The Co-Development of Adiposity, Inflammation and Depressive Symptoms Across Adolescence: A Focus on Sex Differences, Developmental Trajectories and Bidirectional Associations

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Table of Contents

List of Tables and Figures

Tables

Figures

Abstract

There is recognized comorbidity of obesity and depression, and research suggests chronic low-grade inflammation as a potential shared mechanism connecting these two health conditions. However, this hypothesis is mainly based on cross-sectional studies with adult clinical samples, which limits understanding of the developmental nature of these constructs. Furthermore, there is a debate on the directionality of these associations. Recent research also suggests that there are sex differences not only in the individual developmental trajectories of depression, obesity and inflammation across adolescence, but also in the associations among them. Examining the co-development of these constructs in adolescence is particularly important given the high prevalence of first onset-depression during adolescence. Biological mechanisms are critical to consider because obesity and inflammation are associated with endocrine processes which are salient during puberty, and sex differences may be especially apparent during this period. However, few studies have examined these questions in a prospective longitudinal manner throughout adolescent development.

Thus, the current study aimed to examine the co-development of adiposity, inflammation and depressive symptoms in the period from pre-adolescence to early adulthood, and to examine whether these associations differ between boys and girls. These questions were explored in a subset of data from the Avon Longitudinal Studies of Parents and Children (ALSPAC; *N*=6,525). Fat Mass Index (FMI) was used as a measure of general adiposity. C-reactive protein (CRP) was used as a marker of systemic inflammation. Depressive symptoms were assessed by the Short Mood and Feelings Questionnaire (SMFQ; Angold et al., 1995). Each was measured at 4 time points between 9 and 24 years. A combination of both cross-lagged panel analyses and parallel-processes latent growth curve models were used to examine their associations.

The most robust and consistent findings emerged for the relations between FMI and CRP. The development of these two constructs was clearly linked across adolescence, and although girls and boys had different developmental trajectories of FMI and CRP, for both there was greater evidence for earlier adiposity driving later inflammation than for the converse. CRP was not clearly linked with depression across adolescence, and in fact, for both boys and girls, CRP was inversely associated with depression at different points in development. Considering associations with adiposity, the findings from the 3-level cross-lagged model indicated that preadolescents with elevated depressive symptoms may be at greater risk for increasing adiposity, and for girls, increasing inflammation, in the transition into adolescence. However, this pattern does not seem to continue in the later phases of adolescence and emerging adulthood.

These findings demonstrate that the mechanisms underlying the relations between adiposity, inflammation and depression are clearly different in adolescents compared to adults. There is no evidence that systemic inflammation is a shared mechanism between depression and obesity in adolescents. In fact, the null and inverse associations found between CRP and depression in this study call into question the notion that CRP can be used as a biomarker for depression. Consistent with the model proposed by Byrne and colleagues (2015), the study provides limited support to the hypothesis that adiposity and inflammation are consequences rather than antecedents of adolescent-onset depression, and that preadolescent depressed girls may be at greater risk for developing physical health problems in adulthood. To reach a better understanding of the mechanisms at play during adolescence, future research on this topic would benefit from including multiple measures of inflammation and adiposity, measuring sex and stress hormones, and collecting date on diet, exercise, body image, stress and sub-types or symptoms of depression.

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1. Introduction

Obesity and depression are both major public health concerns in children and adults worldwide, and there is recognized comorbidity of these two illnesses, with some data suggesting that obese individuals have about 55% increased odds of developing depression (Luppino et al., 2010), and females with depression having higher risk of being overweight or obese (Linde et al., 2011) and girls having higher risk for both depression and obesity (Quek, Tam, Zhang, & Ho, 2017). Clinical studies with adults show that both obesity and depression are characterized by a state of low-grade inflammation, (Ellulu, Patimah, Khaza'ai, Rahmat, & Abed, 2017; Kiecolt-Glaser, Derry, & Fagundes, 2015), suggesting that this may be a shared biological mechanism explaining the high rates of comorbidity between these two illnesses (Milaneschi, Simmons, van Rossum, & Penninx, 2018). This biological mechanism can also potentially explain the gender difference seen in depression and obesity, since females have stronger immune responses and are more prone to autoimmune diseases (Klein & Flanagan, 2016). However, this hypothesis was primarily developed based on cross-sectional studies with adult clinical samples who already have high levels of inflammation, limiting understanding of how these associations develop over time. Furthermore, research examining these questions amongst adolescents is limited, and it is unclear whether these inter-relations are evident in adolescents and whether they operate in adolescence the same way as in adulthood.

A hallmark of innate immunity, inflammation is one of the body's first lines of defense against pathogens, and involves the joint effects of cytokines and acute-phase reactants in response to infection or injury (Slavich & Angeles, 2015). At a site of infection or tissue damage, cytokines can cause redness, heat, swelling, and pain to promote wound healing, prevent the spread of infection and alert the body to the injury. At a more systemic level, certain cytokines

such as interleukin-6 (IL-6) travel through the blood to the liver, where they stimulate cells to synthesize and secrete the acute-phase protein, C-reactive protein (CRP) (Slavich & Irwin, 2014). CRP and cytokines then act together to increase heart rate, respiratory rate, and body temperature. Acute inflammation is beneficial in the context of an acute physical threat to the body; it accelerates wound healing, kills pathogens and helps the body conserve energy to aid in the recovery from the insult (Slavich & Angeles, 2015). Once the pathogen is cleared, inflammation levels should return to normal. However, when activation of the inflammatory response is altered or prolonged, as in the case of exposure to recurrent or chronic stress, it can cause significant damage to the body (Slavich et al., 2020). This state of chronic inflammation is called "low-grade inflammation" to distinguish these modest elevations from the high elevations of CRP observed in acute inflammation, and it is known to be implicated in a host of major illnesses such as cardiovascular disease, metabolic syndrome, asthma, diabetes, arthritis, and certain cancers (Couzin-Frankel, 2010).

Though higher levels of adiposity and depression are both associated with inflammation, it is not clear how and when associations between these constructs are formed. In adults, two directional hypotheses have been proposed. The first mechanism posits that obesity leads to depression through cytokine-induced mechanisms (Shelton & Miller, 2010). Adipose tissue is an endocrine organ secreting proinflammatory cytokines and fostering a state of low-grade inflammation (Kyrou, Chrousos, & Tsigos, 2006). Proinflammatory cytokines can enter the brain and induce a constellation of "sickness behaviors" which are commonly observed in depression, such as anhedonia, fatigue, pain, sleep problems and social-behavioral withdrawal (Slavich & Irwin, 2014). The second mechanism posits that prior depression may increase the risk for subsequent adiposity through poor diet and sedentary behavior, and greater adiposity then leads

to elevated inflammation (Miller, Freedland, Carney, Stetler, & Banks, 2003). Alternatively, these two pathways can operate in a reciprocal manner, creating a "vicious cycle" in which these constructs are fueling one another, enhancing the development and progression of both depression and obesity and increasing the risk for other inflammation-related diseases (Shelton & Miller, 2011).

Elucidating the pathways of how and when these constructs develop early in life – before the onset of disease – is crucial for developing targeted interventions that prevent later mental and physical health problems. Adolescence is an important period to study these associations because the development of these constructs is closely tied to endocrine changes associated with puberty. Sharp increases in sex hormones and other endocrine factors contribute to rapid changes in adiposity and inflammation over the course of adolescence (Byrne, O'Brien-Simpson, Mitchell, & Allen, 2015). The sharp rise in sex hormones along with the increased stress during pubertal development can lead to depression in vulnerable youth, and inflammation can be stimulated by increased stress through HPA-axis mechanisms (Slavich & Sacher, 2019). Sex differences may be especially apparent during this period, because levels of estrogens and androgens become strongly differentiated between males and females at this point (Byrne et al., 2015; Slavich & Sacher, 2019).

However, to date, studies with adolescent samples have not explored the interrelations between all of these three constructs across adolescent development. Most notably, adolescent studies on inflammation and depression often treat adiposity as a covariate rather than recognizing its important contribution to the development of these two constructs. Yet, there is evidence that low-grade inflammation is associated with symptoms of atypical depression (primarily increased appetite), but not in non-atypical depressive subtypes (Lamers, Milaneschi,

De Jonge, Giltay, & Penninx, 2018). Adolescent-onset depression is more likely to be in the form of atypical depression and is estimated to be four-times more common in females (Singh & Willams, 2006). Thus, adiposity seems to play a key role in the development of the link between depression and inflammation and should be further examined in studies with adolescents.

The limited research examining the interrelations between adiposity, depression and inflammation in adolescents brings many unknowns. First, similar to adult research, there is inconsistency regarding the directionality of these relations. Most studies do not have the capacity to test bidirectional links simultaneously, and many studies do not account for the development of both constructs tested, potentially exaggerating their findings. The inconsistent results may also stem from data collection at different ages, as some of these pathways may emerge at specific developmental periods throughout adolescent development (i.e., early adolescence, mid-adolescence, etc.), though most studies have not addressed this important question. Additionally, it is not clear whether sex differences in these interrelations observed in adults are also evident in adolescents. Some studies only examined girls, while others lacked sufficient power to test sex differences. Considering that women are at higher risk for depression, obesity and elevated inflammation (Derry et al., 2015), it is critical to study when and how this heightened risk develops early in life. Furthermore, the development of inflammation in adolescence is not well understood. Changes in fat mass are hypothesized to be a key mechanism explaining potential sex differences in inflammation (Shanahan et al., 2013), however, most studies on obesity have used Body Mass Index (BMI), a measure that cannot discriminate between fat mass and lean mass. Altogether, these limitations hinder understanding of how these mechanisms operate and unfold over the course of adolescent development.

The current study aims to fill the gap in the literature and to examine the co-development of adiposity, inflammation and depressive symptoms from preadolescence to early adulthood in the Avon Longitudinal Study of Parents and Children (ALSPAC). This prospective study includes repeated measures of fat mass, CRP and depressive symptoms at four time-points that correspond to specific developmental periods: T1 - late childhood/pre-adolescence (ages 9-10), T2 - mid-adolescence (ages 15.5-16), T3 - late adolescence (ages 17.5-18) and T4 - early adulthood (ages 23-24). The prospective, repeated-measures, longitudinal design allows the examination of several aspects related to the co-development of adiposity, inflammation, and depressive symptoms over the course of adolescence. Considering that the directionality of how these associations develop is not well understood, I have used these data to investigate the temporal sequencing of these associations, and to test the idea of bidirectional links. Not only have I tested how each construct influence the other in subsequent waves, I have also tested how initial levels of one construct influence the rate of change of the other construct, as well as how the rate of change of one construct is associated with the rate of change of the other. Additionally, I have examined during which age, or at which developmental period these associations emerge or become stronger. Finally, the large sample size (N = 6,525) have allowed the examination of sex differences in the co-development of these constructs. Elucidating how the associations between adiposity, inflammation and depression develop during adolescence, when they emerge, and who is at a greater risk to form them (i.e., girls or boys), is imperative for informing targeted interventions and preventions efforts for depression, obesity and inflammation-related illnesses.

2. Review of the Literature

In the first three sections of this literature review I have reviewed studies which examine the development of adiposity, inflammation and depressive symptoms during adolescence. These sections examine the development of each construct independently, and highlight sex differences in the development of these constructs during the adolescent period. The following sections review literature on the associations between these constructs in adolescents, examining associations between each pair of constructs. Sex differences in the associations between these constructs are reviewed as well. To best inform my hypotheses on the developmental nature of these constructs, I have highlighted longitudinal research, when available. Given that there are some inconsistencies in the literature depending on the inflammatory measures used, I have focused my review on studies which utilized CRP as their measure of inflammation, as this is the biomarker used in the present study. Research utilizing fat mass as a measure of adiposity is less common, and therefore I have reviewed studies which used other markers of adiposity as well.

2.1. The Development of Adiposity (Fat Mass) During Adolescence

Clinical research shows that during puberty, girls tend to gain more fat mass and boys tend to gain more lean muscle mass, eventually leading to the known sexual dimorphism of adiposity in adulthood (Siervogel et al., 2003). However, the majority of longitudinal studies on the development of adiposity during adolescence have examined BMI trajectories, and relatively few studies have examined the developmental trajectory of fat mass, or fat mass index (FMI). Yet, across these studies, a consistent sex difference emerged, with overall FMI increasing in girls but decreasing in boys during the adolescence years (Eissa et al., 2009; Marshall, Curtis, Cavanaugh, Warren, & Levy, 2020). Further information on the nature of the trajectory of FMI can be obtained from two longitudinal studies. Eissa and colleagues (2009) examined sex and

ethnic differences in the trajectories of fat mass index from ages 8 to 18 in a longitudinal study of 678 children. White boys and girls had similar levels of FMI at age 8 years (4.4 kg/m^2); from then, the trajectories of boys and girls diverged. White girls' FMI increased consistently throughout childhood and early-mid adolescence, until reaching a plateau at late adolescence around age 17 (5.8 kg/m^2). White boys' FMI decreased consistently after reaching a peak around age 10 (4.7 kg/m^2). This study also found ethnic differences, such that Black girls had the highest FMI across all ages compared to all groups, and the sex difference between Black girls and boys was evident early on (Eissa et al., 2009). Similar FMI patterns were observed in a longitudinal study of 469 children which examined trajectories of body composition from age 5 to 17 (Marshall et al., 2020). In boys, FMI increased through childhood, declined in early adolescence and then stabilized during late adolescence. Conversely for girls, FMI increased throughout childhood and adolescence. Notably, neither of these studies extended their data collection beyond adolescence. While their findings suggest that there is stabilization of FMI to some extent during late adolescence, the findings were not entirely consistent, and it is unclear whether this pattern continues through early adulthood.

2.2. The Development of Depression During Adolescence

The risk for first-onset depression is significantly increased during adolescence. While the prevalence of depression in childhood is low (less than 1%), depression rates increase to about 5% during early adolescence, and then climb to as high as 20% by the end of adolescence (Thapar, Collishaw, Potter, & Thapar, 2010). Multiple studies have examined the trajectories of depressive symptoms from childhood to adulthood, revealing a consistent non-linear pattern, with increases in depressive symptoms from childhood through adolescence. A dramatic rise in depressive symptoms is observed across the adolescence period, with a peak around mid-late

adolescence (ages 15-18), which then follows with an overall decline in symptoms in early adulthood (Ferro, Gorter, & Boyle, 2015; Hankin et al., 1998; Natsuaki, Biehl, & Ge, 2009).

In an effort to identify critical points in the development of depression, Kwong (2019) examined the trajectories of depressive symptoms in the ALSPAC cohort (data from this study will be used to perform the following proposed analyses). Results showed that depressive symptoms started to increase around age 13, and continued to increase in subsequent years until reaching a peak at age 18. Consistent with previous research, a decline in depressive symptoms was observed between ages 18-22, but from age 22 depressive symptoms started to rise again (Kwong, 2019). It is possible that previous research did not capture this later increase in depressive symptoms because of limited data on this age group. Nonetheless, results from this study highlight early adolescence as a period with heightened risk for the onset of depressive symptoms.

There is also consistent evidence for sex differences in the trajectories of depressive symptoms during adolescence, with female adolescents overall having higher levels of depressive symptoms compared to male adolescents (Costello, Swendsen, Rose, & Dierker, 2008; Natsuaki et al., 2009). The gender gap widens with puberty, with a two-fold difference in the prevalence of depressive symptoms between adolescent females and males post-puberty, a striking sex difference which persists into adulthood (Adrian Angold & Worthman, 1993). Specifically, Hankin and colleagues (1998) found that the gender differences in depression first emerged between the ages of 13-15, but the greatest increase in this gender difference was observed between 15 and 18 years of age (Hankin et al., 1998).

Another study exploring adolescent trajectories of depressive symptoms from age 10 to 22 in 9301 individuals in the ALSPAC cohort provided corroborating evidence for this sex

difference (Kwong et al., 2019). The findings demonstrated that female and male adolescents had similar levels of depressive symptoms at the beginning of the study (around age 11). However, adolescent females experienced steeper increases in depressive symptoms compared to adolescent males over the course of adolescence until around age 20, when levels of depressive symptoms plateaued and started to decrease in both females and males. This study also examined sex differences in the peak velocity of depressive symptoms, i.e., the age at which depressive symptoms are increasing most rapidly. The results showed that the average peak velocity of depressive symptoms for female adolescents occurred a couple years earlier than the peak velocity for male adolescents. On average, depressive symptoms increased most rapidly at age 13.5 in adolescent females and at age 16 in adolescent males. The age of maximum depressive symptoms did not differ much between adolescent females and males, but was found to occur slightly later than commonly reported in previous studies (age 19.6 for females and 20.4 for males).

2.3. Developmental Changes in Inflammation (CRP) During Adolescence

Research on the developmental changes in CRP during adolescence is scarce. To date, only two studies have characterized the developmental trajectory of CRP in young samples. The overall findings suggest that CRP increases with age, and there is some evidence that the growth of CRP differs between boys and girls. Shanahan and colleagues (2013) examined trajectories of CRP levels from ages 9-21 in 1,420 children in the Great Smoky Mountains prospective study. Their findings revealed sex differences in the developmental trajectory of CRP. In girls, the trajectory of CRP was best described by a quadratic trend; CRP slowly and gradually increased until age 15, and thereafter the rate of increase accelerated significantly, such that levels of CRP nearly doubled between ages 16-19 in girls. Such accelerated increase in CRP was not observed

in boys. In fact, changes in CRP in boys across adolescence were best described by a smaller, linear increase growth pattern (Shanahan et al., 2013).

The second study examined the development of CRP from mid-adolescence to early adulthood across three waves (ages 16, 18 and 20) and found that CRP increased linearly with age. They also found no sex differences in the trajectory of CRP (Chiang et al., 2019). It is possible that the later timing of the measurements, or possibly only having three time points, was not sufficient to reveal the sex differences found in the first study. Alternatively, it is possible that Chiang et al. (2019) did not find sex differences in CRP because they controlled for waist circumference, which is a proxy of abdominal fat. Shanahan et al. (2013) found that BMI, and particularly the associations between BMI and CRP across time, played a large role in explaining the sex differences they have observed in the trajectory of CRP. Specifically, BMI-CRP associations increased with age in girls and decreased with age in boys. Considering that adipose tissue has been found to secrete cytokine and to enhance inflammation (Kyrou et al., 2006), they hypothesized that the differences in BMI-CRP associations between boys and girls were attributable to different amounts of body fat in boys and girls post-puberty (i.e., greater fat mass in girls). However, this hypothesis remained to be empirically tested.

2.4. Associations Between Adiposity and Depression During Adolescence

Findings from cross-sectional research with children and adolescents demonstrate that increased weight is associated with depressive symptoms. Several meta-analyses assessing the prevalence of depression in overweight and obese children and adolescents found that obese youth, in particular, are at a significantly higher risk for having depressive symptoms or clinical depression compared to overweight and normal-weight youth (Quek et al., 2017; Rao et al., 2019, 2020), with stronger associations observed in girls (Quek et al., 2017). Other studies

utilizing continuous measures of adiposity such as percent body fat and BMI, rather than obesity status, also found positive associations between greater adiposity and depressive symptoms in adolescents (Morrison, Shin, Tarnopolsky, & Taylor, 2015; Hillman et al., 2020).

Yet, given the cross-sectional design of these studies, conclusions about the temporal sequencing of these associations cannot be made. Longitudinal studies provide evidence that being overweight or obese during childhood and early adolescence increases the risk for developing depressive symptoms in subsequent periods. Pryor and colleagues (2016) found that being overweight or obese during middle childhood increases the risk of experiencing internalizing symptoms in early adolescence. Likewise, Boutelle and colleagues (2010) found that obese 13-year old girls were at increased risk for developing depressive symptoms in late adolescence (Boutelle, Hannan, Fulkerson, Crow, & Stice, 2010). This risk may be especially prominent in girls, as a longitudinal study found that girls who had been stably overweight since early childhood had the greatest risk to be depressed at age 15, while no associations between any of the obesity trajectories and depression were found in boys (Martin-Storey & Crosnoe, 2015).

Increases in adiposity during childhood have also been found to predict the development of depressive symptoms later on. Felton and colleagues (2010) followed 250 children and adolescents in 6-12 grades and examined whether changes in adiposity predicted depressive symptoms after four months. They found that increases in weight, body mass and body fat were all associated with higher depressive symptoms at follow-up. However, this finding was stronger for older adolescents than younger adolescents. Similar to previous findings, they also found a significant gender effect, such that increases in fat mass were associated with elevated depressive symptoms more strongly for girls (Felton, Cole, Tilghman-Osborne, & Maxwell, 2010).

While the previous studies suggest that obesity and weight gain in childhood and adolescence increase the risk for depression, a couple of studies that investigated bidirectional associations simultaneously provided stronger support for the alternate direction, that depression in adolescence is a risk factor for the development of obesity later on. When examining both paths, these two longitudinal studies found that depression predicted obesity one year later, however, obesity at baseline did not predict symptoms of depression at follow-up assessment (Goodman & Whitaker, 2002; Roberts & Duong, 2013)

The extent to which depression predicts obesity more strongly for girls is unclear, as studies investigating sex differences in this effect yielded mixed results. Indeed, a meta-analysis of longitudinal studies of depression and weight control found that teen girls with depression are about 2.5 times more likely than non-depressed adolescents to have weight gain or obesity status at follow-up assessments (Blaine, 2008). A similar gender effect was found in a longitudinal study that followed black youth from adolescence to adulthood (Assari, Caldwell, & Zimmerman, 2018). Their findings showed that elevated depressive symptoms at age 15 predicted increases in BMI from age 19 to 32, but only in female Black youth.

However, other studies suggest that depression increased the risk for obesity more strongly for boys. One longitudinal study found that depressive symptoms at 10 years old predicted increased BMI, waist circumference and percent body fat at a 3 year follow-up for boys, but not for girls (Aparicio, Canals, Voltas, Hernández-Martínez, & Arija, 2013). Similarly, another study that followed children in grades 2, 6, and 10 found that boys whose depressive symptoms increased had also increases in percent body fat (Olive, Telford, Byrne, Abhayaratna, & Telford, 2017). However, the study of Aparicio at el. (2013) also found that dysthymia predicted increased waist circumference in both sexes. It is possible that the inconsistency in the

observed sex differences stems from variations in the time of measurement or in the type of depression measured.

Interestingly, studies on adolescent girls suggest that bidirectional associations between obesity and depression exist. Anderson and colleagues (2011) followed adolescent girls from 6th to 8th grade, and found that for White girls, depressed mood at 6th grade predicted obesity two years later, and likewise, obesity at baseline predicted depressed mood at 8th grade (Anderson et al., 2011). Additionally, Marmorstein and colleagues (2014) found bidirectional associations between Major Depressive Disorder (MDD) and obesity only in girls, but noted that these reciprocal associations varied over the course of adolescence. Specifically, in girls only, early adolescent-onset depression was associated with elevated risk of obesity, and obesity, particularly during late adolescence, was associated with increased risk of later depression (Marmorstein, Iacono, & Legrand, 2014).

These findings suggest that at least for girls, adolescence is a high-risk period for the development of both depression and obesity, and that the nature of the risk varies over the course of adolescence. These results highlight the importance of studying the development of these constructs simultaneously, with data collection occurring at multiple time points, particularly during important stages of adolescent development. Additionally, given the inconsistency of findings regarding sex differences, future studies should include both boys and girls and test for sex differences in these associations.

2.5. Associations Between Depression and Inflammation (CRP) During Adolescence

Similar to the adult literature, research on younger samples suggests that there is a positive association between depression and inflammation in children and adolescents; however, the findings are mixed. A recent meta-analysis of 22 studies examined the associations between

depression and both IL-6 and CRP (Colasanto, Madigan, & Korczak, 2020). When analyzing cross-sectional studies, a significant positive concurrent association between depression and CRP emerged (overall mean effect size of 0.12). However, this general finding is complicated by studies which found no associations between depression and CRP in adolescents (Byrne et al., 2013; Chaiton, O'Loughlin, Karp, & Lambert, 2010).

Colasanto and colleagues (2020) also reviewed longitudinal research on depression and inflammation in children and adolescents and found that inflammation, measured by CRP or IL-6, predicted future depression. Two additional studies provide further evidence for the predictive effects of CRP on depression. Moriarity and colleagues (2019) examined whether CRP and inflammatory cytokines were associated with changes in depressive symptoms over five follow-up assessments in adolescence. They found that for both boys and girls, elevated CRP predicted increases in depressive symptoms over time. Sex differences were found only in the associations with specific proinflammatory cytokines, and were furthered complicated by the time passed from baseline assessment (Moriarity et al., 2019). There is also evidence from the ALSPAC cohort suggesting that an increasing pattern of CRP from adolescence to early-adulthood was associated with increased risk for moderate/severe depression in early-adulthood (Osimo et al., 2020). However, results were not consistent as another study from the same cohort found that IL-6 at age 9, but not CRP, predicted depression at age 18 years (Khandaker, Pearson, Zammit, Lewis, & Jones, 2014a).

While the previous studies provided some support for the predictive effects of inflammation on depression, there is also evidence that depression predicts inflammation in adolescents. Duivis and colleagues (2015) followed 1164 adolescents from ages 11 to 16 years, and found that persistent depressive symptoms in adolescents over the five years were associated

with higher levels of CRP at age 16; this association was largely mediated by smoking behavior (Duivis et al., 2015). This finding was corroborated by a longitudinal study that investigated the bidirectional associations between CRP and depression in adolescents and young adults. The findings revealed that cumulative episodes of MDD in adolescents predicted later elevated levels of CRP, however, CRP levels did not predict later depression (Copeland, Shanahan, Worthman, Angold, & Costello, 2012). Yet, Colasanto's meta-analysis of longitudinal studies found that depression only predicted IL-6, not CRP (Colasanto et al., 2020). However, the meta-analysis was limited by the small number of longitudinal studies, as well as by small sample sizes, and the authors highlighted the need for future longitudinal research to disentangle the direction of this association.

Taken together, there is some evidence for a positive association between CRP and depression during adolescence; however, the longitudinal association is unclear. There is limited evidence for bidirectional relations; future research should test both paths simultaneously in order to infer directionality. Furthermore, the extent to which the associations between depression and inflammation in adolescence differ by sex is unclear. It is hypothesized that girls will show stronger associations since they have both higher rates of depression and a stronger immune response, especially after puberty (Byrne et al., 2015). During puberty, girls' immune response is stimulated by estrogen which has pro-inflammatory properties (Byrne et al., 2015; Slavich et al., 2015). Additionally, the inflammatory response is activated by stress, and girls tend to be more susceptible to stressors which are known to enhance inflammation, particularly during adolescence (Byrne et al., 2015; Derry et al., 2015). However, to date, there is no study reporting sex differences in the associations between CRP and depression in adolescents.

2.6. Associations Between Adiposity and CRP Across Adolescence

Similar to research with adult samples, evidence from child and adolescent studies also shows a link between adiposity and inflammatory biomarkers. Several cross-sectional studies of children and adolescents have found a positive association between measures of adiposity (BMI, Waist Circumference (WC), Waist-Hip-Ratio (WHR)) and CRP concentrations (Choi, Joseph, & Pilote, 2013; Gillum, 2003; Lambert et al., 2004; Skinner, Steiner, Henderson, & Perrin, 2010). Corroborating evidence from a longitudinal study demonstrated that greater childhood adiposity (ages 5-18) measured by BMI and skinfold thickness predicted elevated CRP levels in young adulthood (Toprak et al., 2011).

Additional longitudinal studies suggest that gains in adiposity during childhood and adolescence predict elevated CRP levels in subsequent periods. Goosby and colleagues (2016) examined whether CRP in early adulthood was predicted by obesity status during birth, adolescence, and emerging adulthood, as well as by body size changes between these different periods. Their findings revealed that body size and obesity status at each developmental period, along with increasing body size between periods, were positively correlated with adult CRP (Goosby, Cheadle, & McDade, 2016). Similar findings were observed in an adolescent follow-up of 600 Chilean infants, investigating the effects of early life adversity on adiposity and inflammation (Reid et al., 2020). The researchers utilized latent growth curve modeling to examine pathways between family adversity experienced during infancy, BMI in childhood (ages 5, 10 and 16 years) and inflammation in adolescence (ages 16-18 years). They found that greater exposure to interpersonal conflict during the first year of life was indirectly associated with increased CRP in late adolescence through the intercept and slope of childhood BMI. Relevant to the current discussion, their model demonstrated that both greater BMI at age 5, and the growth

trajectory of childhood BMI from age 5 to 16, predicted elevated levels of CRP in late adolescence (Reid et al., 2020).

Thus, longitudinal studies suggest that greater adiposity during childhood, as well as increases in body size during childhood, predict elevated inflammation in adolescence and early adulthood. Importantly, just as adiposity contributes to inflammation, elevated inflammation can also contribute to the accumulation of fat over time through HPA-axis activation (Kyrou et al., 2006). However, this hypothesis has not been examined in longitudinal research of children and adolescents.

Compared to adult research demonstrating that the association between adiposity and inflammation is stronger for women than for men (Choi et al., 2013; Thorand et al., 2006), there is limited evidence regarding sex differences in these associations among children and adolescents; yet, these studies also suggest that associations between adiposity and CRP may be stronger for girls. Choi et al. (2012) did not find significant sex differences in the associations between adiposity and CRP in their meta-analysis of a small set of adolescent studies. On the other hand, a cross-sectional study of African-American adolescents found that the associations between adiposity measures and inflammation were somewhat stronger for girls than for boys (Petty et al., 2010). Similarly, Toprack et al. (2011) found that the predictive association between skinfold thickness in childhood to CRP in adulthood was greater for girls than for boys. Finally, results from the longitudinal study of Shanahan and colleagues (2013) reviewed earlier suggested that adiposity, as measured by BMI, explained the sex differences observed in the trajectory of CRP. Specifically, they found that the associations between BMI and CRP increased in girls across adolescence, likely due to greater body fat. Conversely for boys, BMI-CRP associations decreased with age, likely due to increase in lean muscle mass and overall decrease in fat mass.

However, the extent to which sex differences in fat mass explain sex differences in the development of CRP across adolescence is not clear, as most studies on the associations between adiposity and CRP have used other measures of adiposity, most commonly BMI, which cannot distinguish between fat mass and lean muscle mass. Thus, this hypothesis warrants further investigation.

2.7. Aims and Hypotheses

This dissertation was conducted to examine how adiposity, systemic inflammation, and depressive symptoms co-develop across adolescence, and whether these associations differ for boys and girls. The aims and corresponding hypotheses and analyses built upon one another, starting from univariate examinations of the development of each construct individually, followed by bivariate hypotheses and models examining the associations between each two of the three constructs, and finally a tri-variate model including the development of the three constructs together.

Step 1: Characterizing the developmental trajectory of each construct individually via latent growth curve modeling (LGCM) and examining sex differences in each trajectory

Aim 1: To examine the developmental trajectory of depressive symptoms across adolescence and to examine sex differences in the development of depressive symptoms

Hypothesis 1a. Based on previous research on the development of depressive symptoms across adolescence in the ALSPAC dataset, I hypothesized that depressive symptoms will follow a non-linear growth, with great increases during adolescence followed by stabilization into early adulthood.

Hypothesis 1b. Based on previous research in the ALSPAC cohort documenting sex differences in the trajectory of depressive symptoms, I hypothesized that girls will have a faster rate of increasing depressive symptoms across adolescence than boys.

<u>Aim 2:</u> To examine the developmental trajectory of FMI across adolescence and to examine sex differences in the development of FMI

Hypothesis 2a. Based on previous research, I hypothesized that FMI will follow a non-linear growth across adolescence, with most changes in FMI occurring during late childhood and early adolescence, then tending to stabilize during late adolescence and early adulthood.

Hypothesis 2b. Based on previous research, I hypothesized that for girls FMI will increase, and for boys FMI will decrease over the course of adolescence.

<u>Aim 3:</u> To examine the developmental trajectory of CRP across adolescence and to examine sex differences in the development of CRP.

The literature on the development of CRP is very limited, and the two studies reviewed yielded inconsistent results, both in regards to the nature of the developmental trajectory through adolescence and in regards to sex differences in the development of CRP. The only consistent result was that CRP increased with age. Thus, I am hesitant to make *a-priori* predictions about the nature of the developmental trajectory of CRP across adolescence. Since Shanahan et al. (2013) examined CRP development across similar ages to those in this study, I *tentatively* predicted that my results will show a similar pattern.

Hypothesis 3a. I hypothesized that CRP levels will increase with age; CRP levels *may* show a non-linear growth for girls and a linear growth for boys.

Hypothesis 3b. Girls *may* have a faster rate of increasing CRP levels than boys across adolescence.

<u>Step 2:</u> Examining the associations between the overall developmental trajectories of adiposity, inflammation and depressive symptoms via parallel-processes growth curve modeling, and examining sex differences in these associations

<u>Aim 4</u>: To examine associations between the overall developmental trajectories of CRP and depressive symptoms across adolescence

Hypothesis 4a. Based on previous research showing positive associations between CRP and depression, I hypothesized that CRP levels at age 9 will be positively associated with depressive symptoms at age 10.

Hypothesis 4b. Based on some evidence for positive associations between changes of depression and CRP over time, I hypothesized that the development of CRP from age 9 to 24 will be positively associated with the development of depressive symptoms from age 10 to 23.

The limited longitudinal research suggests some evidence for each directional hypothesis, thus my next *tentative* hypotheses reflect bidirectionality:

Hypothesis 4c. CRP in pre-adolescence (9 years) will positively predict the development of depressive symptoms from age 10 to 23.

Hypothesis 4d. Depressive symptoms in pre-adolescence (10 years) will positively predict the development of CRP from age 9 to 24.

Hypothesis 4e. Due to the scarcity in research on sex differences, I am hesitant to make *a-priori* predictions regarding sex differences in these associations. I *tentatively* hypothesized that the associations between the development of CRP and depression will be stronger for girls than for boys.

<u>Aim 5</u>: To examine associations between the overall developmental trajectories of FMI and CRP across adolescence

Hypothesis 5a. Based on previous research showing positive associations between adiposity and CRP, I hypothesized that FMI and CRP will be positively associated at age 9.

Hypothesis 5b. Based on some evidence for positive associations between weight gain and CRP, I hypothesized that the development of FMI and CRP from age 9 to 24 will be positively associated.

Hypothesis 5c. There is strong evidence to support the hypothesis that adiposity predicts later CRP levels rather than CRP predicting adiposity, thus, I did not expect to find bidirectional links. Rather, I hypothesized that FMI in pre-adolescence (9 years) will positively predict the development of CRP from age 9 to 24.

Hypothesis 5d. Based on previous research, I hypothesized that the associations between the developmental trajectories of FMI and CRP will be stronger for girls than for boys.

Aim 6: To examine associations between the overall developmental trajectories of FMI and depressive symptoms across adolescence

Hypothesis 6a. Based on previous research showing positive associations between adiposity and depression, I hypothesized that FMI at age 9 will be positively associated with depressive symptoms at age 10.

Hypothesis 6b. Based on evidence for positive associations between weight gain and depression, I hypothesized that the development of FMI from age 9 to 24 will be positively associated with the development of depressive symptoms from age 10 to 23.

Longitudinal research suggests evidence for both directional hypotheses, thus, my next two hypotheses reflect bidirectionality:

Hypothesis 6c. FMI in pre-adolescence (9 years) will positively predict the development of depressive symptoms from age 10 to 23.

Hypothesis 6d. Depressive symptoms in pre-adolescence (10 years) will positively predict the development of FMI from age 9 to 24.

Hypothesis 6e. While there are some mixed findings regarding sex differences, the majority of studies found stronger associations in girls, thus I *tentatively* hypothesized that the associations between the developmental trajectories of FMI and depressive symptoms will be stronger for girls than for boys.

Step 3: Examining the temporal and directional associations between adiposity, inflammation and depressive symptoms across adolescent development via cross-lagged panel analyses, and examining sex differences in these associations

The following hypotheses are similar to the previous set of hypotheses in terms of predictions regarding directionality and sex differences; hence, explanations will not be repeated. Prior studies had different lengths and different time-points for data collection, with some only reaching until mid-late adolescence, while others only starting from this period, hindering my ability to make predictions regarding sensitive periods for the emergence of associations between adiposity, inflammation and depression. Thus, these follow-up analyses are somewhat exploratory, though I have attempted to make tentative predictions based on theory.

Aim 7: To examine the temporal and directional associations between CRP and depressive symptoms across adolescent development

Hypothesis 7a. I hypothesized to find positive concurrent and bidirectional associations between CRP and depressive symptoms.

Hypothesis 7b. Considering the higher rates of depressive symptoms during adolescence, I hypothesized the associations to be evident during mid-late adolescence.

Hypothesis 7c. Considering that girls tend to have both higher CRP levels and depressive symptoms compared to boys, I hypothesized that the associations will be stronger for girls.

Aim 8: To examine the temporal and directional associations between FMI and CRP across adolescent development

Hypothesis 8a. Considering that adipose tissue secretes cytokines and promotes chronic low-grade inflammation, I hypothesized to find positive concurrent associations between FMI and CRP at each time point.

Hypothesis 8b. Similarly, I hypothesized to find positive transactional associations from FMI to CRP across each time point.

Hypothesis 8c. Considering that girls tend to have greater fat mass compared to boys, I hypothesized that the associations will be stronger for girls, especially during mid-late adolescence when sex differences in both FMI and CRP are most pronounced.

Aim 9: To examine the temporal and directional associations between FMI and depressive symptoms across adolescent development

Hypothesis 9a. I hypothesized to find positive concurrent and bidirectional associations between FMI and depressive symptoms.

Hypothesis 9b. Considering the higher rates of depressive symptoms during adolescence, I hypothesized the associations to be evident during mid-late adolescence.

Hypothesis 9c. Considering that girls tend to have both greater fat mass and higher depressive symptoms compared to boys, I hypothesized that the associations will be stronger for girls.

Aim 10: To examine the co-development of CRP, FMI, and depressive symptoms altogether

3. Methods

3.1. Population and Sample

Participants in this study were drawn from the Avon Longitudinal Studies of Parents and Children (ALSPAC), a population-based prospective longitudinal study of children born to mothers living in Avon county while pregnant. ALSPAC was designed to examine how social, biological, and environmental factors interact to influence pregnancy outcomes and child physical and mental health. Pregnant women were recruited to the study if they had an expected delivery date between April 1, 1991 and December 31, 1992, and lived in the former county of Avon in the UK. The final ALSPAC dataset includes 14,701 children alive at age 1 year.

The researchers utilized various strategies to collect data including parent, child and teacher questionnaires, clinic visits, behavioral observations and clinical interviews. For these set of analyses we have used data for fat mass and CRP from clinic visits occurred at ages 9, 15.5, 17.5, and 24. We have used teen-reported depressive symptoms from questionnaires collected at ages 10, 16, 17.5, and 23. Given that the ages at which variables were collected did not exactly match (and there was also great variability in age within each wave), I have controlled for the age of participants at time of data collection for each of the main variables, at each wave.

The sample for this study included individuals who had at least one data point available for each of the main variables in this study (i.e., fat mass, CRP, depressive symptoms). This was calculated after excluding individuals with extreme values of CRP who also reported having an infection (see more details in the Measures section under the description for CRP). This resulted in a final sample size of N = 6,525 (52.6% females, 98.1% White). The majority of participants had parents with high education (65.3% A-level and university degree), 24.5% had parents with

medium education level (O-level), and 10.3% had parents with low education levels (vocational qualification, CSE or less).

3.2. Procedure

Relevant to this study, participants were assessed at the following approximate time points: ages 9, 10, 15.5, 16, 17.5, 23, and 24 years old. Clinical assessments were completed at ages 9, 15.5, 17.5 and 24. During these clinic visits, blood samples were taken to be later analyzed for CRP among other biomarkers, and fat mass was measured using a DEXA scanner. At ages 10, 16, 17.5 and 23, participants completed several questionnaires (either in the clinic or via postal mail) including a questionnaire assessing depressive symptoms. Relevant covariates for these analyses were drawn from questionnaires filled out by the mother and the teen at additional assessments if not measured at the same time points as the main study variables (more information in Measures). Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Informed consent for the usage of data collected in questionnaires and clinic visits was obtained from all study participants based on guidelines from the ALSPAC Ethics and Law Committee. Consent for biological samples was obtained based on the Human Tissue Act (2004).

3.3. Measures

3.3.1. Main Study Variables

Fat Mass Index (FMI). The marker of adiposity in these analyses was Fat Mass Index (FMI). Fat mass (in grams) was measured using a Lunar Prodigy dual emission x-ray absorptiometry (DEXA) scanner (GE Medical Systems Lunar) during clinic visits at ages 9, 15.5, 17.5 and 24 years. DEXA is considered to be the gold standard for measuring fat mass and is more precise than most other methods assessing adiposity (Gupta et al., 2011; Riddoch et al.,

2009). All scans were manually examined for motion, anomalies and other artifacts. The total mass estimated by the DEXA scan was in strong agreement with the measured mass in this study (R^2>0.99; Riddoch et al., 2009). To account for differences in stature, Fat Mass Index (FMI) was computed as fat mass (in kilograms) divided by height squared (in meters). Height was measured in each clinic visit using a Harpenden stadiometer (Holtain, Crymych, Pembs, UK).

I decided to use fat mass rather than more common measures of adiposity such as BMI because BMI does not discriminate between fat mass and lean mass. Examining fat mass may be crucial for this set of analyses because of the emphasis on sex differences in inflammation. There are known sex differences in body composition which become evident with the onset and progression of pubertal development, i.e., girls gain more fat mass and boys gain more lean muscle mass (Loomba-Albrecht & Styne, 2009), and adipose tissue secretes proinflammatory cytokines and enhances inflammation (Kyrou et al., 2006). Indeed, several studies have recommended the use of FMI rather than BMI for classifying the weight status of children and adolescents (Freedman et al., 2005; Maynard et al., 2001). Additionally, I decided to use Fat Mass Index rather than the absolute amount of fat mass in order to account for individual differences in stature which are prominent during adolescent development. Adjusting the amount of fat for individual's height may be particularly relevant for these analyses considering the emphasis on the development of depressive symptoms during adolescence, which may be influenced by body image issues.

C-reactive protein (CRP). C-reactive protein (CRP) was used as a peripheral marker of systemic inflammation in these analyses. At ages 9, 15.5, 17.5 and 24, participants provided blood samples during the clinic visits. Participants fasted overnight before morning assessments and for 6 hours before afternoon assessments. Blood samples were immediately spun and frozen

at −80°C. Samples were stored for up to 9 months without any intervening freeze-thaw cycles. A high-sensitivity automated particle-enhanced immunoturbidimetric assay was used to quantify hs-CRP (Roche UK, Welwyn Garden City, UK). All inter-assay coefficients of variation were less than 5%. This advanced technique is capable of detecting very low levels of CRP which are often common in children and adolescents.

I was interested in measuring baseline innate immune activity in healthy individuals rather than acute inflammation. CRP values greater than 10 mg/L can indicate current infection or injury which sharply increases CRP levels, and thus, these extreme values are commonly excluded. However, the exclusion of values over 10 mg/L may reduce important variability in the sample as other factors such as obesity can also result in elevated CRP levels, hence excluding these values may remove participants of interest for the current analyses (Mac Giollabhui et al., 2020). We had self-reported data on occurrences of infection at the time of blood collection or in the prior week from the first three clinic visits. Thus, I decided to exclude those who reported an infection and also had CRP levels greater than 10 mg/L (28 cases at T1, 33 cases at T2, 32 cases at T3, and 2 cases at T4 which had values over 150 mg/L). The remaining extreme cases along with additional outliers (i.e., those greater than 3 *SD* from the mean levels) were investigated and winsorized to retain the ordinal values of the data (Horn et al., 2019; Mac Giollabhui et al., 2020). Values below the detection limit of the assay were assigned the value of half of the detection limit as recommended by *Salimetrics* and others (Horn et al., 2019).

Depressive Symptoms. Depressive Symptoms were measured using the Short Mood and Feelings Questionnaire (SMFQ; Angold et al., 1995) which was reported by the child at ages 10, 16, 17.5 and 23. The SMFQ is a 13-item questionnaire designed to measure the occurrence of

depressive symptoms over the past two weeks in children and adolescents. Sample questions include the following: *I cried a lot, I felt Lonely, I felt miserable or unhappy*. The possible responses for each question are *not true* (0), *sometimes* (1), *true* (2). Results are summed up to yield a possible range of 0-26; higher scores indicate more severe depressive symptoms. Research had demonstrated that the SMFQ is a valid and reliable measure of depressive symptoms in youths (Sharp, Goodyer, & Croudace, 2006) and there is good reliability for the depressive symptoms scores that were used in this analysis (Cronbach's alphas 0.80-0.91).

3.3.2. Covariates

I considered a number of individual and family covariates that are known to confound the associations between CRP, adiposity and depression in adolescents (Horn et al., 2019; O'Connor, 2008), including age, parental education, single-family household, and pubertal development. Additional covariates that are known to be associated with CRP (and potentially also with depressive symptoms and FMI) were considered as well. These variables included oral contraceptive use, alcohol use, tobacco use, medication use, and caffeine consumption prior to clinic visit.

Mothers reported their child sex at birth (male, female). A single-family household score (yes, no) was derived from mother report on whether she has a partner, and whether her partner lives with her when the child was 8 years old. At the same assessment mothers also reported on both their and their partner's highest educational attainment (CSE or less, vocational qualification, O-level, A-level, university degree). The highest education score among the parents was chosen (1-5). Participants reported their age at each clinic visit and on every postal questionnaire.

Child's pubic hair tanner stage at age 12 was used as an indicator of pubertal development. It was reported by the parent using tanner stages line drawings. Responses were on a scale of 1-5, from pre-pubertal to fully mature. I chose to control for pubertal status at age 12 because this is the mid-point between the first and second waves (ages 9 and 15) in my analyses, during which period the majority of pubertal development occurs. There was sufficient variability in pubertal status at this age compared to earlier time points.

At each clinic visit, participants reported whether they are taking any medication (yes, no), and whether they had consumed any caffeinated beverages within the past 2 hours (yes, no). Female participants also reported on their use of oral contraceptives (yes, no). Tobacco smoking at ages 15.5, 17.5, and 24 was assessed at each clinic visit based on self-report of smoking in the past 30 days (yes, no), and daily smoking (yes, no). A composite score was created based on the following: 0 = never smoked, 1 = occasional smoker (indicated smoking in the past month but not daily), 2 = daily smoker (indicated smoking daily). Alcohol consumption at ages 15.5, 17.5, and 24 was assessed at each clinic visit based on self-report of frequency of drinking alcohol in the past year. A composite score was created based on the following: 0 = never drink, 1 = occasional drinker (indicated drinking several times in the past month), 2 = frequent drinker (indicated drinking several times in the past week).

Since this is an extensive list of variables, it has the potential to introduce unnecessary heterogeneity and multicollinearity and may reduce power. Thus, as recommended by Horn et al. (2019), I first conducted a series of zero-order bivariate correlations with each of the main variables to examine whether each potential covariate was associated with the main variables. Caffeine consumption prior to clinic visit was the only variable not associated with any of the study main variables (even with the CRP data), and therefore was not included in any of the

models. All other variables had significant correlations with one or more of the main study variables, and therefore were included as covariates in all analyses.

3.4. Statistical Analysis

In order to examine the co-development of adiposity, inflammation and depressive symptoms throughout adolescence, I conducted these analyses in a step-wise fashion, building up from the simplest models to the most complex models. I began by examining the development of each construct separately using latent growth curve modeling (LGCM). I then analyzed the associations between the development of each pair of constructs using parallel-processes latent growth curve modeling. Utilizing latent growth curve modeling analytical approach can provide invaluable insights about the overall developmental trajectories of these constructs and how they relate to one another. For instance, it can demonstrate whether the rate of change of one construct is associated with the rate of change of the other construct. It can also demonstrate whether starting levels of one construct are associated with the rate of change of another construct (Felt, Depaoli, & Tiemensma, 2017).

Yet, this analytic strategy cannot provide information about the temporal associations between these constructs, i.e., whether some of these associations emerge at a certain age or developmental period. Identifying when associations between adiposity, inflammation and depressive symptoms form during development could potentially inform clinical interventions aiming at reducing the risk for obesity, depression and other related diseases. In order to address this question, I conducted a series of cross-lagged panel analyses. The strength of cross-lagged models is that they can be used to test bidirectional associations between variables of interest, while taking into account the development, or stability, of each construct. I first conducted cross-

lagged analyses examining the longitudinal associations between each pair of constructs. I then analyzed a final model which included all three constructs.

Because there are documented sex differences in the development of each one of these constructs - differences that were also confirmed in my preliminary analyses (more information in the Results section) - it does not make sense to attempt to fit a curve to the entire sample, and therefore, I proceeded with conducting all further analyses separately for boys and girls.

The following sections provide further details on each set of analyses. All analyses were conducted in R-studio (R version 3.4.4) using the Lavaan package (Rosseel, 2012). Before performing the main analyses, all variables were examined for outliers and for skewness. The main variables were all positively skewed (skewness statistics > 1), therefore I performed log-transformation on FMI and CRP, and square-root transformation on SMFQ. Full-information maximum likelihood (FIML) estimation was used to estimate missing data and MLR was used for robust estimation.

Step 1. Examining the overall developmental trajectory of each construct using latent growth curve modeling

To examine the developmental trajectories of inflammation (CRP), adiposity (FMI), and depressive symptoms throughout adolescence, I conducted a series of latent growth curve (LGC) analyses within a structural equation model framework (McArdle & Epstein, 1987). LGC analysis uses repeated measures of a construct to estimate its underlying growth trajectory. To characterize the trajectory, the analysis yields two latent factors: the intercept, or the starting point, and the slope, or the rate of change over time. LGC models have the capacity to estimate both within-person and between-person differences in trajectories of growth, and are well-suited for studying change over time in developmental research (Felt et al., 2017).

The first step in this analysis was to characterize the unconditional growth curves of CRP, FMI and depressive symptoms for boys and girls. To estimate the trajectories of CRP and FMI, I used data collected at four clinic visits, when youth were approximately 9, 15.5, 17.5 and 24 years old. To estimate the trajectory of depressive symptoms, I used the four nearest time-points in which youth filled out the SMFQ, i.e., at ages 10, 16, 17.5 and 23 years. The same analytic strategy was followed for all three constructs. I tested a no growth, a linear growth, and a quadratic growth models. The factor loadings of the slopes were computed based on the mean ages at each measurement occasion, and were adjusted to account for the unequal spacing between the four time points. Covariances between the growth factors were estimated as well. The fit of these three models was compared in order to determine the best fitting growth curve. Since these are non-nested models, these models were compared using fit indices such as Akaike Information Criterions (AIC) and Bayesian Information Criterions (BIC), with lower values indicating a better fit (Kuha, 2004).

The fit of each model in theses analyses was also evaluated by examining several fit indices based on common guidelines (Bentler, 1990). The following fit indices were examined: the chi-square (χ^2) goodness of fit statistic (excellent fit if *p*-value is non-significant), the comparative fit index (*CFI* > .95 for excellent fit; *CFI* > .90 for adequate fit), the Tucker-Lewis index (*TLI* > .95 for excellent fit; *TLI* > .90 for adequate fit), the root mean square error of approximating (*RMSEA* < .05 for excellent fit; *RMSEA* < .08 for adequate fit), and the standardized root mean squared residual (*SRMR* < .08 for excellent fit; *SRMR* < .10 for adequate fit.

Because different fit indices are affected by different properties (e.g., the chi-square test is extremely sensitive to sample size and commonly results in a significant *p*-value when the

sample size is large), and it is often the case that some indices indicate excellent fit while others do not, I have assigned fit based on the following criteria: if all fit indices indicated excellent fit, the model was considered to have excellent fit to the data; if some indices indicated excellent or adequate fit, the model was considered to have adequate fit to the data; if all indices indicated that the model does not have an adequate fit, the model was considered to have poor fit to the data.

Step 2. Examining the associations between the overall development of each pair of constructs using parallel-processes latent growth curve modeling

The second step was to examine associations between the growth curves of CRP, FMI and depressive symptoms. Parallel-processes latent growth curve models allow to explore how the development of two constructs relate over time by examining the associations between the growth factors (i.e., intercept and slope) of two different constructs (Felt et al., 2017). Thus, I conducted a total of six parallel processes growth models to test associations between each pair of constructs (i.e., CRP and FMI, FMI and depressive symptoms, CRP and depressive symptoms) separately for boys and girls.

The same analytic strategy was followed for all these models. I regressed each slope on the other construct's intercept to test whether earlier levels of one construct predict the rate of the change of the other construct, and vice versa. I also examined the correlation between the two slopes (i.e., whether the rate of change of one construct is associated with the rate of change of the other), and the correlation between the two intercepts (whether initial levels of two constructs are associated). Considering that quadratic growth terms were also estimated, I also regressed each quadratic slope on the other construct's linear slope. In the second step covariates were added to each model, including the third construct not examined.

Step 3a. Examining the associations between the temporal co-development of each pair of constructs using 2-level cross-lagged panel analyses

In the third step I conducted a total of six crossed-lagged panel analyses to test when associations between constructs emerge, and in which direction. Similar to the previous analyses, I performed each analysis investigating associations between each pair of constructs (i.e., CRP and FMI, FMI and depressive symptoms, CRP and depressive symptoms) separately for boys and girls. The same analytic strategy was followed for each of these models.

Each model tested was a 2-level, 4-wave cross-lagged model investigating concurrent and transactional associations between two constructs across the four waves. Each model included: 1) concurrent paths (correlations) between two constructs within each wave, 2) transactional bidirectional paths between two constructs across subsequent waves, and 3) autoregressive paths between all waves to control for the stability of each construct. In the second step, relevant covariates were added to the model (including the third construct not examined).

Step 3b. Examining the associations between the temporal co-development of all three constructs using 3-level cross-lagged panel analyses

The purpose of the final cross-lagged model was to include all three constructs in one model, and to examine the associations between all three constructs across the different time points (i.e., a 3-level, 4-wave cross-lagged model) separately for boys and girls. This final step was needed in order to check whether the findings from the previous analyses still hold, or whether considering all three constructs together changes the associations observed when investigating only two constructs at a time. The additional benefit of including all three constructs in one cross-lagged panel model is that any potential mediation may be more easily visualized in such a model.

4. Results

4.1. Descriptive Statistics and Zero-Order Correlations

Table 1 depicts the descriptive statistics of the main study variables (i.e., FMI, CRP, and depressive symptoms) across the four waves. There was an overall increase in each one of these constructs with age, and girls tended to have higher values than boys, especially in the later waves. Proportions of participants meeting the clinical cutoff for depression were as follows: 5.9% girls and 5.9% boys at T1, 22.8% girls and 9.8% boys at T2, 24.8% girls and 16.1% boys at T3, and 21.6% girls and 13.5% boys at T4.

Table 2 portrays the zero-order correlations of the main study variables stratified by sex. In general, CRP levels were not significantly correlated with SMFQ scores. There were several significant positive associations between SMFQ scores and FMI scores in girls, however, associations between SMFQ and FMI were not significant in boys. FMI and CRP were significantly positively correlated in both girls and boys (all *p*s < .001).

4.2. Unconditional Growth Curve Models

4.2.1. Depressive Symptoms.

Out of the three models tested for the growth of depressive symptoms over adolescence (i.e., no growth, linear growth, quadratic growth), the best fitting model for both boys and girls was the quadratic growth curve model. Table 3 depicts the unconditional models' estimated parameters.

The quadratic growth model for girls showed good fit (χ^2 (4) = 32.137, $p < .001$, *CFI* = .975, *TLI* = .962, *RMSEA* = .047 [.033, .063], *SRMR* = .044). For girls, the positive estimate of the linear slope mean (M_{slope} = 1.722, $p < .001$) along with a negative estimate of the quadratic slope mean (M_{quad} = -.101, $p < .001$) indicated that girls' depressive symptoms significantly

increased from pre-adolescence to mid-adolescence, and then began to stabilize towards early adulthood. The significant variances around the mean intercept (initial status of depressive symptoms at age 10), the linear slope, and the quadratic slope (all *p*s < .001) indicated there was notable variability in girls' growth trajectories of depressive symptoms across adolescent development. The linear slope was negatively correlated with the quadratic slope, suggesting that adolescent girls who had greater increases in depressive symptoms from pre-adolescence to mid-adolescence were likely to exhibit less of a decline in symptoms during late adolescence and early adulthood.

The quadratic growth model for boys showed acceptable fit (χ^2 (4) = 109.164, $p < .001$, *CFI* = .821, *TLI* = .731, *RMSEA* = .095 [.080, .111], *SRMR* = .058), although not as good as the model fit for girls. For boys, the positive estimate of the linear slope mean (M_{slope} = .166, $p < .05$) along with a positive estimate of the quadratic slope mean (M_{quad} = .003, *ns*) indicated that boys' depressive symptoms significantly increased from pre-adolescence to mid-adolescence, then remained stable during late adolescence and began to increase again during early adulthood. The significant variances around the mean intercept (initial status of depressive symptoms at age 10), the linear slope, and the quadratic slope (all *p*s < .01) indicated there was notable variability in boys' growth trajectories of depressive symptoms across adolescent development. Note that although the quadratic slope was not significant for boys, the fact that the fit of the quadratic model was better than that of the linear model, along with the fact that the variance of the quadratic slope was significant, suggest that some adolescent boys experienced a quadratic growth in their depressive symptoms and that this model should be estimated rather than a linear growth model. The linear slope was negatively correlated with the quadratic slope, suggesting that adolescent boys who increased in depressive symptoms from pre-adolescence to mid-

adolescence were likely to experience an increase in their symptoms from late adolescence trough early adulthood.

Overall, girls showed a sharper increase in depressive symptoms during the transition from pre-adolescence to mid-adolescence, and then their depressive symptoms began to level off. Compared to girls, boys exhibited a more modest increase in depressive symptoms during adolescence, a steady increase which continued into early adulthood.

4.2.2. FMI.

Out of the three models tested for the growth of Fat Mass Index over adolescence (i.e., no growth, linear growth, quadratic growth), the best fitting model for both boys and girls was the quadratic growth curve model. Table 4 depicts the unconditional models' estimated parameters.

The quadratic growth model for girls showed excellent fit (χ^2 (4) = 6.734, p = .151, *CFI* = .999, *TLI* = .999, *RMSEA* = .015[.000, .034] , *SRMR*= .010). For girls, the positive estimate of the linear slope mean (M_{slope} = .372, p < .001) along with a negative estimate of the quadratic slope mean (M_{quad} = -.012, p < .001) indicated that girls' FMI significantly increased from pre-adolescence to mid-adolescence, then began to stabilize with a slower rate of increase from mid-adolescence towards early adulthood. The significant variances around the mean intercept (initial status of FMI at age 9), the linear slope, and the quadratic slope (all ps < .001), indicated there was notable variability in girls' growth trajectories of FMI across adolescent development. The intercept was negatively associated with the linear slope, indicating that pre-adolescent girls with greater FMI at intercept experienced less of an increase in their FMI during adolescence. The linear slope was negatively correlated with the quadratic slope, suggesting that adolescent girls who had greater increases in FMI from pre-adolescence to mid-adolescence were likely to exhibit less of a stabilization in FMI growth during late adolescence and early adulthood. The

intercept and quadratic slope were positively associated, suggesting that pre-adolescent girls with higher FMI at intercept exhibited more stabilization of FMI growth during late adolescence-early adulthood.

The quadratic growth model for boys showed acceptable fit (χ^2 (4) = 127.080, $p < .001$, *CFI* = .969, *TLI* = .954, *RMSEA* = .107 [.091, .123], *SRMR*= .041). Compared to girls, boys showed an opposite pattern in their FMI growth trajectory, i.e., a negative estimate of the linear slope mean (M_{slope} = -.109, $p < .001$) along with a positive estimate of the quadratic slope mean (M_{quad} = .020, $p < .001$), which indicated that boys' FMI did not exhibit an increase from pre-adolescence to late-adolescence, then began to increase during early adulthood. The significant variances around the mean intercept (initial status of FMI at age 9), the linear slope, and the quadratic slope (all *p*s < .001), indicated there was notable variability in boys' growth trajectories of FMI across adolescent development. The intercept was positively associated with the linear slope, indicating that pre-adolescent boys with greater FMI had experienced a greater decrease in their FMI during adolescence. The linear slope was negatively correlated with the quadratic slope, indicating that boys who exhibited less of a decrease (or an increase) in their FMI during adolescence were likely to exhibit an increase in their FMI during early adulthood.

Overall, girls showed an increase in FMI during the transition from pre-adolescence to mid-adolescence, and from then their rate of increase began to level off. Compared to girls, boys' FMI did not increase from pre-adolescence to late adolescence, then began to increase in the transition to early adulthood.

4.2.3. CRP.

Out of the three models tested for the growth of CRP over adolescence (i.e., no growth, linear growth, quadratic growth), the best fitting model for both boys and girls was the quadratic growth curve model. Table 5 depicts the unconditional models' estimated parameters.

The quadratic growth model for girls had an acceptable fit (χ^2 (4) = 99.112, $p < .001$, *CFI* = .846, *TLI* = .769, *RMSEA* = .088 [.073, .103], *SRMR*=.062). For girls, the positive estimate of the linear slope mean (M_{slope} = .460, $p < .001$), along with a negative estimate of the quadratic slope mean (M_{quad} = -.009, $p < .001$) indicated that girls' CRP levels significantly increased from pre-adolescence to mid-adolescence, and then began to stabilize until late adolescence with an additional slower increase towards early adulthood. The significant variances around the mean intercept (initial levels of CRP at age 9) and the quadratic slope (all *p*s < .05), indicated there was notable variability in girls' starting levels and quadratic growth of CRP. Note that the variance of the linear slope was not significant, indicating that there were not significant individual differences in linear growth of CRP. The intercept was negatively associated with the linear slope, suggesting that girls with high starting concentrations of CRP experienced less of an increase in CRP concentrations over adolescence. The intercept was positively associated with the quadratic slope, suggesting that girls with high initial CRP levels exhibited more stabilization (or less of an increase) in CRP levels during the transition from late adolescence to early adulthood.

The quadratic growth model for boys showed excellent fit (χ^2 (4) = 7.457, $p = .114$, *CFI* = .991, TLI= .987, *RMSEA* = .017 [.000, .036], SRMR=.018). For boys, the positive estimate of the linear slope mean (M_{slope} = .785, $p < .001$) along with a negative estimate of the quadratic slope mean (M_{quad} = -.033, $p < .001$) indicated that boys' CRP levels significantly increased from pre-adolescence to mid-adolescence, and then began to stabilize through early adulthood. The

significant variances around the mean intercept (initial levels of CRP at age 9), the linear slope, and the quadratic slope (all *p*s < .01) indicated there was notable variability in boys' growth trajectories of CRP across adolescent development.

The intercept was negatively associated with the linear slope, suggesting that boys with high starting concentrations of CRP experienced less of an increase in CRP concentrations over adolescence. The linear slope was negatively correlated with the quadratic slope, suggesting that adolescent boys who exhibited a greater increase in CRP from pre-adolescence to mid-adolescence were likely to experience less stabilization in CRP levels during late adolescence-early adulthood. The intercept was positively associated with the quadratic slope, suggesting that boys with high initial CRP levels exhibited more stabilization in CRP levels during late adolescence-early adulthood.

Overall, both boys and girls exhibited increases in their CRP levels in the transition from pre-adolescence to mid-adolescence, and from then the rate of growth slowed down. For boys, the increase of CRP leveled off toward early adulthood; however, girls still experienced an increase in CRP concentrations in the transition to early adulthood.

4.3. Parallel-Processes Growth Curve Models

4.3.1. FMI and Depressive Symptoms.

Table 6 presents the results of the adjusted parallel-processes models for FMI and depressive symptoms for boys and girls. The adjusted model for girls had adequate fit (χ^2 (150) = 631.639, $p < .001$, *CFI* = .950, *TLI* = .930, *RMSEA* = .031 [.029, .034], *SRMR* = .038).
For girls, the intercept of depressive symptoms was positively correlated with the linear slope of FMI ($\beta = .088$, $p < .01$), suggesting that pre-adolescent girls with elevated depressive symptoms

at intercept were more likely to have a steeper increase in adiposity during adolescence compared to pre-adolescent girls with lower depressive symptoms.

The adjusted model for boys had adequate fit (χ^2 (138) = 672.981, $p < .001$, *CFI* = .926, *TLI* = .894, *RMSEA* = .036 [.033, .039], *SRMR* = .045). However, no significant associations were found between the cross-constructs growth factors in the models for boys.

4.3.2. FMI and CRP.

Table 7 presents the results of the adjusted parallel-processes models for FMI and CRP for boys and girls. The adjusted model for girls had good fit (χ^2 (150) = 366.766, $p < .001$, *CFI* = .973, *TLI* = .963, *RMSEA* = .021 [.018, .023], *SRMR* = .024). In the model for girls, the intercepts were positively associated ($\beta = .749$, $p < .001$), suggesting that during late childhood, increased adiposity was associated with elevated CRP levels. Similarly, the linear slopes were also positively associated ($\beta = 1.188$, $p < .001$), suggesting that a steeper linear increase in FMI over adolescence was associated with a steeper linear increase in CRP.

I also found significant negative associations between the intercepts and linear slopes. First, the intercept of FMI was negatively associated with the linear slope of CRP ($\beta = -.529$, $p < .001$), suggesting that pre-adolescent girls with elevated FMI were likely to have smaller linear increase in CRP over adolescence compared to those with lower FMI. Similarly, the intercept of CRP was negatively associated with the linear slope of FMI ($\beta = -.502$, $p < .001$), suggesting that pre-adolescent girls with elevated CRP were likely to have a slower linear increase in FMI over adolescence compared to those with lower initial CRP levels.

Finally, I found negative associations between the linear slopes and the quadratic slopes. The linear slope of FMI was negatively associated with the quadratic slope of CRP ($\beta = -.721$, $p < .001$), suggesting that girls with a steeper linear increase in FMI were less likely to have

deceleration in CRP during late adolescence-early adulthood. Similarly, the linear slope of CRP was negatively associated with the quadratic slope of FMI (β = -1.345, $p < .05$), suggesting that girls with a steeper linear increase in CRP were less likely to experience deceleration of FMI during the later adolescence years.

The adjusted model for boys had adequate fit as well (χ^2 (138) = 425.559, $p < .001$, *CFI* = .951, *TLI* = .931, *RMSEA* = .026 [.024, .029], *SRMR* = .024). Similar to girls, the intercepts were positively correlated, suggesting that higher FMI was associated with elevated CRP levels in pre-adolescent boys. The linear slopes were positively associated (β = .072, $p < .001$), suggesting that for boys, over the first half of adolescence, stronger linear increases in CRP were associated with stable or decreasing FMI.

I also found significant negative associations between the intercepts and linear slopes. First, the intercept of FMI was negatively associated with the linear slope of CRP (β = -.139, $p <$ .001), suggesting that similar to girls, pre-adolescent boys with elevated FMI were likely to have smaller linear increases in CRP over the first half of adolescence compared to boys with lower FMI. The intercept of CRP was also negatively associated with the linear slope of FMI (β = -.243, $p < .001$), however considering the negative linear slope of FMI, this suggests that pre-adolescent boys with elevated CRP levels were likely to have increasing FMI (a smaller linear decrease) over the first half of adolescence, compared to boys who started with lower CRP concentrations at intercept.

The correlations between the linear and quadratic slopes were different. The linear slope of FMI was positively associated with the quadratic slope of CRP (β = .220, $p < .001$), suggesting that boys with decreasing or flatter FMI over the first half of adolescence were more likely to have the leveling off in the increase of CRP during late adolescence-early adulthood;

conversely, boys with increasing FMI in earlier adolescence were likely to have continued increases in CRP in later adolescence. The linear slope of CRP was negatively associated with the quadratic slope of FMI (β = -.183, p < .001), suggesting that boys with a steeper linear increase in CRP in earlier adolescence were less likely to experience the increase in FMI during the later adolescent years.

4.3.3. CRP and Depressive Symptoms.

Table 8 presents the results of the adjusted parallel-processes LGC models for CRP and depressive symptoms for boys and girls. The adjusted model for girls had adequate fit (χ^2 (174) = 329.516, p < .001, *CFI* = .971, *TLI* = .960, *RMSEA* = .016 [.014, .019], *SRMR* = .020), however, no significant associations were found between the cross-constructs growth factors. Similarly, the adjusted model for boys had adequate fit (χ^2 (162) = 230.244, p < .001, *CFI* = .979, *TLI* = .971, *RMSEA* = .012 [.008, .015], *SRMR* = .019), however, no significant associations were found.

4.4. Cross-Lagged Panel Analyses

4.4.*1. FMI and Depressive Symptoms.*

Findings from a 2-level, 4-wave cross-lagged panel analysis without covariates revealed bidirectional associations between FMI and depressive symptoms in girls. Specifically, depressive symptoms at T1 positively predicted FMI at T2 (β = .056, p < .001), such that elevated depressive symptoms during pre-adolescence was associated with increased FMI in mid-adolescence. Similarly, FMI at T1 positively predicted depressive symptoms at T2 (β = .056, p < .001), such that increased FMI during pre-adolescence was associated with increased depressive symptoms in mid-adolescence. However, when covariates were entered into the

model, the path from FMI at T1 to depressive symptoms at T2 was no longer significant. The final adjusted model, including fit indices, is presented in Figure 1a.

In boys, depressive symptoms at T1 also positively predicted FMI at T2 (β = .032, p < .05), such that elevated depressive symptoms during pre-adolescence was associated with increased FMI in mid-adolescence. Additionally, FMI and depressive symptoms were negatively associated in late-adolescent boys (β = -.078, p < .01), such that lower FMI was associated with elevated depressive symptoms. These results remained similar when covariates were entered into the model; see Figure 1b.

4.4.2. FMI and CRP.

For both girls and boys, findings from the 2-level, 4-wave cross-lagged analyses without covariates revealed concurrent positive associations between FMI and CRP within each wave (all βs > .203, all ps < .001), such that higher FMI was associated with elevated CRP levels at each wave. Significant unidirectional associations between FMI and CRP were found as well; FMI positively predicted CRP concentrations from each wave to the next, such that higher FMI was associated with increased CRP across each wave (all βs > .131, all ps < .001). These results remained unchanged when entering covariates into the models. The final adjusted model for girls, including fit indices, is presented in Figure 2a; the corresponding model for boys is presented in Figure 2b.

4.4.3. CRP and Depressive Symptoms.

The unconditional cross-lagged panel models for the associations between CRP and depressive symptoms showed different patterns for boys and girls. In girls, depressive symptoms at T1 positively predicted CRP at T2 (β = .067, p < .01), such that elevated depressive symptoms during pre-adolescence was associated with increased CRP concentrations in mid-adolescence.

However, this result was no longer significant after entering covariates into the model. The final adjusted model, including fit indices, is presented in Figure 3a.

In boys, CRP at T1 negatively predicted depressive symptoms at T2 (β = -.056, p < .05), such that lower CRP concentrations in pre-adolescence were associated with elevated levels of depressive symptoms during mid-adolescence. This result also became non-significant after including covariates in the model. The final adjusted model, including fit indices, is presented in Figure 3b.

4.4.4. FMI, CRP and Depressive Symptoms.

The final step was to examine the associations between these three constructs in a 3-level, 4-wave cross-lagged panel model. Similar to the previous models, I examined these associations separately in boys and girls; I first tested the associations between these three constructs without covariates, and then added covariates in the second step. The fully adjusted models are depicted in Figures 4a and 4b for girls and boys, respectively. Both models showed good fit to the data.

For both boys and girls, the associations between FMI and CRP, as well as the associations between FMI and depressive symptoms, remained the same as those obtained from the 2-level cross-lagged analyses reported previously. However, differences were observed in the associations between CRP and depressive symptoms; the paths that lost significance when adding covariates in the 2-level models, along with other trends, became significant in the 3-level model.

Specifically, for girls, depressive symptoms at T1 positively predicted CRP at T2 (β = .050, p < .05), such that elevated depressive symptoms during pre-adolescence were associated with increased CRP concentrations in mid-adolescence. However, from late adolescence to early adulthood, negative associations between CRP and depressive symptoms emerged for girls.

Namely, lower CRP levels in late adolescence predicted elevated depressive symptoms in early adulthood (β = -.062, p < .05), and CRP and depressive symptoms were also negatively associated within early adulthood (β = -.063, p < .05).

For boys, similar negative associations emerged earlier, demonstrated by CRP at T1 negatively predicting depressive symptoms at T2 (β = -.056, p < .05), such that lower CRP concentrations in pre-adolescence were associated with elevated levels of depressive symptoms in mid-adolescence. These results were unchanged when adding covariates to the models.

5. Discussion

Depression and obesity are prevalent in children and adults, and considered as serious public health issues. In light of the high comorbidity of these two illnesses, researchers have examined potential shared mechanisms that could explain the link between obesity and depression. Studies of adults provided some evidence that inflammatory responses may be a key factor that could explain the high comorbidity between depression and obesity. However, the extent to which this mechanism is at play in younger samples is unclear, and it is possible that the mechanism is different considering the significant physiological changes that occur during the pubertal transition and adolescent period. Additionally, research with adults suggests that the inter-relations between obesity, depression and inflammation may be stronger for females; however, the extent to which sex differences are present in these associations in children and adolescents has not yet been fully explored. Thus, the main goals of this study were to examine the development of the inter-relations between adiposity, inflammation, and depressive symptoms from the period of pre-adolescence to early adulthood, and to examine whether these associations differ by sex.

There is limited longitudinal research on these questions in children and adolescents. Previous research investigated these questions of the relations between obesity, depression and inflammation incompletely, by examining two constructs at a time. Most studies were cross-sectional or, if longitudinal, did not have repeated measures and could not control for the stability of one construct in the development of the other, nor could they test two directional paths simultaneously to examine the possibility of bidirectional relations. Finally, many of the studies which attempted to answer these questions had small sample sizes and could not examine sex differences. For this study, I aspired to fill these gaps in the literature and to examine the co-

development of these three constructs in a large prospective cohort study, employing a repeated measure design across multiple time points over the adolescent years. I used a combination of both cross-lagged panel analyses and parallel-processes latent growth curve models to answer these questions, and to examine differences between boys and girls. My findings revealed a more complex set of inter-relations between adiposity, inflammation, and depressive symptoms than has previously been described.

5.1. Individual Latent Growth Curves

My first goal was to examine developmental trajectories of Fat Mass Index (FMI), C-reactive protein (CRP) and depressive symptoms from pre-adolescence to early adulthood in boys and girls. Consistent with previous studies (Eissa et al., 2009; Marshall et al., 2020), I found that girls experienced a non-linear increase in FMI, with a steeper increase during the transition from late childhood to mid-adolescence, and then a slight deceleration in the transition to early adulthood. Boys, in contrast, did not experience an increase in fat mass during adolescence as expected. Previous studies documented a decrease in boys' fat mass during the transition from late childhood to early adolescence (Eissa et al., 2009; Marshall et al., 2020). It is possible that I did not observe the decrease in fat mass because of the different timing of measurements; it may have occurred before the first wave or between the first two waves. Unexpectedly, I observed an increase in males' FMI during the transition to adulthood. This increase may be explained by negative health behavior as young adults finish formal schooling, leave their parents' homes and have more independence over their dietary choices and other related behaviors, including legal alcohol consumption.

Regarding the developmental trajectory of CRP, I found that both boys and girls experienced a non-linear increase in CRP, but the trajectories were slightly different. Both boys

and girls had a steeper increase during the transition to adolescence; from then, the trajectories diverged. Boys' CRP levels tended to stabilize by early adulthood; for girls, the rate of the increase slowed between mid to late adolescence, then accelerated again. The sex differences observed during the transition from late adolescence to adulthood are consistent with results found by Shanahan and colleagues (2013). One potential explanation for the sex differences in CRP during the transition from late adolescence to early adulthood is that females have significantly more fat mass than males at this age (Loomba-Albrecht & Styne, 2009), and it is known that adipose tissue secretes cytokines, CRP, and other proinflammatory factors (Ellulu et al., 2017).

Finally, consistent with previous studies (Ferro et al., 2015; Hankin et al., 1998; Kwong, 2019; Kwong et al., 2019; Natsuaki et al., 2009), both boys and girls experienced a non-linear increase in depressive symptoms, but expected sex differences were observed. Girls had a sharp increase in depressive symptoms from late childhood with a peak in mid-adolescence, and then their symptoms began to decline through late adolescence and early adulthood (although still remained higher than those of boys). Boys, on the other hand, had a more modest increase until mid-adolescence, with a stabilization period until late adolescence, and an additional increase through early adulthood.

5.2. Adiposity and Inflammation

There is scant research on the links between development of obesity and inflammation in adolescents. Few studies have provided some evidence for positive associations between adiposity and inflammation; however, the nature of how and when these associations develop, the directionality of these associations, and whether these constructs develop differently for boys and girls is not clear. I conducted two different analyses, namely, parallel-processes latent

growth models and cross-lagged models, in an attempt to answer this question from different angles. The parallel-processes LGCM provided information regarding the associations between the trajectories of adiposity and inflammation across adolescence, including whether initial levels of one construct predicted the development of the other. The cross-lagged models provided information regarding the temporal order, or directionality of the associations, along with information about the developmental periods at which these associations emerge.

The cross-lagged models allowed me to investigate the possibility that bidirectional associations exist between FMI and CRP, while taking into the account the development of each construct. My findings suggest that adiposity is a robust predictor of systemic inflammation at multiple points during the course of adolescent development, spanning from pre-adolescence to early adulthood. I found positive concurrent associations within each wave, along with unidirectional effects from adiposity at each wave to inflammation in the subsequent wave. My findings suggest that overweight adolescents are likely to have elevated inflammation, and that having increased adiposity at one point is associated with a heightened risk for increase in inflammation in subsequent years. These results were present in both boys and girls. Importantly, C-reactive protein did not predict adiposity at each stage of development.

The positive concurrent associations found between fat mass and CRP are consistent with previous studies which found positive associations between measures of obesity and CRP (Choi et al., 2013). Additionally, the unidirectional effect observed, i.e., greater fat mass predicting greater increases in CRP in subsequent years, is in line with previous studies which found that obesity at younger ages predicts inflammation later on (Goosby et al., 2016; Reid et al., 2020; Toprak et al., 2011). One important note is that these previous studies have used other measures of adiposity, mainly BMI, a measure that cannot discriminate between fat mass and fat-

free mass. This may be important to distinguish when examining sex differences. My study adds to the previous literature by providing evidence that these associations exist with a measure of fat mass. This finding can be explained by the fact that adipose tissue is capable of secreting cytokines and other proinflammatory factors which can promote the production and release of CRP into the bloodstream (Kyrou et al., 2006).

The parallel-processes latent growth models allowed me to examine how change in the development of one construct is related to change in the development of the other construct. Additionally, they also provide information regarding how initial levels of one construct affect the development of the other construct, and vice versa (Felt et al., 2017). Findings from these models revealed some sex differences that were not observed in the cross-lagged models, along with some common findings across genders.

Girls with greater FMI in late childhood also had higher CRP concentrations in late childhood. Perhaps because of this early elevated inflammation, girls with greater FMI in late childhood also showed less of the initial increase in CRP in the transition to adolescence that was typical of females. For girls who did gain more fat mass, there were consequences for later inflammation. Increasing fat mass from late childhood to mid-adolescence was associated with both an initial increase in CRP during the first half of adolescence, and less of the deceleration in CRP during the transition into early adulthood. Therefore, increased fat gain during the first half of adolescence appeared to be a risk factor for increasing inflammation during the transition to adulthood, which in turn could place those girls at risk for other health problems in adulthood.

Similarly, girls who initially exhibited high levels of CRP in late childhood tended to have a smaller increase in adiposity throughout adolescence compared to girls who started with low CRP levels (perhaps due to high initial levels of FMI). For girls who exhibited increases in

CRP concentrations, there were consequences for later adiposity. Increasing CRP from late childhood to mid-adolescence was associated with both an initial increase in adiposity during the first half of adolescence, and less of the deceleration in fat mass during the transition into early adulthood, overall leading to greater adiposity.

The unidirectional effect of adiposity on inflammation was evident in boys as well. Boys with greater FMI in late childhood also had higher CRP concentrations in late childhood. Similar to girls, boys with greater FMI in late childhood also showed less of the initial increase in CRP in the transition to adolescence that was typical of males (perhaps because of early elevated inflammation). In addition, although the overall FMI trajectory for boys was for FMI not to increase in the first half of adolescence, for those boys who did gain more fat mass, there were consequences for later inflammation. Increasing FMI from late childhood to mid-adolescence was associated with less initial change in CRP, but greater subsequent increases in CRP in the transition into early adulthood.

Conversely, boys who started with high levels of CRP tended to have less of a decline (or a greater increase) in fat mass during the first half of adolescence. A steeper increase in CRP during the transition from late childhood to mid-adolescence was associated with a greater decrease in fat mass over the first half of adolescence, followed by a smaller increase in fat mass during early adulthood, overall leading to reduced adiposity.

Therefore, in both boys and girls, early adiposity appeared to be a risk factor for later elevated inflammation, which may increase the risk for other health problems in adulthood. This finding is consistent with the results obtained from the cross-lagged models, which demonstrated that in both boys and girls, adiposity is a robust predictor of subsequent inflammation across adolescence. However, striking differences between boys and girls were found when examining

the influence of inflammation on the development of adiposity across adolescence. In girls, a greater increase in CRP during the first half of adolescence was associated with increased fat gain. Indeed, just as adiposity contributes to inflammation, elevated inflammation can also contribute to the accumulation of fat over time through HPA-axis activation (Kyrou et al., 2006).

However, for boys, a steeper increase in CRP levels during the first half of adolescence was associated with reduced fat gain. These differences could be related to the higher levels of CRP observed in girls versus boys. They could also be due to the fact that girls experience an increase in the amount of fat mass during the pubertal transition, while boys generally experience a relative decrease in the overall amount of fat mass during adolescence while increasing the amount of lean muscle mass (Loomba-Albrecht & Styne, 2009). Indeed, Shanahan and colleagues (2013) found that the association between BMI and CRP increased during adolescence for girls, and decreased during adolescence for boys. They hypothesized that this is due to changes in the amount of fat mass between boys and girls during adolescence. It is possible that I observed positive bidirectional associations between FMI and CRP only in girls because of the strong relations between fat mass and CRP in girls across adolescent development. Shanahan and colleagues (2013) suggested that other factors may have more prominent roles in the development of CRP in boys, such as smoking, drug use, and sex hormones. It also may be the case that measures of abdominal obesity may have stronger relations with CRP in boys, as boys' fat is centered primarily around the abdomen (Loomba-Albrecht & Styne, 2009), and visceral fat is a primary source of cytokines (Ellulu et al., 2017).

Nevertheless, while the parallel-process growth model indicated that the coupling of the development of FMI and CRP also meant that initial CRP concentrations predicted later FMI levels, these findings need to be understood in light of the effects of the cross-lagged models,

which indicated that CRP concentrations were not proximal drivers of change in subsequent adiposity, along with a lack of evidence for this path in the adolescent literature. Potential explanations for this discrepancy could be that the mechanisms by which CRP contributes to fat accumulation take time, or perhaps a certain threshold of CRP is required in order to activate this mechanism, and it should be considered that the majority of participants in this study were young and healthy with low mean levels of CRP.

5.3. Adiposity and Depression

My findings from both parallel-processes LGCM and cross-lagged models provided support for a unidirectional effect of depressive symptoms on the development of adiposity during the first half of adolescence. The result from the LGCM analysis suggests that preadolescent girls with elevated depressive symptoms were likely to have a greater increase in adiposity during the transition to adolescence. The findings from the cross-lagged analyses indicate that this effect was not unique to girls. Specifically, for both boys and girls, elevated depressive symptoms in late childhood predicted increase in adiposity by mid-adolescence. Conversely, adiposity did not predict subsequent depression in both the LGCM and cross-lagged models, neither for boys nor for girls, although there was an unexpected negative correlation between FMI and depression for boys in late adolescence.

Previous research provides evidence for both directional hypotheses, however, two studies which investigated these two paths simultaneously in adolescents found support for the unidirectional effect of depression on increasing the risk for obesity one year later (Goodman & Whitaker, 2002; Roberts & Duong, 2013). My findings provide additional support that experiencing depressive symptoms during late childhood is a risk factor for increasing adiposity during adolescence. My results are also consistent with previous research which found that this

path emerges during the earlier phase of adolescence (Marmorstein et al., 2014). While previous findings regarding sex differences in this association are mixed, my findings suggest that both boys and girls are at increased risk for developing greater adiposity during adolescence if experiencing depressive symptoms in late childhood.

My main finding that experiencing elevated depressive symptoms in late childhood is associated with increased adiposity during mid-adolescence may be explained by the fact that a common type of depression experienced by teens is atypical depression, which is characterized by increased appetite, among other symptoms (Singh & Williams, 2006). This sub-type of depression is also more common in girls than in boys (Singh & Williams, 2006), which may explain the robustness of this finding across models for girls in my study. Additionally, depression is associated with several negative health behaviors which have the potential to result in increased adiposity (e.g., poor diet and eating behaviors, sedentary behavior). Finally, depression is associated with a state of chronic stress, which leads to endocrine and metabolic changes that promote fat accumulation (Miller, Maletic, & Raison, 2009). In order to elucidate the mechanisms underlying the effects of depression on increased adiposity in adolescents, future studies would benefit from examining different subtypes of depression, collecting data on dietary choices, eating behaviors, exercise, and stress, and measuring stress and metabolic biomarkers.

Contrary to expectations, I did not find much evidence to support that increased adiposity in late childhood predicts increase in depressive symptoms during adolescence. This path indeed emerged in girls when I conducted the analysis without covariates, however, as soon as I added covariates such as smoking, alcohol and oral contraceptive use this result became non-significant. Previous studies have found that being overweight or obese during middle childhood increases the risk of experiencing internalizing symptoms in early adolescence (Pryor et al.,

2016), and that obese, but not overweight 13-year old girls were at increased risk for developing depressive symptoms during late adolescence (Boutelle et al., 2010). These studies controlled for relevant confounding factors such as pubertal development and others, however, they did not control for smoking and alcohol use which are associated with both depression and obesity, hence their results may be exaggerated. Additionally, these studies examined the effects of obesity status rather than examining adiposity as a continuous measure. The sample in my study was comprised of healthy adolescents, and it is possible that increased adiposity predicts the development of depressive symptoms in more clinical samples (i.e., in overweight and obese children). This could also explain why I failed to observe positive concurrent associations between depression and adiposity within each wave. Finally, both studies referenced above did not investigate the other directional hypothesis, potentially leading to exaggerated results as well.

One intriguing finding that was unexpected was the negative association between depressive symptoms and adiposity in late-adolescent boys. This finding may be indicative of very lean teen boys who are experiencing body image issues due to not meeting societal expectations of masculinity (i.e., being large and well-muscled). Indeed, previous research have found that 16-year old adolescent boys who viewed themselves as very underweight reported significantly higher levels of depressive symptoms compared to boys who viewed their weight as average (Blashill & Wilhelm, 2015). Considering the key role that body image issues may play in explaining associations between adiposity and depression, future studies would benefit from collecting information on body image and body dissatisfaction. Including additional measures of abdominal adiposity may also aid in elucidating these striking findings, especially since they may be more suitable for investigating effects that are related to body dissatisfaction.

5.4. Inflammation and Depression

Contrary to the adult literature, I did not find many associations between depressive symptoms and C-reactive protein, a general marker of peripheral systemic inflammation, in this sample of healthy adolescents. In fact, in the LGCM and cross-lagged models involving CRP and depression, there were no significant effects that were robust to the inclusion of covariates. Conversely, in the 3-level cross-lagged model that included FMI, there were 5 significant associations between CRP and depression, but 4 of them were counter to the expected positive link. The only significant positive association was found for girls, such that elevated depressive symptoms during late childhood were associated with elevated C-reactive protein concentrations in mid-adolescence. The fact that positive associations between depression and C-reactive protein were only evident in girls may provide one explanation as to why females are at increased risk for developing chronic inflammation and various autoimmune diseases (Klein & Flanagan, 2016).

This finding is consistent with results of two other studies of adolescents which demonstrated the unidirectional effect of depression on later elevated CRP levels (Copeland et al., 2012; Duivis et al., 2015). Duivis and colleagues (2015) found that persistently moderate-high depressive symptoms during late childhood and early adolescence predicted elevated CRP levels in mid-adolescence. Copeland and colleagues (2012) collected data at multiple time points from pre-adolescence to early adulthood, and found that depression at each wave predicted subsequent elevated CRP levels. However, in models adjusting for covariates, only cumulative depressive episodes continued to predict later CRP levels. Thus, it seems that persistent or recurrent episodes of depression exacerbate the risk for developing elevated inflammation later on. This may explain the lack of associations observed in my study during late adolescence and early adulthood.

My findings did not provide evidence for the second directional hypothesis, i.e., elevated CRP levels predicting increased depressive symptoms. I also did not find any significant positive concurrent associations between depression and CRP within each wave. In fact, contrary to expectations, I found several negative associations between CRP and depressive symptoms. In boys, lower concentrations of CRP in late childhood predicted elevated depressive symptoms in mid-adolescence, and in girls the same negative associations were observed from late adolescence to early adulthood, along with a negative concurrent association in early adulthood. These unexpected findings suggest that across adolescence, hypo-activity of the inflammatory response may contribute to the development of depressive symptoms. A potential mechanism that may explain this finding is the immune-suppressant effects of elevated adrenocortical activity resulting from the experience of chronic stress. Suppression of the immune system may increase the risk for various infections and illnesses, and recurrent physical health problems may lead to the feeling of depression in adolescents.

While positive associations between depression and inflammation are widely documented in adults, increasing evidence suggests that this may not be the case in children and adolescents, and the null results observed in this study are consistent with several other studies that did not find significant associations between depression and CRP in children and youths (Baumeister, Akhtar, Ciufolini, Pariante, & Mondelli, 2016; Byrne et al., 2013; Chaiton et al., 2010; Flouri, Francesconi, Midouhas, Papachristou, & Lewis, 2020; Flouri, Lewis, & Francesconi, 2020; Khandaker, Pearson, Zammit, Lewis, & Jones, 2014b; Liu, Ely, Simkovic, Alonso, & Gabbay, 2021). There are a number of potential explanations for the lack of associations observed between CRP and depression in adolescents. The neuroimmune network hypothesis posits that early-life stress activates a neuro-immune crosstalk, which leads to increased threat sensitivity,

inflammation, and unhealthy behaviors, which altogether increases vulnerability to disease (Nusslock & Miller, 2016). Thus, it may be the case that it takes time for the association between depression and chronic low-grade inflammation to form, and that its emergence depends on repeated exposure to stress. In this case, it is possible that I did not observe this association because participants in this study were fairly young, healthy, and from a middle-high socioeconomic backgrounds. It is possible that positive associations will be observed in participants who have experienced early life adversity or those who have experienced persistent and severe depression. It also may be the case that results are not observed due to using a general measure of depressive symptoms rather than examining specific sub-types or symptoms of depression, as there is evidence that low-grade inflammation is associated with specific sub-types or symptoms of depression (Lamers et al., 2018). Importantly, CRP is only one marker of peripheral systemic inflammation, yet, the immune system is complex and has different branches and multiple components. Considering the null associations found between CRP and depression in this study and in other studies of adolescents, it is possible that other immune markers may contribute more significantly to the development of depression (e.g., neuroimmune markers, cytokines, etc.).

5.5 Adiposity, Inflammation and Depression

While studies with adults suggest chronic low-grade inflammation as a potential shared mechanism between depression and obesity, findings from the 3-level cross-lagged model revealed that inflammation is not a mediator of the associations between depression and adiposity across adolescence. In fact, adiposity seems to be the proximal driver of inflammation rather than the converse, and in both boys and girls, adiposity and inflammation were found to be closely linked across adolescence. Furthermore, inflammation was not clearly linked with

depression, and in fact, for both boys and girls, inflammation was inversely associated with depression at different points in development. These findings demonstrate that the mechanisms underlying the relations between adiposity, inflammation and depression are clearly different in children and adolescents compared to adults, and call into question the notion that CRP can be used as a biomarker for depression in younger samples.

Considering associations with adiposity, the findings from the 3-level cross-lagged model indicated that preadolescents with elevated depressive symptoms may be at greater risk for increasing adiposity, and for girls, increasing inflammation, in the transition into adolescence. However, this pattern does not seem to continue in the later phases of adolescence and emerging adulthood. Thus, to the limited extent that depression was associated with adiposity and inflammation, the direction found was more consistent with the model proposed by Byrne and colleagues (2015), which suggests that adiposity and inflammation are consequences rather than antecedents of adolescent-onset depression. The fact that this association was significant in the 3-level cross-lagged model but not in the 2-level cross-lagged model suggests that it was necessary to account for the relations of adiposity with both depression and inflammation in late childhood and mid-adolescence, in order to identify the link between early depression and subsequent inflammation. Byrne and colleagues (2015) proposed that increased adiposity may be a linking mechanism between adolescent-onset depression and the subsequent development of elevated inflammation, although the lack of a measure of adiposity in early adolescence precluded testing that hypothesis in this study. Finally, there is limited evidence to suggest that preadolescent girls with elevated depressive symptoms, in particular, are at heightened risk for developing poor health outcomes that are associated with chronic low-grade inflammation in adulthood.

5.6. Limitations

My findings should be interpreted in light of several study limitations. First, this study did not have an exact match in the occasions at which the depression variables were collected and when the clinic measures were collected (i.e., fat mass, blood test for CRP assays). There was also great variability in the ages of participants even within the same clinic visit. Thus, I controlled for the age of participants at each measurement collection. Second, this study did not have a data collection point during early adolescence. This is especially important because there is a great variability in pubertal development during early adolescence, and pubertal development is known to affect each of the main study variables. To account for this, I have included pubertal development at age 12 as a covariate in all my models. Third, this study have utilized self-reported symptoms of depression rather than a clinical diagnosis of depression. Although the validity of the Moods and Feelings Questionnaire used in this study is well-established (Turner, Joinson, Peters, Wiles, & Lewis, 2014), the self-report may have introduced bias into the study. Fourth, I did not formally test for sex differences, therefore the observed findings for girls and boys should not be interpreted as statistically significant differences. Finally, the findings from this study cannot be generalized to other populations, as the sample in this study was comprised of mostly White participants from middle-high socioeconomic backgrounds in the United Kingdom. Future studies should investigate these questions in individuals from diverse backgrounds.

5.7. Conclusion and Future Directions

This dissertation study provides evidence for the existence of concurrent and predictive relations among adiposity, peripheral inflammation and depressive symptoms across adolescent development, however, the mechanisms seem to be different than those observed in adults. First, inflammation was not found to be a mediator of neither adiposity, nor depression. In fact, across

adolescence, adiposity seems to be the proximal driver of inflammation rather than the converse. Furthermore, the null and inverse associations found between CRP and depression call into question the usage of CRP as a biomarker of depression, at least for children and adolescents. Consistent with the model proposed by Byrne and colleagues (2015), the findings provide limited support for the hypothesis that depression experienced in late childhood increases the risk for the development of adiposity, and in girls, inflammation, during the transition into adolescence. While the associations observed were more similar than different across genders, the developmental trajectories of each construct looked very different between boys and girls.

Considering the scarcity of research on these questions in younger samples and the overall mixed findings in the adolescent literature on this topic, further longitudinal research on children and adolescents is warranted. Future studies on this topic should employ a repeated-measures design, and should aim at collecting the same study variables at key stages over the course of adolescent development. As mentioned earlier, it would be beneficial to collect several types of adiposity measures, including measures of both general and abdominal adiposity, as well as different types of immune markers such as cytokines. Additionally, it would be important to collect data on depression subtypes and symptoms. In order to reach a better understanding of the mechanisms at play, future studies should include behavioral measures on diet, exercise, body image, and stress. Additional biological measures that could shed light on the mechanisms are sex hormones, nutrition, and stress biomarkers.

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7. Tables and Figures

Table 1

Descriptive Statistics of Main Study Variables Across Four Waves

Variable	M_{Age}	Sex	*N*	*M*	*SD*	*Min*	*Max*
FMI variables							
FMI T1	9.859	Males	2741	3.647	2.207	.733	15.420
		Females	2898	4.871	2.329	.926	18.146
FMI T2	15.446	Males	2102	3.694	2.648	.714	19.021
		Females	2306	6.945	2.936	1.369	22.764
FMI T3	17.798	Males	1864	4.317	3.009	.515	20.096
		Females	2320	7.848	3.404	1.379	27.913
FMI T4	24.483	Males	1278	6.398	3.015	1.753	23.242
		Females	2048	9.006	3.860	.628	28.492
hs-CRP variables							
hs-CRP T1	9.859	Males	2325	.475	.948	.015	6.077
		Females	2379	.680	1.069	.015	6.078
hs-CRP T2	15.446	Males	1592	.893	1.366	.080	7.646
		Females	1719	.888	1.350	.070	7.645
hs-CRP T3	17.798	Males	1532	.943	1.405	.015	9.188
		Females	1660	1.428	1.876	.060	9.187
hs-CRP T4	24.483	Males	1204	1.313	2.117	.050	14.182
		Females	1822	2.195	3.070	.050	14.183
Depression variables							
MFQ T1	10.650	Males	2818	4.080	3.401	0.000	23.000
		Females	2959	3.908	3.541	0.000	20.000
MFQ T2	16.681	Males	1596	4.241	4.514	0.000	26.000
		Females	2276	6.946	6.013	0.000	26.000
MFQ T3	17.840	Males	1670	5.578	4.739	0.000	26.000
		Females	2184	7.211	5.455	0.000	26.000
MFQ T4	22.888	Males	1085	5.286	4.954	0.000	26.000
		Females	1994	6.620	5.744	0.000	26.000

Note. The table presents descriptive statistics of the main study variables before transformation (i.e., raw values). FMI = Fat Mass Index; hs-CRP = high-sensitivity C-reactive protein; MFQ= Moods and Feelings Questionnaire. T1 = pre-adolescence, T2 = mid-adolescence, T3 = late adolescence, T4 = early adulthood. *N* = 6,525; 3,434 females; 3,091 males.

Table 2

Zero-Order Correlations of Main Study Variables Stratified by Biological Sex

Variable	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.
1. FMI T1	-----	.753***	.693***	.566***	.455***	.306***	.206***	.205***	.005	.049*	.048*	.055*
2. FMI T2	.753***	-----	.832***	.685***	.345***	.385***	.246***	.235***	.067**	.086***	.045	.053*
3. FMI T3	.715***	.838***	-----	.725***	.311***	.324***	.335***	.304***	.072**	.053*	.036	.052*
4. FMI T4	.594***	.614***	.728***	-----	.267***	.263***	.238***	.413***	.078**	.134***	.044	.055*
5. hs-CRP T1	.411***	.310***	.276***	.224***	-----	.363***	.318***	.343***	.040	.019	.009	.006
6. hs-CRP T2	.273***	.338***	.302***	.185***	.281***	-----	.365***	.319***	.076**	.022	.003	.038
7. hs-CRP T3	.242***	.276***	.352***	.238***	.262***	.310***	-----	.357***	.039	.058*	.036	-.019
8. hs-CRP T4	.208***	.229***	.319***	.407***	.240***	.287***	.333***	-----	.033	.034	-.036	-.044
9. MFQ T1	-.011	.015	-.003	.001	-.028	.022	-.019	.022	-----	.270***	.224***	.192***
10. MFQ T2	-.008	-.017	-.032	.005	-.066*	.005	-.023	.005	.220***	-----	.513***	.456***
11. MFQ T3	-.015	-.022	-.043	-.024	-.015	.007	-.055*	.011	.226***	.497***	-----	.425***
12. MFQ T4	.000	.041	-.021	-.009	-.063	-.036	-.059	-.016	.188***	.389***	.382***	-----

Note. Correlations for boys are below the diagonal and for girls are above the diagonal. FMI=Fat Mass Index (log-transformed); hs-CRP=high-sensitivity C-reactive protein (log-transformed); MFQ=Moods and Feelings Questionnaire (square-root transformed). *N*=6,525; 3,434 females; 3,091 males. T1=pre-adolescence, T2=mid-adolescence, T3=late adolescence, T4=early adulthood.
* $p < .05$. ** $p < .01$. *** $p < .001$.

Table 3

Parameter Estimates of the Unconditional Univariate Latent Growth Curve Model of Depressive Symptoms in Boys and Girls

Parameter	Girls		Boys	
	Mean (SE)	Variance (SE)	Mean (SE)	Variance (SE)
Intercept	1.725*** (.018)	.309*** (.035)	1.802*** (.017)	.177*** (.038)
Linear slope	1.722*** (.066)	2.715*** (.485)	.166* (.075)	2.540*** (.603)
Quadratic slope	-.101*** (.005)	.013*** (.003)	.003 (.007)	.014** (.004)
Intercept-linear slope covariance	.013 (.093)	------	.122 (.104)	------
Linear slope-quadratic slope covariance	-.175*** (.037)	------	-.180*** (.049)	------
Intercept-quadratic slope covariance	-.005 (.006)	------	-.009 (.008)	------

Note. All coefficients are unstandardized. Factor loadings intercept (1,1,1,1), factor loadings linear slope (0, .603, .719, 1.224), factor loadings quadratic slope (0, 3.636, 5.170, 14.982).
*$p < .05$. **$p < .01$. ***$p < .001$.

Table 4

Parameter Estimates of the Unconditional Univariate Latent Growth Curve Model of Fat Mass Index (FMI) in Boys and Girls

Parameter	Girls		Boys	
	Mean (SE)	Variance (SE)	Mean (SE)	Variance (SE)
Intercept	.641*** (.004)	.037*** (.001)	.494*** (.004)	.046*** (.001)
Linear slope	.372*** (.006)	.052*** (.004)	-.109*** (.010)	.078*** (.008)
Quadratic slope	-.012*** (.000)	.000*** (.000)	.020*** (.001)	.000*** (.000)
Intercept-linear slope covariance	-.020*** (.002)	------	.018*** (.002)	------
Linear slope-quadratic slope covariance	-.003*** (.000)	------	-.005*** (.001)	------
Intercept-quadratic slope covariance	.001*** (.000)	------	-.002*** (.000)	------

Note. All coefficients are unstandardized. Factor loadings intercept (1, 1, 1, 1), factor loadings linear slope (0, .559, .794, 1.462), factor loadings quadratic slope (0, 3.125, 6.304, 21.374).
*$p < .05$. **$p < .01$. ***$p < .001$.

Table 5

Parameter Estimates of the Unconditional Univariate Latent Growth Curve Model of C-Reactive Protein (CRP) in Boys and Girls

Parameter	Girls		Boys	
	Mean (SE)	Variance (SE)	Mean (SE)	Variance (SE)
Intercept	-.484*** (.010)	.099*** (.010)	-.672*** (.010)	.108*** (.011)
Linear slope	.460*** (.029)	.140 (.092)	.785*** (.029)	.252** (.096)
Quadratic slope	-.009*** (.002)	.001* (.000)	-.033*** (.002)	.001** (.000)
Intercept-linear slope covariance	-.061** (.023)	------	-.112*** (.026)	------
Linear slope-quadratic slope covariance	-.010 (.006)	------	-.014* (.006)	------
Intercept-quadratic slope covariance	.004** (.001)	------	.006*** (.001)	------

Note. All coefficients are unstandardized. Factor loadings intercept (1, 1, 1, 1), factor loadings linear slope (0, .559, .794, 1.462), factor loadings quadratic slope (0, 3.125, 6.304, 21.374).
*$p < .05$. **$p < .01$. ***$p < .001$.

Table 6

Parameter Estimates of Parallel Processes Latent Growth Models of Fat Mass Index (FMI) and Depressive Symptoms

Parameter	Girls		Boys	
	Estimate	SE	Estimate	SE
Intercepts covariance	-.017	.003	-.008	.004
Linear Slopes covariance	-.022	.004	-.002	.005
FMI intercept predicting MFQ linear slope	.032	.179	.010	.014
MFQ intercept predicting FMI linear slope	**.088*****	.008	.017	.226
FMI linear slope predicting MFQ quadratic slope	-.006	.019	-.004	.019
MFQ linear slope predicting FMI quadratic slope	.027	.000	-.021	.000

Note. Significant effects are in bold. Standardized coefficients are presented. The models were adjusted for the effects of age at the different time points, highest parental education, single-family household, pubertal development, medication use, tobacco smoking, alcohol use, oral contraceptive use (only in girls), and C- reactive protein. FMI = Fat Mass Index (log-transformed); MFQ= Moods and Feelings Questionnaire (square-root transformed). N = 6,525; 3,434 females; 3,091 males.
*p < .05. **p < .01. ***p < .001.

Table 7

Parameter Estimates of Parallel Processes Latent Growth Models of Fat Mass Index (FMI) and C-Reactive Protein (CRP)

Parameter	Girls		Boys	
	Estimate	SE	Estimate	SE
Intercepts covariance	**.749*****	.002	**.604*****	.002
Linear Slopes covariance	**1.188*****	.007	**.072*****	.002
FMI intercept predicting hs-CRP linear slope	**-.529*****	.125	**-.139*****	.066
hs-CRP intercept predicting FMI linear slope	**-.502*****	.045	**-.243*****	.025
FMI linear slope predicting hs-CRP quadratic slope	**-.721*****	.014	**.220*****	.006
hs-CRP linear slope predicting FMI quadratic slope	**-1.345***	.015	**-.183*****	.001

Note. Significant effects are in bold. Standardized coefficients are presented. The models were adjusted for the effects of age at the different time points, highest parental education, single-family household, pubertal development, medication use, tobacco smoking, alcohol use, oral contraceptive use (only in girls), and depressive symptoms. hs-CRP = high-sensitivity C-reactive protein (log-transformed); FMI = Fat Mass Index (log-transformed). N = 6,525; 3,434 females; 3,091 males.
*p < .05. **p < .01. ***p < .001.

Table 8

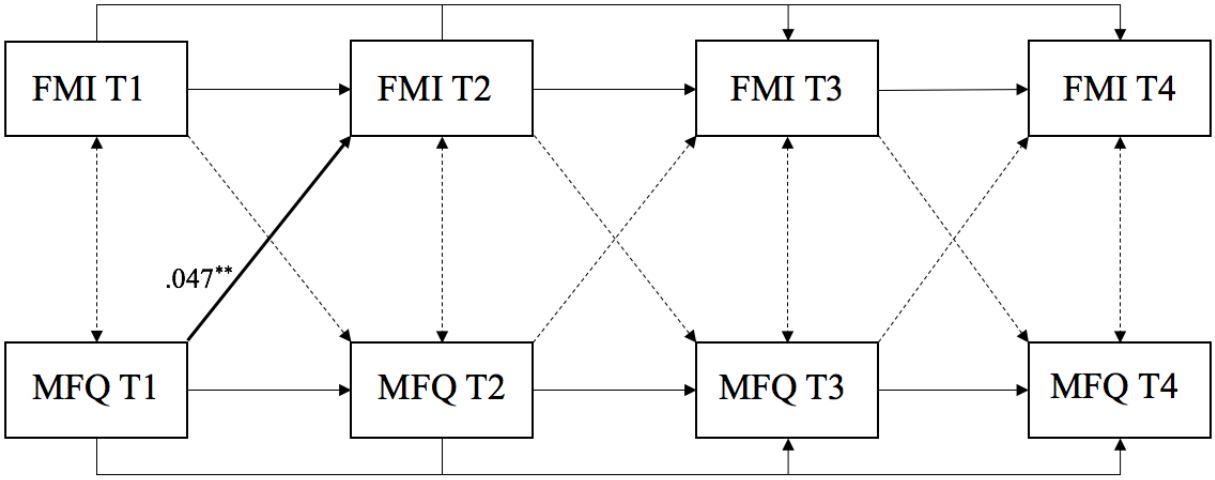
Parameter Estimates of Parallel Processes Latent Growth Models of C-Reactive Protein (CRP) and Depressive Symptoms

Parameter	Girls		Boys	
	Estimate	SE	Estimate	SE
Intercepts covariance	.068	.008	-.099	.007
Linear Slopes covariance	-.012	.015	-.008	.015
hs-CRP intercept predicting MFQ linear slope	-.008	.216	-.046	.370
MFQ intercept predicting hs-CRP linear slope	-.042	.029	.067	.047
hs-CRP linear slope predicting MFQ quadratic slope	.086	.023	-.009	.029
MFQ linear slope predicting hs-CRP quadratic slope	-.003	.001	.019	.001

Note. Significant effects are in bold. Standardized coefficients are presented. The models were adjusted for the effects of age at the different time points, highest parental education, single-family household, pubertal development, medication use, tobacco smoking, alcohol use, oral contraceptive use, and Fat Mass Index. hs-CRP = high-sensitivity C-reactive protein (log-transformed); MFQ= Moods and Feelings Questionnaire (square-root transformed). N = 6,525; 3,434 females; 3,091 males.
*$p < .05$. **$p < .01$. ***$p < .001$.

Figure 1a

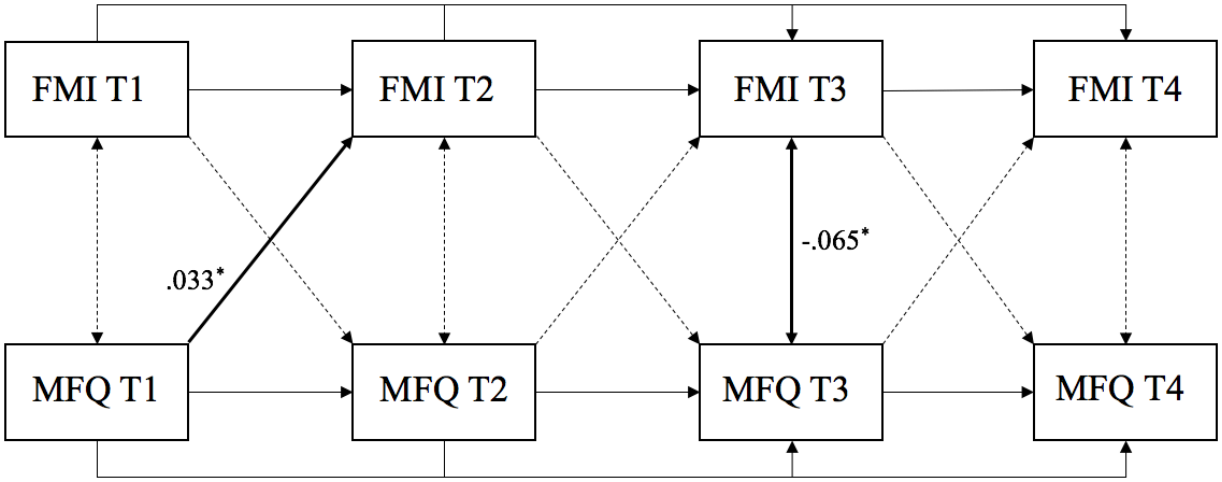
Concurrent and Transactional Associations between Fat Mass Index (FMI) and Depressive Symptoms in Girls from Preadolescence to Early Adulthood



Note. Bold lines represent significant paths; dashed lines represent non-significant paths. Only standardized coefficients on significant paths are presented for clarity. The model was adjusted for the effects of age at the different time points, highest parental education, single-family household, pubertal development, medication use, tobacco smoking, alcohol use, oral contraceptive use, and C-reactive protein. All autoregressive paths were positive and significant. FMI= Fat Mass Index (log-transformed); MFQ = Moods and Feelings Questionnaire (square-root transformed). T1 = pre-adolescence (ages 9-10), T2 = mid-adolescence (ages 15-16), T3 = late adolescence (ages 17-18) and T4 = young adulthood (ages 23-24). N = 3,434. Fit indices: χ^2 (153) = 563.708, $p < .001$, *CFI* = .959, *TLI* = .936, *RMSEA* = .028 [.026, .031], *SRMR*= .025. *$p < .05$. **$p < .01$. ***$p < .001$.

Figure 1b

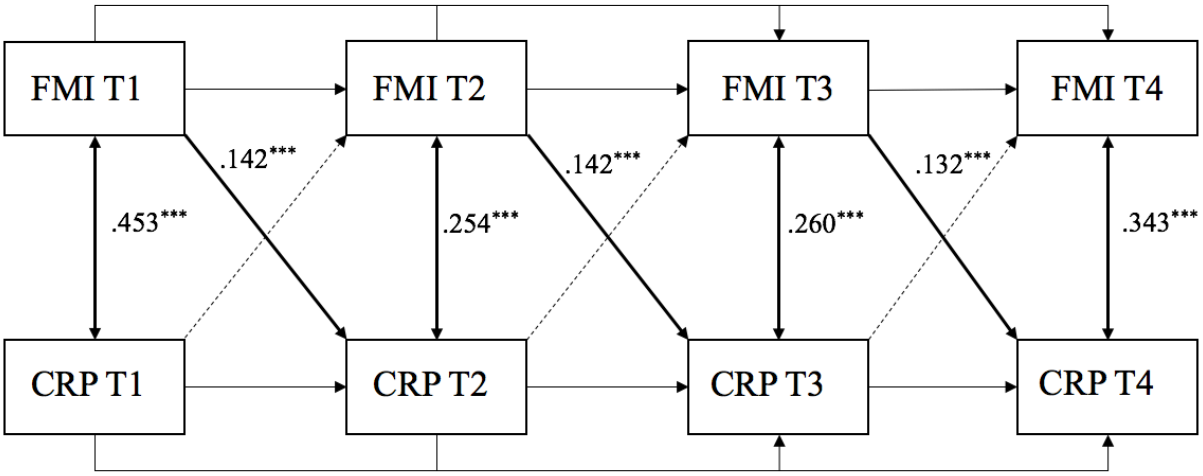
Concurrent and Transactional Associations Between Fat Mass Index (FMI) and Depressive Symptoms in Boys from Preadolescence to Early Adulthood



Note. Bold lines represent significant paths; dashed lines represent non-significant paths. Only standardized coefficients on significant paths are presented for clarity. The model was adjusted for the effects of age at the different time points, highest parental education, single-family household, pubertal development, medication use, tobacco smoking, alcohol use, and C-reactive protein. All autoregressive paths were positive and significant. FMI= Fat Mass Index (log-transformed); MFQ = Moods and Feelings Questionnaire (square-root transformed). T1 = pre-adolescence (ages 9-10), T2 = mid-adolescence (ages 15-16), T3 = late adolescence (ages 17-18) and T4 = young adulthood (ages 23-24). N = 3,091. Fit indices: χ^2 (141) = 389.916, $p < .001$, *CFI* = .966, *TLI* = .947, *RMSEA* = .024 [.021, .027], *SRMR*= .028
*$p < .05$. **$p < .01$. ***$p < .001$.

Figure 2a

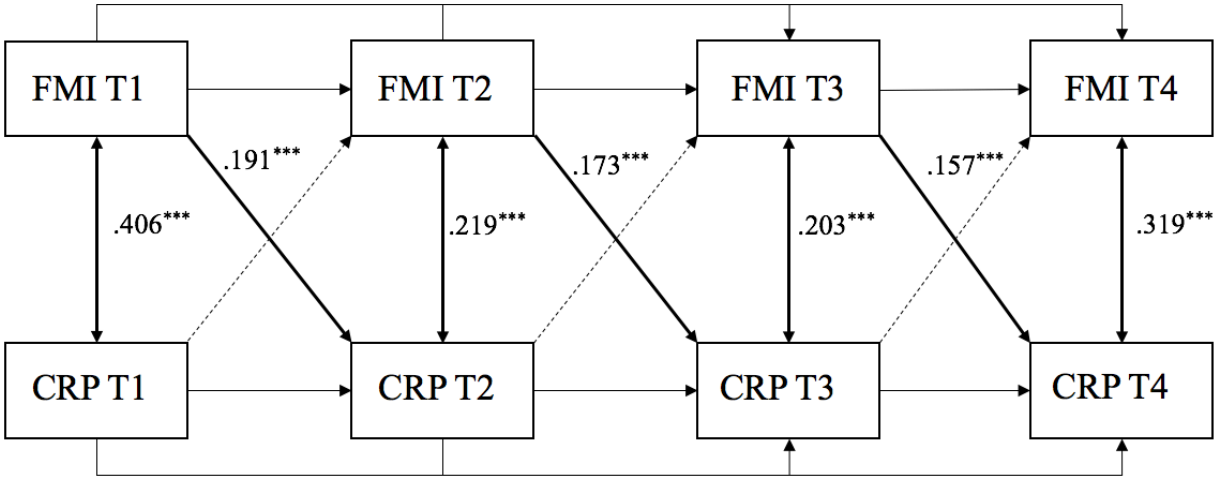
Concurrent and Transactional Associations Between Fat Mass Index (FMI) and C- Reactive Protein (CRP) in Girls from Preadolescence to Early Adulthood



Note. Bold lines represent significant paths; dashed lines represent non-significant paths. Only standardized coefficients on significant paths are presented for clarity. The model was adjusted for the effects of age at the different time points, highest parental education, single-family household, pubertal development, medication use, tobacco smoking, alcohol use, oral contraceptive use, and depressive symptoms. All autoregressive paths were positive and significant. FMI= Fat Mass Index (log-transformed); CRP = C-reactive protein (log-transformed). T1 = pre-adolescence (ages 9-10), T2 = mid-adolescence (ages 15-16), T3 = late adolescence (ages 17-18) and T4 = young adulthood (ages 23-24). N = 3,434. Fit indices: χ^2 (128) = 382.112, $p < .001$, *CFI* = .969, *TLI* = .948, *RMSEA* = .024 [.022, .027], *SRMR*= .024 *$p < .05$. **$p < .01$. ***$p < .001$.

Figure 2b

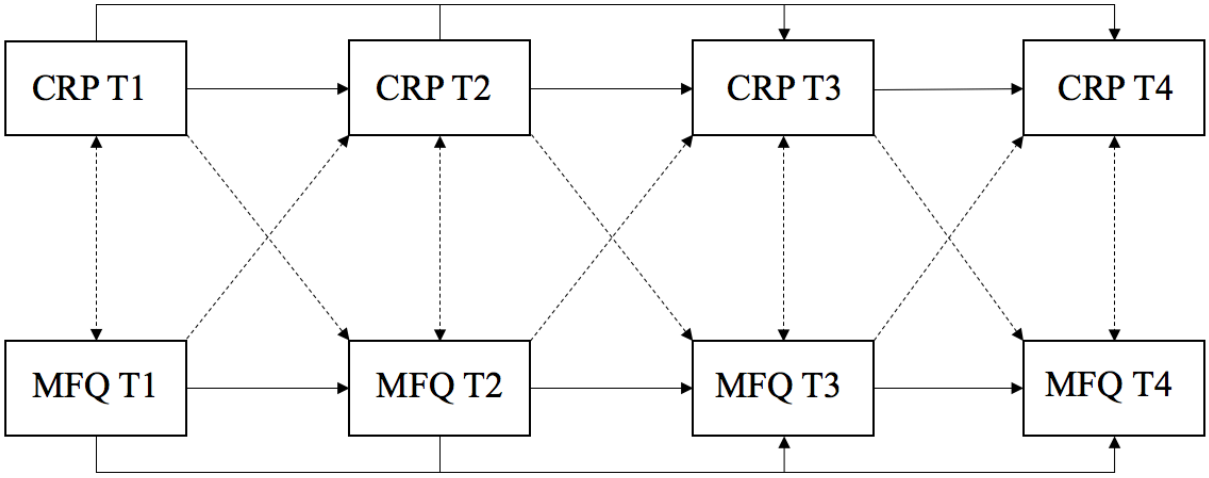
Concurrent and Transactional Associations Between Fat Mass Index (FMI) and C-Reactive Protein (CRP) in Boys from Preadolescence to Early Adulthood



Note. Bold lines represent significant paths; dashed lines represent non-significant paths. Only standardized coefficients on significant paths are presented for clarity. The model was adjusted for the effects of age at the different time points, highest parental education, single-family household, pubertal development, medication use, tobacco smoking, alcohol use, and depressive symptoms. All autoregressive paths were positive and significant. FMI= Fat Mass Index (log-transformed); CRP = C-reactive protein (log-transformed). T1 = pre-adolescence (ages 9-10), T2 = mid-adolescence (ages 15-16), T3 = late adolescence (ages 17-18) and T4 = young adulthood (ages 23-24). N = 3,091. Fit indices: χ^2 (116) = 224.306, $p < .001$, *CFI* = .982, *TLI* = .969, *RMSEA* = .018 [.014, .021], *SRMR*= .022.
*$p < .05$. **$p < .01$. ***$p < .001$.

Figure 3a

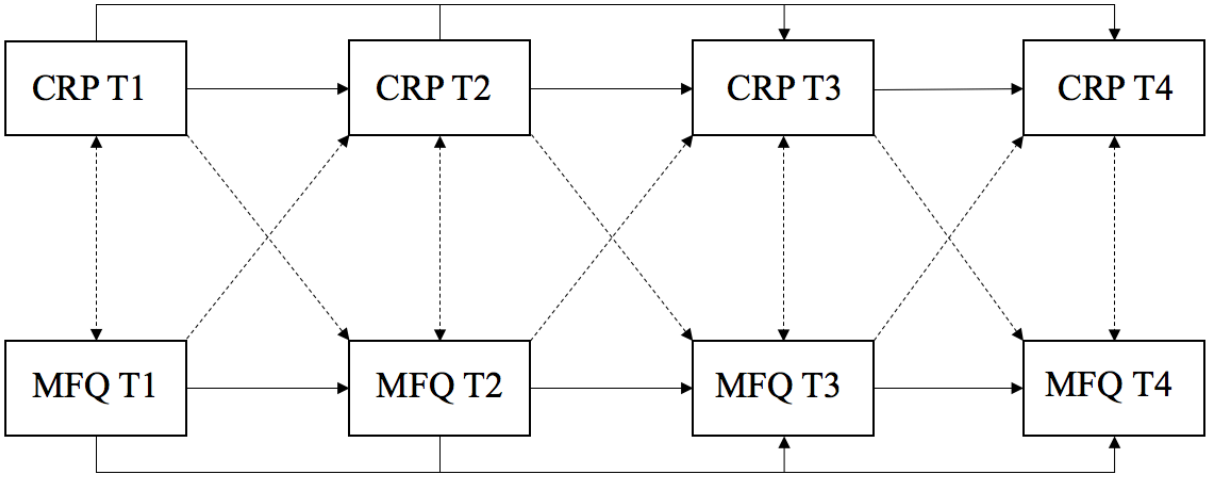
Concurrent and Transactional Associations Between C-Reactive Protein (CRP) and Depressive Symptoms in Girls from Preadolescence to Early Adulthood



Note. Bold lines represent significant paths; dashed lines represent non-significant paths. Only standardized coefficients on significant paths are presented for clarity. The model was adjusted for the effects of age at the different time points, highest parental education, single-family household, pubertal development, medication use, tobacco smoking, alcohol use, oral contraceptive use, and Fat Mass Index. All autoregressive paths were positive and significant. MFQ= Moods and Feelings Questionnaire (square-root transformed); CRP = C-reactive protein (log-transformed). T1 = pre-adolescence (ages 9-10), T2 = mid-adolescence (ages 15-16), T3 = late adolescence (ages 17-18) and T4 = young adulthood (ages 23-24). N = 3,434. Fit indices: χ^2 (153) = 359.491, $p < .001$, *CFI* = .961, *TLI* = .940, *RMSEA* = .020 [.017, .023], *SRMR*= .019. *$p < .05$. **$p < .01$. ***$p < .001$.

Figure 3b

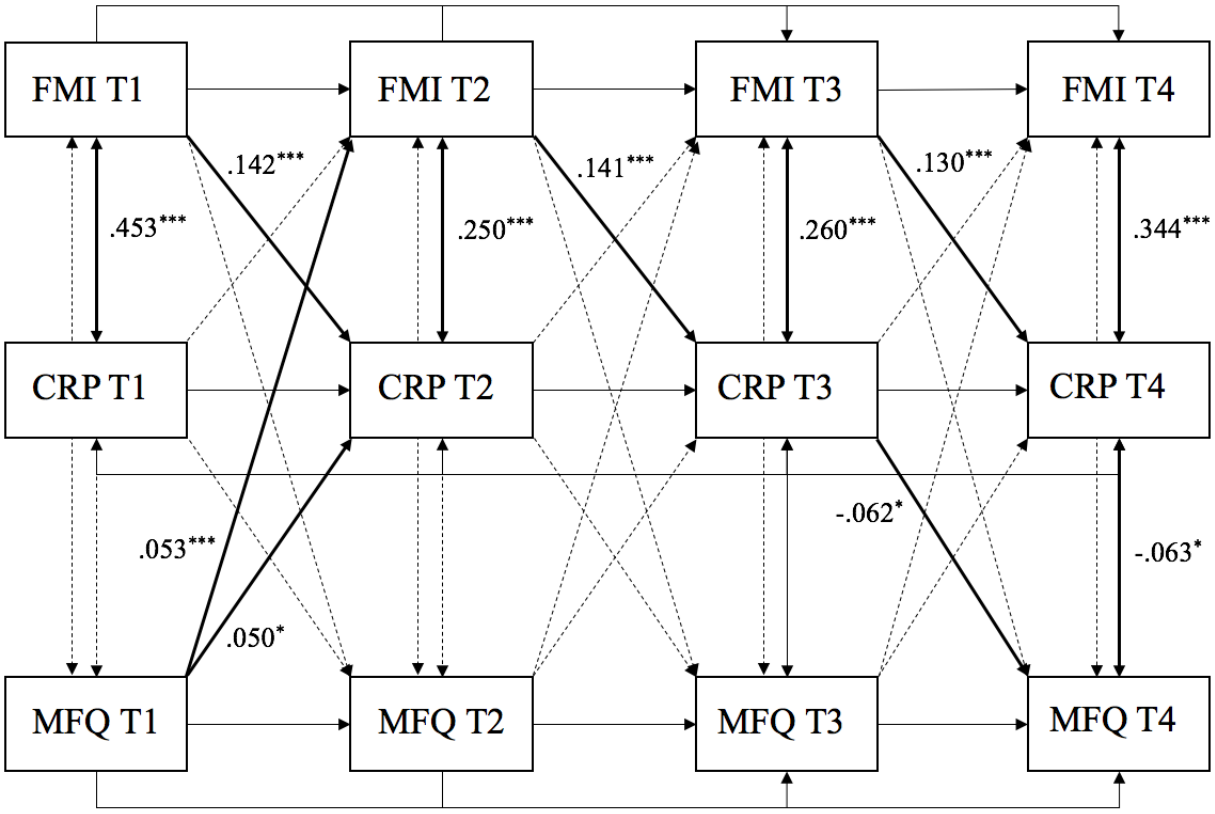
Concurrent and Transactional Associations Between C-Reactive Protein (CRP) and Depressive Symptoms in Boys from Preadolescence to Early Adulthood



Note. Bold lines represent significant paths; dashed lines represent non-significant paths. Only standardized coefficients on significant paths are presented for clarity. The model was adjusted for the effects of age at the different time points, highest parental education, single-family household, pubertal development, medication use, tobacco smoking, alcohol use, and Fat Mass Index. All autoregressive paths were positive and significant. MFQ= Moods and Feelings Questionnaire (square-root transformed); CRP = C-reactive protein (log-transformed). T1 = pre-adolescence (ages 9-10), T2 = mid-adolescence (ages 15-16), T3 = late adolescence (ages 17-18) and T4 = young adulthood (ages 23-24). N = 3,091. Fit indices: χ^2 (141) = 214.503, $p < .001$, *CFI* = .977, *TLI* = .965, *RMSEA* = .013 [.009, .017], *SRMR* = .018.
*$p < .05$. **$p < .01$. ***$p < .001$.

Figure 4a

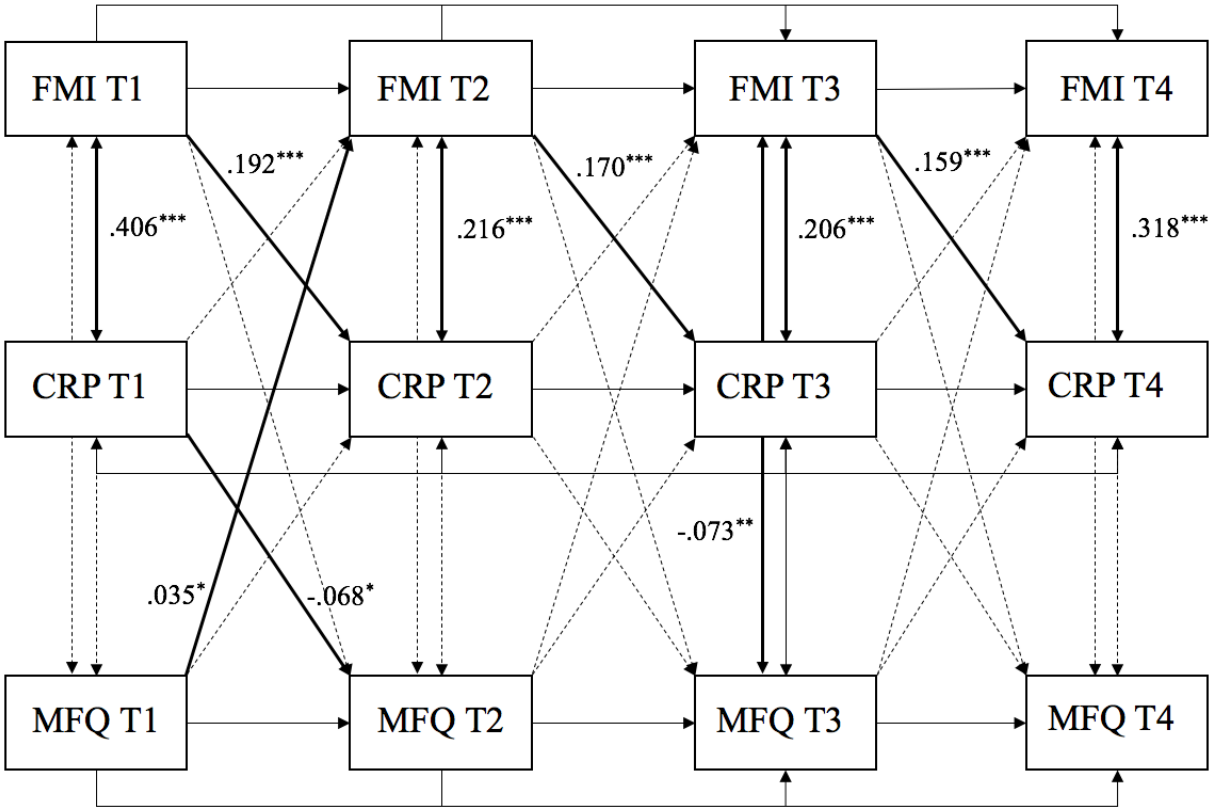
Concurrent and Transactional Associations Between Fat Mass Index (FMI), C-Reactive Protein (CRP) and Depressive Symptoms in Girls from Preadolescence to Early Adulthood



Note. Bold lines represent significant paths; dashed lines represent non-significant paths. Only standardized coefficients on significant paths are presented for clarity. The model was adjusted for the effects of age at the different time points, highest parental education, single-family household, pubertal development, medication use, tobacco smoking, alcohol use, and oral contraceptive use. All autoregressive paths were positive and significant. FMI = Fat Mass Index (log-transformed); CRP = C-reactive protein (log-transformed); MFQ= Moods and Feelings Questionnaire (square-root transformed). T1 = pre-adolescence (ages 9-10), T2 = mid-adolescence (ages 15-16), T3 = late adolescence (ages 17-18) and T4 = young adulthood (ages 23-24). N = 3,434. Fit indices: χ^2 (202) = 504.178, $p < .001$, *CFI* = .973, *TLI* = .956, *RMSEA* = .021 [.019, .023], *SRMR* = .026.
*$p < .05$. **$p < .01$. ***$p < .001$.

Figure 4b

Concurrent and Transactional Associations Between Fat Mass Index (FMI), C-Reactive Protein (CRP) and Depressive Symptoms in Boys from Preadolescence to Early Adulthood



Note. Bold lines represent significant paths; dashed lines represent non-significant paths. Only standardized coefficients on significant paths are presented for clarity. The model was adjusted for the effects of age at the different time points, highest parental education, single-family household, pubertal development, medication use, tobacco smoking, and alcohol use. All autoregressive paths were positive and significant. FMI = Fat Mass Index (log-transformed); CRP = C-reactive protein (log-transformed); MFQ= Moods and Feelings Questionnaire (square-root transformed). T1 = pre-adolescence (ages 9-10), T2 = mid-adolescence (ages 15-16), T3 = late adolescence (ages 17-18) and T4 = young adulthood (ages 23-24). N = 3,091. Fit indices: χ^2 (184) = 326.227, $p < .001$, *CFI* = .982, *TLI* = .970, *RMSEA* = .016 [.013, .019], *SRMR* = .025. *$p < .05$. **$p < .01$. ***$p < .001$.