Chapter 7

General discussion
Against the background of a dramatic rise in overweight and obesity prevalence at the end of the 20th century, the American Academy of Pediatrics (AAP) recommended pediatricians in 2003 to routinely assess and guide children in their diet and physical activity practices [1]. Diet and physical activity are considered the main drivers of the obesity epidemic. Since the beginning of this century, the effect of sedentary behavior (i.e., any waking behavior characterized by a very low energy expenditure while sitting, reclining or lying) has increasingly been evaluated and targeted by overweight and obesity prevention programs in children [2]. However, effects of programs tackling these behaviors on overweight and obesity prevention and reduction are only modest, encouraging researchers to think beyond these classic determinants of overweight and obesity [3]. An increasing body of research now examines the role of psychosocial stressors in the development of overweight and obesity [3,4]. An important psychosocial stressor in this context is the experience of adverse life events. Adverse life events are events such as childhood abuse, illness or death of a family member or friend and parental divorce. The focus of this dissertation was on the relation between adverse life events and body mass index (BMI) in children, adolescents and young adults.

In this chapter, I will provide a summary of the main findings of this dissertation and discuss their implications. I will provide explanations for why certain associations between accumulation of adverse life events and BMI and between childhood abuse and BMI were identified, while others were not. Firstly, I will focus on factors that could influence the relationship between adverse events and BMI. Secondly, the existence of a time lag between exposure and outcome will be considered. Thirdly, gender differences in the associations between adverse life events and BMI will be discussed. Suggestions for obesity prevention and intervention programs and areas for future research will be given. This chapter will conclude with methodological considerations in accumulation of adverse events research.

**MAIN FINDINGS**

The first research question of this dissertation was whether there was an association between accumulation of adverse life events and measures of overweight in childhood, adolescence and young adulthood. The results of the systematic review and meta-analysis indicated a small positive association between accumulation of adverse life events and measures of overweight (i.e. overweight, obesity and BMI) in childhood and adolescence (chapter 2). However, the number of included studies was small and heterogeneity between studies with regard to measurement of adverse life events and construction of an accumulated adverse life events measure was large. In addition, longitudinal cohort studies investigating the association between accumulation of adverse life events and overweight measures in adolescence were scarce. In a longitudinal investigation using TRAILS data, a
Dutch cohort study following adolescents into young adulthood, no associations were found between accumulation of adverse life events and BMI in children and adolescents (chapter 3). Using the same data, different trajectories of BMI development from adolescence to young adulthood (i.e. trajectories characterized by low increases in BMI and trajectories characterized by high increases in BMI) were identified. These trajectories were also not differentially associated to the number of adverse life events children experienced (chapter 4). Little to no evidence was thus found for a relation between accumulation of adverse life events and BMI, overweight and obesity in childhood and adolescence. However, associations between accumulation of adverse life events and BMI were identified in young adulthood (age 22 years). Adverse events in different life phases, shortly as well as long before young adulthood, were associated with BMI in young adulthood. Accumulation of adverse events in childhood was associated with a higher BMI in young adulthood and accumulation of adverse life events at the end of adolescence and beginning of young adulthood was associated with a lower BMI in young adulthood. The first association was attributable to adverse health events, such as illness or death of a family member and hospitalization, while the second association was attributable to adverse relationship and victimhood events, such as conflicts with friends or family, break-ups and being a victim of bullying (chapter 3). This shows that the direction of the association between adverse events and BMI in young adulthood may depend upon the type of experienced adverse events and the life phase in which these events were experienced. It also shows that adverse events may have an effect on BMI development long after their occurrence.

The second research question was whether a particularly severe adverse childhood event, childhood abuse, was associated with BMI in young adulthood. The association was investigated in a Dutch sample (chapter 5) and in a nationally representative sample from the United States (chapter 6). Of the three types of childhood abuse (i.e. sexual, physical and verbal abuse), only sexual abuse was related to BMI in Dutch young adult females, while only verbal abuse was related to BMI in US young adult females. Associations were thus only identified between particular types of childhood abuse and BMI in young adults and only in females. Important to note is that sexual abuse in Dutch females was not only associated with higher BMI at the beginning of young adulthood, but also with a higher increase in BMI in young adulthood. This again shows that adverse life events may influence BMI development long after their occurrence.

The third research question of this dissertation was whether the association between childhood abuse and BMI in young adulthood was mediated by depression and/or anxiety disorders. The identified association between sexual abuse and BMI in young adult females was partially explained by diagnosis of major depressive disorder (MDD) before young adulthood, but not by diagnosis of generalized anxiety disorder (GAD) (chapter 5). The
prevalence of MDD before young adulthood was increased in males and females who experienced childhood abuse and the occurrence of MDD, in turn, was related to a higher BMI in young adult females. The association between MDD and BMI was not identified in males. In addition, MDD before young adulthood was not related to higher increases in BMI in young adulthood, neither in females nor in males. While the prevalence of GAD was increased in both young adult females and young adult males who experienced abuse, GAD was not associated with BMI in young adults of either sex. GAD thus did not mediate the relation between childhood abuse and BMI in young adults.

The fourth and final research question of this dissertation was whether the association between childhood abuse and body mass index in young adulthood was moderated by personality traits. Evidence was found for moderation of the association between childhood abuse and BMI by personality traits in a US sample (chapter 6). Abuse- and personality trait-specific effects were identified in males and females. Low extraversion was a risk factor for higher BMI in verbally abused males and females. Additionally, in physically and verbally abused females, high agreeableness was a risk factor for higher BMI. In physically abused males, in turn, high conscientiousness and high openness were risk factors for higher BMI. Finally, high neuroticism was a risk factor for higher BMI in sexually abused males. Individuals who were more likely to experience inner distress thus seem most prone to BMI changes in response to abuse.

The main findings of this dissertation are summarized in Figure 1. In females, accumulation of adverse life events in childhood is related to overweight and obesity in young adulthood. In addition, associations are identified between childhood abuse and BMI in young adult females. An association between sexual abuse and BMI is identified in Dutch young adult females and between verbal abuse and BMI in US young adult females. The relationship between sexual abuse and BMI in Dutch young adult females is partly mediated by a diagnosis of major depressive disorder (MDD) at the end of adolescence. In addition, there is moderation of the relationship between childhood physical and verbal abuse and BMI by personality traits in young adult females. In males, accumulation of adverse life events in childhood is related to overweight and obesity in young adulthood. No associations between childhood abuse and BMI are identified in young adult males. However, personality traits moderate the association between childhood abuse and BMI in young adult males. In the remainder of this general discussion, I will reflect on the identified associations and on explanations for why certain associations were not identified.
A. Females

B. Males

Figure 1. Summary of the findings of this dissertation (per chapter) for females (A) and males (B).
FACTORs INFLUENCING THE ASSOCIATION BETWEEN ADVERSE EVENTS AND BMI

The associations identified in the first decades of life between accumulation of adverse life events and overweight measures and between childhood abuse and overweight measures were few in number and small in size. As the findings exemplify, this could be caused by the fact that the association between adverse life events and BMI is influenced by the presence or absence of other, tertiary, factors [5]. The relation between adverse life events and BMI could be influenced by child characteristics, life phase characteristics and event characteristics (Figure 2).

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**Figure 2.** Factors that can influence the association between adverse life events and body mass index (BMI).

**Child characteristics**

Some individuals will be exposed to many adverse life events without experiencing detrimental changes to their BMI, while other individuals will experience BMI changes after exposure to relatively few adverse life events [3]. Differences in resilience and coping between individuals are considered the most likely explanation to underlie differences between children in BMI changes following adverse life events [3]. Resilience and coping are intertwined concepts. Resilience is “positive adaptation within the context of significant adversity” [6]. Coping is defined as “the conscious volitional effort to regulate emotion, cognition, behavior, physiology, and the environment in response to stressful events or circumstances” [7]. Children with high resilience and effective coping strategies may not experience changes in BMI in response to the occurrence of adverse events, while children with low resilience and ineffective coping strategies may [3].

A factor related to coping is personality [8]. Personality traits are enduring patterns of thinking, feeling and behavior that differ between people [9]. Personality could serve both as a factor influencing someone’s appraisal of an event as well as someone’s response to an event [10]. The relationship between various types of childhood abuse and BMI was influenced by specific personality traits (chapter 6). Scoring high on personality traits characterized by being more trusting of others, more orderly, prone to distress and more likely to keep distressed feelings inside was shown to serve as a risk factor for higher BMI after the experience of abuse. The reverse was often also true: the same type of abuse was
related to lower BMI in participants who were less trusting of others, less orderly, less prone to distress and more likely to express distressed feelings. For example, verbal abuse was not only related to higher BMI in females scoring high on agreeableness, but was also related to lower BMI in females scoring low on agreeableness. Childhood abuse was thus related to increases in BMI as well as to decreases in BMI, depending on someone’s personality. In line with this finding, childhood abuse has been related to overweight and binge eating as well as to underweight, skipping meals, vomiting and other eating pathology [11–14]. Accumulation of adverse events has also been related to both binge eating and extreme weight control behaviors in adolescents and young adults [15]. Adverse life events can thus be related to higher BMI as well as to lower BMI and the direction of the association may depend upon child characteristics such as personality.

Other child characteristics that could influence the presence and direction of an association between adverse life events and BMI are dietary intake, physical activity and weight status. Individuals who display obesogenic behaviors and have a high weight status may be more likely to increase their weight when stressed, whereas individuals who display no obesogenic behaviors and have a normal or low weight status may be more likely to maintain or even decrease their weight when stressed [16,17]. Adverse life events are related to higher BMI in children who have high sweet food intake, but not in children with low intake of sweet foods [18]. In addition, the relationship between adverse life events and BMI is weaker in adolescents with high physical activity levels than in adolescents with low physical activity levels [19]. The idea that weight status may influence the relation between adverse events and changes in BMI is supported by a study in adults [20]. In this study, weight status influenced the relation between the impact of the most severe experienced event and changes in weight. With an increase in the reported impact of the adverse event, overweight adults showed a tendency for weight gain, while adults with a healthy weight showed a tendency for weight reduction. A different response to adverse events by children with a different weight status is also a possible explanation for the fact that we did not observe an association between the number of adverse life events children experienced and the BMI trajectories identified in the study in chapter 4 (i.e. the ‘normal weight’, ‘early onset overweight’ and ‘late onset overweight’ trajectories). When adolescents in the higher BMI trajectories (the ‘early onset overweight’ and the ‘late onset overweight’ trajectory) respond to adverse events by increasing their weight, while adolescents in the ‘normal weight’ trajectory respond to adverse events by maintaining or even decreasing their weight, no relationship between accumulation of adverse events and BMI trajectory will be identified. Health behavior characteristics and weight status of children experiencing adverse events
may thus influence the presence and direction of an association between adverse life events and BMI.

Life phase characteristics
The presence and direction of a relation between adverse events and BMI could also be influenced by the examined life phase. In chapter 3, accumulation of adverse events in childhood was related to higher BMI in young adulthood, while accumulation of adverse life events in adolescence and young adulthood was related to lower BMI in young adulthood. Childhood may thus be a sensitive period for stress to induce elevations in BMI, while in adolescence stress may be more likely to have BMI lowering effects. Childhood and adolescence are different stages of development, biologically as well as psychologically, and this could cause the effect of events on body and behavior to be different. For example, different brain areas are most vulnerable to outside influences in different phases of development [21]. Stress in early childhood has greater effects on the hippocampus than on the prefrontal cortex, while adolescent stress has greater effects on the prefrontal cortex than on the hippocampus [21–23]. These differential vulnerabilities of brain areas to stress in different life phases may result in different effects of stress on health in the different life phases. Another biological difference between adolescents and children is that adolescents are exposed to higher levels of circulating sex hormones than children. Sex hormones influence the reactivity of the hypothalamic-pituitary-adrenal axis (HPA axis), a central system in the stress response [24]. The higher levels of sex hormones in adolescence compared to childhood could cause differences in the effects of stressors on HPA axis activity in the different life phases [24]. In addition, brain maturation and sex hormones can influence the experience of stress [25]. These different stress experiences in response to adverse events in the different life phases can cause differences in the association between adverse life events and BMI. In conclusion, differences in the vulnerability of different brain areas to outside influences, in the effects of sex hormones on the HPA axis and in the experience of stress could cause the association between adverse life events and BMI to be different in childhood and adolescence.

Event characteristics
Another explanation for the differences in the association between accumulation of adverse life events and BMI in the different life phases could be that in our study different events were measured in childhood and adolescence. In childhood, a limited number of adverse events were measured, including parental illness, parental death, parental divorce and out-of-home placement. At the end of adolescence many more events were measured, including miscarriage, conflicts with friends or family and unemployment. Different types of events
can have different effects. Many event types may only result in acute stress [20]. However, specifically chronic stress is believed to result in overweight and obesity [26]. Accumulation of adverse events would be assumed to reflect chronic rather than acute stress due to it being a measure of subsequent, repeated exposure to stress [27]. However, when many minor events exerting only acute stress are included, accumulation may not necessarily reflect chronic stress [28]. Measurement of different events can thus lead to differences in the association between accumulation of adverse events and health. This idea is supported by the fact that in our study the positive association between accumulation of adverse events in childhood and BMI in young adulthood was attributable to adverse health events, while the negative association between accumulation of adverse events at the end of adolescence and BMI in young adulthood was attributable to adverse relationship and victimhood events. However, while in our study adverse health events were measured in childhood, adolescence and the beginning of young adulthood, only adverse health events in childhood were associated with BMI. In addition, in our study similar adverse events were measured both at the start and at the end of adolescence and only the latter were related to BMI. Measurement of different adverse events in the different life phases does thus not fully explain the differences in the identified relations. Moreover, if the type of event would be crucial for the existence of a relation between adverse events and BMI, one would expect childhood abuse, one of the most severe adverse events, to be related to BMI [28]. In contrast, we identified few associations between childhood abuse and BMI in young adulthood (chapter 5 and chapter 6).

In this dissertation, the relation between various types of childhood abuse and BMI in young adulthood was examined. While only a relation between sexual abuse and BMI was identified in young adult females in a Dutch cohort (chapter 5), only an association between verbal abuse and BMI was identified in young adult females in a nationally representative sample from the United States (chapter 6). Differences in the results of both studies could be caused by the fact that the data came from different countries, with highly differing living conditions, policies and health-care systems. Differences could also be caused by the fact that the sample from the US was several years older than the Dutch sample. In addition, differences could be caused by the fact in the two studies different tools were used to measure abuse. In the US study (chapter 6), abuse was measured by one question assessing only severe abuse, while in the Dutch study (chapter 5) multiple questions, also assessing less severe forms of abuse, were used. It is thus possible that the measures used for childhood abuse contain abuse experiences that do not all have an equally large impact. The fact that, in chapter 5, one or more occurrences of verbal abuse were reported by about 75% of the sample, an extremely high percentage, supports this idea. It may be that only the
less common, and presumably more severe, forms of verbal abuse, such as threatening a child, are related to BMI [29].

Another event characteristic that could influence the relation between adverse life events and BMI is the duration of adverse events [30,31]. The longer the duration of an adverse event, the more likely an event is to exert chronic stress rather than acute stress and hence BMI changes. For example, a conflict with family or friends can be quickly resolved or can be drawn-out. When a conflict is quickly resolved, the conflict is most likely to result in acute stress only, while it is more likely to result in chronic stress when the conflict is drawn-out. Previous studies showed that individuals that needed a longer time to process the events they experienced and individuals that experienced events at multiple time points had a lower physical health and were more likely to be overweight [32,33]. The time someone is exposed to events may thus influence the relation between adverse life events and physical health. The type of adverse events measured and the duration of the measured adverse events could thus explain why different associations between accumulation of adverse life events and BMI were identified in the different life phases.

**DELAY IN THE EFFECT OF ADVERSE EVENTS ON BMI**

In both studies on accumulation of adverse life events and studies on childhood abuse in this dissertation, associations with BMI changes were primarily found at the end of adolescence and in young adulthood. A study examining differences in obesity rates between sexually abused females and non-sexually abused females in childhood and young adulthood similarly only identified a difference in young adulthood as a result of a higher increase in BMI between childhood and young adulthood in sexually abused females [34]. In addition, in a meta-analysis on childhood abuse and obesity, an association was identified with obesity in adulthood, but not with obesity in childhood and adolescence [35]. A likely explanation for these findings is that there is a delay in the effects of childhood abuse on BMI. This dissertation suggests that some associations between childhood abuse and BMI (have) come to expression in young adults. This is in line with previous studies identifying no or few associations in young adults [36,37].

There may be a time lag between the occurrence of adverse life events and changes in BMI, because of the time it takes for intermediary processes to take place. As mentioned in the introduction, psychosocial stressors are assumed to affect BMI via two mechanisms: via health behaviors and via the body’s biology [26,38]. Obviously, when health behaviors are affected, this does not result in immediate changes in BMI. Moreover, health behaviors in childhood may not be influenced at all, because of the strong influence of parents on children’s health behaviors [39]. However, as children become adolescents and young adults their health behaviors may be influenced by adverse events. This is because in these life
phases health behaviors increasingly come under their own control and responsibility [39]. Adolescence and young adulthood may thus be the life phases in which adverse childhood events come to expression via alterations in health behaviors. However, even this will not immediately result in changes in BMI. If psychosocial stressors influence BMI via an effect on health behaviors, an association with BMI is probably not seen until adulthood.

When psychosocial stressors exert an effect on BMI via alterations in biological reactions in the body, a time lag between event exposure and BMI changes is also likely to exist. For example, hippocampal volume changes in response to childhood stress are generally not observed in childhood, but are shown in adulthood [31]. There can thus be a long lag before biological alterations in response to adverse events come to expression and translate into adverse health [40]. If psychosocial stressors influence BMI via an effect on biological reactions, effects may thus not be seen until adulthood.

Finally, when the relation between adverse events and changes in BMI is dependent upon other, intermediary, health conditions, a time lag between both factors is also likely to exist. In this dissertation, depression and anxiety disorders were considered as intermediate health conditions that could connect adverse life events to changes in BMI.

THE ROLE OF DEPRESSION IN THE RELATION BETWEEN ADVERSE EVENTS AND BMI
In the study described in chapter 5, a rise in major depressive disorder (MDD) and generalized anxiety disorder (GAD) rates following the occurrence of childhood abuse was noted. The occurrence of GAD was not related to BMI in young adulthood. The occurrence of MDD was also not related to BMI in young adult males. However, the occurrence of MDD before young adulthood was related to higher BMI at the beginning of young adulthood in females. The relation between childhood sexual abuse and BMI in females was partially explained by the occurrence of MDD. It is important to note, however, that the possibility of reverse causation in the relation between MDD and BMI cannot be completely ruled out. It is possible that instead of MDD before young adulthood contributing to a higher BMI at the beginning of young adulthood, a higher BMI in childhood or adolescence actually contributed to the development of MDD before young adulthood [41].

Mediation of the relation between childhood abuse and BMI by MDD
Depression and BMI may be associated via the same two mechanisms that were also mentioned to explain the association between adverse events and BMI. Firstly, they may be associated via unhealthy behaviors [42]. For example, depression has been associated with emotional eating (e.g. eating in response to negative emotions) [43,44] and emotional eating has been associated with higher unhealthy dietary intake [45,46] and higher BMI [43,44,46,47]. Here, emotional eating serves as a mediator of the relation between
depression and BMI [43,44]. Depression has also been related to lower physical activity and lower physical activity self-efficacy [44,48]. Lower physical activity and lower physical activity self-efficacy, in turn, have been related to increased adiposity and BMI [44,48]. Physical activity and physical activity self-efficacy also serve as mediators of the relation between depression and BMI [44,48]. Thus, unhealthy behaviors may serve as a mechanism connecting depression to BMI.

A second explanation for the association between depression and BMI may be that the conditions are biologically related. Dysregulation of the HPA axis, a system of biological reactions in the body that plays a central role in the stress response, has been implicated in both obesity and depression [49]. Altered activity of the HPA axis has been shown in depressed patients [49] and cortisol, the end product of the HPA axis, is suggested to lead to increased unhealthy food intake and fat deposition in the body [17,50,51]. Depression and obesity may thus be related via alterations in biological reactions in the body.

On the preceding pages, several mechanisms have been described that are suggested in the literature to connect adverse events and BMI. In Figure 3, a graphical summary of these mechanisms is given. Adverse events may be related to BMI via changes in health behaviors and biological reactions in the body. Adverse events can also be associated with BMI via mental health conditions. Mental health conditions and BMI may be associated via changes in health behaviors and biological reactions.

![Figure 3](image-url)

**Figure 3.** Graphical summary of proposed relation between adverse life events and body mass index (BMI). Note: (1) moderating factors are not displayed in this figure and (2) the timeline in this figure provides an indication of the timing of the different elements in the framework, but timing may vary across individuals.
Moderation of the relation between MDD and BMI by childhood abuse

Next to evidence for mediation of the relation between childhood sexual abuse and BMI by MDD, we also found evidence for moderation of the relation between MDD and BMI by childhood sexual abuse. In females who experienced childhood sexual abuse, MDD and BMI were associated, while no evidence for an association was identified in females who did not experience childhood sexual abuse. As mentioned before, dysregulation of the HPA axis has been implicated in both obesity and depression [49]. In addition, dysregulation of the HPA axis has been suggested to be a consequence of childhood abuse [52]. MDD and changes in BMI may thus be the result of related alterations in biological reactions in the body in response to childhood abuse [38,42]. The biological profile of MDD and obesity in response to childhood abuse may therefore be different from the biological profile of MDD and obesity arising from different causes. In line with this idea, MDD in response to childhood abuse has been shown to differ biologically from MDD from other causes [53]. Research found that individuals who experienced childhood abuse and who suffered from depression had a smaller hippocampal volume, higher inflammatory biomarkers and a higher stress response than depressed individuals who did not experience childhood abuse [54–58]. This biological profile of depression in response to childhood abuse may also be associated with changes in BMI. The relation between MDD and BMI, presented in Figure 2, may therefore be specifically present in individuals who experienced childhood abuse.

GENDER DIFFERENCES

Several associations in this dissertation were identified among women, but not among men. Previous research also only detected associations between childhood abuse and obesity in females, more readily detected associations in females or detected stronger associations in females [35,37,59].

Gender differences in the association between childhood abuse and BMI may be explained by differences in health behaviors between the sexes. Women are shown to score higher than men on emotional eating and stress-related eating and lower than men on physical activity self-efficacy [44,60]. These health behaviors and beliefs about the ability to perform health behaviors are suggested to mediate the relation between adverse events and BMI. Therefore, the relation between adverse events and BMI may be more pronounced in women than in men.

Gender differences in the association between depression and BMI may also explain differences in the association between childhood abuse and BMI. Depression is more often associated with weight gain in women than in men [61]. This may be due to differences in health behaviors between women and men with depression. Depression is associated with
emotional eating [43,44] and an association between emotional eating and unhealthy dietary intake has been identified in females with depression, but not in males with depression [45]. Therefore, depression could be specifically related to a higher BMI via emotional eating and unhealthy dietary intake in women. A stronger relation between depression and BMI in females may explain why associations between childhood abuse and BMI are detected in young adult females, but not in young adult males.

Besides via health behaviors and health conditions, adverse events and BMI may also be related via biological reactions. Biological differences between the sexes in brain maturation and functioning during childhood and adolescence may lead to gender differences in the appraisal of events in these life phases [25]. In addition, differences between the sexes in the timing of puberty onset, in the effect of sex hormones on the stress response and in interactions of sex hormones with stress on brain development could serve as explanations for why the relationship between childhood abuse and BMI is different for women and men [62]. In line with the idea of puberty and sex hormones influencing the reaction to stress, gender differences in functioning of the HPA axis seem to emerge in adolescence [25]. Female sex hormones are suggested to particularly influence the HPA axis [25]. Therefore, the relation between adverse life events and BMI may be more pronounced in women. Differences in health behaviors and biology between the sexes may thus explain why childhood abuse is related to BMI in women, but not in men.

STRATEGIES TO PREVENT CHANGES IN BMI IN RESPONSE TO ADVERSE EVENTS

To my knowledge, no studies into prevention of obesity following the experience of adverse events have been performed. However, cohort studies and intervention studies to reduce depression and depressive symptoms in response to adverse events provide suggestions for obesity prevention strategies following adverse events. As depression and BMI changes following childhood abuse are related, strategies to prevent depression following childhood abuse may also prevent changes in BMI. Ideally of course, adverse events in childhood, especially severe events causing high levels of stress, should be prevented [63]. However, if prevention of these adverse events is not possible, preventing health problems associated with adverse events holds a higher promise and is likely more cost-effective than treatment of health problems later in life [63,64]. In all these efforts, the possible cause of the health problems needs to be taken into account. Prevention efforts aimed at MDD need to be different when MDD is the result of childhood abuse than when MDD has a different cause, as the clinical course of and treatment success in MDD is influenced by adverse childhood experiences [53,65,66]. Obesity prevention strategies for children who experienced adverse events may therefore also need to have a different content than overweight and obesity prevention strategies in general [38]. Studies suggest that increasing acceptance of negative
emotions, resilience, engagement in health behaviors, effective family functioning and social support are all promising strategies to reduce adverse health outcomes in individuals who experienced adverse life events. In addition, changing DNA methylation patterns may be a biological strategy to reduce depression and changes in BMI following the experience of adverse events (Figure 4). Below, all these factors will be discussed in more detail.

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Figure 4. Factors that can be targeted in overweight and obesity prevention programs following the experience of adverse events.

Factors to target in intervention programs
Firstly, child characteristics can be targeted in prevention and intervention programs to reduce adverse health conditions in response to adverse events. This dissertation shows that personality traits can be a fruitful target for obesity prevention strategies after the experience of adverse events. For example, increasing extraversion could prevent increases in BMI in verbally abused children low on extraversion. Increasing children’s acceptance (as opposed to children’s avoidance) of negative emotions may also result in better mental and physical health following adverse events. Individuals who were more accepting of negative emotions did not experience an increase in depressive symptoms in reaction to adverse events, whereas individuals who were less accepting of negative emotions did show increases in depressive symptoms in response to adverse events [67]. In addition, the experience of adverse events is related to a lower depression score in individuals who score higher on resilience than in individuals who score lower on resilience [68]. Physical activity levels were also increased by an intervention to increase resilience and health behaviors, pointing to a possible physical health benefit of increasing resilience as well [69].

Not only factors related to the child can be targeted, but the social environment of children who experienced adverse events can also be targeted to decrease adverse effects on health. Factors such as family dysfunction and social support are important. Programs that increase children’s exposure to safe, stable and nurturing environments and relationships by providing assistance to parents, in terms of social support and teaching them responsible health behaviors and child-rearing and management skills, have been shown to reduce children’s exposure to adversity and improve children’s cognitive and
social-emotional development [64]. In addition, changes in HPA axis activity were not seen in children in foster care that participated in an intervention aimed at stimulating a warm environment, positive behavior and social and developmental competencies, while they were seen in children in foster care that did not receive the intervention [70]. In line with stimulating a warm environment, social support could be an important factor to increase in children who experienced adverse events [71]. Adults who experienced childhood maltreatment and were diagnosed with a mental disorder less often reported participation in sports clubs, having had friends and the presence of a support figure outside the home in childhood than adults who were maltreated as children, but who were not diagnosed with a mental disorder [71].

A potential biological target in prevention and intervention programs is DNA methylation. Differences in susceptibility to depression after trauma exposure may be traced back to differences in DNA methylation following trauma exposure [72]. DNA methylation can cause so-called silencing of genes: genes cannot be transcribed and translated into proteins, because of alterations (i.e. the addition of methyl groups) made to the DNA structure. These different DNA methylation and gene expression patterns may result in altered biological processes in the body following childhood abuse, such as an altered stress response [73] and reflect the risk of developing MDD following childhood abuse [72]. These DNA methylation patterns may additionally reflect the risk of developing BMI changes following childhood abuse. Targeting DNA methylation profiles using pharmaceutical or nutritional interventions may therefore be a promising route to prevent depression and obesity following adverse events [72]. Future studies should examine whether this approach is safe and indeed results in reduced rates of depression and obesity following adverse events.

**Timing of interventions**

For most interventions, the optimal time frame would be childhood or, at the latest, adolescence. Childhood and adolescence are periods of increased brain plasticity [74]. In these time periods, the brain is especially vulnerable to exposures that can cause alterations, such as stressors [74]. Therefore these periods may also be the best periods to reverse the effect of stressors. In addition, the fact that MDD and GAD rates in response to childhood abuse are already elevated in adolescence (chapter 5) and the fact that it is more difficult to reverse adverse health behavior patterns once they are established warrants prevention and intervention efforts as early as possible [63].
Chapter 7

METHODOLOGICAL CONSIDERATIONS IN ACCUMULATION OF ADVERSE EVENTS RESEARCH

There are several methodological considerations when performing studies on the accumulation of adverse events. One inherent limitation of studies on accumulation of adverse events is the lack of a universally accepted method for measuring adverse events and constructing an accumulated adverse events measure. Results of existing studies assessing the association between accumulated adverse events and overweight, obesity and BMI in childhood are heterogeneous (chapter 2). Differences in the methods used to measure adverse events and to construct an accumulated adverse events measure likely partially explain these differences. While studies often use some type of sum score, the included adverse events, the way information on these adverse events is generated and the way in which sum scores are created differ strongly between studies. Below, I will first focus on aspects to consider when measuring adverse events and I will subsequently focus on aspects to consider when constructing an adverse events score.

Measuring accumulation of adverse events

There are several measurement aspects to carefully consider when studying accumulation of adverse events. Firstly, to truly study accumulation of adverse events, measurement of a large number of different types of events is advisable. When studying only a small number of events, results can be driven by the presence or absence of a particular event rather than by accumulation of events. Further, if a limited range of event types is included in the adverse events score, one is examining adverse events experienced in a certain domain, rather than accumulation of adverse events in general. To exclude the possibility that events in a certain domain drive associations, researchers can create sum scores of the different types of adverse events in addition to creating an overall adverse event score. The association between these different accumulated adverse events scores and overweight, obesity or BMI can subsequently be determined, as we did in chapter 3 and chapter 4.

A second aspect to consider when measuring adverse events is the length of the recall period. The period over which adverse events are recalled should be long enough for measures to truly reflect which individuals experienced more adverse events and which individuals experienced fewer adverse events. In addition, the recall period should be long enough for changes in overweight, obesity or BMI to become apparent. The recall period should, however, not be too long either. The length of the recall period should not raise questions about whether adequate and reliable recall of adverse events is possible.

A third aspect to consider when measuring accumulation of adverse events is which informant to use. As the child is the most likely informant to know exactly which events it encountered, the child is the best informant to report on adverse life events in its own life, if
age permits [75]. Only if the child is too young or the period studied is a period of which the child has no conscious recollection, someone close to the child should report on the adverse events the child has experienced.

A final important aspect to consider when measuring adverse events is which measurement method to use. Information on adverse events can be collected in an interview or by using a self-administered questionnaire. In interviews, information can be collected on a more complete set of events than can be done through most questionnaires [75]. However, the downside of interviewing is that individuals may not mention adverse events for which they feel embarrassment [75]. Nonetheless, using an interview serves the advantage of being better able to judge the reliability, the context and the exact content of the reported adverse events than can be done using a questionnaire [75]. When possible, the use of an interview is therefore advised.

**Construction of an accumulated adverse event measure**

With regard to the construction of the accumulated adverse events measure, two aspects should be considered. The first aspect is whether to use a continuous accumulated adverse events measure or to apply cut-offs and use a categorical accumulated adverse childhood events measure with a limited number of categories. Creating an accumulated adverse events measure with a limited number of categories by applying cut-offs is discouraged [76]. In our systematic review and meta-analysis, results of studies on accumulation of adverse events and overweight in childhood that used a categorical accumulated adverse events measure were heterogeneous, while results of studies that used a continuous accumulated adverse events measure were not heterogeneous (chapter 2). Contrasting individuals who experienced high and low numbers of adverse events may indeed result in the identification of larger associations with health, but there likely is considerable variability in the exposure within the contrasted groups [76]. Therefore, the clinical relevance of these contrasts and the usefulness of the results in daily practice can be questioned. Children who experienced a certain threshold of adverse events cannot easily be identified and prevention strategies aimed at these children are difficult to implement. The use of a continuous adverse childhood events measure is advised [76].

The second aspect to consider with regard to the construction of the accumulated adverse events measure is whether or not to weigh the experienced adverse events based on their severity. Using a severity rating, based on reports of the person who experienced the adverse events, could be crucial for the identification of a relationship between adverse life events and BMI as the experienced severity may mimic one’s physiological reaction or may influence one’s behavioral reaction to adverse events [77]. However, a study examining the relation between a combination measure of the number of experienced adverse life
events, the severity of the events and chronicity of the events did not show a relation between this measure and BMI [77]. In addition, an overall score of mother-reported impact of adverse events was not related to overweight in adolescents [33]. Whether measures of accumulated adverse events that include a severity rating serve as a better predictor of BMI is thus debatable, definitely if the severity rating is not made by the respondent. In addition, researchers should consider the possibility that factors moderating the relation between adverse life events and BMI, such as personality, can influence the severity rating of the respondent. Moderators may thus not be identified when a severity rating is applied. When one truly wants to study the relationship between accumulation of adverse events and BMI, without attenuating the effect of moderating factors, a severity rating should therefore not be used in the accumulated adverse life events measure.

CONCLUSION
This dissertation shows that accumulation of adverse life events in childhood and adolescence is related to BMI in young adulthood, while it is not related to BMI in childhood and adolescence. In addition, childhood abuse has few associations with initial BMI in young adulthood and is most strongly associated with increases in BMI in young adulthood. These last associations are gender-specific: they are identified in females, but not in males. There thus likely is a delay in the effect of adverse life events in childhood on BMI. In addition, the association is more pronounced in females than in males. If adverse life events indeed get under the skin at an early age and slumber there for years before they come to expression as serious health conditions, targeting children is crucial for prevention of these conditions. Prevention and intervention efforts aimed at reducing overweight and obesity development in response to adverse life events would benefit from a better understanding of child and event characteristics that influence the relation between adverse life events and BMI and from a better biological understanding of the relation.
REFERENCES


Chapter 7


