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

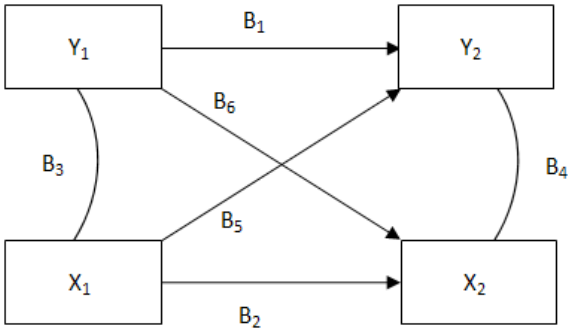

Figure 10.1. A prototypical cross-lagged model.

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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