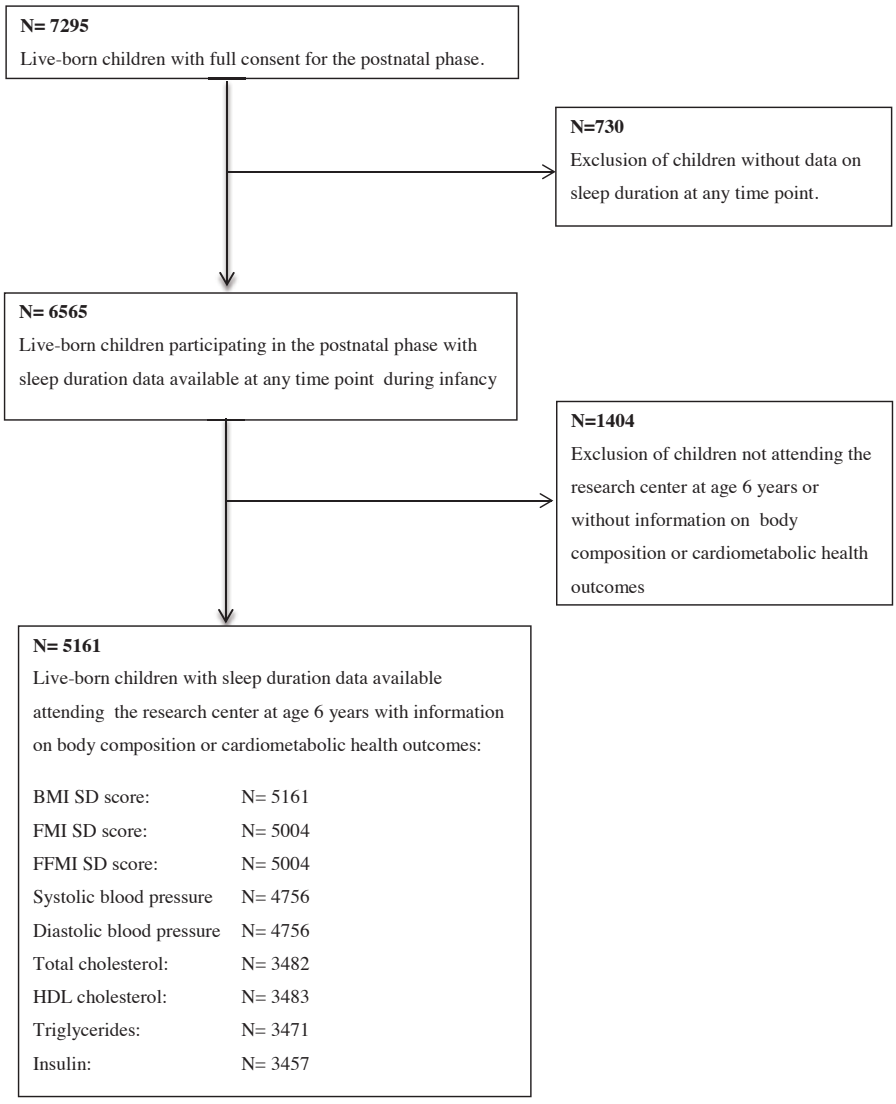
SUPPLEMENT

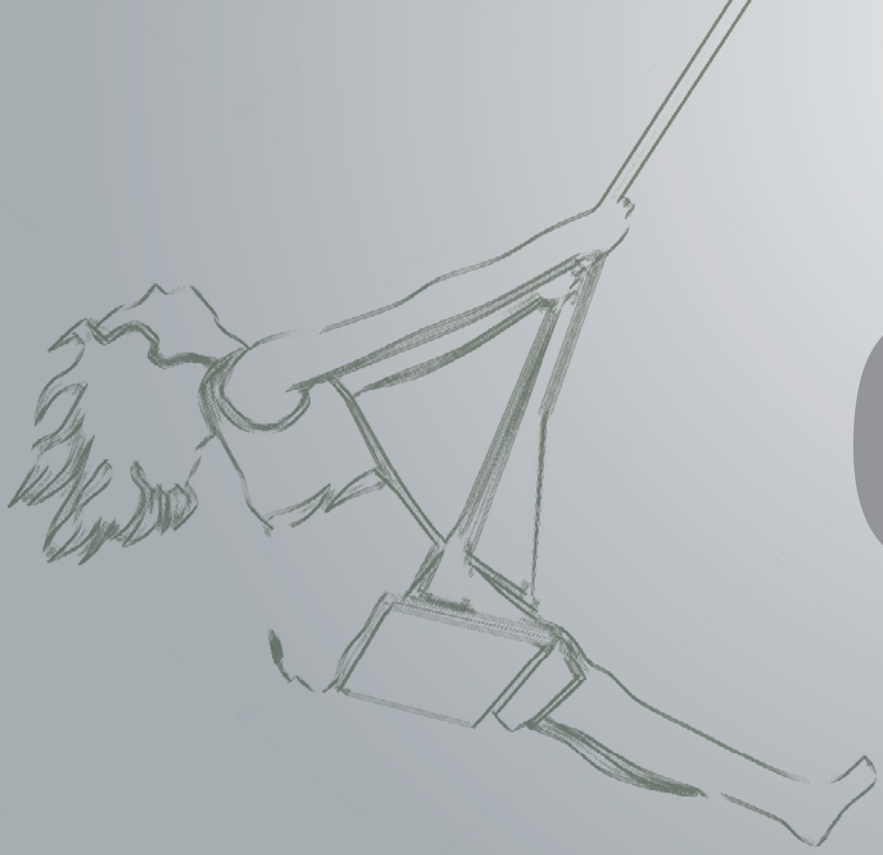


Supplementary Figure 5.1. Flowchart of the study population

Supplementary Table 5.1. Correlation coefficients between sleep duration at different time points and metabolic risk factors at the age of 6 years

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. Sleep duration at 2 months	1												
2. Sleep duration at 6 months	0.31*	1											
3. Sleep duration at 24 months	0.15*	0.22*	1										
4. Sleep duration at 36 months	0.08*	0.13*	0.30*	1									
5. BMI SD score	−0.08*	−0.07*	−0.06*	−0.06*	1								
6. FMI SD score	−0.09*	−0.07*	−0.06*	−0.02	0.82*	1							
7. FFMI SD score	−0.02	−0.03	−0.05*	−0.08*	0.73*	0.32*	1						
8. Systolic blood pressure	−0.06*	−0.03	−0.03	−0.03	0.23*	0.20*	0.13*	1					
9. Diastolic blood pressure	−0.05*	−0.03	−0.02	−0.02	0.07*	0.09*	−0.03	0.63*	1				
10. Total Cholesterol	−0.03	−0.04	−0.01	0.01	0.07*	0.09*	−0.01	0.07*	0.04	1			
11. HDL cholesterol	0.01	−0.06*	−0.01	−0.02	−0.03	−0.05*	−0.01	0.05*	0.03	0.29*	1		
12. Triglycerides	0.03	0.02	0.00	0.01	0.03	0.04*	0.03	−0.02	−0.03	0.15*	−0.39*	1	
13. Insulin	0.01	−0.01	0.03	−0.02	0.12*	0.09*	0.09*	0.06*	−0.03	−0.02	−0.06*	0.19*	1

Values represent Pearson correlation coefficients and Spearman rank correlation coefficients (triglycerides and insulin). * P-value<0.01.



6

Associations of infant sleep duration with body composition and cardiovascular health to mid-adolescence: The PEAS Kids Growth Study

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ABSTRACT

Background: Short sleep duration in childhood has often been linked with obesity in later childhood or adolescence. However, whether infant sleep duration affects body composition trajectories and cardiovascular health through to mid-adolescence remains unknown.

Methods: Participants were 336 adolescents from a community-based prospective birth cohort in Melbourne, Australia. Mothers completed 24-hour time diaries including infant sleep in 5-minute intervals at ages 2, 4 and 12 months. BMI and body composition outcomes were measured 6-monthly between 4 and 6.5 years and at 10 and 14 years. Cardiovascular outcomes at 14 years comprised blood pressure, pulse wave velocity, retinal arteriole-to-venule ratio and carotid intima-media thickness. We used multivariable linear regression and multinomial logistic regression analyses adjusted for sex, age, BMI at birth, gestational age, ethnicity, maternal education, maternal BMI and neighborhood socioeconomic position.

Results: At two months, infants slept on average 14.1 hours (SD 1.9), decreasing to 13.4 hours (SD 2.0) by 12 months. We observed no associations between the different sleep duration time points in infancy and later BMI or body composition. Moreover, a shorter sleep duration did not increase the odds of being on a high body composition trajectory compared to longer sleep (e.g. OR per hour of sleep at 4 months 0.85, 95% CI 0.65, 1.11). Infant sleep duration was also not associated with cardiovascular function or large or small artery structure at 14 years of age.

Conclusions: We found no evidence that sleep duration very early in life affects adolescent body composition or cardiovascular health.

INTRODUCTION

Links between short sleep duration and obesity have been extensively studied in children and adolescents.[1-3] A recent meta-analysis of prospective studies showed that short sleep duration increased the risk of later obesity by 45% in children and adolescents.[4] Mechanisms proposed to underlie a relationship between inadequate sleep and increased weight include an increased appetite, less physical activity due to tiredness, and parents possibly offering extra food when children are awake.[1,4,5]

Results of studies on sleep duration in very early life (i.e. infancy) on later weight development are, however, partially inconsistent. Several studies showed an association between short sleep in infancy and higher BMI up to 7 years of age,[6-12] while other studies found no association.[13,14] Chaput et al.[15] concluded in a systematic review that despite this negative association in most studies, the quality of evidence remained low. Studies generally used parent-estimated mean sleep duration per day, which is considered less accurate than prospective diary-reported sleep duration or sleep duration as measured with actigraphy.[16] Moreover, none of these studies have followed up beyond 7 years of age, so whether effects of short sleep duration in infancy on obesity development persist into late childhood or adolescence remains unknown.

Short sleep duration might also affect later cardiovascular health outcomes, potentially through central sympathetic mechanisms and inflammation[17] and/or the early cardiovascular health impacts of sleep-associated obesity itself. In children, the few papers that have examined relationships between sleep duration and cardiovascular health are mostly cross-sectional. A review of cross-sectional studies in children and adolescents from Matthews and Pantesco[18] and a follow-up review by Fobian et al.[19] showed that shorter sleep duration is often associated with higher blood pressure, while the only two longitudinal studies yielded mixed results. Furthermore, Navarro-Solera et al.[20] reported a cross-sectional relationship of short sleep with mean arterial pressure in children aged 7-16 years with obesity, but no studies have examined cardiovascular indicators other than blood pressure in a community sample.

The current study examined the prospective association of sleep duration, measured repeatedly across infancy by 24-hour sleep diaries, with BMI and body composition throughout childhood and with cardiovascular health in mid-adolescence in a community cohort of Australian children. Furthermore, we examined whether short sleep in infancy poses a risk for being on a high BMI or fat mass trajectory from childhood onwards. We expected that shorter sleep duration in infancy is associated with (trajectories of) higher BMI and fat mass and with adverse cardiovascular outcomes in mid-adolescence.

METHODS

Study design and participants

This study drew on data from the PEAS Kids Growth Study, which commenced as a prospective quasi-experimental study and followed-up as a prospective community-based cohort focused on growth and cardiovascular health in Australian children. Parents provided written consent at each phase of the study. At the age of 14 years, adolescents also gave written consent. The PEAS Study and the PEAS Kids Growth Study were approved by The Royal Children's Hospital Human Ethics Research Committee (HREC 28135).

Between June 1998 and February 2000, all first-time mothers were approached when their baby was aged 2 weeks in three local government areas of Melbourne (urban, suburban and semirural) to participate in the Parent Education and Support (PEAS) Study. This program was a non-randomized quasi-experimental trial, delivered through existing universal government-funded Maternal and Child Health (MCH) program visits. Both the intervention group and control group received routine visits available to all Melbourne babies throughout the first 2 years of life, namely at 2 weeks and at 2, 4, 8, 12, 18 and 24 months. Parents of the intervention group received additional advice on a wide range of common parenting problems, including cry-fuss behavior and sleep problems. At the 4 and 8 month scheduled visits, the intervention group discussed infant sleep with maternal and child health nurses who gave guidance notes on nighttime sleep routines and simple strategies to encourage good sleep patterns. Groups were similar in baseline and end-of-trial child health and behavior, including sleep, and were therefore followed-up as a combined cohort from the age of 4 years onwards in the PEAS Kids Growth Study.[21] Participating families still residing in Melbourne were invited for six follow up visits between 4.5 and 6 years, followed by visits at 10 and 14 years.

Originally, 493 mother-child dyads were recruited, of whom 469 children completed the PEAS Study at 24 months. At the age of 4 years, 402 mother-child dyads continued to participate in the PEAS Kids Growth Study. The final sample for the current study included those with at least one assessment of infant sleep duration and one outcome assessment later in childhood (4, 6 or 10 years) or early adolescence (14 years), in order to keep the study sample as large as possible (n=336). Of those, 276 children had sleep duration information available at all three assessments (82.1%). The study sample was smallest at the age of 14 years (n=195), due to participant withdrawal or loss to follow-up (Flowchart: Supplementary Figure 6.1).

Procedures and Measurements

During each wave, parents completed written questionnaires. Additionally, objective physical health measures were collected by MCH nurses from 2 weeks to 2 years (as part of their usual service), by trained researchers during home visits from 4 to 10 years, and

again by researchers at a clinic visit at Melbourne's Royal Children's Hospital or home visit at 14 years of age.

Infant sleep duration

Infant sleep duration at 2 months, 4 months and 12 months was measured with infant sleep/fuss diaries, originally developed by Barr et al.[22] At each age, parents completed a single 24-hour diary (from 8.00 am to 8.00 am) by reporting whether the infant was sleeping, being fed, awake/content or crying/fussing at each 5-minute interval over a 24-hour period.

BMI and body composition

Six-monthly between the ages of 4 and 6.5 years, and at 10 and 14 years, anthropometrics of the participants were measured during in-person visits in light clothing with bare feet. Height was measured twice in centimeters (recorded to the nearest 0.1 cm) using a portable rigid stadiometer (IP0955; Invicta; Leicester, UK). The mean of two height measurements was used unless these differed by >0.5cm, in which case height was measured a third time and the mean of three measurements was used. Weight was measured using a digital scale (4 to 6.5 years: Tanita TI-THD 646; 10 and 14 years Tanita BC-351, Tokyo Japan). BMI was calculated as kg/m^2 for each time point.

Body composition was measured unfasted using Bioelectrical Impedance Analysis (BIA). Measurements between 4 and 6.5 years utilized 4-limb multiple frequency bioelectrical impedance analysis (MFBIA; Bodystat QuadScan analyser; Bodystat Ltd; Isle of Man, United Kingdom). MFBIA was performed with the child lying still and adhesive electrodes applied to the right wrist, hand, foot and ankle. The Schaefer equation was used to calculate percent fat variables from the MFBIA output.[23] At 10 and 14 years, BIA was measured unfasted using portable 2-limb BIA scales (BC-351; Tanita, Japan). Percent fat is calculated by these scales using proprietary impedance equations not in the public domain. Fat mass (kg) was calculated as total weight (kg) × percent fat, while lean mass was calculated as total weight (kg) – fat mass (kg). Fat Mass Index (FMI) was calculated as fat mass (kg)/ height $(m)^2$, and Lean Mass Index (LMI) as all non-fat mass (kg)/ height $(m)^2$.

Cardiovascular function and structure outcomes

Cardiovascular function and structure outcomes were assessed during clinical assessments at Melbourne's Royal Children's Hospital or at home at the age of 14 years. Blood pressure and pulse wave velocity (PWV) were assessed using the Automated SphygmoCor XCEL device (AtCor Medical, NSW, Australia). Brachial systolic and diastolic blood pressure were measured three times to the nearest 1 mmHg, after the child had been lying down quietly for 2 minutes, with 1-minute breaks between measurements. Carotid-femoral PWV was then measured once to the nearest 0.1 m/sec. Pulse transit time (sec)

was determined by the SphygmoCor XCEL as the time between the bottom of the carotid and femoral pulse waveforms with corrections made for the femoral pulse wave being measured on the thigh. The SphygmoCor XCEL calculates PWV as distance (m)/ pulse transit time (sec).[24]

Equipment for macro- and micro-vascular structure outcomes was not available for the home visits and therefore only children who attended the clinic-based visit have these data available. Retinal arteriole-to-venule ratio (AVR) was measured from one of four retinal photographs taken with a digital nonmydriatic camera (CR-DGi with EDS 30D SLR camera back, CERA, Melbourne, Australia) and saved for later analysis. Retinal vascular caliber was measured from the right-eye retina-centered photo using the Interactive Vessel Analysis (IVAN) software which measures all microvessels in the half- to one-disk diameter from the optic disc.[25] The "big 6" methodology summarizes the largest six arterioles and the largest six venules as the Central Retinal Artery Equivalent (CRAE) and the Central Retinal Vein Equivalent (CRVE) respectively.[26] AVR was calculated as CRAE/CRVE. Carotid intima-media thickness (cIMT) was measured by Vivid i portable ultrasound with linear array probe for vascular ultrasound and ECG (Vivid i BT06, GE Healthcare, Buckinghamshire, UK). cIMT was measured 1 cm proximal to the carotid bulb at the R wave using automated Carotid Analyzer 6 program (MIA, Iowa). These methods have been reported in detail elsewhere.[27]

Covariates

Several potential confounders were identified *a priori*. At baseline, mothers reported child sex, date of birth, child place of birth (Australia versus other) and highest maternal level of completed education (did not complete high school, completed high school, completed tertiary education). Gestational age and BMI at birth were retrieved from the parent-held Child Health Record, completed at birth. Neighborhood socioeconomic status was based on the neighborhood disadvantage score (SEIFA Index of Relative Socioeconomic Disadvantage) for the residential postcode, derived from Australian census data; the Australian national mean is 1000 (SD 100), with lower scores reflecting more disadvantage.[28] Mothers reported their own height (cm), and weight was assessed at the 4-year visit, from which BMI was calculated as weight (kg)/ height $(m)^2$.

Statistical analyses

Body composition trajectories from 4 to 14 years of age

Body composition trajectories were identified for children with at least one cardiovascular outcome measured at 14 years. For each of the three separate body composition variables, latent class analysis (LCA) was used to assign children to their most likely trajectory class. Model fit parameters (Supplementary Table 6.1) were assessed to determine the

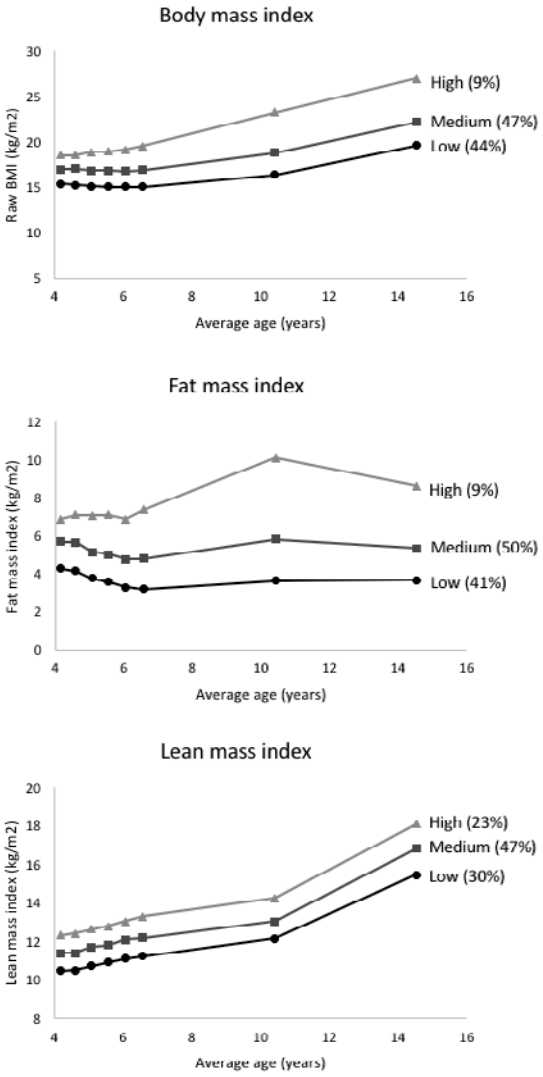

Figure 6.1. Trajectories of BMI, fat mass index and lean mass index as derived with Latent Class Analysis. Total n=194 for BMI trajectories, and n=193 for fat mass index and lean mass index trajectories.

optimal number of latent classes. Model fit parameters considered included the following information criteria; the model entropy, which we aimed to maximize; the sample size of the smallest trajectory category, which we aimed to keep above 10% of the total sample; the significance of the Vuong-Lo-Mendall-Rubin likelihood ratio test; and the interpretability of the resulting trajectories. Consideration of these factors resulted in a three-class solution for all three trajectory analyses i.e. *low*, *medium* or *high* BMI, FMI and LMI (Figure 6.1). Latent Class Analyses were performed with Mplus version 5.[29]

Associations of infant sleep duration with body composition and cardiovascular function and structure

To examine the relationship of sleep duration in infancy with body composition (ages 4, 6, 10 and 14 years) and cardiovascular phenotypic outcomes (age 14 years), multivariable linear regression analyses were conducted, adjusted for the above-mentioned covariates. Secondly, we examined whether sleep duration in infancy was associated with trajectories of BMI, FMI and LMI across childhood and adolescence (age 4 – 14 years), using multinomial logistic regression analysis adjusted for the covariates.

We checked for non-linearity by adding a quadratic term of sleep duration in the models with BMI. Further, we repeated our analyses with trajectories based on sex- and age adjusted BMI z-scores instead of raw BMI trajectories. To include as many cases as possible, missing data on confounders were estimated by multiple imputation techniques (fully conditional specification method). All study variables were included as predictors, and results are based on pooled results of 20 datasets. Analyses were performed with IBM SPSS version 24.

RESULTS

Sample characteristics are provided in Table 6.1. Most of the children included had an Australian background (87.9%), and mothers had a mean BMI of 24.6 (SD 4.7) at the 4-years visit. At the age of 2 months, children slept on average 14.1 hours (SD 1.9), and this decreased to 13.4 hours (SD 2.0) at 12 months of age. Mean BMI at 4 and 6 years was 16.5 kg/m^2 (SD 1.4) and 16.3 kg/m^2 (SD 1.6) respectively, increasing to 21.5 kg/m^2 (SD 3.5) at 14 years.

Table 6.2 shows associations between infant sleep duration at 2, 4 and 12 months and later outcomes. Overall, neither the point estimates nor the confidence intervals suggested associations between sleep duration in infancy and later BMI, body composition, or adolescent cardiovascular health indicators (systolic and diastolic blood pressure, PWV, cIMT and AVR).

None of the associations between infant sleep duration and body composition trajectories reached significance. With the low trajectory as the reference in each case, estimates were in the expected direction for all three infant sleep time points for the high BMI and high FMI trajectories, but in the opposite to expected direction for the medium BMI and FMI trajectories. For example, compared to those with shorter sleep durations, children with longer sleep duration tended to have a lower odds of being in the: a) high BMI trajectory (e.g. OR=0.86, 95% CI= 0.69, 1.06, per hour of sleep at 12 months) and b) high FMI trajectory (e.g. at 12 months: OR=0.91, 95% CI= 0.74, 1.12) while c) simultaneously having a higher odds of being in a trajectory with high LMI (e.g. at 2 months: OR= 1.30,

Table 6.1. Characteristics of the study sample.

Characteristics	Total Sample (n=336)	
	n	Value
Child characteristics		
Male sex (%)	166	49.4
Birth weight, kg (mean, SD)	322	3.5 (0.5)
BMI at birth (mean, SD)	313	13.7 (1.3)
Gestational age at birth (mean, SD), weeks	325	39.6 (1.6)
Place of birth (%)		
Australian	290	87.9
Other	40	12.1
Sleep duration at age 2 months (mean, SD)	317	14.1 (1.9)
Sleep duration at age 4 months (mean, SD)	306	14.1 (1.9)
Sleep duration at age 12 months (mean, SD)	312	13.4 (2.0)
BMI at age 4 years (mean, SD)	333	16.4 (1.4)
BMI at age 6 years (mean, SD)	315	16.3 (1.6)
BMI at age 10 years (mean, SD)	258	18.2 (2.7)
BMI at age 14 years (mean, SD)	195	21.5 (3.5)
Mother characteristics		
Education level (%)		
High school not completed	71	21.7
High school completed	121	37.0
Tertiary education completed	135	41.3
BMI (mean, SD)	320	24.6 (4.7)
Neighborhood socioeconomic status, SEIFA (median, IQR)	200	1051.9 (28.3)

Characteristics are based on original data. IQR= interquartile range, SD= standard deviation.

95% CI= 0.95, 1.75). We did not observe a quadratic relationship of infant sleep duration with subsequent BMI. Finally, analyses with trajectories based on BMI z-scores yielded similar findings: no associations were observed between sleep duration in infancy and trajectories of BMI z-scores.

DISCUSSION

Findings from this community-based Australian study showed that 24-hour diary-reported sleep duration at three different time points in infancy was not associated with body composition and cardiovascular function and structure up to mid-adolescence, despite a weak suggestion of relationships with the highest adiposity trajectories of BMI and FMI from 4 to 14 years.

Table 6.2. Associations of sleep duration in infancy with body composition and cardiovascular outcomes up to age 14 years

Outcomes	n	Adjusted regression coefficients (95% CI) by infant sleep duration in hours				
Body composition		**2 months**	**n**	**4 months**	**n**	**12 months**
BMI (kg/m^2)						
4 years	314	−0.04 (−0.12, 0.05)	304	−0.01 (−0.09, 0.06)	309	0.01 (−0.07, 0.08)
6 years	296	−0.04 (−0.13, 0.06)	289	0.04 (−0.05, 0.13)	292	−0.02 (−0.12, 0.09)
10 years	241	0.04 (−0.15, 0.22)	238	0.10 (−0.06, 0.27)	241	−0.06 (−0.24, 0.12)
14 years	182	0.15 (−0.12, 0.42)	185	0.09 (−0.18, 0.37)	183	−0.04 (−0.29, 0.22)
FMI (kg/m^2)						
4 years	302	−0.02 (−0.09, 0.06)	292	0.02 (−0.05, 0.09)	297	0.01 (−0.06, 0.08)
6 years	294	−0.02 (−0.10, 0.06)	287	0.03 (−0.05, 0.11)	290	0.00 (−0.09, 0.09)
10 years	239	0.01 (−0.16, 0.19)	236	0.05 (−0.11, 0.21)	239	−0.08 (−0.25, 0.09)
14 years	182	0.08 (−0.10, 0.27)	184	0.10 (−0.09, 0.29)	182	−0.04 (−0.21, 0.14)
LMI (kg/m^2)						
4 years	303	−0.02 (−0.07, 0.03)	293	−0.02 (−0.08, 0.03)	298	−0.01 (−0.05, 0.04)
6 years	294	−0.01 (−0.06, 0.04)	287	0.01 (−0.04, 0.06)	290	−0.02 (−0.07, 0.03)
10 years	239	0.02 (−0.05, 0.09)	236	0.04 (−0.02, 0.11)	239	0.02 (−0.05, 0.09)
14 years	182	0.07 (−0.04, 0.17)	184	0.01 (−0.11, 0.12)	182	0.01 (−0.10, 0.11)
Cardiovascular phenotype at age 14 years						
Systolic blood pressure (mmHg)	181	−0.15 (−0.87, 0.57)	184	0.04 (−0.69, 0.78)	182	0.28 (−0.40, 0.96)
Diastolic blood pressure (mmHg)	181	−0.32 (−0.81, 0.17)	184	0.27 (−0.24, 0.77)	182	−0.20 (−0.66, 0.26)
PWV (m/s)	172	0.05 (−0.01, 0.11)	176	0.06 (0.00, 0.12)	174	−0.02 (−0.07, 0.04)
AVR (ratio)	100	0.00 (−0.01, 0.01)	100	0.00 (−0.01, 0.01)	98	−0.00 (−0.01, 0.00)
cIMT (mm)	96	0.00 (−0.01, 0.01)	96	0.00 (−0.01, 0.01)	94	0.00 (−0.00, 0.01)

Table 6.2. Associations of sleep duration in infancy with body composition and cardiovascular outcomes up to age 14 years (*continued*)

Outcomes Body composition	n	Adjusted odds ratios (95% CI) by infant sleep duration in hours				
		2 months	n	4 months	n	12 months
Trajectories from 4 to 14 years						
BMI						
Low	81	(ref)	80	(ref)	79	(ref)
Medium	82	1.07 (0.88, 1.28)	86	1.05 (0.87, 1.27)	85	1.04 (0.87, 1.24)
High	17	0.93 (0.70, 1.25)	17	0.85 (0.65, 1.11)	17	0.86 (0.69, 1.06)
FMI						
Low	85	(ref)	88	(ref)	85	(ref)
Medium	78	1.09 (0.90, 1.31)	75	1.06 (0.88, 1.27)	77	1.07 (0.89, 1.28)
High	17	0.96 (0.71, 1.30)	19	0.95 (0.72, 1.24)	18	0.91 (0.74, 1.12)
LMI						
Low	71	(ref)	71	(ref)	72	(ref)
Medium	80	1.10 (0.90, 1.34)	81	1.14 (0.92, 1.40)	79	0.83 (0.69, 1.01)
High	29	1.30 (0.95, 1.75)	30	1.10 (0.78, 1.54)	29	0.92 (0.63, 1.32)

All models are adjusted for child sex, age at outcome visit (trajectories are not adjusted for age) ethnicity, BMI at birth, gestational age, maternal education, maternal BMI and neighborhood socioeconomic status. Abbreviations: FMI= Fat Mass Index, LMI= Lean Mass Index, cIMT= Carotid intima-media thickness, PWV = Carotid-femoral pulse wave velocity, AVR= retinal Arteriole-to-Venule Ratio.

It is recommended that infants until one year of age sleep 12 to 16 hours per 24 hours.[30] Variability in infant sleep duration can be explained by individual differences in sleep need, but can also be due to parents influencing the sleep-wake cycle, for instance by set bed times, bedtime routines and strategies used in response to night waking.[31,32] In our sample, there was considerable variability in sleep duration and on average 10% of our infants slept less than 12 hours per day, which is comparable to the prevalence of sleep problems during infancy.[33] Despite this variation, we did not observe that short sleep duration in infancy was associated with increased adiposity across childhood.

Results of this study do not align with the mounting number of papers linking sleep duration with BMI across the life course.[2,4,6,34] This may partly relate to the high quality of our infant sleep measure. Most studies have used global maternal reports of infant sleep duration, which typically overestimate actual daily sleep duration.[16] We used prospective, validated 24 hour time diaries recording sleep in 5-minute intervals, known to provide more precise estimations.[16] Although likely still less accurate than objective sleep measures, such as polysomnography or actigraphy, diaries are more feasible in larger community-based settings. In this study, parents had to report every 5 minutes what their infant was doing (sleeping, being fed, awake and cry/fuss) over a 24-hour period. The use of these diaries for assessing patterns of crying and fussiness was validated against audiotape recordings, and showed that diaries provide valid reports.[22] Although promising, such validation is lacking for sleep estimates. However, misclassification of sleep is only problematic if the degree of sleep overestimation differs between different groups of parents (e.g. by socioeconomic or ethnic background), as this may distort the association between child sleep and BMI. Secondly, it might be that infant sleep only affects weight development within early or mid-childhood (the follow-up window of previous studies). However, we did not observe a relationship of infant sleep duration with BMI and body composition at age 4 years nor with trajectories of BMI from 4 years onwards. Further, our findings are in line with randomized intervention trials focused on improving infant sleep. These studies reported no improvement of sleep duration, or no beneficial effect on the child's later BMI status,[35,36] or had only marginal impacts.[37,38]

Few infant sleep studies have distinguished between the outcomes of fat and lean mass, despite the assumption that short sleep is mainly obesogenic.[39] Sleep duration has been associated with a higher skinfold thickness at 3 years and fat mass levels at 6, 7 and 13 years, and an association with both fat mass and lean mass in children aged 3-4 years has also been reported.[7,8,12,39-41] We did not show prospective associations of sleep duration with any marker of body composition at 4, 6, 10 and 14 years, nor did shorter sleep duration have any meaningful effect on FMI or LMI trajectories across childhood.

We did not observe an association between infant sleep and adolescent structural and functional cardiovascular outcomes. To our knowledge, this study is the first to examine such relationships from infancy. Within the adult literature, those reporting a short sleep

duration had a higher risk of developing or dying from coronary heart disease (CHD) (48%) or stroke (15%) compared to adults with normal sleep duration.[42] Child and adolescent studies examining sleep duration and high blood pressure are conflicting.[18] For example, in a large Chinese population, short sleep duration was only associated with higher blood pressure in 11-14 year-old boys, but not in girls or children at other ages.[43] Prospective studies with sleep duration in infants are scarcer. One previous study reported that infant sleep duration at age 2 months (but not at later ages up to 36 months) was inversely associated with systolic blood pressure at 6 years.[12] Plumptre et al.[44] reported no association between sleep duration in children aged 12-36 months and systolic blood pressure in mid-childhood. Perhaps shorter sleep duration only at later ages alters cardiovascular health.

This study was strengthened by the repeated use of valid, prospective 5-minute interval diaries to report infant sleep duration, its 14-year follow-up, the ability to use body composition trajectories and detailed cardiovascular health outcomes at mid-adolescence. A necessary consequence of such precise and intensive assessments of sleep duration and health outcomes is a relatively small sample, reducing the power of the study to confirm small true associations. However, even though our confidence intervals were not narrow, the point estimates did not suggest any meaningful associations. The number of participants in the trajectory groups may have also reduced the power to detect associations between sleep duration and body composition trajectories. This emphasizes the need for replication in larger samples. Differential loss to follow-up in less privileged participants may affect the generalizability of the results. However, 336 (68%) of the original children could be included in analyses and both predictor and outcomes showed expected variability for a community sample, suggesting that the influence of selective follow up on our findings was minimal.

Conclusions

From this Australian prospective community-based study, we conclude that 24-hour, diary-assessed infant sleep duration was not associated with body composition or cardiovascular health from mid-childhood to mid-adolescence. Larger observational studies that accurately measure infant sleep (using actigraphy or sleep diaries) are needed to confirm whether shorter sleep duration is a risk factor for later adverse health outcomes or not. However, this study suggests that at most such effects would be small - if they exist at all. Therefore, it still seems premature to implement intervention programs that aim to increase infant sleep in order to prevent childhood obesity.

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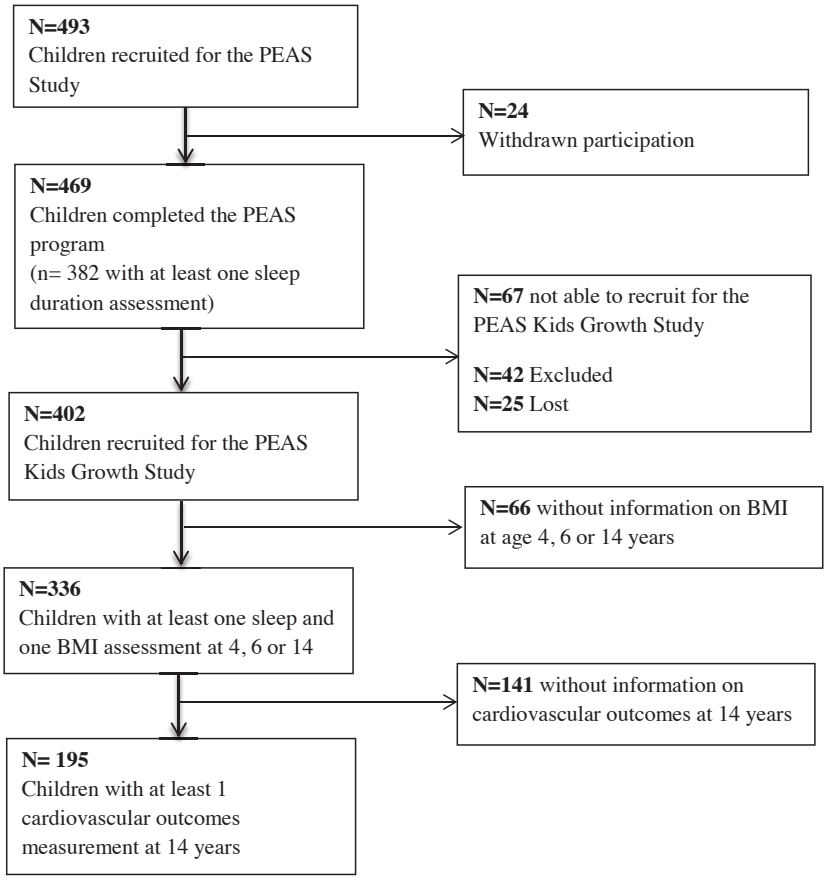
SUPPLEMENT



Supplementary Figure 6.1. Flowchart of the study sample

Supplementary Table 6.1. Model fit criteria used to identify optimal number of classes

Number of latent classes	AIC	BIC	Adjusted BIC	Entropy	VLMR likelihood ratio test	Size of smallest class, %
Body mass index trajectories						
2	5186.2	5268.2	5189.0	0.92	0.19	45.4
3	4702.0	4813.1	4705.4	0.96	0.23	9.3
4	4447.7	4588.2	4452.0	0.95	0.15	8.8
5	4260.4	4430.4	4265.6	0.96	0.35	1.0
Fat mass index trajectories						
2	4773.4	4855.0	4775.8	0.94	0.12	26.9
3	4299.1	4410.1	4302.4	0.97	0.15	8.8
4	4150.2	4290.5	4154.3	0.93	0.47	4.7
5	4031.3	4201.0	4036.2	0.94	0.35	1.0
Lean mass index trajectories						
2	3369.6	3451.2	3372.0	0.91	0.04	42.5
3	3033.4	3144.3	3036.6	0.91	0.26	22.8
4	2807.6	2947.9	2811.7	0.95	0.03	4.1
5	2709.7	2879.3	2714.6	0.92	0.20	4.1

AIC: Akaike's Information Criteria; BIC: Bayesian Information Criteria; VLMR: Vuong-Lo-Mendell-Rubin.

The model fit statistics (AIC, BIC, Adjusted BIC) decreased with the addition of extra classes (i.e. going from a 2-class model to a 3-class model steeply decreased the values for AIC, BIC, Adjusted BIC). All 3-, 4-, and 5-trajectory class models had an acceptable level of entropy (>0.90). The VLMR likelihood ratio test was statistically significant for the 4-class LMI model (p=0.03). All other models were not statistically significant.

We aimed for our smallest latent class to include approximately 10% of the sample to ensure maximize the power of subsequent analyses. The 4- and 5-class solutions for all models led to the identification of small latent classes; however, the 2-class solution (high, low) offered little novel interpretability. Therefore, we present a 3-class model solution for all latent class analyses. This weighs the need for sufficient class size to perform regression analyses, whilst optimizing model fit statistics, increasing entropy, and minimizing the VLMR LRT.

7

Testing bidirectional associations between childhood aggression and BMI: Results from three cohorts

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ABSTRACT

Objectives: We examined the prospective, potentially bi-directional, association of aggressive behavior with body mass index (BMI) and body composition across childhood in three population-based cohorts.

Methods: Repeated measures of aggression and BMI were available from the Generation R Study between 6 and 10 years (*N*=3,974), the Netherlands Twin Register between 7 and 10 years (NTR, *N*=10,328) and the Swedish Twin Study of Child and Adolescent Development between 9 and 14 years (TCHAD, *N*=1,462). In all samples aggression was assessed with the Child Behavior Checklist. Fat mass and fat-free mass were available in the Generation R Study. Associations were examined with cross-lagged modeling.

Results: Aggressive behavior at baseline was associated with higher BMI at follow-up in the Generation R Study (β=0.02, 95%CI 0.00;0.04) in NTR (β=0.04, 95%CI 0.02;0.06), and in TCHAD (β=0.03, 95%CI −0.02;0.07). Aggressive behavior was prospectively associated with higher fat mass (β=0.03, 95%CI 0.01;0.05), but not fat-free mass. There was no evidence that BMI or body composition preceded aggressive behavior.

Conclusions: More aggressive behavior was prospectively associated with higher BMI and fat mass. This suggests that aggression contributes to the obesity problem, and future research should study whether these behavioral pathways to childhood obesity are modifiable.

INTRODUCTION

Childhood obesity is a worldwide public health problem, with an increasing prevalence expected to reach 9% of children in 2020.[1] Although accumulating evidence suggests that children with overweight show more externalizing behavioral problems – e.g. aggressive, oppositional behaviors - than children with normal weight,[2,3] the directionality of the association between high Body Mass Index (BMI) and aggressive behavioral problems in childhood remains unclear.

Four longitudinal population-based studies have previously examined the potential bi-directional association between externalizing behavior problems – consisting of aggressive behavior and/or attention-deficit/hyperactivity (ADHD) problems[4] – and high BMI in childhood.[5-8] These studies yielded mixed results, raising questions about the directionality of effects. Two prospective studies reported that early externalizing behavior problems predicted higher BMI in early childhood[8] and early adolescence,[6] while no association between childhood BMI and subsequent increases in externalizing behavior was found. Conversely, two other prospective population-based studies observed no longitudinal associations between externalizing behavior and BMI in children aged 2 years at baseline and 12 years at follow-up,[5] or in toddlers aged 18 months at baseline and 36 months at follow-up.[7] These conflicting findings call for further investigations into the potential bi-directionality of this association. While it is well-known that ADHD poses a risk for developing obesity,[9] there is a particular need to elucidate the association between aggressive behavior and BMI in childhood. Aggressive behaviors are the most common reasons for referral to child and adolescent mental health services, and they are substantially predictive to poorer long-term functioning and high societal costs.[10] And although ADHD is often comorbid with aggression, no study has yet examined their independent prospective associations with BMI, which could provide further insight into the specific behavioral mechanisms of the development of obesity in childhood. Furthermore, previous studies have focused on BMI only, while adequately distinguishing fat mass from fat-free mass may benefit determining specificity of associations.[11]

The aim of the current study was to examine the prospective, potentially bi-directional, associations between aggressive behavior and BMI across childhood. Insights obtained from this study will contribute to a better understanding of the behavioral – and potentially modifiable – pathways to obesity risk in childhood. Here, we assessed the direction of association between aggressive behavior and BMI in three large population-based cohorts from early childhood (ages 6-7 to 10 years) to early adolescence (ages 9 to 14 years). Furthermore, in one cohort we also assessed the directionality of associations of aggressive behavior with fat mass and lean mass in order to examine more in-depth weight-related obesity indicators. Sensitivity analyses were conducted with additional adjustment for co-occurring attention, social, and internalizing problems at baseline.

We hypothesized that aggressive behavior would be associated with higher BMI and fat mass at later ages rather than vice versa, as behavioral inhibition deficits associated with aggression might increase the risk for unhealthy life styles and, therefore, higher BMI.[12]

METHODS

Study design and Population

Three population-based cohort samples were included in the current study that collaborate under the European Union Seventh Framework Program–Aggression in Children: Unravelling Gene-Environment Interplay to Inform Treatment and Intervention Strategies consortium.[13] First, primary analyses were conducted in the Generation R Study, a prospective cohort from fetal life onwards in Rotterdam, The Netherlands. The study has been designed to investigate early environmental and genetic pathways leading to normal and abnormal growth, development and health.[14] The study was approved by the Medical Ethical Committee of the Erasmus Medical Center, Rotterdam. For the current study, children with data on BMI, body composition, and aggressive behavior at both ages 6 and 10 years were included, resulting in a study sample of 3,974 children.

Independent replication of the relationship between BMI and aggressive behavior was performed in the Netherlands Twin Register (NTR; *n*=10,328, assessed at ages 7 and 10 years)[15,16] and the Swedish Twin Study of Child and Adolescent Development (TCHAD; *n*=1,462, assessed at ages 9 and 14 years)[17]. Both twin cohorts are designed to investigate the genetic and environmental effects on children's cognitive functioning, health, and emotional and behavioral problems during development. For the current analyses, both twins from each twin pair were included in the analyses, and these analyses were adjusted for family relatedness. Written informed consent and assent was obtained for all participants from all cohorts. Previous research in both twin cohorts has shown higher twin correlations for aggressive behavior in monozygotic (range, r = 0.48-0.84) versus dizygotic (range, r = 0.35-0.78) twins,[18,19] indicating moderate-to-high twin heritability. Similarly, the twin heritability for BMI has been estimated to be moderately high in childhood.[20]

Measurements

Aggressive behavior

The subscale Aggressive behavior of the Child Behavior Checklist (CBCL) was employed in all three studies. The CBCL was completed by the mothers and rated on a three-point Likert scale (0=not true, 1=somewhat true, sometimes true, 2=very true, often true). The CBCL is a reliable, valid measurement of emotional and behavior problems,[21] including

affective, anxiety, attention and aggression problems, and generalizable across societies worldwide.[22] Moreover, the CBCL has been shown to be a valid screening instrument for *Diagnostic and Statistical Manual of Mental Disorders,4th Edition* externalizing disorders.[23] In the Generation R Study, the CBCL/1.5-5 was used to measure aggressive behavior at mean age 6 years.[24] This version of the CBCL was chosen as it was expected most children would be younger than 6 years at assessment. Indeed, 57.4% of the children were 5 years old at the assessment wave, the remainder were 6 years (37.7%) or 7 years or older (4.9%), and we used the CBCL 1½–5 version for all children during this assessment wave to enhance comparability across all children, as recommended in the Achenbach System of Empirically Based Assessment manual.[24] The items of the aggressive behavior problems scale largely overlap with the CBCL/6-18 (e.g. "physically attacks" and "stubborn, sullen or irritable"). Earlier work from the Generation R Study has demonstrated that the internal consistency (Cronbach alpha) was similar for all syndrome scales for children aged 5 years versus children older than 5 years,[25] indicating that the CBCL/1.5-5 assesses aggressive behavior problems similarly in 5-year-old children and 6-7-year-old children. At the age of 10 years, aggressive behavior was measured with the CBCL/6-18, which was also used in the NTR cohort at both waves. In the TCHAD sample, the CBCL/4-18, which is an earlier version of the CBCL but with identical items that assess aggressive behavior problems, was used to assess aggressive behavior.

Child BMI and body composition

At the age of 6 and 10 years, child weight and height were measured at the Generation R research center. The obtained BMI (kg/m^2) was standardized into Body Mass Index Standard Deviation Scores (BMI-SDS) by correcting for sex and age, using the Dutch national reference in the Growth Analyzer program (http://www.growthanalyser.org). In the NTR and TCHAD cohorts, height (m) and weight (kg) data were based on mother-reports, which were used to calculate BMI.

In the Generation R Study, body composition at both ages was measured with Dual-energy X-ray absorptiometry (DXA) scanner (iDXA, GE-Lunar, 2008, Madison, WI, USA). Fat Mass Index (FMI) and Fat-Free Mass Index (FFMI) were converted into sex- and age-adjusted standardized scores.

Covariates

Based on prior studies,[2,3] the following sociodemographic covariates were included in the analyses. With respect to Generation R, sex and birth weight were determined using data from medical records. Maternal age, maternal education and ethnicity of the child were assessed using questionnaires. Ethnicity of the child was categorized as Western and non-Western national origin. Highest attained maternal educational level was categorized into low, medium and high educational level. Maternal psychopathology symptoms

were determined through a self-reported questionnaire using the reliable and validated Brief Symptom Inventory (BSI),[26] which includes 53 items encompassing a spectrum of psychiatric symptoms, comprising all subscales such as depression, anxiety and hostility. Maternal BMI was measured at the research center when children were 6 years old.

In the NTR and TCHAD samples, similar covariates were available for adjustment of the models, namely gender, age at baseline, ethnicity of the child, birth weight, maternal educational level, maternal BMI (NTR only), and gestational age (NTR only). These data were derived from parent-reported questionnaires.

Statistical analyses

Cross-lagged structural equation modeling in Mplus 7.0 was used to examine the bi-directional relation between aggressive behavior and BMI/body composition over time. The cross-lagged model consisted of stability paths across two consecutive time points for each variable, cross-sectional paths between aggressive behavior and BMI, and cross-lagged paths between behavior and BMI over two time-points. The cross-lagged paths indicated the extent to which aggressive behavior or BMI/body composition at time point 1 predicted scores on the other measure at time point 2, while accounting for stability and cross-sectional paths. In all three cohorts, separate sensitivity analyses were conducted with additional adjustment for attention problems, internalizing problems and both at baseline. Social problems are not assessed with the CBCL/1.5-5 and, therefore, sensitivity analyses with additional adjustment for social problems at baseline were only performed in the NTR and TCHAD cohorts. Furthermore, we repeated our analyses in the Generation R Study after excluding all twin participants (n=114) to ensure there was no overlap between this sample and NTR. Finally, to increase the interpretability of results, the cross-lagged model of aggression with BMI in the Generation R study was repeated using weight status categories (underweight/normal weight vs. overweight/obese) instead of BMI continuously at 6 and 10 years. For the twin cohorts, the 'complex option' of Mplus (clustering corrected robust maximum likelihood estimation) was used to take family dependency of the observations into account. To determine the model fit, Root Mean Square Error of Approximation (RMSEA≤0.08), Comparative Fit Index (CFI≥0.95), and Tucker Lewis Index (TLI≥0.95) were used as indices to determine good model fit.[27] In all samples, Full Information Maximum Likelihood was used to account for missing data. Standardized estimates are presented throughout.

RESULTS

Study sample demographics

The baseline characteristics of the three samples were comparable (Table 7.1). Of note, the Generation R Study included more children with a non-Western ethnic background than

the replication samples, reflecting the urban population base of the former. As expected, averages for gestational age and birth weight were lower for the twin cohorts than in the Generation R Study.

Bi-directional association of aggressive behavior with BMI

Figure 7.1 shows the results of the cross-lagged model of aggressive behavior and BMI in the three cohorts. In the Generation R Study, BMI was highly stable over time (β=0.80, 95%CI 0.79-0.81), while aggressive behavior was moderately stable across the two time points (β=0.56, 95%CI 0.54-0.59). No cross-sectional associations were observed between aggressive behavior and BMI. With regards to the longitudinal relationships, aggressive behavior at age 6 years was associated with higher BMI at age 10 years (β=0.02, 95%CI 0.00-0.04). No such association was observed in the opposite direction, i.e. BMI at 6 years was not predictive of subsequent increases or decreases in aggressive behavior problems at 10 years. In the NTR sample, aggressive behavior was associated with BMI at both time points in cross sectional analysis (β=0.03, 95%CI 0.01-0.06 and β=0.03, 95%CI 0.01-0.05, respectively). Even following adjustment for this cross-sectional relationship, aggressive behavior at 7 years was prospectively associated with subsequent higher BMI at 10 years (β=0.04, 95%CI 0.02-0.06), but, conversely, BMI at 7 years was not associated with subsequent more aggressive behavior at age 10 years. With respect to the TCHAD sample, no cross-sectional association between aggressive behavior and BMI was observed at age 10 years; this association was only observed at age 14 years (β = 0.06, 95% CI: 0.01 to 0.11). Prospectively, aggressive behavior at 10 years was not significantly associated with subsequent higher BMI at age 14 years, although the effect estimate had a magnitude

(β = 0.03, 95% CI: −0.02 to 0.07) similar to those in the other two cohorts. An association in the reversed direction was not observed. Fit statistics of the cross-lagged models indicated good model fit in all three samples.

Bi-directional association of aggressive behavior with fat mass and fat-free mass

In the Generation R Study, aggressive behavior at 6 years was associated with a subsequent higher fat mass index at 10 years (Figure 7.2, β=0.03, 95%CI 0.01-0.05). Again, this association was not seen in the opposite direction. No associations were observed between aggressive behavior and fat-free mass index in either direction. Fit indices for the cross-lagged models pertaining to body composition both indicated good model fit.

Sensitivity analyses

Further analyses with additional adjustment for co-occurring attention problems, internalizing problems, or both yielded similar results as the main findings (Supplementary Figure 7.1-7.6). This was the case for the analyses pertaining to BMI, fat mass index as well as fat-free mass index. Similarly, analyses in NTR and TCHAD with additional adjustment for

Table 7.1. Demographic characteristics of the included study populations

	Generation R (*n* = 3,974)		NTR (*n* = 10,328)		TCHAD (*n* =1,462)	
	6 years	**10 years**	**7 years**	**10 years**	**9 years**	**14 years**
Child characteristics						
Sex, % female	50.4		51.2		51.6	
Age, y, mean (SD)	6.08 (0.40)	9.75 (0.28)	7.42 (0.40)	10.05 (0.37)	8.67 (0.47)	13.67 (0.47)
Ethnicity, %						
Dutch/Swedisch	67.0		94.3		92.2	
Other Western	8.8		2.9		5.9	
Other Non-Western	24.2		2.9		1.9	
Birth weight, gram, mean (SD)	3425.83 (567.20)		2508.97 (536.97)		2615.75 (526.39)	
Gestational age, mean (SD)	39.80 (1.85)		36.73 (2.47)		N/A	
BMI, kg/m^2, mean (SD)	15.99 (1.62)	17.34 (2.52)	15.35 (1.73)	16.40 (2.16)	16.25 (2.06)	19.06 (2.74)
FMI, kg/m^2, mean (SD)	3.89 (1.20)	4.68 (1.91)	N/A	N/A	N/A	N/A
FFMI, kg/m^2, mean (SD)	11.93 (0.89)	12.55 (1.05)	N/A	N/A	N/A	N/A
Aggressive behavior score, median (IQR)	4.00 (6.00)	2.00 (4.00)	4.00 (6.00)	3.00 (5.00)	3.00 (6.00)	2.00 (5.00)
Maternal characteristics						
Age mother at baseline, mean (SD)	37.98 (4.50)		N/A		N/A	
BMI mother, (kg/m^2), mean (SD)	25.27 (4.67)		23.59 (3.66)		N/A	
Maternal psychopathology symptoms, median (IQR)	0.10 (0.19)		N/A		N/A	
Maternal educational level, %						
Low	8.9		2.6		10.6	
Medium	29.2		51.2		56.1	
High	61.6		46.2		33.3	

Values are based on original, unimputed data. Abbreviations, SD: standard deviation; IQR: interquartile range; BMI: body mass index; FMI: fat mass index; FFMI: fat-free mass index, N/A: not applicable. Missingness was highest for maternal psychopathology symptoms in Generation (24.3%), for maternal BMI in NTR (22.6%) and for ethnicity in TCHAD (7.5%).

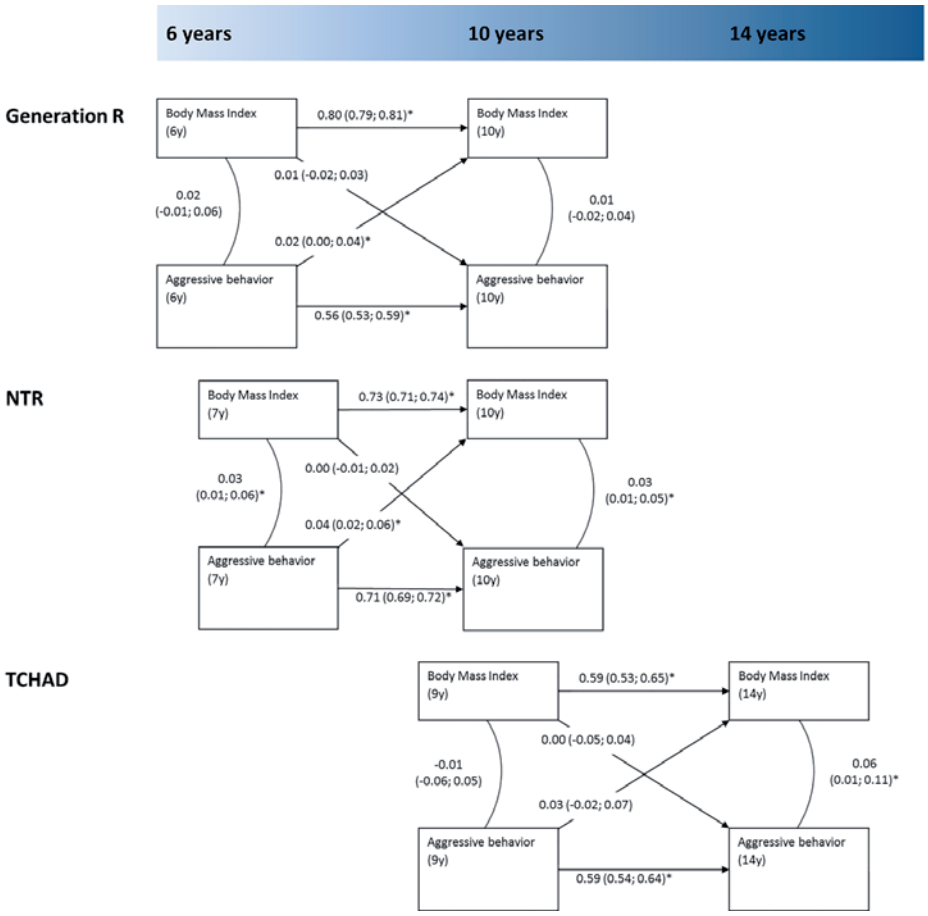

Figure 7.1. Cross-lagged association model for the association between aggressive behavior and body mass index in three population-based samples across childhood. Estimates denote standardized β coefficients. All models were adjusted for sample-specific covariates. Fit indices: Generation R sample (N =3,974), Root Mean Square Error of Approximation (RMSEA) = 0.06, Comparative Fit Index (CFI) = 0.95, and Tucker Lewis Index (TLI) = 0.90; NTR sample (N = 10,328), RMSEA = 0.03, CFI = 0.98, and TLI = 0.95; TCHAD sample (N = 1,462), RMSEA = 0.02, CFI = 0.99, and TLI = 1.00. * Significant at P < 0.05; numbers in between brackets denote 95% confidence intervals.

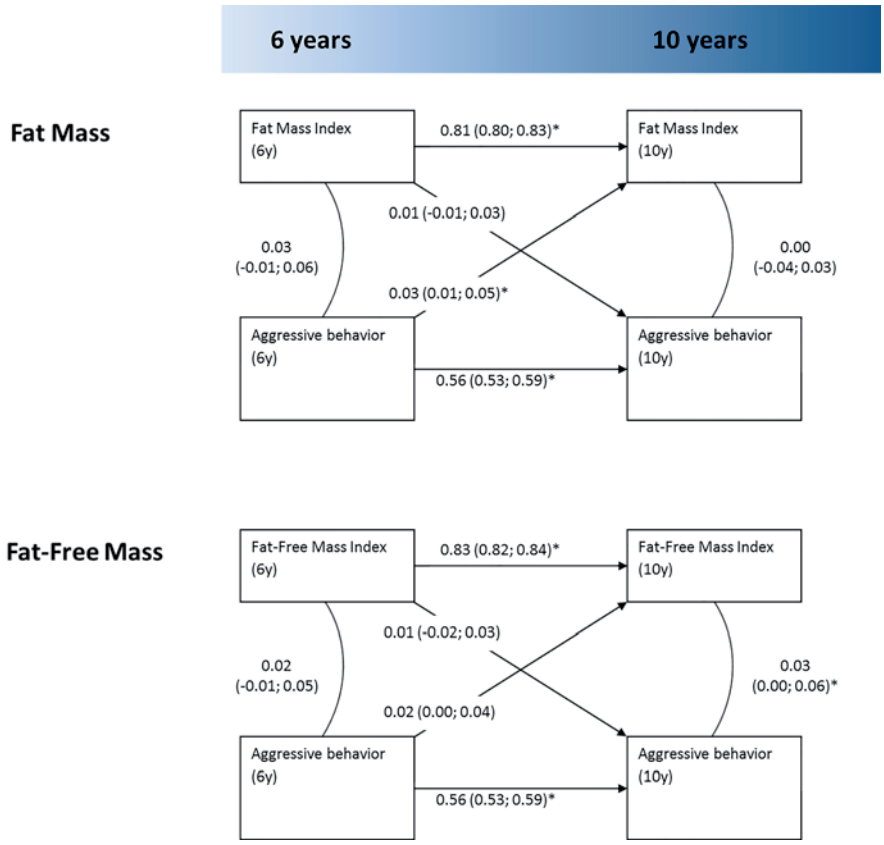

Figure 7.2. Cross-lagged association model for the association of aggressive behavior with fat mass and fat-free mass in the Generation R sample (N = 3,974). Estimates denote standardized β coefficients. All models were adjusted for sample-specific covariates Fit indices: fatt mass, Root Mean Square Error of Approximation (RMSEA) = 0.07, Comparative Fit Index (CFI) = 0.94, and Tucker Lewis Index (TLI) = 0.86; fat-free mass, RMSEA = 0.05, CFI = 0.96, and TLI = 0.92. * Significant at $P < 0.05$; numbers in between brackets denote 95% confidence intervals.

social problems resulted in similar associations (Supplementary Figures 7.7-7.8). Analyses excluding twin participants from the Generation R Study yielded results comparable to the main findings (data not shown). Finally, in analyses using categories of normal weight versus overweight/obesity, a 1-unit increase in aggressive behavior scores was associated with a greater odds of overweight/obesity (odds ratio = 1.03, 95% CI: 1.01 to 1.05, data not shown).

DISCUSSION

We observed that early aggressive behavior problems was associated with subsequent higher BMI later in childhood in three independent population-based cohorts. We also demonstrated that aggressive behavior was specifically associated with subsequent higher fat mass but was not associated with higher fat-free mass. No associations were observed in the opposite direction, i.e. higher BMI or fat mass at baseline did not predict more aggressive behavior problems at follow-up. These observations were robust to additional adjustment for comorbid attention, social and internalizing problems.

Although several studies have examined ADHD symptoms or the broader concept of externalizing problems in relation to BMI, to our knowledge, this is the first study focusing on the prospective relation between aggressive behavior and children's BMI. The estimates of the association between aggressive behavior – a component of externalizing problems – and increase in BMI were all relatively small in magnitude but consistent. Small effect estimates were expected given the relationship studied and the use of cross-lagged model analyses, which are adjusted for cross-sectional and longitudinal stability paths as well as covariates. Nonetheless, estimates were small to modest, indicating that higher levels of aggressive behavior are only marginally predictive of higher BMI at follow-up, which is not surprising for composite complex phenotypes with many risk determinants such as BMI.[28] Our findings in the Generation R sample of aggressive behavior predicting a higher BMI were replicated in the NTR sample of similar ages. Effect estimates in the older and smaller TCHAD sample were comparable in size to those observed in the other cohorts, although these associations were non-significant. Our findings extend previous studies showing associations between externalizing behavior and subsequent increases in BMI in children of younger and older ages,[5-8] but these previous studies, similar to our study, did not find an association in the direction from BMI to subsequent higher externalizing problems. Our present study extends these investigations by providing a specific focus on aggressive behavior, which is important given that aggressive behaviors predict substantial societal costs in terms of health and social service use.[10] The results from the aforementioned studies which examined externalizing problems more generally, could have been clouded by the well-established association between ADHD symptoms and obesity.[9] Importantly, our findings remained in sensitivity analyses with additional adjustment for baseline attention problems, further suggesting a specific prospective link between aggressive behavior and higher BMI.

Thus, our findings suggest that aggressive behavior problems constitute one of the many contributing components of obesity in childhood. Although small in magnitude, the relatively modest effects obtained in the current study are of interest as these associations might be indicative of one of the many likely pathways to increased weight and obesity later in life. Of note, the association between aggressive behavior and subsequently higher

BMI was not statistically significant in the TCHAD sample of young adolescents. This lack of replication might potentially be due to the smaller sample size of the TCHAD cohort, which is not impossible considering the small estimates observed in the Generation R and NTR samples. These studies were larger in sample size, with corresponding lower standard errors and, hence, narrower confidence intervals around regression estimates. Future examinations from childhood and adolescence into adulthood are required in order to determine specific developmentally sensitive periods, which is needed considering the stability of weight status across the life course.[1]

We observed an association of aggressive behavior with subsequent higher fat mass and not fat-free mass, indicating that aggressive behavior is specifically associated with weight-related physical health. This more in-depth finding of body composition adds to the existing literature, which typically has focused on BMI more generally.[5-8] No associations were observed from baseline fat mass or lean mass to future changes in aggressive behavior problems, which further supported our main findings with regards to BMI. These findings lend support to the observation that aggressive behavior might also be considered in the multidisciplinary assessment of childhood obesity. Future research should focus on other behavioral indices of cardiometabolic health and the potential modifiability of these purported risk indicators.

A potential mechanism underlying the observed association might be that children who exhibit more aggressive behavior could also have more problems with behavioral self-regulation and inhibitory control.[29] Deficits in self-regulation, specifically emotion regulation and behavioral inhibition, arise from executive functioning deficits.[30] Children with deficits in self-regulation potentially do not have the ability to respond adequately to their internal feelings of hunger or satiety cues, which in turn leads to overeating,[12] resulting in weight gain and potentially obesity in the long term. Indeed, studies indicated that the neural pathways controlling appetite and behavioral inhibition are interrelated.[31] In addition, temperament, behavior traits, taste preferences, and appetite are regulated by the dopaminergic system.[32-34] Moreover, evidence suggested that traits such as eating behavior[35,36] and aggressive behavior[37] are both regulated via the same neurotransmitter pathways. Furthermore, aggressive behavior and BMI might share genetic vulnerabilities, which possibly explains the phenotypic associations identified in this study. Recent work has demonstrated common pathophysiological mechanisms for depressive symptoms and obesity,[38] and this could potentially also apply to other psychiatric problems such as aggressive behavior, which are (genetically) related to depressed mood.[39,40]

Another potential mechanism that could explain the association between aggressive behavior and increased BMI and fat mass, comprises inadequate coping mechanisms of parents in response to the challenging aggressive behavior of their child. Parents may allow their child to consume more sweets or unhealthy food, might accept more easily their child's refusal of healthy food, and may allow their children to exhibit sedentary activities

such as watching television to avoid difficult behavior of their children.[41] These actions may eventually, if performed regularly, result in a relatively high weight gain of children,[42] and could thus mediate the relationship between aggressiveness and subsequent high BMI.

Strengths of the present study include the prospective study design of all three pediatric community cohorts with an identical instrument of aggressive behavior. Moreover, we were able to analyze body composition in addition to BMI. However, several limitations should be noted. First, our analyses relied solely on mother reports of the CBCL, which could be subject to reporter bias. Repeated multiple informant assessments of aggressive behavior would be preferred, but this was not achievable in the current population-based design. Moreover, the CBCL is a valid and reliable measurement for aggressive behavior,[22] and has good diagnostic accuracy for clinical disruptive behavior disorders.[23] In addition, our analyses in the Generation R Study were adjusted for maternal BMI. Second, as all population-based studies, the included cohorts experienced attrition. However, albeit affecting prevalence, selective loss to drop-out often does not influence the strength of association.[43] Third, it is well-established that not only obesity is important for determining physical health. Other factors, such as physical activity, also pose a significant risk for poorer physical health. Here, we were not able to examine the directionality and possible mediation mechanisms between aggressive behavior, physical activity, and obesity and further research is required to address these, potentially modifiable, pathways of risk. Fourth, measures of maternal psychopathology were unavailable in the NTR and TCHAD cohorts. However, adjustment for psychiatric symptoms of the mother only marginally affected our estimates in the Generation R Study. Fifth, the CBCL/1.5-5 was also used for children aged 6-7 years in the Generation R Study, which might not be appropriate for this age. However, internal consistency of the aggressive behavior scale was similar for 5-year-olds versus 6/7-year-olds,[25] and the multi-dimensional factor structure of the aggression behavior scale is also comparable to the CBCL/6-18.[44] Finally, we suggested a causal association from aggressive behavior to subsequent higher BMI and fat mass instead of vice versa. However, actual causal inference of composite phenotypes such as obesity is complex,[28] and is restricted in this observational study.

Conclusion

The present study showed a small association between aggressive behavior and subsequent increased BMI and fat mass in childhood. This association indicates that aggressive behavior problems observed by mothers are part of one of the many composite risks for obesity in childhood, which also includes other behavioral mechanisms such as coping strategies, self-control, and impulsivity, as well as lifestyle-related behaviors such as snacking, sedentary behaviors, and sports participation. Hence, it might be helpful to carefully screen for aggressive and other behavioral problems in children with increased

risk of obesity. Moreover, our findings signal a need for conducting trials[45] assessing the extent to which treating behavior problems in children improves their physical health and well-being. In general, professionals as well as parents and other people involved in the care for children with weight difficulties should be aware of the possible behavioral mechanisms associated with higher BMI and fat mass. Most importantly, future research should examine the extent to which these behavioral pathways to childhood obesity are modifiable, although bearing in mind that effects might be small, as observed in the current study.

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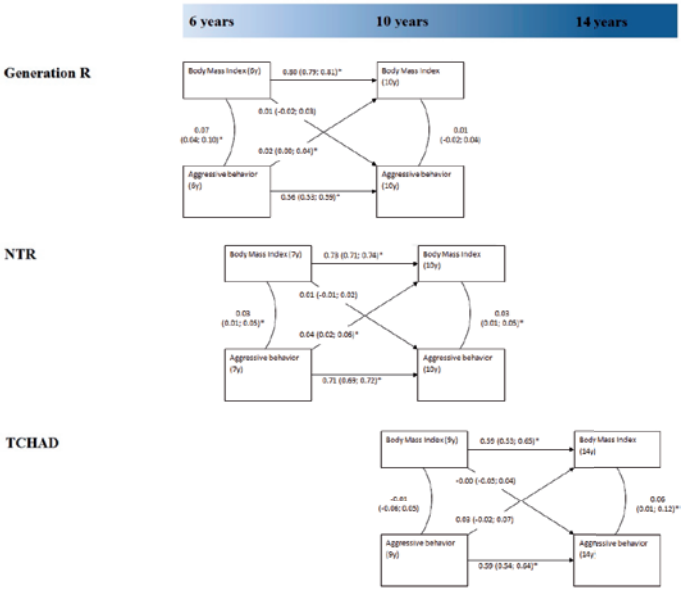
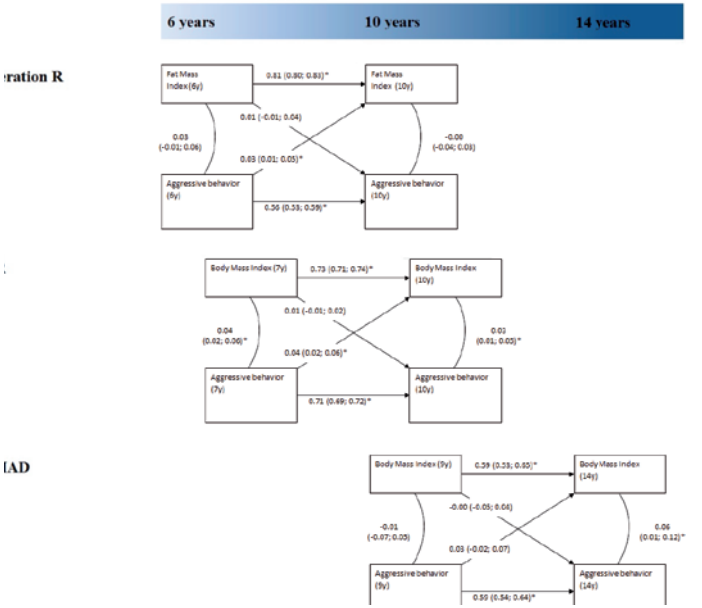
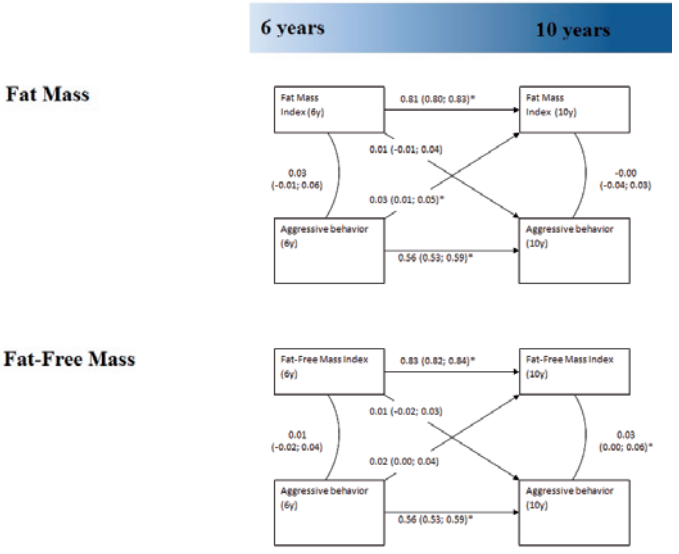


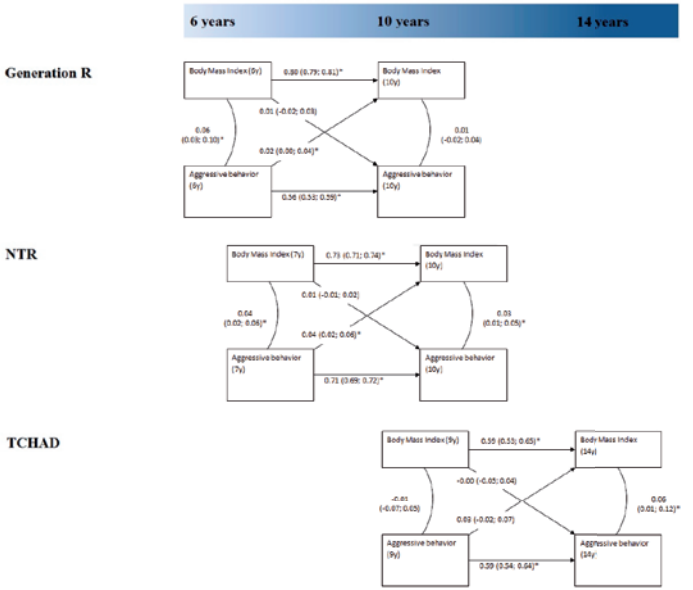
Supplementary Figure 7.2. Cross-lagged association model for the association between aggressive behavior and body mass index in three population-based samples across childhood, additionally adjusted for co-occurring internalizing problems. Note: Estimates denote standardized β coefficients. All models were adjusted for sample-specific covariates. Fit indices: Generation R sample (*N* =3,974), Root Mean Square Error of Approximation (RMSEA) = 0.06, Comparative Fit Index (CFI) = 0.97, and Tucker Lewis Index (TLI) = 0.92; NTR sample (*N* = 10,328), RMSEA = 0.03, CFI = 0.98, and TLI = 0.96; TCHAD sample (*N* = 1,462), RMSEA = 0.02, CFI = 0.99, and TLI = 0.99. * Significant at $P < 0.05$; numbers in between brackets denote 95% confidence intervals.



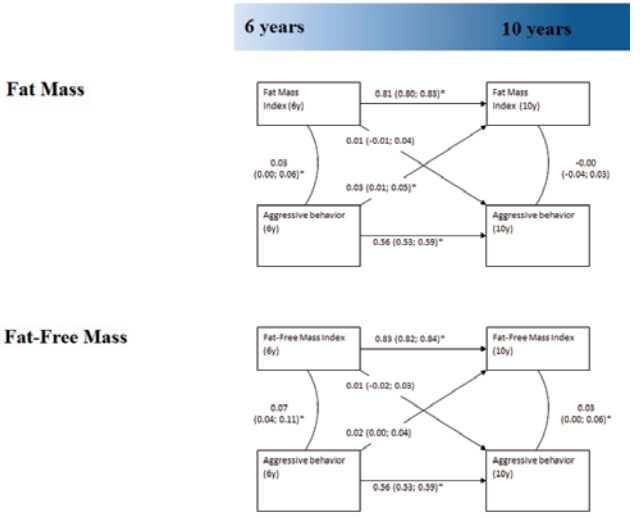
Supplementary Figure 7.1. Cross-lagged association model for the association between aggressive behavior and body mass index in three population-based samples across childhood, additionally adjusted for co-occurring attention problems. Note: Estimates denote standardized β coefficients. All models were adjusted for sample-specific covariates. Fit indices: Generation R sample (*N* =3,974), Root Mean Square Error of Approximation (RMSEA) = 0.06, Comparative Fit Index (CFI) = 0.96, and Tucker Lewis Index (TLI) = 0.91; NTR sample (*N* = 10,328), RMSEA = 0.03, CFI = 0.98, and TLI = 0.96; TCHAD sample (*N* = 1,462), RMSEA = 0.02, CFI = 0.99, and TLI = 0.99. * Significant at $P < 0.05$; numbers in between brackets denote 95% confidence intervals.



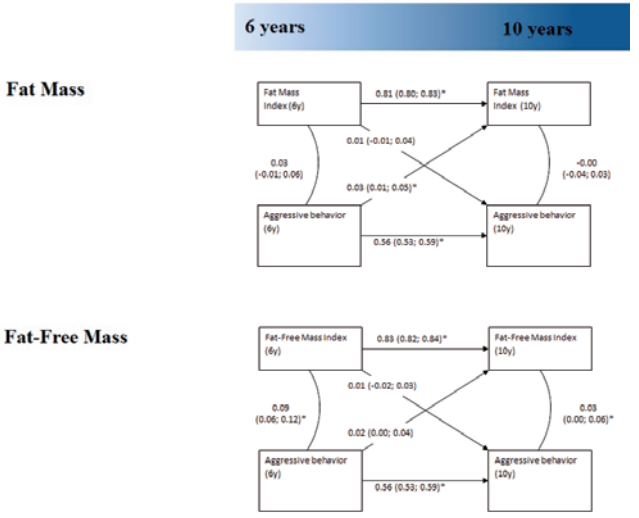
Supplementary Figure 7.4. Cross-lagged association model for the association of aggressive behavior with fat mass and fat-free mass in the Generation R sample (N = 3,974), additionally adjusted for co-occurring attention problems. Note: Estimates denote standardized β coefficients. All models were adjusted for sample-specific covariates Fit indices: fatt mass, Root Mean Square Error of Approximation (RMSEA) = 0.06, Comparative Fit Index (CFI) = 0.95, and Tucker Lewis Index (TLI) = 0.88; fat-free mass, RMSEA = 0.05, CFI = 0.97, andTLI = 0.93. * Significant at $P < 0.05$; numbers in between brackets denote 95% confidence intervals.



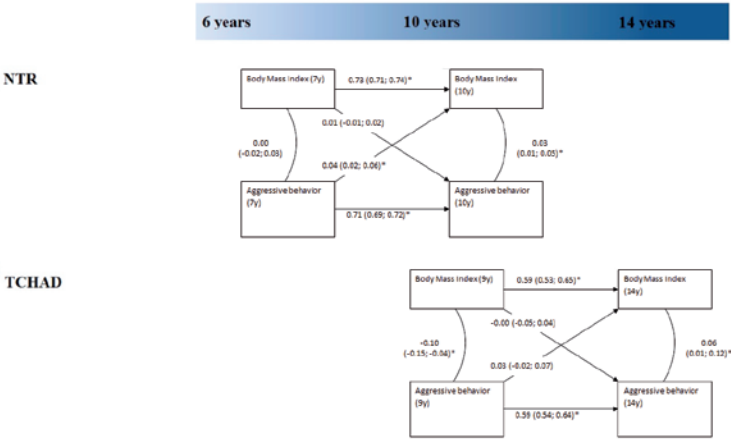
Supplementary Figure 7.3. Cross-lagged association model for the association between aggressive behavior and body mass index in three population-based samples across childhood, additionally adjusted for co-occurring attention *and* internalizing problems. Note: Estimates denote standardized β coefficients. All models were adjusted for sample-specific covariates. Fit indices: Generation R sample (N =3,974), Root Mean Square Error of Approximation (RMSEA) = 0.05, Comparative Fit Index (CFI) = 0.97, and Tucker Lewis Index (TLI) = 0.92; NTR sample (N = 10,328), RMSEA = 0.03, CFI = 0.98, and TLI = 0.96; TCHAD sample (N = 1,462), RMSEA = 0.02, CFI = 0.99, and TLI = 0.98. * Significant at $P < 0.05$; numbers in between brackets denote 95% confidence intervals.



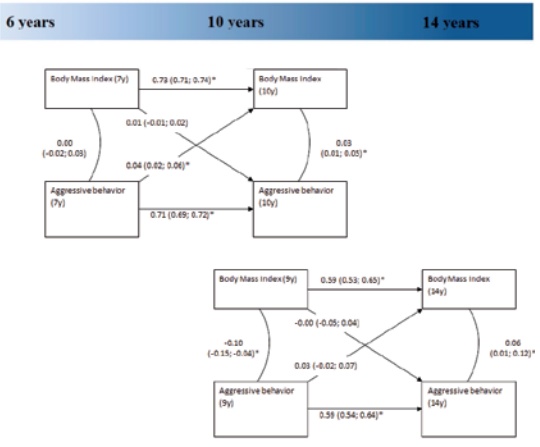
Supplementary Figure 7.6. Cross-lagged association model for the association of aggressive behavior with fat mass and fat-free mass in the Generation R sample (N = 3,974), additionally adjusted for co-occurring attention *and* internalizing problems. Note: Estimates denote standardized β coefficients. All models were adjusted for sample-specific covariates Fit indices: fatt mass, Root Mean Square Error of Approximation (RMSEA) = 0.06, Comparative Fit Index (CFI) = 0.96, and Tucker Lewis Index (TLI) = 0.91; fat-free mass, RMSEA = 0.05, CFI = 0.97, andTLI = 0.94. * Significant at $P < 0.05$; numbers in between brackets denote 95% confidence intervals.



Supplementary Figure 7.5. Cross-lagged association model for the association of aggressive behavior with fat mass and fat-free mass in the Generation R sample (N = 3,974), additionally adjusted for co-occurring internalizing problems. Note: Estimates denote standardized β coefficients. All models were adjusted for sample-specific covariates Fit indices: fatt mass, Root Mean Square Error of Approximation (RMSEA) = 0.06, Comparative Fit Index (CFI) = 0.96, and Tucker Lewis Index (TLI) = 0.90; fat-free mass, RMSEA = 0.05, CFI = 0.97, andTLI = 0.94. * Significant at $P < 0.05$; numbers in between brackets denote 95% confidence intervals.



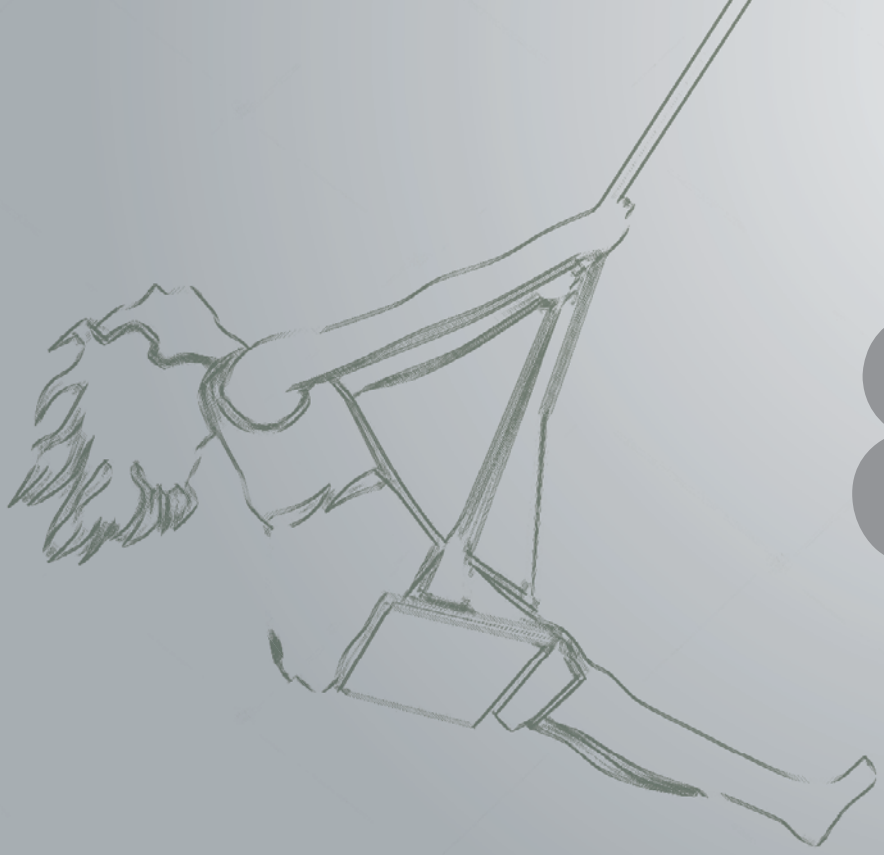
Supplementary Figure 7.8. Cross-lagged association model for the association between aggressive behavior and body mass index in two population-based samples across childhood (NTR and TCHAD samples), additionally adjusted for co-occurring social, attention, and internalizing problems. Note: Estimates denote standardized β coefficients. All models were adjusted for sample-specific covariates. Fit indices: NTR sample (N =10,328), Root Mean Square Error of Approximation (RMSEA) = 0.03, Comparative Fit Index (CFI) = 0.98, and Tucker Lewis Index (TLI) = 0.96; TCHAD sample (N = 1,462), RMSEA = 0.02, CFI = 1.00, and TLI = 0.99. * Significant at $P < 0.05$; numbers in between brackets denote 95% confidence intervals.



Supplementary Figure 7.7. Cross-lagged association model for the association between aggressive behavior and body mass index in two population-based samples across childhood (NTR and TCHAD samples), additionally adjusted for co-occurring social problems. Note: Estimates denote standardized β coefficients. All models were adjusted for sample-specific covariates. Fit indices: NTR sample (N =10,328), Root Mean Square Error of Approximation (RMSEA) = 0.03, Comparative Fit Index (CFI) = 0.98, and Tucker Lewis Index (TLI) = 0.96; TCHAD sample (N = 1,462), RMSEA = 0.01, CFI = 1.00, and TLI = 0.99. * Significant at $P < 0.05$; numbers in between brackets denote 95% confidence intervals.

PART III

MATERNAL FEEDING PRACTICES AND CHILD BODY COMPOSITION



8

Testing the direction of effects between child body composition and restrictive feeding practices: results from a population-based cohort

Ivonne P.M. Derks, Henning Tiemeier, Eric J.G. Sijbrands, Jan M. Nicholson, Trudy Voortman, Frank C. Verhulst, Vincent W.V. Jaddoe, Pauline W. Jansen.

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ABSTRACT

Background: Parental restrictive feeding (i.e. limiting food intake of children) has been linked to childhood overweight. However, the directionality of the causal pathway remains unknown.
Objective: The objectives of this study were to examine the bidirectional association of maternal restrictive feeding with children's weight and body composition across childhood, and to explore a possible mediating role of maternal concern about child weight.
Design: Data were available for 4689 mother-child dyads participating in Generation R, a prospective birth cohort in the Netherlands. At ages 4 and 10 years, restrictive feeding was assessed with the parent-reported Child Feeding Questionnaire and children's BMI was measured. At age 6 years, Fat Mass Index (FMI) and Fat Free Mass Index (FFMI) were measured with Dual-energy X-ray absorptiometry (DXA). Both directions of the relation between restriction and child body composition were examined with multivariable linear regression analyses and cross-lagged modeling. Mediation analyses were performed to examine concern about child weight (mother-reported at child age 10 years) as a potential mediator.
Results: Higher child sex- and age-adjusted BMI SD scores (zBMI) at age 4 years predicted more restrictive feeding at age 10 years, adjusted for confounders and restrictive feeding at age 4 years (B=0.15, 95%CI: 0.11, 0.18). Both zFMI and zFFMI at 6 years were also positively associated with restrictive feeding at 10 years. Maternal concern about child weight partially mediated these associations from child body composition to restrictive feeding (e.g. for zBMI at 4 years: $B_{indirect}$ = 0.10, 95%CI: 0.07, 0.13). There was no temporal association from restrictive feeding at 4 years to child zBMI at 10 years after adjustment for baseline zBMI.
Conclusions: The continued use of restrictive feeding practices at age 10 years appeared to be primarily a response of mothers to an unhealthy weight of their child rather than a cause of children's overweight. Guidelines discouraging restrictive feeding for preventing childhood overweight should therefore be reconsidered.

INTRODUCTION

Parents have an important influence on children's food intake which in turn affects weight development.[1] Parents can regulate food intake by using different feeding strategies, including restrictive feeding. With this strategy, parents attempt to regulate and limit the types and amount of food that children eat.[2]

It has been postulated that restrictive feeding is a risk factor for overweight,[3] as it may hamper the development of a healthy self-regulation of food intake, and therefore lead to overeating when foods are freely available. Also, the attractiveness of restricted foods may increase, as shown in experimental studies.[4,5] Cross-sectional studies confirmed that restrictive feeding was associated with greater snack and sugar-sweetened beverage intake[6,7] and higher child weight,[8-11] but longitudinal studies found no temporal associations in the general population.[12-17] A longitudinal association of more restriction with higher BMI was only found in specific samples of children with low inhibitory control[18,19] or a predisposition to obesity,[20-23] in African-American children[24] and in girls.[23]

An alternative explanation for the reported cross-sectional findings is that parents use restrictive feeding in response to their child's eating behavior and overweight.[3,25] Parents are generally sensitive to their children's hunger and satiety cues, and adapt their feeding strategies when needed.[26] Thus, if children develop obesogenic eating habits or excess weight, parents may limit the availability of high-fat or high-sugar products in their homes, and set rules about snacking. However, this hypothesis was examined only a few times with contradicting findings. A longitudinal study in a U.K. cohort found no evidence for this hypothesis,[12] while in the Dutch Generation R and Portuguese Generation XXI cohorts, associations between child weight and later restriction were found.[27,28] It can be speculated that parental concern about children becoming overweight might drive the restriction of children's food intake. Indeed, results of Webber et al.[29] supported this hypothesis, by showing that the cross-sectional association between parental restriction and BMI in children aged 7 to 9 years was mediated by parental concern about child weight. However, because of the cross-sectional design of this study, temporality and causality of the associations could not be determined.

The inconclusive findings of studies so far highlight the need for longitudinal research with repeated assessments of both restrictive feeding and BMI to better understand the positive, cross-sectional association reported previously.[8-11] This study aimed to examine the direction of effects between restrictive feeding and child adiposity in a large prospective cohort in the Netherlands. We previously reported on the feeding - BMI association when children were 2 to 6 years old using only one assessment of restrictive feeding at age 4 years.[27] We now report on repeated measures of both restriction and child BMI at ages 4 and 10 years, enabling us to examine bi-directionality. We also examined more precise measures of body composition (fat and fat free mass) and the role of maternal concern about child weight.

METHODS

Study design and population

This study was embedded in the Generation R Study, a population-based cohort from fetal life onwards, which was described previously in detail.[30] In brief, all pregnant women living in Rotterdam, the Netherlands with an expected delivery date between April 2002 and January 2006 were invited for participation by health care workers during pregnancy and shortly after birth of their child (participation rate: 61%). The study was approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam and written informed consent was obtained from all participating children and their parents. Data used for the current study were prospectively collected at multiple time points. At the age of 4 years, restrictive feeding was measured by postal questionnaire and BMI data was retrieved from the Municipal Health Centers. At the age of 6 years, children visited our research center where body composition was measured. At 10 years of age, children visited the research center for the second time for body composition measures and at the same time point, feeding practices were measured by postal questionnaire.

At the age of 10 years, 8548 children and parents were invited to participate in an assessment, of whom 5862 children visited the research center for detailed follow-up measures. Children were excluded from the current analyses when they had missing data at 10 years on BMI (n=176) or maternal feeding practices (n=997), resulting in a study sample of 4689 children and their mothers. Missing data on BMI (n=2046), body composition (n=394) and feeding practices (n=1226) from previous waves and missing data on covariates were dealt with using multiple imputation (Supplementary Figure 8.1). A comparison of the study sample (n=4689) with excluded participants (n=3858) showed that the study population included more girls (p=0.01), and more children with a Dutch background (p<0.01) and higher family income (p<0.01).

Measures

Maternal restrictive feeding and concern about child weight

Restrictive feeding practices were measured when children were 4 and 10 years old with the use of the restrictive feeding subscale of the Child Feeding Questionnaire (CFQ). This subscale measures how much a parent controls his/her child's food consumption by restricting eating and by using food as reward for good behavior. Research has demonstrated adequate validity and reliability of the English language version,[31] which had been translated into Dutch by using the standard forward-backward translation method. When the children were 4 years old, mothers reported on their own use of restrictive feeding practices regarding the study child (89% mother-report). The subscale consists of 8 items, e.g. "If I did not guide or regulate my child's eating behavior, he/she would eat too many

of his/her favorite foods" and "I offer my child his/her favorite food in exchange for good behavior". All item responses were rated on a five point scale, from "1. disagree", indicating no restriction, to "5. agree" indicating high restriction. Sum scores were calculated when at least 6 items were answered (62 mothers had 1 or 2 items missing). Internal consistency in our study population was considered as acceptable (Cronbach's $\alpha = 0.73$). At the age of 10 years, mothers reported again on the CFQ restriction subscale (Supplementary Table 8.1). Two items of the original subscale were omitted due to space limitations in the questionnaire. Sum scores were calculated when mothers (98% mother-report) answered at least 5 items (69 mothers had 1 item missing). When children were 10 years old, mothers additionally reported on a shortened version of the CFQ subscale 'concern about child weight'. This two-item scale (originally three-item scale) assesses a mother's concern about her child becoming overweight, with the following items: "How concerned are you about your child having to diet to maintain a desirable weight?" and "How concerned are you about your child eating too much when you are not around?" Answers were given on a five-point scale ("1. not concerned at all" to "5. extremely concerned") from which a sum score was calculated. Internal consistencies on both shortened scales were very acceptable (Restriction, Cronbach's $\alpha = 0.74$; Concern about child weight, Cronbach's $\alpha = 0.79$), and similar to the internal consistency of the original full scales.[31]

Child BMI and body composition

At the age of 4 years, children's height and weight were measured by trained staff at the municipal Child Health Centers as part of routine health care. At the age of 10 years, participating children were invited to our research center where their growth characteristics were obtained. Height was measured with a stadiometer (Holtain Limited, Crosswell, Crymych, UK) to the nearest 0.1 cm, and weight was measured to the nearest 0.1 kg using an electronic scale (Seca 888, Almere, The Netherlands). At both ages, sex and age adjusted BMI (kg/m^2) standard deviation scores (zBMI) were calculated by using the Dutch reference growth curves (http://www.growthanalyser.org).[32]

At the age of 6 years, height was measured with a stadiometer (Holtain Limited, Crosswell, Crymych, UK) and children's body composition was assessed at our research center by trained staff using the Dual-energy X-ray absorptiometry (DXA) scanner (iDXA, GE-Lunar, 2008, Madison, WI, USA). While children were lying down in horizontal position, without shoes and metal objects, total and regional body fat mass, lean mass and bone mass were measured. From this, Fat Mass Index (FMI) was calculated as fat mass (kg)/ height $(m)^2$, and Fat Free Mass Index (FFMI) was calculated as fat-free mass (kg)/ height $(m)^2$. Sex- and age specific standard deviation scores (zFMI and zFFMI) were calculated for the total study population with body composition data available.

Covariates

The following covariates were considered as possible confounders in the association between restrictive feeding and child BMI: child's age, sex, ethnicity, birth weight, duration of breastfeeding, maternal education level, household income, maternal BMI and maternal depression and anxiety symptoms. Children's sex and birth weight were derived from medical records filled out by obstetricians and community midwifes. In prenatal questionnaires, the country of birth of both biological parents was assessed, from which child ethnicity was derived. Maternal educational level was also obtained by prenatal questionnaire. Maternal anxiety symptoms and depressive symptoms were obtained with two subscales of the validated Brief Symptom Inventory (BSI) when children were 3 years old.[33] Duration of breastfeeding was based on repeated questionnaires in the first year of children's lives. Information on household income was obtained by questionnaire when the children were 6 years old. Maternal weight and height were measured during the 6-years visit of the children from which maternal BMI was calculated as kg/m^2.

Statistical analyses

Restrictive feeding and concern about child weight measures were transformed into standardized scores (z-scores) for effect-size comparison purposes. The association between child zBMI or body composition with restrictive feeding was studied in both directions using multiple linear regression analyses. First, the crude association was tested, and in a second step, covariates were included in the model. Covariates were only included if they influenced the feeding-BMI association by more than 5%. As a result, maternal education, maternal anxiety symptoms and duration of breastfeeding were not included in the models. As a third step, the association between restrictive feeding at 4 years and child zBMI at 10 years was additionally adjusted for zBMI at baseline (4 years), in order to examine whether restrictive feeding predicted the change in zBMI. Likewise, the association between child zBMI at 4 years and restrictive feeding at 10 years was additionally adjusted for restrictive feeding at baseline (4 years) to examine whether BMI predicted change in restrictive feeding. Interaction effects with sex were studied for all the above associations by adding an interaction term to the models. A sensitivity analysis was performed to study whether children in different weight categories respond differently to maternal restriction. Child zBMI at age 4 years was categorized according to BMI status (underweight, normal weight and overweight/obese). Subsequently, a stratified multivariable linear regression was performed to examine the association between maternal restrictive feeding at age 4 years and child zBMI at 10 years.

A cross-lagged modeling approach was used to further investigate the association between child zBMI and restrictive feeding. In this type of path analysis, all associations are accounted for each other, confounding factors, stability effects and cross-sectional correlations, and, stepwise, the mutual prospective associations between restrictive

feeding and child zBMI. In order to find the best-fitting model, we first tested the stability model, that only included the stability paths and cross-sectional associations, with confounders regressed at the two baseline assessments (model 1). Next, we included the lagged association from restrictive feeding at 4 years to zBMI at 10 years (model 2) in the stability model, and in a separate model the lagged association from child zBMI at age 4 to restrictive feeding at age 10 years (model 3). Finally, both lagged associations were entered in the full model simultaneously (model 4). The best-fitting model was chosen based on model improvement tested with the Satorra-Bentler χ^2-difference test for maximum likelihood estimation.[34] By using this method, the created models are not judged on the overall model fit since the aim is not to best predict the outcomes, but rather to examine which of the models with alternative pathways provide the best fit to the data.

In a final analysis, we examined the possible mediating role of parental concern about child weight in the association between child zBMI and restrictive feeding. With mediation analysis, we estimated the direct effect of child zBMI on restrictive feeding, as well as the indirect effect via parents' concern about child weight. Similar mediation analyses were conducted with zFMI and zFFMI at the age of 6 years as predictors of restrictive feeding at 10 years. All mediation models were adjusted for confounders.

Multiple imputation (full conditional specification) was used to account for missing values in the predictors and confounders in the multiple regression analyses. Information on all variables included in the study as well as child zBMI at ages 1, 2, 3, 4, 6, 11 and 14 months, and at age 1.5, 2, 2.5, 3 and 6 years, and other CFQ subscales at age 4 years were used to estimate imputations. Analyses were based on pooled results of 20 imputed data sets. For the cross-lagged and mediation analyses, Full Information Maximum Likelihood (FIML) was used to deal with missing values. When only including children with data available on all predictors and outcomes (n=2268), we found similar results as observed in the imputed data. Multiple linear regression analyses were performed with SPSS version 21.0 (IBM Corp, Armonk, NY, USA), and the cross-lagged- and mediation analyses were performed with Mplus, version 7.11 (Muthén & Muthén, Los Angeles, CA, USA).

RESULTS

Non-imputed characteristics of the study sample are shown in Table 8.1. Most children were Dutch (65.1%), and grew up in families with a household income of 1600-4000 euros per month (49.8%). Mothers' average BMI was 25.3 kg/m^2. Maternal restrictive feeding declined over time, with a mean item score of 2.97 (SD=0.77) when children were 4 years old, towards a mean item score of 2.46 (SD=0.92) when children were 10 years old.

Table 8.1. Characteristics of the study sample (n = 4689)[a]

Child characteristics	**n**	**Values**
Sex, % male	4689	49.5%
Age at 10-years visit in years, mean (SD)	4689	9.76 (0.29)
Ethnicity, %		
Dutch	3022	65.1%
Other Western	411	8.9%
Non-Western	1208	26.0%
Birth weight (standardized score), mean (SD)	4642	−0.05 (1.01)
BMI (kg/m^2) at 4 years, mean (SD)	2643	15.80 (1.31)
BMI (kg/m^2) at 10 years, mean (SD)	4689	17.38 (2.53)
FMI (kg/m^2) at age 6 years, mean (SD)	4295	3.92 (1.22)
FFMI (kg/m^2) at age 6 years, mean (SD)	4295	11.93 (0.89)
Maternal characteristics		
Maternal BMI (kg/m^2), mean (SD)	4347	25.34 (4.74)
Household income, %		
Low, <1600€ per month	504	12.4
Medium, 1600-4000€ per month	2023	49.8
High, >4000€ per month	1538	37.8
Maternal depressive symptoms (score), mean (SD)[b]	3354	0.12 (0.29)
Restrictive feeding at 4 years (mean item score), mean (SD)	3463	2.97 (0.77)
Restrictive feeding at 10 years (mean item score), mean (SD)	4689	2.46 (0.92)
Concern about child weight at 10 years (mean item score), mean (SD)	4689	1.24 (0.55)

[a] Data was missing for child ethnicity (n=48), birth weight (n= 47), child BMI at age 4 years (n=2046), child body composition at age 6 years (n=394), maternal BMI (n=342), household income (n=624), maternal depressive symptoms (n=1335), and restrictive feeding at age 4 years (n= 1226).
[b] Maternal depressive symptoms were derived from the Brief Symptom Checklist (BSI).
FMI: Fat Mass Index, FFMI: Fat Free Mass Index

Cross-sectionnaly, maternal restrictive feeding had a stronger association with child zBMI at the age of 10 years (B= 0.24, 95%CI: 0.21, 0.27), than at the age of 4 years (B= 0.10, 95%CI: 0.06, 0.14) (not tabulated). In Table 8.2, the confounder-adjusted longitudinal relations between child zBMI, body composition, restrictive feeding and maternal concern about child weight as obtained with linear regression analyses are shown. Only confounder adjusted results are presented, as together, the confounders, child ethnicity, birth weight, household income, and maternal BMI and depressive symptoms, hardly affected effect sizes. A higher level of restrictive feeding at the age of 4 years was associated with a higher child zBMI at 10 years (B=0.05, 95%CI: 0.01, 0.10). However, this association attenuated to null after adjusting for child zBMI at 4 years. In contrast, a higher child BMI at 4 years was related to more restrictive feeding at age 10 years, even after

Table 8.2. Associations between child BMI, body composition, restrictive feeding and concern about child weight (n = 4689)[a]

Outcomes at age 10 years	Predictors	B (95% CI)	p-value
Child zBMI	Restrictive feeding (4y)	0.05 (0.01, 0.10)	0.03
	Restrictive feeding (4y)[b]	0.00 (−0.04, 0.05)	0.88
Restrictive feeding	Child zBMI (4y)	0.18 (0.14, 0.21)	<0.01
	Child zBMI (4y)[c]	0.15 (0.11, 0.18)	<0.01
	Child zFMI (6y)	0.25 (0.22, 0.29)	<0.01
	Child zFFMI (6y)	0.13 (0.10, 0.16)	<0.01
Concern about child weight	Restrictive feeding (4y)	0.10 (0.05, 0.14)	<0.01
	Child zBMI (4y)	0.29 (0.25, 0.32)	<0.01
	Child zFMI (6y)	0.56 (0.53, 0.60)	<0.01
	Child zFFMI (6y)	0.19 (0.16, 0.22)	<0.01

[a] Values are linear regression coefficients derived from multivariable linear regression analyses. Restrictive feeding and concern about child weight sum scores were transformed into z-scores. All models are adjusted for child ethnicity, birth weight, maternal depressive symptoms, maternal BMI, and household income. Effect sizes of unadjusted associations did not materially differ from the confounder adjusted effect sizes and are therefore not presented. zBMI, sex-and age-adjusted BMI SD scores; zFFMI, sex-and age-adjusted fat-free mass index SD scores; zFMI, sex-and age-adjusted fat mass index SD scores.

[b] Additionally adjusted for zBMI at age 4 y.

[c] Additionally adjusted for restrictive feeding at age 4 y.

adjustment for restrictive feeding at age 4 years (B=0.15, 95%CI: 0.11, 0.18). zFMI and zFFMI were also prospectively associated with restrictive feeding practices, of which the association for zFMI was stronger (e.g., zFMI: B=0.25, 95%CI: 0.22, 0.29). More maternal restrictive feeding at 4 years of age was associated with more maternal concern about child weight at the age of 10 years (adjusted B=0.10, 95%CI: 0.05, 0.14). Furthermore, a higher zBMI at 4 years and zFMI and zFFMI at 6 years were each prospectively associated with more maternal concern about the child's weight (e.g. zFMI: adjusted B=0.56, 95%CI: 0.53, 0.60). The association between child zBMI, zFMI and zFFMI with maternal concern about child weight, was stronger for girls than for boys; e.g. per 1 z-score increase in BMI, maternal concern increased by 0.33 z-score for girls (95%CI= 0.28, 0.38), and by 0.21 z-score for boys (95%CI= 0.19, 0.28). No other sex differences were found for any associations we examined. The association between maternal restrictive feeding at age 4 years and zBMI at age 10 years did not differ by child weight status at age 4 years since restriction was not associated with future zBMI in either of the weight status categories (Supplementary Table 8.2).

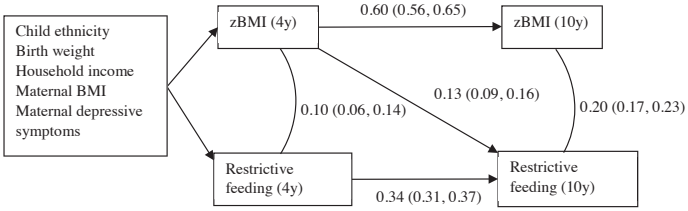


Figure 8.1. The lagged model of associations between restrictive feeding and child BMI from age 4 to 10 years (n=4689). Values represent standardized linear regression coefficients (95% CI's) derived from path analysis and adjusted for covariates.

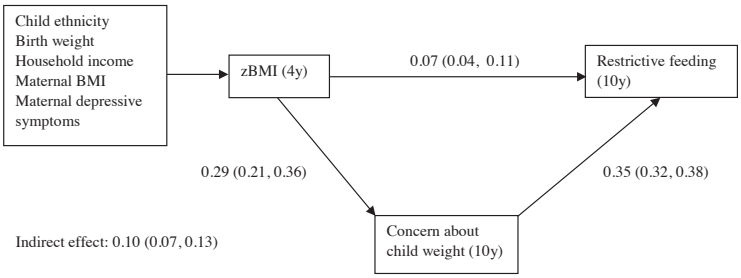
The best-fitting lagged model of associations between restrictive feeding and child zBMI is shown in Figure 8.1. This model included only lagged effects from a higher child zBMI at 4 years towards more restrictive feeding at 10 years (model 3) (B= 0.13 95% CI: 0.09-0.16). The stability paths showed moderate stability over time for both child zBMI and parental restrictive feeding. The reversed path (from restriction to zBMI, model 2) had a less fit and adding both paths (model 4) was not a significant addition to model 3. The other models, model fit indices and results of the Satorra-Bentler χ^2-difference test are presented in Supplementary Table 8.3 and Supplementary Figures 8.2A-C.

In a final step, we examined whether maternal concern about child weight mediated the association from body composition to restrictive feeding that we observed in the cross-lagged model (Figure 8.2A-C). Figure 8.2A shows that the relation between child zBMI at 4 years and restrictive feeding at 10 years was mediated by maternal concern about child weight ($B_{indirect}$ =0.10, 95% CI: 0.07, 0.13). Likewise, Figures 8.2B and 8.2C show that the relation of child zFMI and zFFMI with restrictive feeding at 10 years was also mediated by maternal concern about child weight status. However, the mediation effect of maternal concern about child weight was significantly larger for child zFMI than for zFFMI, as indicated by non-overlapping confidence intervals (for zFMI, $B_{indirect}$ =0.20, 95%CI: 0.18, 0.22; for zFFMI, $B_{indirect}$ =0.08, 95 CI%: 0.06, 0.09).

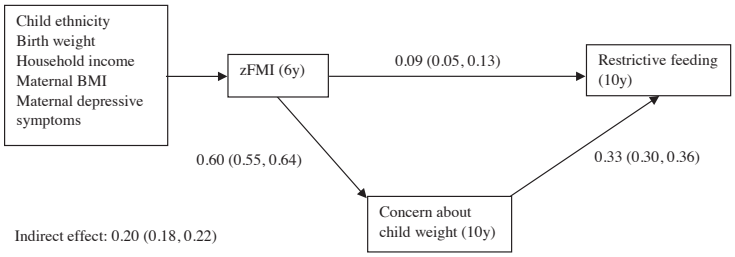
DISCUSSION

The findings from this large population-based study showed that children's higher zBMI and fat mass at ages 4 and 6 years prospectively predicted more use of restrictive feeding by mothers when the children were 10 years old, while in general, the use of restrictive feeding declined over the childhood years. This indicates that restrictive feeding is primarily a response of mothers to children's excess weight, largely - as shown in our analyses - because mothers are concerned about their child's weight. Our results do not

A.



B.



C.

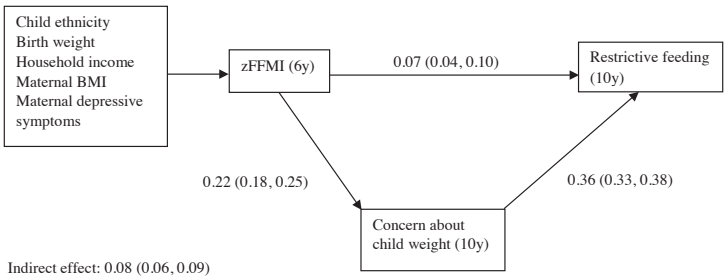


Figure 8.2A-C. Mediation models between child body composition, concern about child weight and restrictive feeding (n = 4689).

Values were derived from mediation analyses and represent linear regression coefficients (95% CI's), adjusted for covariates. Model fit indexes were considered as sufficient to good (Comparative Fit Index: 0.83, 0.98, 0.86, and Root Mean Squared Error of Approximation: 0.051, 0.025, 0.054, for figures A, B, C, respectively). FMI: Fat Mass Index, FFMI: Fat Free Mass Index.

support the hypothesis that restrictive feeding is a risk factor for childhood obesity, since restriction did not predict a change in zBMI.

The finding that a higher zBMI in early childhood predicted more restrictive feeding six years later is in line with a child-responsive model. Apparently, mothers are sensitive to their child's weight status and adapt their feeding practices accordingly, probably with the intention to reduce children's food intake and improve health and well-being.[29] This result is in line with results from a Portuguese longitudinal study,[28] and also corresponds with research on other controlling feeding practices, which showed that parents use more coercive feeding strategies when their child is very thin.[27,35]

Besides supporting the child-responsive hypothesis, our results also extend previous findings by using detailed measurements of body composition. Only very few longitudinal studies examined body composition beyond BMI in relation with restrictive feeding in either direction, and showed inconsistent results.[12,16,24] Our analyses with specific body composition measures showed that fat mass was more predictive of restrictive feeding than fat free mass. This suggests that parents respond differently in their feeding practices when children are chubby or have a rather large frame.

Mothers' concern about child weight appeared as an important mediator in the association between child weight and restriction. This is an important extension of previous cross-sectional findings of Webber et al.,[29] who observed that parental concern about child weight mediated the cross-sectional association between child BMI and restriction. Beyond Webber's research, this specific mediation pathway was not studied before. However, related research on part of the pathways showed that mothers who are concerned about their child becoming overweight are more likely to restrict intake of unhealthy foods by their children.[36] Furthermore, Keller et al.[37] found that the android/gynoid body fat ratio in children, a measure of fat distribution around the belly and hip area, explained 47% of the variance in parental concern about child weight. Together, these findings suggest that parental concern about their child's body weight is an important driver of feeding behavior, although it did not fully explain the relation between child weight and restriction. Additional explanatory mechanisms might include parents' potential concerns about dietary intake and general health of children, which may also drive parents' control over children's food-intake.

Our study found no evidence for restrictive feeding at the age of 4 years influencing weight development, similar to other longitudinal studies in the general population.[12-17] However, this contrasts with longitudinal studies among children at-risk for overweight and with experimental studies.[4,5,18-24] Together these findings might imply that there is a direct effect of restrictive feeding on eating behavior, but that at the longer term, restrictive feeding is only a risk factor for overweight among those who are susceptible to overweight. However, our findings could not confirm this since the (lack of) effect of restriction was similar for children who were underweight, normal weight or overweight/

obese at age 4 years. A possible reason why parental restriction does not influence weight status at the age of 10 years might be that during this school-age period, children start eating more outside of their homes with peer influences and food availability at school and sports facilities becoming more important influences. This might also explain the decline of maternal restrictive feeding over time, as observed in our study. Mothers of heavier children, however, might maintain greater restriction in later childhood because they have concerns about their child's weight, while during early childhood mothers might have other reasons to restrict their child's eating, as indicated by a less strong cross-sectional association at the age of 4 years.

As stated before, in the general population, the influence of restrictive feeding on child BMI seems absent, although future research is needed to unravel whether this accounts for all aspects of restrictive feeding. The CFQ restriction scale that was used in our study only measures overt control (i.e., controlling food intake by directly influencing child eating),[38] but not covert control (controlling food intake in a way that cannot be detected by a child, e.g. not bringing snacks in the house). These aspects of control may have differential associations with child BMI[39,40] and are potentially also differentially associated with maternal factors, such as sociodemographics and BMI. Moreover, an in-depth examination of the level of restriction is needed, since mild restriction of unhealthy foods might be beneficial for a child with overweight, whereas more intrusive and extreme restriction might have adverse effects.[38]

Strengths of this study are its population-based longitudinal design and repeated measurements of both feeding and BMI, and objectively measured body composition. There are also limitations that should be discussed. First, as noted above, the restriction subscale of the CFQ only measures overt restriction, precluding any conclusions on covert restriction. Secondly, parental concern about child weight was measured in parallel with restrictive feeding practices at the age of 10 years, while restrictive feeding was not assessed when zFMI and zFFMI were measured. This limits our conclusions regarding directionality of the (mediating) pathways. Third, at the age of 10 years, the restrictive feeding and concern about child weight subscales were shortened. However, internal consistencies of the scales were very acceptable, and similar to the original full scales.[31] Furthermore, generalizability of the results might be limited since the non-response analysis showed differences between included and excluded parents and children. As reported, those who were lost to follow up relatively often came from non-Dutch families with a low household income, which are known risk factors for child overweight.[41] However, we assume that the influence of this differential drop-out is limited, because these factors were accounted for in the analyses and hardly affected the reported associations. Also, there were missing data on determinants and covariates of the included children. The findings with imputed data were, however, similar to findings including only children with full data on determinants and outcomes (data not shown). Finally, in our study,

mothers reported on the use of restrictive feeding, whereas additional information from fathers could give more insight in the feeding strategies within families and the complementary effects of mothers and fathers.

In conclusion, our findings do not support the often assumed adverse effect that restrictive feeding causes excess weight gain in children. Instead, we found strong evidence that restrictive feeding is a response of mothers to their child having a relatively high zBMI or fat mass and that this response is largely driven by concerns of parents about child weight. Thus, restrictive feeding seems to reflect understandable intentions of parents who are worried that their child has an unhealthy weight. Current guidelines and recommendations in the context of childhood overweight, such as provided by Public Health England and the Dutch Center for Youth Health (Nederlands Centrum Jeugdgezondheid) generally discourage restrictive parenting in food-related situations. Instead, recommending that children need to regulate their own nutritional needs, supported by authoritative parenting methods.[38,42-44] This might need to be reconsidered, particularly if our findings are replicated in future studies.

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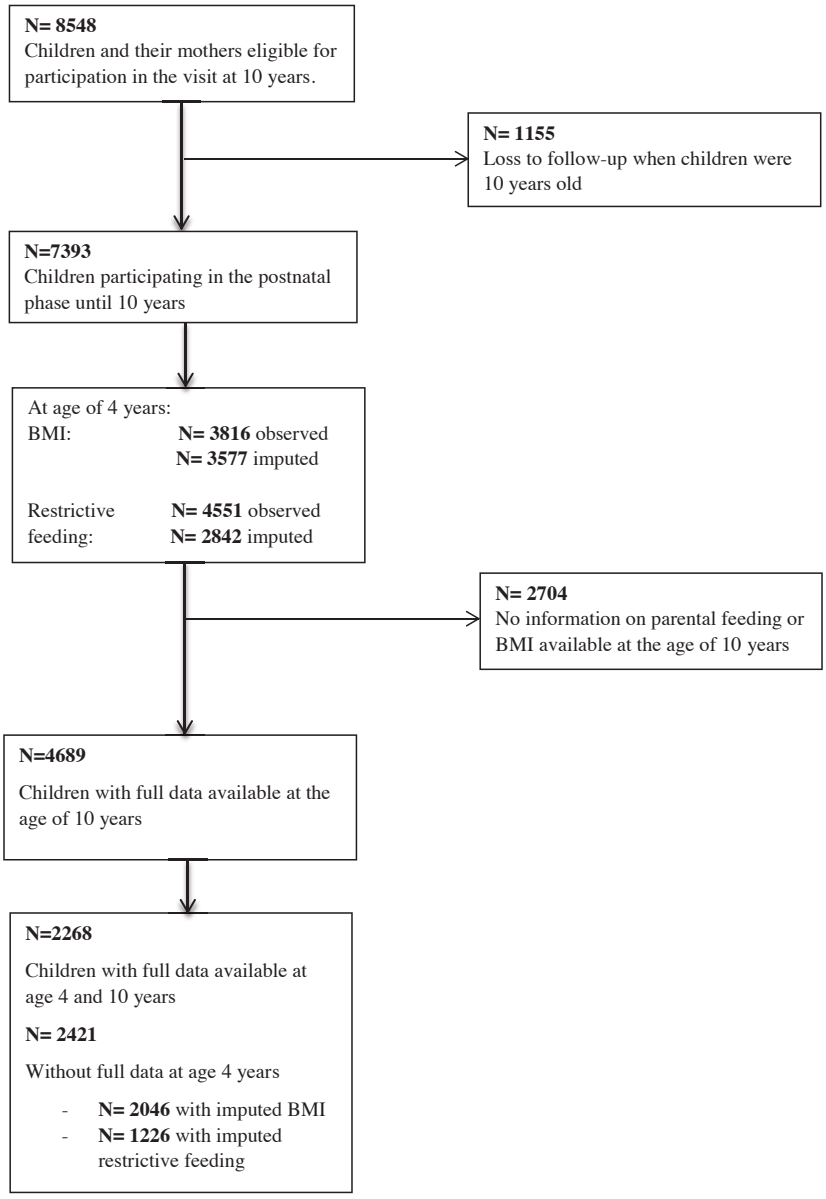
SUPPLEMENT



Supplementary Figure 8.1. Flowchart of the study sample.

Supplementary Table 8.1. Items of the CFQ restriction subscale

Item
1. I have to be sure that my child does not eat too many sweets (candy, ice cream, cake or pastries)
2. I have to be sure that my child does not eat too many high-fat foods
3. I have to be sure that my child does not eat too much of his/her favorite foods*
4. I intentionally keep some foods out of my child's reach
5. I offer sweets (candy, ice cream, cake, pastries) to my child as reward for good behavior
6. I offer my child his/her favorite foods in exchange for good behavior
7. If I did not guide or regulate my child's eating, he/she would eat too many junk foods*
8. If I did not guide or regulate my child's eating, he/she would eat too much of his/her favorite foods

*Item not included in the assessment at age 10 years

Supplementary Table 8.2. Associations between maternal restrictive feeding at 4 years and child zBMI at 10 years, stratified by child BMI category at 4 years (n= 4689)[a]

Restrictive feeding	Child zBMI at age 10 years	
	B (95% CI)	p-value
BMI category at age 4 years		
Underweight (n= 474)	−0.03 (−0.14, 0.09)	0.66
Normal weight (n= 3803)	0.03 (−0.02, 0.08)	0.22
Overweight (n= 412)[b]	−0.01 (−0.10, 0.09)	0.91

[a] Values are standardized linear regression coefficients derived from stratified multivariable linear regression analyses. Models were adjusted for child ethnicity, birth weight, maternal depressive symptoms, maternal BMI and household income. [b] Including obesity (n=59).

Supplementary Table 8.3. Model fit indices for the cross-lagged analyses between restrictive feeding and child BMI.

Model fit indexes	Model 1 (Stability model)	Model 2 (Stability model + lagged restriction → BMI)	Model 3 (Stability model+ lagged BMI → restriction)	Model 4 (Cross-lagged model)
χ^2 (df)	523.30 (16)***	526.24 (15)***	479.07 (15)***	484.09 (14)***
χ^2 Δ test, indicating difference from Model 1 (df)[a,b]	-	2.37 (1)	41.64 (1)***	44.71***
CFI	0.759	0.757	0.780	0.777
RMSEA	0.082	0.085	0.081	0.085

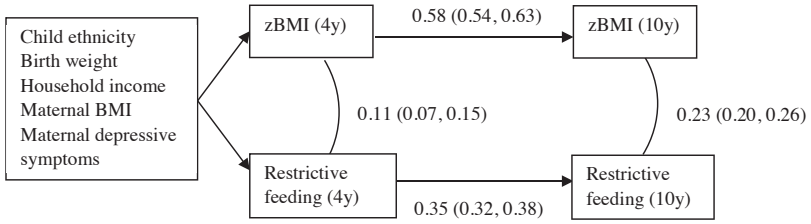
* p-value <0.05, ** p-value <0.01, *** p-value <0.001.

[a] Result of the Satorra-Bentler χ^2 difference test.

[b] Model 4 did not show an improved model fit over best-fitting Model 3, χ^2 difference 1.70, p-value:0.19.

CFI: Comparative Fit Index, RMSEA: Root Mean Squared Error of Approximation, df: degrees of freedom

A.



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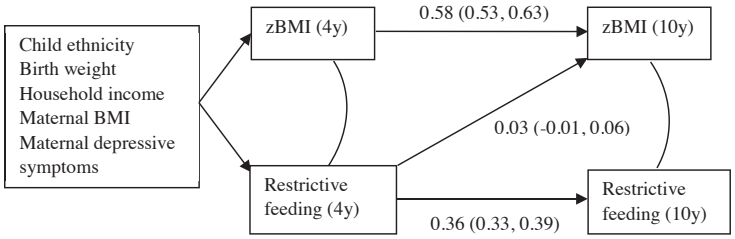
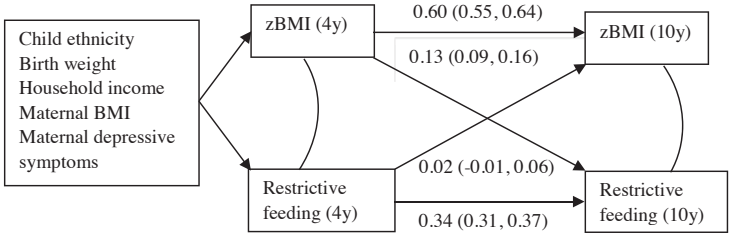


C.



Supplementary Figure 8.2A-C. The stepwise models of associations between child BMI and restrictive feeding from age 4 to 10 years (n=4689). Results of the lagged model of associations between restrictive feeding and child BMI from age 4 to 10 years. Values represent standardized linear regression coefficients (95% confidence intervals) derived from path analysis and adjusted for covariates. A: Stability model. B: Stability model + lagged association from restriction to child zBMI. C. Cross-lagged model.

9

Using food to soothe in infancy is prospectively associated with childhood BMI in a population-based cohort

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ABSTRACT

Background: Feeding practices have been implicated in childhood overweight, but the long-term effects of using food to comfort a distressed child remain unknown.
Objective: This study examined whether the use of food to soothe in infancy was associated with later body composition, and whether children's eating behaviors mediate this relation.
Methods: Participants were 3960 children of Generation R, a population-based birth cohort in the Netherlands. Parents reported on the use of food to soothe when infants were 6 months old and on child eating behavior (food responsiveness, emotional eating) at ages 4 and 10 years. Body Mass Index, fat mass and fat-free mass were measured at ages 6 and 10 years. Linear regression and mediation analyses were conducted, accounting for various potential confounding factors.
Results: The use of food to soothe when infants were 6 months old predicted a higher BMI from age 6 onwards, independently of infant weight, maternal BMI and other confounders. Specifically, frequent use was associated with a 0.13 higher BMI z-score at age 10 years (95% CI: 0.03, 0.22) as compared with never use. Children's emotional eating mediated this association (indirect effect B=0.04, 95% CI: 0.02, 0.06). The feeding – body composition association was most evident for fat mass (p for trend= 0.014) and somewhat less for fat-free mass (p for trend= 0.079).
Conclusions: The use of food to comfort a distressed infant was consistently associated with obesogenic eating behaviors and an unhealthy body composition throughout middle and late childhood. As our design precludes conclusions on causal associations, we recommend further studies with precise, repeated assessments of infant feeding practices. Such research can help ascertaining the direction of effect, which is needed for establishing evidence-based guidelines for parents regarding the use of food to soothe early in life.

INTRODUCTION

Childhood overweight is a worldwide public health problem, given its high prevalence and adverse health consequences.[1] Eating behaviors and appetitive traits play a key role in dietary intake and maintaining a healthy weight.[2,3] The roots for these behaviors most often lie early in life.[4]

In early childhood, parents shape child behavior to a large extent.[5-8] In particular, feeding strategies may contribute to children's development of both healthy and unhealthy eating behaviors.[5,7,8] Research on feeding mostly focused on controlling feeding practices, used to influence quality and quantity of children's food intake.[5,7-9] Less attention has been paid to parents' use of food for non-nutrient purposes, including the use of food to soothe which is the tendency of parents to give their child food or a drink when the child is crying, anxious, angry, distressed or upset.[10] The immediate effects of offering food to soothe (also called emotional feeding) are often positive, as the child's negative mood quickly diminishes.[11] However, through repeated exposure to this feeding practice, children may learn that eating food can effectively soothe distress.[12] Moreover, as the food offered usually contains high levels of sugar,[10] it has been postulated that emotional feeding could be a risk factor for obesity.

Nevertheless, studies evaluating this hypothesis were restricted to infancy and toddlerhood, mostly had a cross-sectional design and reported contradicting findings.[10, 12-18] While some studies showed that the use of food to soothe a distressed infant or toddler was associated with a higher BMI in early childhood[13] or with weight gain in infancy,[14] others found no relation.[10,15-21] A few researchers also reported that the use of food to soothe was associated with more (emotional) overeating,[12,17,21,22] snacking and a preference for sweet, fatty foods in childhood.[18,19] Because such behaviors contribute to the development of overweight,[2] a possible effect of the use of food to soothe on child BMI could potentially be explained by these eating behaviors.

In this large, population-based study, we evaluated whether the use of food to soothe in infancy is prospectively associated with BMI and fat mass across childhood. We hypothesized that more often use of food to soothe predicts a higher BMI and fat mass in later childhood, and that this association is mediated by children's tendencies towards external and emotional eating.

METHODS

Design and study population

This study was embedded in Generation R, a population-based cohort on health and development from fetal life onwards.[23,24] All pregnant women living in Rotterdam, the

Netherlands, with an expected delivery date between April 2002 and January 2006 were invited to participate (participation rate: 61%). The study was conducted in accordance with the guidelines proposed in the World Medical Association Declaration of Helsinki and has been approved by the Medical Ethical Committee of the Erasmus Medical Center Rotterdam. Written informed consent was obtained from parents of all children.

Full consent for the postnatal preschool phase of the Generation R Study was obtained from 7 295 children and their parents. Children without information on parents' use of food to soothe when infants were 6 months old (n=2 683, 36.8%) and those with missing data on BMI at all four follow-up assessments (3, 4, 6 and 10 years, n=652, 8.9%) were excluded, yielding a sample of 3 960 mother-child dyads for the current study (54.3%, Supplementary Figure 9.1). Because data on the outcomes is not complete for all children, the study population varies slightly per analysis.

Comparison of the included and excluded children indicated that children with missing data on the use of food to soothe or all BMI assessments (n=3 335) were more often of non-Western origin and had lower educated mothers (both $p<0.001$) than children with information on feeding and BMI (n=3 960). The children with missing data also had a lower birth weight (3 375 vs. 3 436 gram, $p<0.001$).

Measures

The use of food to soothe

Emotional feeding was assessed when children were 6 months old using a single item question. In a postal questionnaire, mothers were asked whether they had tried to comfort their child by giving something to eat or drink in the last two weeks. Three answering options were provided: never, sometimes and often. This question was part of an assessment of diverse soothing techniques that parents may use to calm their crying infants.[25]

Child body composition

Children´s growth characteristics were measured at the municipal Child Health Centers as part of a routine health care program at ages 3 and 4 years. At ages 6 and 10 years, children´s growth characteristics and body composition were measured at the Generation R research center. At all assessments, trained staff measured children´s height and weight using standard procedures. Height was measured in standing position using a Harpenden stadiometer. Weight was measured with light clothing using a mechanical personal scale. BMI was calculated as weight/height^2 (kg/m^2).

Body composition was measured at ages 6 and 10 years by Dual-energy-X-ray absorptiometry (DXA) scans (iDXA, GE-Lunar. 2008, Madison, WI, USA), using encore software v13.6. Measurements included body fat mass, bone mass and lean mass. Fat mass index (FMI) was calculated as total fat mass (kg) divided by squared height (m^2).

Children's fat free mass index (FFMI) was calculated as the sum of bone and lean mass (kg) divided by squared height (m^2).

Child eating behavior

Eating behavior of children was assessed with the validated Children's Eating Behavior Questionnaire (CEBQ).[26] Parents were asked to fill in this questionnaire twice, when children were 4 and 10 years old. Two eating behavior dimensions of the CEBQ were included in this study: emotional overeating (4 items, e.g. 'My child eats more when anxious') and food responsiveness (5 items, e.g. 'Even if my child is full up, s/he finds room to eat his/her favorite food'). Parents (mothers in 89% of the children) answered the items on a five-point Likert scale from 1=never to 5=always. Continuous scale scores were standardized to facilitate effect size comparisons. The CEBQ has good psychometric properties, including good test-retest reliability, internal consistency and concurrent validity with actual eating behavior.[26,27] Internal consistency in the Generation R study population was high for emotional overeating (α=0.85 and 0.92 at ages 4 and 10 years, respectively) and food responsiveness (α=0.84 and 0.86 at ages 4 and 10 years, respectively).[3]

Covariates

Several possible confounding factors were included in the analyses. Information on maternal age and child gender was obtained from hospital/midwife registries. Maternal ethnicity (categorized as Dutch, Western and Non-western) and educational level were assessed by postal questionnaire during pregnancy. In the same period, maternal psychopathology symptoms were assessed using the Brief Symptom Inventory, a 53-item validated self-report on a diverse range of psychiatric symptoms.[28,29] Mothers' height and weight were measured at the Generation R research center, which was used to calculate maternal BMI (kg/m^2). Information on whether children were breastfed or not (ever breast fed and breast feeding at 6 months) was obtained from postal questionnaires in the first year of children's lives. Infant weight and height at 6 months was measured at the municipal Child Health Centers as part of routine health care, and was used to calculate infant BMI.

Statistical analyses

The body composition measures and the CEBQ scales were standardized. For BMI, sex- and age- adjusted z-scores were calculated according to the Dutch reference growth curves by using a growth analyzer program (www.growthanalyzer.nl).[30] For fat mass, fat free mass and the CEBQ scales, the standardization was based on internal references (i.e. the Generation R cohort), as external references were not available. Associations between the use of food to soothe in infancy and covariates were examined using ANOVAs for continuous variables and χ^2 test for categorical variables. Next, the association between

feeding, and children's eating behavior and BMIz were explored using Pearson correlation coefficients. Then, linear regression analyses were conducted to examine (1) associations of feeding with child BMIz and body composition measures at the various ages, and (2) associations of feeding with eating behavior, separately for each CEBQ scale at 4 and 10 years. Analyses were first conducted unadjusted, and then repeated while accounting for potential confounding factors. Covariates were only included in the multivariate analyses if they changed the effect estimates of the associations by >5%. The linear regression analyses were repeated including using food to soothe as a continuous rather than categorical variable in order to obtain p-values for trend.

Next, we conducted mediation analyses to test whether the feeding – BMI relation was explained by differences in children's eating behaviors. Direct effects of the use of food to soothe an infant on later BMIz and indirect effects via eating behavior were calculated using the 'MODEL CONSTRAINT' command in Mplus 7.2 for multiple imputation datasets. Models were estimated using the maximum likelihood estimation with robust standard errors (MLR) to account for non-normality of the data.[31]

Multiple imputations were performed to estimate missing values of the covariates. The presented effect estimates are the pooled results of 20 imputed datasets. Missing values ranged from n=1 for breast feeding to n=764 for maternal psychopathology. All statistical analyses, except the mediation analyses, were performed with SPSS version 23.0.

Results

General characteristics of the mother-child dyads are shown in Table 9.1. The majority of mothers indicated to sometimes have used food to soothe their infant (53.0%), 22.7% 'often' and 24.3% 'never' used this feeding strategy. Women with a non-Dutch or low educational background used emotional feeding relatively more often ($p<0.001$, and $p=0.002$, respectively). The vast majority of infants were breast fed for some time (92.2%). At 6 months, a third of the infants were still breast fed, with only 1.2% of the infants receiving solely breast milk.

Table 9.2 shows the correlations between determinants, outcomes and mediators. Most of the correlations represented small effect sizes ($r<0.30$). The use of food to soothe an infant, body composition measures at ages 6 (BMIz) and 10 years (BMIz, FFMIz, FMIz), and emotional overeating at ages 4 and 10 years all correlated positively with each other. Food responsiveness was significantly correlated with body composition at all ages, but not with the use of food to soothe the infant. Therefore, this eating scale was not considered a potential mediating factor in further analyses.

Table 9.3 shows that the use of food to soothe was positively associated with BMI, FFMI and FMI z-scores at ages 6 and 10 years, while no significant relations were found with BMIz at ages 3 and 4 years. Particularly often use of food to soothe predicted a higher BMIz and higher FMIz in later childhood, after accounting for potential confounders

Table 9.1. General characteristics of the 3960 study participants[a]

Maternal characteristics	% or mean ± SD				
	Total study population (n=3960)[a]	By using food to soothe category			
		Never (n=961)	Sometimes (n=2099)	Often (n=900)	P-value[b]
Ethnicity (%)					<0.001
Dutch	61.6	27.4	53.5	19.1	
Western	8.9	22.3	52.3	25.4	
Non-western	29.5	18.8	52.0	29.2	
Educational level (%)					0.001
High	31.9	26.1	54.0	19.9	
Mid-high	24.3	24.6	54.8	20.6	
Mid-low	28.3	25.2	52.0	22.8	
Low	15.5	19.5	52.2	28.3	
Age in years	31.2 ± 4.7	31.4 ± 4.3	31.3 ± 4.6	30.8 ± 5.3	0.02
BMI (kg/m^2)	24.5 ± 4.3	24.7 ± 4.3	24.4 ± 4.2	24.5 ± 4.4	0.10
Psychopathology score[c]	0.25 ± 0.33	0.21 ± 0.28	0.24 ± 0.32	0.30 ± 0.40	<0.001
Child characteristics					
Gender (% boys)	49.3	48.3	48.8	51.7	0.27
BMI at 6 months	17.2 ± 1.40	17.2 ± 1.42	17.1 ± 1.37	17.3 ± 1.44	0.05
BMIz at 6 months	0.11 ± 1.00	0.12 ± 1.01	0.08 ± 0.99	0.18 ± 1.01	0.06
Ever breastfed (% yes)	92.2	90.4	92.2	94.3	0.007
Breastfeeding at 6 months (% yes)	33.6	23.5	34.4	42.8	<0.001
Exclusive breastfeeding at 6 months (% yes)	1.2	1.2	1.3	0.9	0.59

[a]Values are percentages for categorical variables and means ± SDs for continuous variables. Some variables had missing values: ethnicity (n=40), educational level (n=165), maternal BMI (n=299), psychopathology score (n=764), child BMI (BMIz) at 6 months (n=726) and breast feeding (n=1). Descriptive values of the imputed data was very similar.[b]P-value for heterogeneity: ANOVA for continuous variables, χ^2 for categorical variables.[c]Assessed with the Brief Symptom Inventory.[28, 29]

(e.g. B for FMI z-score at 10 years=0.11, 95% CI: 0.03, 0.20). The significant association between emotional feeding and FFMI z-score attenuated to statistical non-significance after adjustment for confounders.

Results of the regression analyses with the use of food to soothe and emotional overeating are shown in Table 9.4. More frequent use of food to soothe an infant was associated with higher levels of children's emotional overeating at ages 4 and 10 years, compared to children whose parents never used food to soothe. These associations attenuated slightly after accounting for potential confounders (e.g. at 10 years, B attenuated from 0.26 [95%CI 0.15, 0.36] to 0.23 [95% CI: 0.13, 0.34]), but remained statistically significant.

Table 9.2. Correlations between the use of food to soothe, child BMI and eating behavior in 3960 children of the general population[a]

		Pearson correlation coefficients						
	Mean ± SD	Use of food to soothe at 6 months	BMI z-score				FFMI z-score 10 years M=−0.10 (SD=0.92)	FMI z-score 10 years M=−0.02 (SD=0.95)
			3 years M=0.11 (SD=0.96)	4 years M=0.08 (SD=0.97)	6 years M=0.21 (SD=0.88)	10 years M=0.19 (SD=1.0)		
Use food to soothe at 6 months			0.03	0.01	0.04*	0.06*	0.04*	0.07**
Child eating behavior								
At 4 years								
Emotional Overeating	5.8 ± 2.4	0.05*	0.05*	0.03	0.06*	0.06*	0.11	0.07**
Food Responsiveness	8.9 ± 3.4	0.01	0.25**	0.23**	0.21**	0.15**	0.15**	0.12**
At 10 years								
Emotional Overeating	6.0 ± 2.7	0.09*	0.10**	0.09**	0.14**	0.16**	0.11**	0.17**
Food Responsiveness	9.2 ± 3.9	0.04	0.25**	0.23**	0.35**	0.37**	0.27**	0.36**

[a] Values are means ± SDs and Pearson correlation coefficients. FFMI: Fat free mass index. FMI: Fat mass index. * p-value <0.05, ** <0.001.

Table 9.3. Association of the use of food to soothe with body composition in 3960 children of the general population[a]

Use of food to soothe at 6 months	B (95%CI) for body composition z-scores at different ages					
	BMI z-score at 3 years (n=2819)[b]	BMI z-score at 4 years (n=2464)[b]	BMI z-score at 6 years (n=3416)[b]	BMI z-score at 10 years (n=3075)[b]	Fat free mass index z-score at 10 years (n=3028)[b]	Fat mass index z-score at 10 years (n=3028)[b]
Model 1: Unadjusted						
Never	Reference	Reference	Reference	Reference	Reference	Reference
Sometimes	0.01 (−0.08, 0.09)	−0.02 (−0.11, 0.08)	0.00 (−0.07, 0.07)	−0.00 (−0.09, 0.08)	−0.03 (−0.11, 0.05)	0.01 (−0.07, 0.09)
Often	0.09 (−0.01, 0.20)	0.03 (−0.08, 0.14)	0.12 (0.03, 0.20)*	0.18 (0.08, 0.29)*	0.11 (0.01, 0.21)*	0.18 (0.09, 0.28)*
P for trend	*0.087*	*0.61*	*0.010*	*0.001*	*0.043*	*<0.001*
Model 2: Adjusted[c]						
Never			Reference	Reference	Reference	Reference
Sometimes			0.02 (−0.04, 0.08)	0.02 (−0.06, 0.10)	0.01 (−0.08, 0.08)	0.02 (−0.05, 0.09)
Often			0.08 (0.01, 0.17)*	0.13 (0.03, 0.22)*	0.09 (−0.01, 0.18)	0.11 (0.03, 0.20)*
P for trend			*0.065*	*0.011*	*0.079*	*0.014*

*p-value <0.05

[a] Values are regression coefficients (95% CI).

[b] N varied per analysis due to different number of missing BMI assessments per time point.

[c] Adjusted for maternal education, ethnicity, age, BMI and psychopathology score, and child gender, BMI at 6 months and breast feeding.

Table 9.4. Association of the use of food to soothe with emotional overeating in 3960 children of the general population[a]

Use of food to soothe at 6 months	B (95%CI) for emotional overeating z-scores	
	4 years (n=3217)	10 years (n=2838)
Model 1: Unadjusted		
Never	Reference	Reference
Sometimes	0.09 (0.01, 0.17)*	0.09 (−0.00, 0.17)
Often	0.15 (0.05, 0.25)*	0.26 (0.15, 0.36)**
P for trend	*0.003*	*<0.001*
Model 2: Adjusted[b]		
Never	Reference	Reference
Sometimes	0.08 (−0.01, 0.16)	0.09 (0.01, 0.18)*
Often	0.10 (0.01, 0.20)*	0.23 (0.13, 0.34)**
P for trend	*0.038*	*<0.001*

* p-value <0.05, ** <0.001.

[a] Values are regression coefficients (95% CI).

[b] Adjusted for maternal education, ethnicity, age, BMI and psychopathology score, and child gender, BMI at 6 months and breast feeding.

In mediation analyses (presented in Figure 9.1), a significant indirect effect of the use of food to soothe an infant on child BMI z-score via emotional eating was found (e.g. indirect effect on child BMIz at 10 years: B=0.04, 95% CI: 0.02, 0.06). Besides, a direct effect of frequent use of food to soothe on children's BMI z-score was also observed (e.g. direct effect on child BMIz at 10 years: B=0.14, 95% CI: 0.04, 0.24).

DISCUSSION

Children, who were soothed by their parents with food and drinks in infancy, displayed more obesogenic eating behaviors and an unhealthier body composition when they were ten years old. In particular, these children had a higher mean BMI and a greater accumulation of fat mass. Although the mean increase in BMI z-score of 0.13 due to emotional feeding (often vs never, corresponding with 0.40 BMI points, 95% CI: 0.15, 0.64) may appear small, this is very comparable to the protective effect of breast feeding, which is estimated to reduce BMI z-score in childhood by 0.18.[32] Thus, our findings suggest that the use of food to soothe might contribute to the development of obesity.

Our findings provide support for the hypothesis that the practice of offering food for non-nutrient purposes influences weight development of children. The adverse effect of the use of food to soothe a distressed infant or child on weight development was

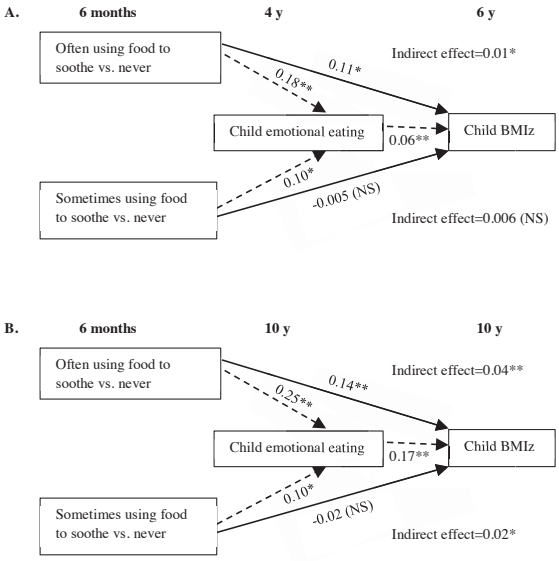

Figure 9.1. Mediation analyses representing the direct effect of the use of food to soothe in infancy on (Panel A) BMI at age 6 y and the indirect effect via emotional eating at 4 y, and on (Panel B) BMI at age 10 y and the indirect effect via emotional eating at 10. Values represent regression coefficients derived from Mplus 7.2. Figure 1A: n=3416, Figure 1B: n=3075. Adjusted for maternal education, ethnicity, age, BMI, psychopathology score, and child gender, BMI at 6 months and breast feeding.
* p-value <0.05, ** <0.001.

not reported in longitudinal population-based studies before.[17,20] Only one small study in the U.S. (n=135) showed that emotional feeding predicted weight gain from 6 to 18 months.[10] Our results add substantially to this study by showing that the use of food to soothe predicted a higher child BMI z-score and particularly the accumulation of body fat over a ten-year period, independently of initial body weight. The current study also suggests that parents' use of food to soothe in infancy is associated with later emotional eating. This supports previous work reporting similar associations in cross-sectional[21,22] or longitudinal studies with a one-year follow up only.[17]

Different explanations for the reported association between the use of food to soothe distressed infants and body composition in childhood are conceivable. First, we showed that children's tendencies to emotional eating mediated the feeding – body composition association. This finding could be interpreted as evidence for the hypothesis[12] that being fed as a way to provide comfort and consolation may specifically teach children to associate food with emotions and to cope with negative emotions by eating, even at times when they are not hungry. We showed that the use of food to soothe was related with emotional eating at ages 4 and 10 years, while the association with body composition was only evidenced in late and not in early childhood. This suggests that the effects of using food

to soothe on child weight via emotional eating may not become evident until children have more free access to food. Free access makes it possible to act upon the inclination to eat and snack in response to distress. This hypothesis is supported by work showing that emotional eating is a risk factor for excessive weight gain in school-aged children from about age 6 years onwards,[27,33] but not at younger ages.[19,34] Alternatively, subtle differences in BMI due to feeding practices may first be masked by individual differences in timing of the adiposity rebound, and only become apparent after this transition period (>5-6 years).[35]

An alternative explanation for the reported feeding – body composition association is that parents who use food to soothe their infants may years later also be more indulgent to give their children something to eat or snack. In line with this reasoning, we acknowledge the possibility that the feeding – body composition relation is explained by other factors not included in the analyses. Possibly, families using food in non-nutrient ways may also be families with unhealthier lifestyle habits or a less affluent background. Although the analyses were adjusted for several possible confounding factors, residual confounding cannot be ruled out.

Reverse causality is another mechanism that must be considered. Previously, we showed that parents tend to use specific feeding practices in response to child weight or eating behavior.[36] Plausibly, parents of food-oriented or reward sensitive children may realize that offering food is an efficient way to quickly soothe their child's distress. By adjusting the analyses for initial weight, we attempted to rule out the direction of effect that heavy children with a large appetite were more likely to be exposed to emotional feeding. However, only a randomized controlled trial can definitely confirm the current findings and demonstrate direction of causation.

The current study is strengthened by its large sample size of mother-child dyads and the use of objective measurements of body composition. Furthermore, we relied on a prospective design using data collected in multiple assessment waves, making it possible to infer on the longer-term effects of a specific feeding practice. Limitations of our study include

our relatively healthy, affluent sample, due to selective participation[37] and loss to follow-up, which was more substantial in those of lower socio-economic and ethnic minority backgrounds. Moreover, our sample showed a lower rate of exclusive breastfeeding at 6 months postpartum as compared to a large representative sample of Dutch mothers in the same period.[38] Another limitation is the reliance on mother reports of emotional feeding and children's emotional eating. Mothers may have provided socially desirable or biased reports on her own parenting strategies and her child's eating behavior. However, findings for emotional overeating and child BMI – which was objectively measured – were rather similar. Moreover, the validity of the CEBQ has been proven with a variety of observations of actual eating behaviors.[26] The assessment of emotional feeding was

also limited by its single item assessment. Although a single item can be effectively used to capture a global construct, a multi-item questionnaire could have assessed situational aspects of feeding and the relevant emotional states of children in more detail. Furthermore, we only assessed emotional feeding at a single time point in infancy, when milk and perhaps fruit and vegetable puree are the main components of a child's diet. It is unclear whether emotional feeding practices in these circumstances remain the same or change as children grow older, thus limiting more general conclusions on parental feeding practices across childhood.

In conclusion, this longitudinal population-based study is the first, to our knowledge, to suggest that the use of food to soothe in infancy contributes to unhealthy weight development throughout childhood. However, given our assessment of emotional feeding using a single item at only one time point in infancy, we emphasize the need for replication of our findings in future longitudinal studies, preferably with precise, repeated assessments of feeding practices, as well as experimental studies. Such studies can better demonstrate (direction of) causation. However, the burden of the overweight epidemic urges us to translate findings – even if representing small effects – into clinical practice.[1] Thus, we recommend health professionals involved in the care of young parents, like midwives and professionals at baby-well clinics, to inform parents about adequate strategies to soothe distressed infants, such as distraction and comforting through talking, singing, walking and rocking. These strategies are positive in any case and such advice needs only a minimal time effort if given along with the standard recommendations about breast feeding. Once the negative effects of emotional feeding are confirmed by future studies, health care professionals should then be advised to guide parents to use emotional feeding strategies to a limited extend only.

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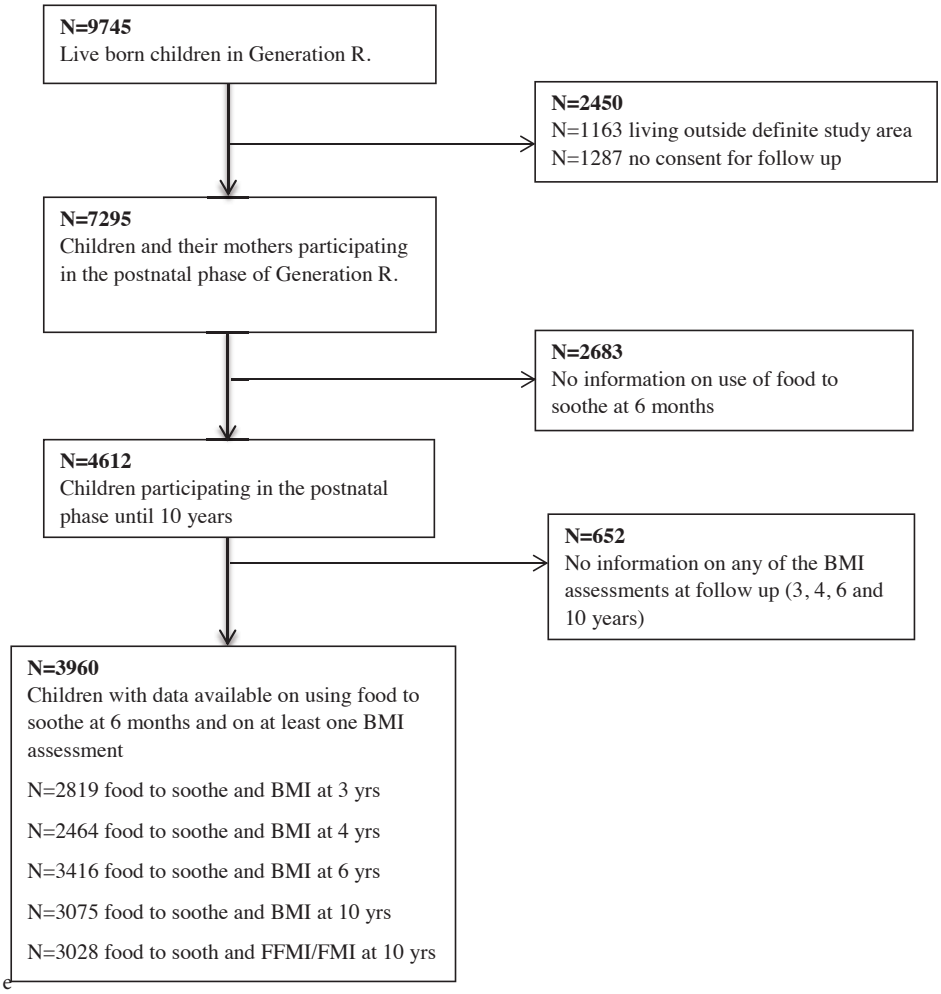
SUPPLEMENT



Supplementary Figure 9.1. Flowchart of the study sample

10

General Discussion

RATIONALE AND MAIN FINDINGS

A better understanding of the relationship between behavior and obesity development in children is of key importance in order to reduce the alarmingly high rates of overweight and obesity and to prevent new cases. Behavioral traits are modifiable and presumed to be closely related to obesity development. The overall aim of this thesis was to examine the relationship of parental and child behaviors with adiposity and cardiometabolic health across childhood.

In **Part I** of this thesis, we provided insight in the development of eating behaviors in children by first studying the course of several eating behaviors across childhood and second, examining potential determinants of these eating behaviors. In **Chapter 2**, the course of eating behaviors in children from age 4 years to 10 years was studied with a person-centered approach in order to identify subgroups of children with distinct eating behavior patterns. Although most children followed a stable low pattern of obesogenic eating behaviors, some children developed distinct and more unhealthy patterns of emotional overeating and food responsiveness. Patterns of enjoyment of food and satiety responsiveness were similar for all children and fairly stable across childhood. These findings suggest that emotional overeating and food responsiveness are dynamic behaviors in the first years of life that can change during childhood. Using an explorative approach, a range of potential predictors of these eating behavior patterns were examined. Results indicated that children's overweight status and emotional and behavioral problems at the age of 3 years correlated with more unhealthy eating behavior patterns from 4 years to 10 years, along with maternal controlling feeding practices. A different potential predictor of unhealthy eating behavior was examined in **Chapter 3**. Here, associations of impaired gestational glucose tolerance as measured with 2-stage glycemic screening (i.e. isolated hyperglycemia, impaired glucose tolerance and gestational diabetes mellitus) with offspring eating in the absence of hunger in early adolescence were examined. Adjusted for a range of socio-demographic and prenatal covariates, sex-specific associations were observed: Girls exposed to maternal hyperglycemia or impaired glucose tolerance during pregnancy reported a higher level of eating in the absence of hunger, while boys exposed to impaired glucose tolerance during pregnancy reported less eating in the absence of hunger. Comparable sex-specific associations of impaired gestational glucose tolerance were found for intake of sugar-sweetened beverage intake and the consumption of energy dense low-nutritive foods. Finally, the level of eating in the absence of hunger was not cross-sectionally associated with body composition in early adolescence.

In **Part II**, we studied longitudinal and potentially bi-directional associations between different child behaviors, body composition and cardiometabolic health. In **Chapter 4**, we examined bi-directional associations between eating behavior and body composition. Children who had already developed a higher weight and more fat mass at the age of

4 years were at higher risk for more obesogenic eating behavior at the age of 10 years, as shown by higher levels of food responsiveness, enjoyment of food and less satiety responsiveness. However, eating behaviors at 4 years were not related with weight status 6 years later. For emotional overeating, a bi-directional relationship was identified: more emotional overeating at 4 years was associated with higher BMI and fat mass at 10 years, as well as vice versa. Next, in **Chapters 5 and 6**, the relationship of infant sleep duration with body composition and cardiovascular or cardiometabolic health later in childhood or adolescence were investigated in two populations. In **Chapter 5**, sleep duration in infancy was assessed with questionnaires, and only a small association of shorter sleep duration at 2 months with higher BMI, fat mass and systolic blood pressure was observed, while sleep duration at other time points were not associated with body composition or cardiometabolic health at 6 years of age. In **Chapter 6**, we conducted a similar study in which sleep duration in infancy was assessed with 24-hour diaries, an instrument evaluated as a more precise measure compared with estimated average sleep duration. Again, infants with a shorter sleep duration did not have an increased likelihood of being on a high weight trajectory until the age of 14 years, nor did they have a heightened risk for adverse cardiovascular health outcomes. In **Chapter 7**, bi-directional associations between aggressive behavior and body composition across childhood were investigated. A small association between aggressive behavior and subsequent increased BMI and fat mass throughout childhood was found in three cohorts, while children with a high BMI at baseline had no heightened risk of more aggressive behavior at follow-up.

Finally, in **Part III**, the role of different maternal feeding practices on adiposity development was investigated. In **Chapter 8**, we described the relationship between the use of restrictive feeding practices and body composition across childhood in a longitudinal and bi-directional design. Results indicated that a having higher BMI at 4 years and higher fat mass and fat free mass at 6 years of the child increased the likelihood of more restrictive feeding at 10 years. Maternal concern about the weight status of their child partially mediated these associations. Yet, no temporal associations between restrictive feeding at 4 years and subsequent body composition were found. Taken together, these results suggest that the use of restrictive feeding practices appeared to be primarily a response of mothers to the high weight status of their child. In **Chapter 9**, a different feeding strategy was examined: emotional feeding (i.e. using food to soothe a distressed child). When mothers frequently used food to comfort their child in infancy, children had a higher BMI and body composition at 6 and 10 years of age. Emotional overeating of the child partially mediated this association, which suggests that children might also learn to comfort themselves with food, and thus affecting their weight gain.

INTERPRETATION OF FINDINGS

In this thesis, we only found limited evidence for behavioral determinants of adiposity development across childhood. Rather unexpected, results of this thesis revealed that some behavioral characteristics were likely to be consequence of the adiposity level of the child or that prospective associations were absent. Below, we will discuss some of our main findings more in-depth.

Childhood adiposity as a precursor for the development of eating behaviors

The link between eating behaviors and obesity has been widely examined throughout the life-course, and consistently showed that obesogenic eating behaviors were related to weight status from childhood onwards.[1-13] Up to this moment, evidence was pointing towards a Behavioral Susceptibility Theory of Obesity. According to this theory, eating behaviors are heritable characteristics that together with the obesogenic environment create individual differences in adiposity levels.[3,14] As foods are easily accessible in the current obesogenic environment, individuals with inherited low food avoidant and high food approaching eating behaviors are prone to weight gain while others with a more balanced appetite regulation are not. Evidence for a genetic basis of eating behaviors comes from the Gemini Study, which observed moderate to high heritability of 63% for satiety responsiveness and 75% for food responsiveness in 8-11-year-old twins.[15] The observed gradient relationship between eating behaviors and adiposity further implies a behavioral susceptibility.[3,7] Though, prospective studies that ruled out the influence of reversed causality in the relationship between eating behaviors and adiposity were mostly lacking.

Our findings regarding the relationship between adiposity and eating behaviors described in this thesis foremost suggest reversed causality is indeed the case: Twice, we observed an association between adiposity and subsequent eating behaviors, rather than the reversed association. First, being overweight or obese at the age of 3 years was a predictor of increasing trajectories of food responsiveness and emotional overeating from 4 years onwards (chapter 2), and second, a higher BMI at 4 years and a higher fat mass at 6 years were associated with more food approaching and less food avoidant eating behaviors at 10 years of age, while no associations in the other direction were observed (chapter 3). Although this direction of effects seems counterintuitive, a few other studies reported results in line with our findings.[16-21] Furthermore, important evidence in favor of our findings further comes from a Mendelian Randomization study that reported a causal influence of adiposity on the level of disordered eating in adolescence and adulthood.[22] Finally, children who were on a high BMI trajectory from 6 years onwards were more likely to develop eating disorders, including binge eating disorder, bulimia nervosa and purging disorder.[23]

The results described above highlight the importance of a healthy weight status early in childhood to prevent the development of obesogenic eating behaviors. Interestingly, bi-directional or unidirectional relationships from adiposity to eating behaviors were reported in studies conducted in mid-childhood or later. However, prospective studies conducted in early childhood, before the age of 4 years, mostly observed a relationship between unhealthy eating behavior and later weight gain,[16,24-27] while at later ages a prospective relationship was not found,[28] or not studied. This might suggest that the relationship between eating behaviors and adiposity is more complex than initially assumed, with potential time-varying effects of adiposity on eating behaviors and vice versa. Future studies should therefore use repeated assessments of eating behaviors and adiposity from infancy to adulthood and examine time-varying effects over the life course.

Various mechanisms might explain the observed associations between adiposity and subsequent eating behaviors. Distinguishing fat mass from fat free mass in the relationship between weight status and subsequent eating behaviors provided further indication on how adiposity affects eating behavior. In a study by Steinsbekk et al.[18] a higher fat mass predicted an increase in food responsiveness, while more muscle mass predicted a decrease in satiety responsiveness. The authors suspected distinct relationships of muscle mass and fat mass with the homeostatic appetite control system versus hedonic eating. Although we observed that associations of fat mass with the hedonic eating system (food responsiveness, emotional overeating and enjoyment of food) were stronger than that of fat-free mass, we did not observe distinct relationships for different components of body composition. A high adiposity level early in childhood might upregulate appetite through a higher set point of energy balance.[29,30] Further, accumulating fat mass decreases the inhibitory effect of "satiety-hormone" leptin, resulting in more food intake.[31-34] Eating behaviors, mainly satiety responsiveness, are associated with common genetic variants in BMI or the expression of the FTO gene, and therefore, eating behaviors and adiposity may also share genetic vulnerabilities.[14,35-37] I carefully speculate that the timing of expression of this genetic vulnerability might be different for obesity and appetite with children first develop higher adiposity levels and subsequently developing unhealthy eating behaviors. Finally, in early childhood, children largely depend on their parents as they are not able to make their own decisions while later in childhood they gain more autonomy regarding food intake. Parents might first offer children unhealthy foods which might result in higher adiposity already early in childhood and later in unhealthy eating behaviors because children adopted eating habits from their parents.

Emotional overeating as a determinant and consequence of childhood adiposity

Unlike other eating behaviors that were examined in this thesis, emotional overeating was the only eating trait that might contribute to the development of childhood obesity as it

was shown to be bi-directionally associated with BMI, and particularly fat mass, across childhood (chapter 3). Emotional overeating can be considered as a coping strategy in order to reduce the level of negative feelings, resulting in feelings of reward and hedonism.[38,39] Engaging in emotional overeating may eventually result in weight gain because foods consumed during emotional overeating are often highly palatable.[40,41] In turn, a higher weight status may contribute to low self-esteem, a potential driver of emotional overeating. Importantly, engagement in emotional overeating in childhood is mentioned as an antecedent of eating disorders, such as binge eating disorder,[42] which are likely to develop in adolescence. In most cases, binge eating disorder and obesity co-occur and reinforce each other through negative feelings, a similar association as observed here in childhood. It can be hypothesized that children already getting trapped in this vicious circle of emotional overeating and a higher weight might ultimately develop binge eating disorder and obesity.

As recently suggested by Herle et al.,[43-45] emotional overeating was explained by environmental factors in childhood rather than reflecting heritability, and therefore considered as a learned behavior, shaped by the home environment. Emotional overeating was previously shown to increase with age,[44,46] and in the Generation R Study, we identified a subgroup of children who strongly increased in their emotional overeating from 4 to 10 years. We showed that factors associated with this increase in emotional overeating might be embedded in the psychological context: children's emotional and behavioral problems as well as maternal psychiatric symptoms were associated with an increasing emotional overeating patterns from 4 to 10 years (chapter 2). Children experiencing emotional and behavioral problems might have poor emotion-regulation skills and therefore use eating in order to reduce feelings of stress, anxiety and sadness, which has been shown previously in young adolescents.[47] Studies showed that psychological problems and adiposity are interrelated from early childhood onwards. Emotional and behavioral problems heighten the risk for obesity,[48-50] or the level of adiposity heightens the risk for emotional and behavioral problems,[51] or both.[52,53] Emotional overeating is likely to play an intermediate role in this relationship.[54] Further, the observation that aggressive behavior was - to some extent - associated with BMI and fat mass across various cohorts also emphasizes the role of emotional and behavioral problems as risk factors for weight gain (chapter 7). Since emotion dysregulation often underlies aggressive behavior in children,[55] these children might therefore also exhibit emotional overeating. However, whether emotional overeating plays a role in the relation between aggression and BMI is yet to be discovered. Further, in line with Herle et al.,[44] our results provided an indication that emotional overeating is shaped within the family situation. Results showed that maternal- but not paternal- psychiatric symptoms were associated with increased emotional overeating, as well as the use of more restrictive feeding practices, while monitoring of food intake had a protective effect. However, our study on potential predictors of eating behaviors used an explorative approach without adjustment for confounding, and therefore we cannot conclude on independent effects.

The marginal role of sleep duration in infancy

In this thesis, we only found marginal effects of sleep duration in infancy on later body composition and cardiovascular and metabolic health up to mid adolescence. This, largely negative finding, was consistent across two different cohorts and two different assessment methods of sleep duration (chapter 5 and 6). In chapter 5, sleep duration was assessed by questionnaires, asking mothers to report the average sleep duration of their infant in the last week. This can be difficult for parents to estimate, as infants often do not sleep through the night and take naps during the day. To overcome this, we analyzed sleep duration assessed with diaries in chapter 6, a prospective method instead of retrospective questionnaire.

Our findings on the role of sleep duration in infancy contradict many previous studies that suggest a causal relationship between short sleep, high adiposity and adverse cardiometabolic health over the lifespan.[56-61] One of the reasons why we did not observe an effect of short sleep duration on adiposity might be the age period we examined. Indeed, pathways proposed through which sleep affects adiposity might only be applicable from childhood onwards. For example, one of the often-proposed behavioral pathways is that shorter sleep unavoidably leads to more time to eat. This results in more snacking and obesogenic eating behavior, already previously shown in young children.[62,63] A related biological mechanism that might underlie the relationship between short sleep and adiposity includes discrepancies in the appetite-regulatory hormones leptin and ghrelin, which results in increasing appetite.[64,65] Both postulated mechanisms posit that short sleep results in more food intake and subsequent weight gain. However, infants are dependent on feedings provided by the parents or other caregivers, thus short sleep duration might not affect future weight gain if parents do not provide feeding anymore. A second reason might be the length of the follow-up. Previous studies examining the influence of sleep in infancy on subsequent weight gain until 7 years,[66-69] we extended this by examining whether there is an association present with body composition or cardiometabolic health until the age of 14 years. However, we neither found an association of sleep duration with body composition at the age of 4 years (chapter 6). Infancy is a very particular period, and it can be debated whether sleep duration at this young age would already have lasting direct effects or whether it can be seen as an early marker for later sleep problems. Indeed, the level of stability in sleep duration from 2 to 36 months was not very high (chapter 5). Thus, regression dilution may occur, as the effect of short sleep during infancy might be washed-out because children may sleep normal hours after this period.

Parental feeding practices as a response to children's needs

It is commonly believed that parental feeding practices can negatively influence children's adiposity level, including restrictive and emotional feeding strategies. Against the theoretical background of the child-responsive model we explored different types of feeding:

Parents may adjust their feeding practices towards the needs of the child. Restrictive feeding and emotional feeding strategies can be used for different intentions and needs of the child and may therefore relate differently to children's weight status.

Restrictive feeding was generally assumed to negatively affect children's weight by hindering the development of self-regulation in eating and making the consumption of restricted foods more appealing.[70,71] In this thesis, we found no evidence for this. Instead, parents were more likely to use restrictive feeding in response to a high BMI or fat mass. Parents who were likely perceiving their child as being too heavy seem to intervene by limiting food intake to prevent further weight gain or to support weight loss. The use of restrictive feeding was largely explained by the level of maternal concern about the weight status of the child, indicating that if mothers do perceive their child as overweight and are concerned, they will likely use restriction.[72] So far, studies that examined bi-directionality also concluded that restrictive feeding is more likely to be a response to a higher BMI or to accumulating fat mass.[73-76] Further, a recent twin analysis showed the degree to which parents restrict food intake is related to children's genetic predisposition for obesity.[77] Now that it becomes evident that parents use restriction as a response to high weight, the question arises whether it is an effective strategy for weight loss. Although we observed that restrictive feeding did not predict a higher weight status, we neither observed a reduction in BMI due to more restrictive feeding over time, nor did other studies observe such a relation. Apparently, restriction causes no harm with respect to children's weight, but future research should examine to what extend restriction might be beneficial for children's weight status. Finally, it should be noted that extreme restriction might still have counterproductive effects on adiposity development.

Emotional feeding is used for non-nutritional purposes, namely to comfort the child when he or she is in distress. It can be argued that this also fits the child-responsive model: parents try to soothe the distressed child by offering food. However, whether this is a healthy method to comfort your child can be disputed. In this thesis, we showed that the use of emotional feeding as early as 6 months has a long-term negative effect on adiposity development, as indicated by higher levels of BMI and body composition at 6 and 10 years (chapter 9). This long-term effect was partially explained by the children's use of emotional overeating, as was shown in mediation analyses. This suggests that emotional feeding might teach children that food provides consolation when experiencing negative feelings and to develop emotional overeating as coping mechanism. This is compatible with our previous observations that in a subgroup of children increases in emotional overeating and the bi-directional nature of emotional overeating with BMI (chapter 2 and 4). Further support for our findings on emotional feeding comes from a study with an experimental design: children of mothers who offer children food for emotion-regulation purposes ate more in the absence of hunger as measured with calorie intake, and this was exaggerated when children themselves experienced a negative mood.[78] Nevertheless,

more studies should investigate the influence of emotional feeding on child development, particularly with an improved and repeated assessment of emotional feeding. Here, we studied emotional feeding based on only 1 item and we cannot rule out reversed causality as seen by restrictive feeding.

METHODOLOGICAL CONSIDERATIONS

Bi-directionality in observational studies

An often-reported limitation in observational studies that restricts inferring on causality is the potential problem of reversed causality. Usually, when an association is examined in an observational setting, researchers generate an *a priori* hypothesis on the direction of effects, in which factor X is hypothesized to have an influence on outcome Y. However, researchers cannot rule-out the possibility of reversed causality in which X is actually the result of Y at an earlier stage, and in many instances, a justified hypothesis for this reversed pathway can be thought of. Ignoring the possibility of reversed causation in epidemiological studies can lead to false inferences on causality and ultimately lead towards non-effective, or even harmful, intervention or treatment strategies.

Cross-lagged modeling

In this thesis, we examined the role of reversed causality in relationships between behaviors and adiposity by studying reciprocal effects simultaneously and thus provide more insight in the directionality of these relationships. A common method to study reciprocal effects is by using a cross-lagged modeling approach, also mentioned as a cross-lagged panel model or autoregressive cross-lagged panel model. Cross-lagged modeling is a technique within structural equation modeling (SEM) for which longitudinal data is needed. This method was first introduced by Campbell in 1963 as a quasi-experimental design, and later referred to as cross-lagged panel correlation. In the 1970's, Kenny studied and refined this methodology extensively and concluded that it was a suitable technique to provide an indication of causal predominance from one direction over the other.[79,80] Since then, cross-lagged modeling is commonly used to study the possibility of bi-directional relationships within the field of developmental psychology.[81]

A cross-lagged analysis represents a simultaneous comparison and requires that two variables of interest are assessed concurrently at two time points (or more), from which six pathways can be estimated: two stability paths, two cross-sectional paths, and two lagged paths. In figure 1, a prototypical cross-lagged model is presented. The coefficients of the stability (or autoregressive) paths show the association of a trait between two time points, represented in Figure 1 as B_1 and B_2. The cross-sectional paths between X_1 and Y_1, and between X_2 and Y_2 are represented as B_3 and B_4. Finally, the cross-lagged parameters,

from time point 1 to time point 2 are represented as B_5 and B_6. The lagged parameters can therefore be interpreted as the between-person effect of X_1 on Y_2, while controlling for stability in both variables, cross-sectional relationships between both variables and the reversed lagged effect.[79] In this thesis, we used different methods to evaluate whether one direction of effects is stronger than the other. In chapter 8, we searched for the best fitting model: a stability model was first created, including the stability paths and the cross-sectional paths. As a next step, we added the lagged effect in one direction, and repeated this separately for the lagged path in the opposite direction. Finally, a full cross-lagged model including the six paths was obtained. One of the four models described above was chosen based on model improvement tested with the Satorra-Bentler chi-square test using maximum likelihood estimation. In contrast, in chapter 4 , we conducted the full cross-lagged model at once and compared the strength of the two lagged effects by using the Wald test. A significant Wald test result indicates that the pathways significantly differ in strength, predominating one path over the other. The cross-lagged modeling approach can thus provide an indication of the direction of the association between the two variables by comparing the standardized lagged effects.

Although the cross-lagged model is a widely applied modeling strategy, it has also recently been debated and alternative techniques are proposed. It is argued that the regular cross-lagged modeling approach fails to differentiate within-person from between-person levels. Berry and Willoughby[81] state that there might be a mismatch between developmental theory and the statistical models we use to examine this theory. In studying bi-directional relationships, there is an interest in studying intra-individual changes – whether or not a persons' behavior changes over time or remains stable –, while as for all variable-centered approaches, the cross-lagged model examines bi-directional within- and between-person relationships (i.e. compared to children who have a lower BMI, children with a higher BMI might tend to eat more in response to external food cues). Berry and Willoughby argued that development is a within-person expedition and more attention should be given

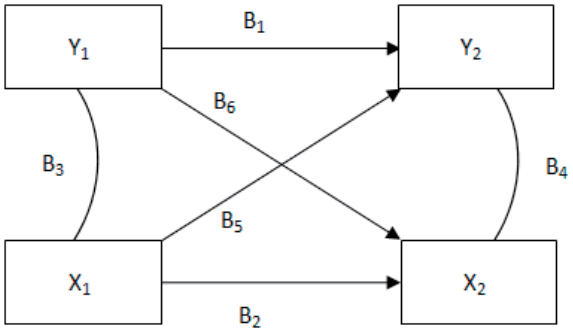


Figure 10.1. A prototypical cross-lagged model.

to within-person variation (i.e. eat more food in response to external food cues relative to one's own normal amount).[81] Similar critiques come from Hamark et al. (2015)[82] and Mund and Nestler (2019, *in press*).[83] Another related point of discussion for cross-lagged models is that the inclusion of the autoregressive effect between time points will fail to adequately control when the variable is too time-invariant and trait-like.[82] In order to differentiate for within-person variability and between-person variability and therefore also to overcome trait-like individual differences, alternatives for the cross-lagged model have been proposed.[81-83] The Random Intercept Cross-Lagged Panel Model (RI-CLPM) is able to represent the within-person level by modeling a random intercept for each person in the variables to capture trait-like between-person effects. Furthermore, the Autoregressive Latent Trajectory Model with Structured Residuals is also able to consider both within- and between-person differences by including a latent intercept factor and a latent slope factor to capture linear change for both variables. Therefore, the model estimates all relationships between intercept factors, slope factors and intercept and slope factors.[83] Comparing effect estimates between the regular cross-lagged model, the RI-CLPM and the Autoregressive Latent Class Trajectory Model with Structured Residuals (ALT-SR) shows that the 'traditional' cross-lagged model can over- or underestimate effects of the lagged paths. Yet, applying a Random Intercept Cross-Lagged model or an Autoregressive Latent Trajectory with Structured Residuals approach was not feasible in our studies, as they require at least three or four time points, respectively, which means we have to wait for future waves to obtain data for these analyses of eating and feeding behaviors. Furthermore, Hamaker et al.[82] state that, when the constructs are not too trait-like or time-invariant, adding the random-intercept of the RI-CLPM does not substantially affect the results and therefore a regular cross-lagged model can be applied. In regard to our constructs, different type of behaviors and body composition, it can be argued that BMI and body composition might be trait-like, with standardized coefficients ranging from 0.61 to 0.83 between time points. However, no standard on when a construct is too trait-like is provided, leaving us speculating whether this might be the case.

Assessment of feeding practices and eating behaviors in parents and children

In most instances, we used validated questionnaires for measuring dimensions of eating and feeding, the Child Eating Behavior Questionnaire and Child Feeding Questionnaire, respectively.[4,12,84-87] The validity and reliability of the dimensions that were constructed in these questionnaires have been examined extensively in different populations, at different ages of the child and across the spectrum from underweight to obesity. These psychometric properties assure us that the questionnaires are measuring what they are supposed to measure in a precise, reliable and accurate way. In this thesis, we also relied on other eating and feeding measurements that were assessed with only 1 or 2 items in two studies, which might be prone to some problems.

Eating in the absence of hunger

In chapter 3, we examined the relationship between maternal gestational glucose tolerance and eating in the absence of hunger in early adolescent offspring. Originally, the construct of eating in the absence of hunger was developed in a research lab setting as an observational measurement, a procedure that is still used these days. In short, children are invited to visit the laboratory for a range of measurements. During the visit, children were served with an ad-libitum lunch of a generous portion. After this, only children who indicated to be full were given access towards a room were a large variety of sweets and salty snacks were freely available. Children were told that they could eat whatever they wanted. The amount of foods consumed during the period of free-access was calculated, indicating the level of eating in the absence of hunger, and resembling disinhibition in eating.[71,88-90] Although this observational method of assessing the level of eating in the absence of hunger precisely reflects how much a child eats on this specific occasion, this is often not feasible in large population-based studies because it is too time consuming. Furthermore, it can be questioned whether the assessment of eating behavior in a lab setting is representable for eating behavior in the home environment. It can be argued that in the field of childhood obesity, researchers want to investigate the extent of eating in the absence of hunger in children in day-to-day life. Therefore, children's self-report on how often and to what extent they eat without hunger might provide more insight than the observational method used within the laboratory-paradigm.

In chapter 3, eating in the absence of hunger was assessed by self-report of the children based on only two items, which might have been prone to some problems. The two items that were used in this thesis to assess eating in the absence of hunger were derived from the Eating in the Absence of Hunger in Children and Adolescents Questionnaire (EAH-C), developed by Tanofsky-Kraff to conquer the laboratory-paradigm by creating a questionnaire.[91] This questionnaire consisted of 14 items, with 7 items starting with "*Imagine that you are eating a meal or snack at home, school, or in a restaurant. Imagine that you eat enough of your meal so that you are no longer hungry.*", followed by "*In this situation, how often do you keep eating because …*", or secondly, "*In this situation, how often do you start eating again because …?*" after which for each seven items a reason for eating is provided, focusing on the dimensions of eating in the absence of hunger, namely, external and emotional reasoning, and boredom. The use of only two modified items derived from the EAH-C has the disadvantage that the reliability and validity is unknown. This might induce misclassification because children did not understand the questions correctly or provided social desirable answers.[92] However, the original EAC-C showed to have good internal consistency, convergent validity with emotional overeating and loss of control in eating, and temporal stability.[91] This might also hold for the items that we used here, because only the stimulus indicating why children would eat in the absence of hunger was omitted. This does not affect the question of interest in our study on how

often children engage in eating in the absence of hunger, but might help the children to understand the questions better and provide more information on situations in which children would eat more in the absence of hunger. Another reason for concern about the construct that we used comes from the fact that in our sample, the level of eating in the absence of hunger was not correlated with the amount of consumed snacks and the level of adiposity of children which could have been expected.

Emotional feeding

In chapter 9, emotional feeding was assessed with one item for which misclassification might have occurred. Assessing a behavior like emotional feeding might be prone to social desirability, because parents are likely to be aware that offering food is not an encouraged method to soothe your child. Furthermore, the question "*In the past two weeks, have you tried to comfort your child by giving something to eat or drink?*" provides not enough information on the context. Mothers might have reported to comfort their child by offering food or milk when the child is crying because it was simply time to feed. This potential misinterpretation of the question might result in false-positive answers. Furthermore, assessing in which situations emotional feeding is used, what types of foods and drinks are offered to the child, and by which emotional states of the child might provide more in-depth information on situations where this strategy is used. Future studies should use validated questionnaires to measure emotional feeding as a construct. It is unclear how the above issues affected our results regarding the relationship between emotional feeding and adiposity.

In sum, the use of modified items of questionnaires or single items in epidemiological studies creates uncertainty on the validity and reliability of the measurements. This could have affected the results. However, it is unclear whether the above reported issues imply differential misclassification and whether this would result in an over- or underestimation of effects.

PERSPECTIVES FOR PREVENTION AND INTERVENTION

The complex etiology of obesity in children makes it extremely difficult to find an effective solution to curb this ongoing epidemic. So far, numerous strategies focused on behavioral and lifestyle changes were developed and implemented, but long-term successes in weight gain prevention or weight loss were not achieved. In 2017, the US Preventive Services Task Force (USPSTF) presented the following new recommendation: "The USPSTF recommends that clinicians screen for obesity in children and adolescents 6 years and older and offer or refer them to comprehensive, intensive behavioral interventions to promote improvements in weight status".[93] This intervention should include 26 contact hours or more over a period of 2 to 12 months in children who have obesity. Yet,

the USPSTF based this recommendation on intervention studies that reported a only a moderate beneficial effect on children's BMI SD score (mean reduction of −0.20 BMI SD score, which is considered the minimum clinically relevant threshold[94]) at a maximum of 12 months follow-up. Further evidence is needed to confirm the maintenance of weight loss.[93] The latter touches upon the problem of the absence of long-term successes with current behavioral intervention strategies. Indeed, a recently conducted, large, multicenter randomized controlled trial including 610 children aged 3-5 years at risk for obesity showed no positive effects on weight after 3 years follow-up of a multicomponent behavioral intervention in children.[95] Thus, the ongoing struggle to find effective intervention strategies based on changing health behaviors in school-aged children raises the question whether we are heading in the right direction.

The findings discussed in this thesis have some implications for prevention and intervention strategies. First, we propose that behavioral prevention strategies should be introduced as early as possible. Current programs to prevent excessive weight gain early in life mainly focus on responsive parenting, sleep hygiene and early feeding practices, and so far, results seem to be more effective compared to intervention programs implemented from mid-childhood onwards.[96-101] Moderately positive results on responsive feeding practices, eating behavior and weight of the child have been reported. Although these interventions early in life might be promising, more evidence for the effectiveness of early prevention is needed.[102] Though, starting preventive interventions in a community setting as early as possible, for instance by maternity care providers or healthcare practitioners at the Municipal Health Centers might be more effective than intervening later in childhood in children who are already developing obesity. One of the factors that could be included in these early-life interventions for parents is guidance on the use of food to soothe the infant when it's distressed and provide information on healthier alternatives.[97] Second, findings of this thesis might provide an explanation for the struggle to develop effective behavioral interventions for the prevention of weight gain or weight reduction in mid childhood by addressing eating behaviors. Using a population-based approach, we found no evidence for longitudinal associations between eating behaviors and subsequent weight gain from 4 years onwards, although changing eating habits often is the focus of intervention strategies.[103] Indeed, while many interventions address school-aged children, this can be too late, since many children are already overweight or obese when first attending school.[104]

A growing body of evidence suggests that restrictive feeding does not contribute to the development of obesity.[73-77] Policy makers should therefore consider removing this recommendation arguing that restrictive feeding should be avoided, as it is stated in the guidelines of the Dutch Center for Health in Youth (Nederlands Centrum Jeugdgezondheid). Discouraging parental restriction might have an adverse effect in overweight children, because their intake of palatable foods will not be controlled although this

might be necessary in children developing overweight. This study showed that restricting children's intake of snacks is a 'natural' and probably adequate response of parents of children with high adiposity as an attempt to hamper further weight gain. Yet, whether the use of restriction can influence weight reduction still needs to be examined but results in this thesis strongly suggest that there is no beneficial effect.

While the majority of our findings in this thesis emphasized the absence of a prospective influence of child behaviors on increasing adiposity, other findings suggest there is a window of opportunity for obesity prevention and intervention. Emotional overeating was bi-directionally associated with adiposity across childhood. This indicates a vicious circle in which children engaged in emotional overeating gain weight, and subsequently, use more emotional overeating because of negative feelings regarding their weight.[105] It is therefore of key importance to break this vicious circle, as it is affecting both children's physical and mental health state. In a population-based setting, our findings indicated that a subgroup of children strongly increased in their level of emotional overeating from 4 to 10 years. These children will be at high risk for obesity- or might already be obese- and are prone to develop binge eating disorder. First symptoms of binge eating (i.e. eating a large amount of food in a short period while experiencing loss of control in eating) can already occur in late childhood or early adolescence.[106,107] Episodes of binge eating arise as extreme maladaptive strategies in emotion-regulation to reduce the feelings of anger, anxiety or depression, as was shown in children aged 8-13 years who experienced at least one episode of loss of control in eating in the past 3 months.[108] Healthcare practitioners should therefore be aware of the risks of emotional overeating and detect its early signs. Furthermore, children at risk for obesity should be monitored regarding emotion regulation skills and the use of emotional overeating.[109] Other coping mechanisms for dealing with negative emotions should be introduced in children with as early as possible. In line with this, more attention should be paid to the physical risks of children with psychological problems as it becomes more and more clear that psychological problems of the child contribute to developing higher adiposity.[48,49,53] Although reported effect sizes are generally small, it is worthwhile to raise awareness of the risks of weight gain in these children. Perhaps, treatment of emotional and behavioral problems might also have beneficial effects on weight status of the child to some extent, but studies reporting this are lacking.

A final remark for policy makers in the field of obesity and other lifestyle related diseases should be provided. The genetic vulnerability for obesity will only express itself in combination with the environment. Therefore, providing the child with a healthy environment in the prenatal period and first years of life is key for a future healthy life. Yet, parents carry a massive responsibility for the upbringing of a healthy child while in the meantime the environment continuously seduces people to live unhealthy, with cheap palatable food and reinforcing a sedentary lifestyle. Changing the obesogenic environment should therefore be the first priority in obesity prevention.

FUTURE SCIENTIFIC CONSIDERATIONS

Taken everything together, some noteworthy recommendations for future research can be given. Because the results of this thesis foremost emphasize on the complex interrelation between adiposity and behavior, more studies are needed to examine whether these findings can be replicated.

In this thesis, we examined the relationship between adiposity with eating behaviors and feeding in children aged 4 years or older and results strongly raised the question what is happening before this age, as children who already a higher BMI as toddlers developed more unhealthy eating behaviors and parents applied more restriction as an attempt to reduce the high weight status. Therefore, studying environmental and behavioral aspects of adiposity from birth - or even before - onwards will help to determine why children at the age of 4 years are already overweight. Furthermore, as we hypothesize based on the results of this thesis that relationships between child eating behaviors and adiposity vary over time, repeated assessments of eating behaviors and adiposity from early childhood onwards are needed to further unravel this complex association. Although results from bi-directional studies provided more insight in the direction of effects, we are hesitant to make any inferences on causality based on cross-lagged models and more advanced methods are needed to create stronger conclusions on causality, such as a Mendelian Randomization Study should be carried out.[110]

Finally, as the children of the Generation R Study grow older, they are able to report on their own eating behaviors instead of relying solely on caregivers' reports. Studying relationships between psychological problems, behavior and obesity in early adolescents will be of interest to further disentangle these complex relationships throughout adolescence. New methods, such as Ecological Momentary Assessments, can assess detailed information on within-person changes in emotions by reporting mood fluctuations during the day and can provide more insight in when children start eating for emotional reasons and how this is associated with obesity and psychological problems.[111,112]

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A

Appendices

SUMMARY

Obesity is affecting many children worldwide and can have detrimental physical and psychological consequences throughout the life-course. The complex etiology of the development of adiposity in childhood involves many underlying factors, including genetic predisposition, the obesogenic environment, and physical and behavioral components. This makes it extremely difficult to develop effective prevention and intervention strategies in order to tackle this ongoing epidemic. Parental- and child health behaviors are of key interest in these strategies because behaviors can be considered as directly modifiable risk factors. However, these strategies have shown to be only moderately effective so far. Therefore, a better understanding of underlying behavioral components of adiposity is needed, as well as the examination on whether these behaviors are either determinants or consequences of a high weight status. The aim of this thesis was to examine the relationship of parental- and child behaviors with the development of adiposity and cardiometabolic health in children, and to provide more insight in the direction of the associations by using data of prospective population-based studies in high-income populations. Most studies described in this thesis were embedded in The Generation R Study, a prospective population-based cohort study situated in Rotterdam, the Netherlands.

In **part I**, we provided insight in the development of different eating behaviors across childhood. Eating behaviors are suggested to develop in early childhood and remain stable thereafter. Yet, whether different patterns of eating behaviors can be detected in children from 4 years onwards was unknown. In **chapter 2**, three distinct patterns of emotional overeating and five patterns of food responsiveness were identified. Regarding emotional overeating, patterns revealed that, although the majority of children remained low in their emotional overeating, some children developed a tendency towards more eating in response to emotions across childhood. For food responsiveness however, a small group of children already scored relatively high at the age of 4 years. A part of these children decreased in their sensitivity to external food cues by the age of 10 years while others remained stable at this high level. Opposed to this, other children increased moderately or strongly in their food responsiveness after the age of 4 years. We did not observe distinct patterns of enjoyment of food and satiety responsiveness from 4 to 10 years of age. An explorative examination of potential predictors of these distinct eating behavior patterns indicated that a higher weight status and more psychological problems in early life, as well as maternal controlling feeding strategies were correlated with the development or maintenance of a unhealthy eating behavior pattern. This knowledge might help identifying children at risk of developing obesogenic eating behaviors.

Offspring exposed to maternal impaired glucose tolerance during pregnancy has been shown to be at higher risk for obesity, perhaps by affecting the development of appetite regulation. In **chapter 3**, the relationship between maternal gestational glucose tolerance

and offspring eating in the absence of hunger in early adolescence was examined. We found sex-specific associations of exposure to impaired gestational glucose tolerance with eating in the absence of hunger in early adolescence: girls exposed to isolated hyperglycemia or impaired gestational glucose tolerance during pregnancy reported more eating in the absence of hunger, while boys exposed to impaired gestational glucose tolerance reported less eating in the absence of hunger. Furthermore, eating in the absence of hunger was not related to body composition in early adolescence. These findings suggest that exposure to impaired gestational glucose tolerance might affect sex-specific intrauterine programming and long-term appetite dysregulation.

In **part II,** prospective and bi-directional relationships of several child behaviors with body composition and cardiometabolic health were investigated. We showed that children with a higher BMI at the age of 4 years had an increased risk of developing unhealthy eating behaviors at 10 years, including more food responsiveness, more enjoyment of food and less satiety responsiveness (**chapter 4**). Associations in the opposing direction, from eating behavior to subsequent BMI, were not observed. Emotional overeating was shown to be bi-directionally associated with BMI, which indicates that children who engage in more emotional overeating have a higher risk of higher adiposity, and vice versa. Disentangling fat mass from fat free mass showed that effects of fat mass on eating behaviors were stronger than of fat free mass. This suggests that the development of more unhealthy eating behaviors might be a result a high weight status early in life instead of being a predictor for future weight gain.

In **chapter 5 and 6**, the influence of sleep duration in infancy on body composition and cardiometabolic health later in childhood and adolescence was investigated. In **chapter 5**, sleep duration was assessed by parental-reported questionnaires at 4 time points during infancy and early childhood. A small effect of shorter sleep duration at 2 months on BMI, fat mass and systolic blood pressure at 6 years was found, but not at other ages or other indicators of cardiometabolic health. In **chapter 6** the same relationship was examined in a different population in which sleep duration was assessed three times in the first 12 months by 5-minute interval diary reports. Results showed that sleep duration in infancy did not affect later body composition and cardiovascular health up to the age of 14 years, neither was sleep duration associated with body composition trajectories from 4 to 14 years. From these studies, we can conclude that infant sleep only plays a marginal role in the development of adiposity and cardiometabolic health later in life.

In **chapter 7**, the role of aggressive behavior in children and its potential bi-directional relationship with adiposity was investigated. Previous studies showed that attention problems increase the risk of obesity in children, but whether aggressive problems are also associated with an increased weight in children is unknown. It was shown in three population-based cohorts that children with more aggressive behavior in mid childhood had an increased risk of a higher adiposity level at 10 or 14 years, although effect sizes

were small. In turn, a higher adiposity level in mid childhood did not affect children's aggressive behavior. This implies that aggressive behavior might be one of the many factors that contribute to the development of adiposity in children.

In **part III**, the role of different parental feeding strategies on eating behavior and adiposity development of the child was explored. In **chapter 8**, we investigated the direction of effects of the use of restrictive feeding practices and childhood adiposity. Results indicated that mothers used more restrictive feeding practices at the age of 10 years when the child had a higher BMI at the age of 4 years. The level of concern of the mother about the weight of the child partially mediated the observed relationship. No temporal relationship between restrictive feeding at 4 years and subsequent adiposity level of the child was observed. These results therefore suggest that the level of restriction a mother applies in feeding is more likely to be a response to a higher weight status of her child.

The influence of emotional feeding in infancy on eating behaviors and weight status later in childhood was examined in **chapter 9**. We showed that children of mothers who often used food for soothing purposes during infancy were more likely to have a higher BMI and body composition at 6 and 10 years of age. These children also showed higher levels of emotional overeating at 4 years, which partially explained the relationship between emotional feeding and the development of adiposity. This suggests that mothers who use food to comfort their distressed child might teach children that eating is a method to cope with negative emotions, and therefore enhances a higher weight status.

Finally, in **chapter 10** , the main results of this thesis are discussed, as well as some important methodological considerations such as the use of cross-lagged models to study bi-directional relationships. Implications for prevention and intervention are provided as well as recommendations for future research.

NEDERLANDSE SAMENVATTING

In dit proefschrift staat de relatie tussen de verschillende gedragsfactoren en de ontwikkeling van overgewicht bij kinderen centraal. In de afgelopen 40 jaar zijn de prevalenties van overgewicht en obesitas bij kinderen en jongeren wereldwijd sterk gestegen. In Nederland heeft gemiddeld 13.5% van alle kinderen overgewicht en is nog eens 2.8% van alle kinderen gediagnosticeerd met obesitas. Het hebben van overgewicht of obesitas als kind kan vergaande gevolgen hebben voor de gezondheid in het latere leven. Eerder onderzoek heeft reeds aangetoond dat kinderen met overgewicht of obesitas een hogere kans hebben op het behoud van een verhoogd lichaamsgewicht gedurende de adolescentie en volwassenheid. Daarbij hebben zij meer kans op gerelateerde ziekten als diabetes type 2, hart- en vaatziekten en psychische problemen. Ook op jonge leeftijd kunnen kinderen al last hebben van de consequenties van overgewicht: ze worden vaker gepest en hebben vaker sociale en emotionele problemen vergeleken met kinderen met gezond gewicht. Bovendien zijn soms de eerste verschijnselen van het metabool syndroom al zichtbaar.

Om de epidemie van overgewicht en obesitas bij kinderen een halt te kunnen roepen, is het van belang dat de etiologie goed begrepen wordt om zo effectieve preventie en interventiestrategieën te kunnen ontwikkelen. Tot op heden is dit een grote uitdaging omdat één enkele directe oorzaak meestal niet aantoonbaar is maar het juist een complexe interactie van allerlei genetische-, omgevings-, biologische- en gedragsfactoren blijkt te zijn. Het is hierdoor lastig aan te tonen waardoor het ene kind wel overgewicht ontwikkeld en het andere kind niet. De algehele stijging van het voorkomen van overgewicht is wel verklaarbaar: de huidige, obesogene omgeving zorgt ervoor dat er een overvloed aan ongezond eten beschikbaar is en er zo weinig mogelijk lichaamsbeweging nodig is.

Gezond gedrag geniet op dit moment veel aandacht in de ontwikkeling van preventie en interventieprogramma's. De reden hiervoor is dat gedrag in principe veranderd kan worden. Tot dusver heeft met name cross-sectioneel onderzoek aangetoond dat gedragsfactoren, zoals eetgedrag, slaapduur en gedragsproblemen, en overgewicht met elkaar gerelateerd zijn. Ook werd aangetoond dat verschillende voedingsstrategiëen, de manier van eten geven, die toegepast worden door ouders gerelateerd zijn aan het gewicht van het kind. Deze bevindingen kunnen echter niets zeggen over de richting van het waargenomen verband: is gedrag een voorspeller van overgewicht, of blijkt juist het gedrag van kinderen en ouders te veranderen als gevolg van een hoger gewicht? Prospectieve onderzoeken met herhaalde metingen kunnen helpen in het beantwoorden van dit vraagstuk door de richting van het effect te onderzoeken.

Het doel van dit proefschrift was om meer inzicht te geven in de relatie tussen verschillende gedragsfactoren van ouders en kinderen en de ontwikkeling van overgewicht gedurende de kindertijd. In dit proefschrift werd niet alleen BMI als maat voor gewichtsstatus onderzocht maar kon ook een belangrijk onderscheid gemaakt worden tussen

vetmassa en vetvrije massa, die samen de lichaamssamenstelling vormen. Allereerst hebben we gekeken naar de ontwikkeling van eetgedrag bij kinderen (deel I), vervolgens werd de relatie van verschillende gedragsfactoren met het gewicht, de lichaamssamenstelling en de cardio-metabole gezondheid van kinderen onderzocht (deel II), en als laatste onderzochten we de rol van verschillende voedingsstrategiëen van moeders op de ontwikkeling van het gewicht en lichaamssamenstelling van kinderen (deel III).

Om bovenstaand doel te kunnen onderzoeken is gebruik gemaakt van data van verschillende grote bevolkingsonderzoeken wereldwijd. De meeste studies zijn uitgevoerd binnen het bevolkingsonderzoek genaamd de Generation R Studie. Dit onderzoek is opgezet om de ontwikkeling en gezondheid van een nieuwe generatie Rotterdammers te onderzoeken. Tussen 2002 en 2006 werden alle zwangere vrouwen in Rotterdam uitgenodigd om deel te nemen. Na de geboorte vulden ouders regelmatig vragenlijsten in over de ontwikkeling en gezondheid van hun kinderen. Op 6- en 10-jarige leeftijd werden de kinderen uitgenodigd bij het onderzoekscentrum in het Sophia Kinderziekenhuis om deel te nemen aan diverse lichaamsmetingen en gedragsonderzoeken. Naast de Generation R Studie zijn er ook studies uitgevoerd binnen soortgelijke bevolkingsonderzoeken in andere landen met een hoog inkomen zoals de Verenigde Staten, Australië en Zweden.

Deel I. De ontwikkeling van eetgedrag in kinderen

Het eerste gedeelte van dit proefschrift is gewijd aan het onderzoek naar de ontwikkeling van eetgedrag in de kindertijd. Eerdere onderzoeken suggereerden dat het eetgedrag van een persoon in de vroege kindertijd ontwikkeld wordt en daarna redelijk stabiel blijft gedurende de rest van het leven. In **hoofdstuk 2** werd bestudeerd of kinderen tussen de leeftijd van 4 jaar tot 10 jaar kunnen veranderen in hum eetgedrag door groepen met verschillende patronen in eetgedrag te identificeren. Hierbij werd gekeken naar 4 dimensies van eetgedrag: de mate waarin kinderen reageren op externe eetsignalen, zoals het zicht en de reuk, de mate waarin kinderen responsief zijn naar hun verzadigingsgevoel, de mate van plezier tijdens het eten en de mate van emotioneel overeten. Er werden vijf verschillende groepen kinderen geïdentificeerd die verschillen in de mate waarop zij reageren op externe eetsignalen. De meeste kinderen (66.7%) lieten over de tijd een stabiel patroon van lage scores zien maar twee groepen kinderen lieten een toename zien van dit gedrag (23.3%) en weer een andere groep kinderen een afname (6.7%). Verder was er een kleine groep die over de leeftijd van 4 tot 10 jaar een stabiele hoge mate van reactie op externe eetsignalen liet zien (3.2%). Bij emotioneel overeten kwamen andere patronen naar voren: op de leeftijd van 4 jaar scoorden alle kinderen relatief laag. De meeste kinderen lieten dit nog steeds zien op de leeftijd van 10 jaar (63.7%) maar de rest van de kinderen nam toe: 29.3% van de kinderen nam gematigd toe in hun emotioneel overeten, en de overige kinderen lieten een sterke toename in emotioneel overeten zien van 4 tot 10 jaar (7.0%). Alle kinderen lieten echter een vergelijkbaar en redelijk stabiel traject van responsiviteit op verzadiging en de mate van

plezier tijden het eten zien over een periode van 6 jaar. Vervolgens werd in dezelfde studie exploratief onderzocht welke factoren gecorreleerd zijn aan de ontwikkeling van ongezond eetgedrag. Met name overgewicht en emotionele en gedragsproblemen van het kind op 3-jarige leeftijd waren gerelateerd aan de ontwikkeling van ongezondere eetgedrag, samen met voedingsstrategieën van de ouders. Deze kennis kan helpen bij het identificeren van kinderen met een hoog risico op het ontwikkelen van obesogeen eetgedrag.

Kinderen die zijn blootgesteld aan verstoorde glucosetolerantie van de moeder tijdens de zwangerschap hebben een hoger risico op de ontwikkeling van overgewicht. Dit verhoogde risico zou verklaard kunnen worden door een verstoring in de ontwikkeling van de eetlustregulatie. In **hoofdstuk 3** werd de relatie tussen maternale glucosetolerantie tijdens de zwangerschap en de mate van eten zonder hongergevoel van hun kinderen op de leeftijd van 13 jaar onderzocht. Maternale glucosetolerantie werd gemeten tijdens de zwangerschap door middel van een glucose-challenge test en een glucosetolerantie test waarbij resultaten in vier categorieën werden ondergebracht: normale glucose tolerantie, geïsoleerde hyperglycemie, verstoorde glucose tolerantie en zwangerschapsdiabetes. Geslacht-specifieke relaties tussen maternale hyperglycemie tijdens de zwangerschap en het eten zonder hongergevoel bij de kinderen werden geobserveerd. Meisjes die blootgesteld werden aan geïsoleerde hyperglycemie of verstoorde glucosetolerantie tijdens de zwangerschap rapporteerden vaker hogere waarden van eten zonder hongergevoel dan meisjes die blootgesteld werden aan een normale glucosetolerantie tijdens de zwangerschap. Voor jongens werd een tegenovergestelde relatie gevonden: blootstelling aan een verstoorde glucose tolerantie tijdens de zwangerschap was geassocieerd met minder eten zonder hongergevoel. Als laatste werd er geen verband gevonden tussen de mate van eten zonder hongergevoel en BMI, vetmassa of vetvrije massa geobserveerd op 13-jarige leeftijd. De geslacht-specifieke bevindingen zouden verklaard kunnen worden door een verschil in sensitiviteit op de intra-uteriene omgeving waardoor er verschillen in de ontwikkeling van eetlust-regulatie kunnen ontstaan.

Deel II. Gedrag, lichaamssamenstelling en cardiometabole gezondheid in kinderen

Deel II beschrijft het onderzoek naar de prospectieve relatie, en waar mogelijk de richting van deze relatie, tussen verschillende gedragsfactoren met het gewicht, de lichaamssamenstelling en cardiometabole gezondheid. Uit het onderzoek beschreven in **hoofdstuk 4** bleek dat kinderen met een verhoogd BMI op de leeftijd van 4 jaar een hogere kans hadden op meer ongezond eetgedrag op de leeftijd van 10 jaar, namelijk het vaker reageren op externe eetsignalen, het hebben van meer plezier om te eten en een verminderde responsiviteit op het verzadigingsgevoel. Dit resultaat kwam naar voren door de bidirectionele relatie te onderzoeken tussen eetgedrag en BMI. Er werd echter geen bewijs gevonden voor dat ongezond eetgedrag een verhoogd BMI zou kunnen voorspellen. De

mate van emotioneel overeten was bi-directioneel geassocieerd met BMI gedurende de kindertijd, waarbij meer emotioneel overeten gerelateerd was aan een hoger BMI op latere leeftijd en andersom een hoger BMI tevens meer emotioneel overeten voorspelde. Een onderscheid in de lichaamssamenstelling liet zien dat de relatie tussen vetmassa en eetgedrag sterker was dan de relatie tussen vetvrije massa en eetgedrag. Verklaringen voor deze prospectieve relatie tussen een hoger gewicht en de ontwikkeling van ongezond eetgedrag later in de kindertijd kan liggen in het behoud van een verhoogd lichaamsgewicht waardoor er meer energie nodig is, net als een verminderde sensitiviteit voor het verzadigingshormoon leptine en een verminderde sensitiviteit voor het hormoon dopamine wat het beloningsgevoel van eten verminderd.

Veel studies hebben laten zien dat een korte slaapduur invloed heeft op de ontwikkeling van overgewicht bij kinderen, adolescenten en volwassenen. Minder is bekend over de invloed van slaapduur in de eerste jaren van het leven. In **hoofdstuk 5 en 6** worden de resultaten van twee onderzoeken naar de relatie tussen slaapduur in de vroege kindertijd (tot 3 jaar) met het gewicht, de lichaamssamenstelling en cardiometabole of cardiovasculaire gezondheid later in de kindertijd en adolescentie beschreven. In **hoofdstuk 5** was slaapduur op 4 momenten in de eerste 3 jaar van het kind gemeten door middel van vragenlijsten. Een kortere slaapduur op een leeftijd van 2 maanden had een klein effect op BMI, vetmassa en systolische bloeddruk op 6-jarige leeftijd. Daarentegen werd geen relatie gevonden voor andere tijdspunten waarop slaapduur was gemeten in combinatie met andere cardio-metabole uitkomsten op de leeftijd van 6 jaar. In **hoofdstuk 6** werd slaapduur in baby's tot de leeftijd van 12 maanden 3 keer gemeten met behulp van dagboeken. In deze studie werd geen verband tussen slaapduur, gewicht en lichaamssamenstelling op verschillende leeftijden in de kindertijd en adolescentie gevonden. Tevens was slaapduur in het eerste levensjaar niet geassocieerd met cardiovasculaire uitkomsten toen kinderen 14 jaar oud waren. Uit de resultaten van deze twee hoofdstukken kan geconcludeerd worden dat slaapduur in het vroege leven weinig invloed lijkt te hebben op de ontwikkeling van overgewicht en cardiometabole uitkomsten later in de kindertijd of adolescentie.

In het laatste hoofdstuk van deel II (**hoofdstuk 7**) onderzochten we de prospectieve en potentiele bi-directionele relatie tussen agressief gedrag en BMI en lichaamssamenstelling bij kinderen. Uit eerdere studies werd geconcludeerd dat aandachtsproblemen het risico op het ontwikkelen van overgewicht of obesitas kan verhogen maar of dit ook het geval is voor agressief gedrag, dat beiden onder de gedragsproblematiek valt, is niet bekend. Om deze relatie te onderzoeken werd gebruik gemaakt van drie verschillende bevolkingsonderzoeken met dezelfde metingen op bijna dezelfde leeftijden, van 6-9 jaar naar 10 of 14 jaar. In alle drie de cohorten werd een klein effect van meer agressief gedrag op een hoger BMI waargenomen. Een onderscheid tussen vetmassa en vetvrije massa in de lichaamssamenstelling liet zien dat agressief gedrag gerelateerd was aan een hogere

vetmassa, maar niet aan vetvrije massa. Er werd geen prospectieve relatie in tegenovergestelde richting, dat BMI of vetmassa vooraf gaat aan agressief gedrag, gevonden. Deze bevindingen impliceren dat agressief gedrag mogelijk bijdraagt aan de ontwikkeling van overgewicht en obesitas bij kinderen.

Deel III. Voedingsstrategieën van de moeder en lichaamssamenstelling van het kind

In deel III onderzochten we ten slotte de rol van verschillende voedingsstrategieën van de moeder op het gewicht en de lichaamssamenstelling van het kind. In **hoofdstuk 8** werd het beperken van de inname van ongezond eten bij kinderen door hun ouders onderzocht. Eerdere studies toonden aan dat een beperkende voedingsstrategie van ouders gerelateerd was aan een hoog gewicht van het kind. Dit zou verklaard kunnen worden doordat kinderen op deze manier hun eigen regulatie van eetlust niet goed ontwikkelen, waardoor ze meer eten wanneer er wel mogelijkheid tot ongezond eten is. Wij vonden echter geen bewijs voor deze assumptie. Het beperken van de voedselinname door de moeder op 4-jarige leeftijd was namelijk niet geassocieerd met gewicht en lichaamssamenstelling later in de kindertijd. Resultaten lieten echter zien dat wanneer kinderen een hoger BMI en lichaamssamenstelling op 4-jarige leeftijd hebben, moeders vaker een beperkende voedingsstrategie toepassen op de leeftijd van 10 jaar. De bezorgdheid van moeders over het gewicht van het kind verklaarde deels deze relatie. Deze resultaten laten zien dat ouders geneigd zijn de voedselinname van het kind te beperken als een reactie op de hoge gewichtsstatus van het kind.

In **hoofdstuk 9** werd de rol van een andere voedingsstrategie onderzocht: het gebruik van eten om het kind te kalmeren wanneer het huilt, boos of angstig is. Deze manier van eten geven heeft een gunstig korte termijn effect om het kind te sussen maar kan mogelijk lange termijn gevolgen hebben voor het eetgedrag en gewicht van het kind. Resultaten lieten zien dat kinderen van moeders die aangaven deze manier voeden regelmatig toe te passen wanneer hun kind 6 maanden oud was, kans hadden op een hoger BMI op 6 en 10-jarige leeftijd. De mate van emotioneel overeten van het kind op 4-jarige leeftijd bleek een belangrijk deel van deze relatie te verklaren. Dit kan betekenen dat ouders op deze manier hun kinderen zouden kunnen leren om emoties 'weg te eten', dat vervolgens kan bijdragen aan de ontwikkeling van adipositas. Het is raadzaam om daarom ouders andere strategieën te leren om hun baby te kalmeren wanneer ze huilen, bijvoorbeeld door te wiegen, wandelen, praten of zingen.

Tot slot worden in de discussie (**hoofdstuk 10**) de belangrijkste resultaten bediscussieerd, methodologische overwegingen besproken, zoals het gebruik van cross-lagged modellen voor het onderzoeken van bi-directionele relaties, en vervolgens perspectieven voor preventie en interventie gegeven. Als laatste worden aanbevelingen voor verder onderzoek gegeven.

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LIST OF PUBLICATIONS

This Thesis

Derks IPM, Kocevska D, Jaddoe VWV, Franco OH, Wake M, Tiemeier H, Jansen PW. Longitudinal associations of sleep duration in infancy and early childhood with body composition and cardiometabolic health at the age of 6 years: The Generation R Study. *Childhood Obesity*. 2017;13(5):400-408

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ABOUT THE AUTHOR

Ivonne Derks was born on the 7th of January, 1990 in Ravenstein, the Netherlands. She is the second child of four from Mat Derks and Bets Bardoel. Together with her sisters Marloes and Jeanette, and brother Peter, she enjoyed her childhood in Ravenstein, where she also attended primary school. She graduated from pre-university in 2008, with the specialization in Science and Health. In the same year, she started her bachelor program in Health Sciences at Maastricht University. During her bachelor, she chose to follow the Mental Health track, and additionally participated in the minor Health and Law at the Maastricht University School of Law. After obtaining her bachelor degree in 2011, she travelled through South America for four months. Inspired by her travels and research ambitions, she started the Health Sciences Research Master with the Global Health specialization at Maastricht University in 2012. During her master program, she performed two research internships focused on type 2 diabetes. First, In 2013, she spend three months in Arizona, US, to study the role of traditional medicine and health behaviors in Native Americans with type 2 diabetes, supervised by Prof.dr. Rob de Bie. In the second year of her master program, Ivonne performed a full-year research internship at the department of Social Medicine, Maastricht University, where she examined the relationship between early life socioeconomic conditions and type 2 diabetes, using data from the Maastricht Study and supervised by Prof.dr. Hans Bosma. After graduation in 2014, she started her PhD program supervised by Dr. Pauline Jansen and Prof.dr. Henning Tiemeier at the department of Child and Adolescent Psychiatry/Psychology and The Generation R Study Group at the Erasmus MC in Rotterdam, from which the results are presented in this thesis. During her PhD, she obtained a postgraduate master degree in Clinical Epidemiology from the Netherlands Institute of Health Sciences and she performed a research project as a visiting research fellow at Harvard Medical School and Harvard Pilgrim Health Care Institute, in Boston, USA. In 2019, she started as postdoctoral researcher at the Department of Psychology, Education and Child Studies, Erasmus University Rotterdam, where she combines her research with teaching.

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Name PhD student:	Ivonne PM Derks
Department at Erasmus Medical Centre:	Child & Adolescent Psychiatry/Psychology
Research School:	Netherlands Institute for Health Sciences (NIHES)
PhD period:	August 2014 – August 2018
Promotor:	Prof. Dr. H Tiemeier
Co-promotor:	Dr. PW Jansen

	Year	Workload (ECTS)
1. PhD Training		
General courses		
Master of Science in Health Sciences, specialisation Clinical Epidemiology, Netherlands Institute for Health Sciences, Erasmus University Rotterdam, the Netherlands		
Core curriculum		
Study design	2014	4.3
Biostatistical methods II. Classical regression models	2014	4.3
Clinical Epidemiology	2015	7.5
Methodological topics in epidemiological research	2014	1.4
Electives		
Psychiatric Epidemiology	2015	1.1
Missing values in Clinical Research	2015	0.7
Principles of Epidemiological Data-analysis	2015	0.7
Maternal and Child Health	2015	0.9
Women's Health	2016	0.7
Erasmus Summer Program		
Principles of Research in Medicine and Epidemiology	2014	0.7
Methods of Public Health Research	2014	0.7
Clinical Trials	2014	0.7
Health Economics	2014	0.7
The Practice of Epidemiological Analysis	2014	0.7
Fundamentals of Medical Decision Making	2014	0.7
Methods of Clinical Research	2015	0.7
Social Epidemiology	2015	0.7
Causal Inference	2015	0.7
Causal Mediation Analysis	2015	0.7
Logistic Regression	2015	1.4

	Year	Workload (ECTS)
Skill courses		
Biomedical writing and communication, Erasmus MC, Rotterdam	2016	2.0
EAS Sensitivity training, Leiden University, Leiden	2015	1.5
Stralingshygiëne voor röntgentoestellen, Erasmus MC, Rotterdam	2014	1.0
Research Integrity, Erasmus MC, Rotterdam	2016	0.3
Conference presentations		
International Society of Behavioral Nutrition and Physical Activity, Victoria, Canada (oral presentation)	2017	1.2
Developmental Origins of Health and Disease (DOHaD), Rotterdam, The Netherlands (oral presentation)	2018	1.2
Developmental Origins of Health and Disease (DOHaD), Rotterdam, The Netherlands (poster presentation)	2018	0.6
Sophia Research Day, Erasmus MC, Rotterdam, the Netherlands	2017	0.5
Workshops, Meetings and Symposia		
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Generation R Research Meetings, Erasmus MC, Rotterdam, The Netherlands (oral presentation)	2014-2019	1.0
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Supervising Master's theses		
Monica Walhout (Pedagogy and Education/ Family Pedagogy, Erasmus University Rotterdam)	2015	2.0
Maternal sensitivity and food fussiness in early childhood: A Generation R Study		
Cora Moerland (Clinical Psychology, Erasmus University Rotterdam)	2015-2016	2.0
Inhibitory control and parenting styles in the prediction of overweight in children		
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The association between religion and bullying behaviour involvement in children from Dutch national origin at the age of six years		
Zeynep Yalcin (Clinical Psychology, Erasmus University Rotterdam)	2016-2017	2.0
Childhood weight and obesity in relation to aggressive behaviour symptoms		

	Year	Workload (ECTS)
Other Teaching Activities		
Teaching assistant Principles of Research in Medicine and Epidemiology, Erasmus Summer Program, Erasmus MC, Rotterdam, the Netherlands	2016 and 2017	2.0
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Research Fellowship at the department of Population Medicine, Harvard Medical School- Harvard Pilgrim Health Care Institute, Boston, USA	2017-2018	
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Bio Art and Design Awards, ZonMW, NAW	2017	1.5
1 ECTS (European Credit Transfer System) is equal to a workload of 28 hours		

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Adiposity is affecting many children worldwide and can have detrimental physical and psychological consequences throughout the life-course. The complex etiology of the development of adiposity in childhood involves many underlying factors, including genetic predisposition, the obesogenic environment, and physical and behavioral components. This makes it extremely difficult to develop effective prevention and intervention strategies in order to tackle this ongoing epidemic. Parental- and child behaviors are of key interest in these strategies because behaviors can be considered as directly modifiable risk factors. However, so far these strategies have shown to be only moderately effective. Therefore, a better understanding of underlying behavioral components of childhood adiposity is needed, as well as the investigation of whether these behaviors are either determinants or consequences of a high weight status. The aim of this thesis was to examine the relationship of parental- and child behaviors with adiposity development and cardiometabolic health in children, and to provide more insight in the direction of the associations by using data of prospective population-based studies in high-income populations. Most studies described in this thesis were embedded in The Generation R Study, a prospective population-based cohort study situated in Rotterdam, the Netherlands.