DEPRESSION AND ITS DETERMINANTS IN YOUTH WITH OBESITY

DEPRESSION AND ITS DETERMINANTS IN CHILDREN AND ADOLESCENTS WITH OBESITY

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LAY ABSTRACT

Obesity has a significant impact on depression in children and adolescents. Inflammation – the body's response to injury – is measured through markers in the blood and leptin – the marker of body fat – have shown to be related to depression. Research indicates that depression influences these factors to act on obesity. However, research on the interactions of biological and socio-demographic factors with depression in youth with obesity is lacking. Therefore, our objective was to explore the impact of these factors on depression in obese youth entering into a weight management program. Using a depression-screening tool, we studied 244 youth under 18 years and confirmed that household income and body fat were important factors of depression. However for the first time, we found leptin influenced depression regardless of the amount of fat present suggesting that depression acts on obesity through leptin but it is uncertain how this occurs and further research is warranted.

ABSTRACT

There is increasing recognition of the relationship between depression and obesity in the pediatric population and recently, there has been a focus on inflammation as a potential link. Both conditions are considered to be pro-inflammatory states, and certain inflammatory markers are linked to depression in obese adults and vice versa. Leptin has also been implicated in depression as a potential mediator between inflammation and depression. Brain derived neurotrophic factor (BDNF), which is associated with depression and obesity, is influenced by inflammation and leptin in animal models as well.

Few studies have examined the interactions between depression, adiposity, and biological markers in obese youth and therefore, our objective was to explore the determinants of depression in obese youth in a clinical setting. We studied 244 youth aged 8-17 years (125 girls, 119 boys) at the time of entry to a weight management program, as part of a prospective, longitudinal study. The CES-DC depression-screening tool was used to assess depressive symptoms, and a participant was classified as having high depressive symptoms if the CES-DC score ≥15 or taking antidepressants. Questionnaires assessed socio-demographic factors and puberty while adiposity was measured using dual-energy X-ray absorptiometry (DXA). Inflammatory markers (IL-6, TNFα, CRP, IL-10), leptin, and BDNF were quantified by immunoassays.

Of the 244 participants, 8 were on antidepressants and 88 (36.4%) met the criteria for high depressive symptoms. We confirmed previous findings that household income and body fat were important determinants of depressive symptoms. However for the first time, it was identified that leptin levels predicted CES-DC score independent of body fat.

Neither inflammatory markers nor BDNF were significantly related to depression scores. Our findings suggest that leptin may mediate the relationship of adiposity and depression but it is uncertain if this is related to direct action or to the phenomenon of leptin resistance.

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LIST OF ABBREVIATIONS

APA	American Psychiatric Association
BBB	Blood-Brain Barrier
BDI-Y	Beck's Depression Inventory – Youth version
BDNF	Brain derived neurotrophic factor
BMI	Body mass index
CCHS	Canadian Community Health Survey
CDC	Centers for Disease Control
CDI	Children's Depression Inventory
CES-D	Center for Epidemiological Studies – Depression Scale for adults
CES-DC	Center for Epidemiological Studies – Depression Scale for children
CSF	Cerebrospinal fluid
CRP	C-reactive protein
CV	Coefficient of Variation
DIO	Diet-induced obesity
DSM	Diagnostic and Statistical Manual of Mental Disorders
DXA	Dual-energy X-ray absorptiometry
ELISA	Enzyme-linked immunosorbent assay
FST	Forced swim test
HPA	Hypothalamic-pituitary-adrenal
hs	High-sensitivity
ICD	International Classification of Diseases
IDO	Indoleamine 2,3-dioxygenase
IFNα	Interferon-α
IL	Interleukin
IOTF	International Obesity Task Force
LepRb	Leptin receptor-b
LOD	Limit of detection
LPS	Lipopolyssacharide
MDD	Major depressive disorder
mRNA	messenger RNA

MRI	Magnetic resonance imaging
NHANES	National Health and Nutrition Examination Survey
SES	Socio-economic status
TNFR	Tumor necrosis factor receptor
TNFα	Tumor necrosis factor-α
trkB	Tropomyosin receptor kinase B
Val66Met	Valine-66-Methionine
VIF	Variance inflation factor
WAGR	Wilms tumor, aniridia, genitourinary anomalies, mental retardation
WC	Waist circumference
WHO	World Health Organization

DECLARATION OF ACADEMIC ACHIEVEMENT

Vivian Vaughn-Williams and research staff previously collected data, and my contributions entailed cleaning and verifying the data to be analyzed. I also conducted the assays for IL-10 and BDNF and performed all data analyses myself with consultations from statisticians in the McMaster University Department of Pediatrics. I completed a statistics course to familiarize myself with conducting statistical tests in SPSS. I was also involved in drafting the manuscript for the mental health paper published recently (Morrison, Shin, Tarnopolsky, & Taylor, 2015).

CHAPTER 1: LITERATURE REVIEW

Almost a third of children and adolescents in Canada are considered overweight or obese (Roberts, Shields, de Groh, Aziz, & Gilbert, 2012), and pediatric obesity is associated with multiple health risks including type 2 diabetes and fatty liver disease (Daniels, 2009). In the last decade, the relationship between obesity and depression has been recognized in the pediatric population, particularly in clinic-based studies. Obese youth presenting to weight management programs have higher body mass indexes (BMIs) and higher rates of depression compared to obese youth in population-based studies (Britz, et al., 2000; Van Vlierberghe, Braet, Goossens, & Mels, 2009). Given the increase in prevalence of depression in this population, it is critical to understand the determinants of depression, both socio-demographic and biological, to assist in the identification of 'at risk' children and adolescents.

1.1 Obesity

1.1.1 Prevalence & Determinants of Obesity

In the latest population survey conducted by Statistics Canada, Roberts *et al.* (2012) reported that approximately 20% of children and adolescents aged 5-17 years were considered overweight, and 11.7% classified as obese based on the World Health Organization (WHO) guidelines.

Obesity is the result of complex interactions of genetics, metabolic factors, environment and lifestyle that have yet to be fully understood. Genetic disorders such as Prader-Willi syndrome and Wilms tumor, Aniridia, genitourinary anomalies, and mental retardation (WAGR) syndrome have been associated with obesity (Holm, et al., 1993;

Han, et al., 2008) while sedentary habits and high-fat, energy-dense diets have steadily increased (Jimenez-Pavon, Kelly, & Reilly, 2010). Although the mechanisms underlying the development of obesity are not fully understood, we know that obesity occurs when energy intake exceeds energy expenditure (Dehghan, Akhtar-Danesh, & Merchant, 2005). Poor diet, sedentary behaviours, decreased participation in sports and physical education, parental obesity, socioeconomic status (SES), and ethnicity have all been associated with increased risk of obesity in children and adolescents (Troiano, Briefel, Carroll, & Bialostosky, 2000; Tremblay & Willms, 2003; Whitaker, Deeks, Baughcum, & Specker, 2000; Wang & Lim, 2012; Utter, et al., 2010; Popkin & Gordon-Larsen, 2004).

1.1.2 Obesity Definitions

Currently, there is no single universally accepted definition for overweight and obesity in children and adolescents. While many countries including Canada are adopting the 2007 WHO classification system, others still continue to use different guidelines (Dietitians of Canada, Canadian Paediatric Society, College of Family Physicians of Canada, Community Health Nurses of Canada, & Secker , 2010). A simple definition of obesity for children is difficult to characterize due to changing body composition with age and growth. However, the rising prevalence of childhood obesity in Canada and worldwide calls for a standardized definition of obesity to quantify and compare trends both nationally and internationally (WHO, 2011). There are three commonly used definitions: the 2007 WHO growth references, 2000 International Obesity Task Force (IOTF) reference curves, and 2000 US Centers for Disease Control (CDC) growth curves and all use BMI to assess obesity (Appendix A, pg. 91). Previously, it was recommended

that Canada use the 2000 CDC growth charts however at that time, limitations were noted that these charts were growth references describing how a sample population of children grew regardless if their growth rate was optimal or not. Therefore, when the WHO updated their growth charts for older children and adolescents in 2007 to better address the growing epidemic of childhood obesity, an executive statement was made recommending the transition to WHO guidelines (Dietitians of Canada, Canadian Paediatric Society, College of Family Physicians of Canada, Community Health Nurses of Canada, & Secker , 2010).

When comparing the three systems, the highest prevalence rates of childhood obesity were seen using the WHO classification while IOTF tended to yield the lowest rates (Shields & Tremblay, 2010; Twells & Newhook, 2011). Overall, the WHO and CDC tend to report small differences in prevalence rates and these differences may have been due to methodological differences in the three classification systems. The most current rates of obesity in youth reported by Roberts *et al.* (2012) were based on the 2007 WHO cutoffs. However, with 2000 IOTF guidelines, the prevalence was lower at 16.4% and 8.4%, respectively, providing further evidence that the IOTF classification underestimates obesity relative to WHO (Reilly, Kelly, & Wilson, 2010).

1.1.3 Assessment Tools for Body Composition

Adding to the confusion of measuring obesity in children and adolescents, there are a number of methods to quantify adiposity. Two types of measures include: 1) direct measures such as scanning using magnetic resonance imaging (MRI); and 2) indirect measures including anthropometric methods such as waist circumference (WC) and BMI.

Direct measures such as MRI are more accurate than indirect measures but are not practical for population level screening or clinical management (Kipping, Jago, & Lawlor, 2008). MRIs use magnetic fields to differentiate between fat mass and lean mass but can also assess regional distribution of fat (Sweeting, 2007) but these instruments are costly (Rodriguez, et al., 2004). Dual energy x-ray absorptiometry (DXA) uses two x-ray energies to measure the amount of x-rays absorbed by bones and tissues of an individual to determine bone density, lean and fat mass (Pietrobelli, Formica, Wang, & Heymsfield, 1996). Measurements of lean and fat mass completed by DXAs are highly correlated with those from MRIs, and so have been utilized in clinical and research settings because of their low radiation exposure (Bigornia, LaValley, Benfield, Ness, & Newby, 2013; Albanese, Diessel, & Genant, 2003).

Indirect measures provide estimates of adiposity and are often used in both research and clinical settings (Kipping, Jago, & Lawlor, 2008). Although anthropometric measures are widely used because they are practical and easy to obtain tools to screen for overweight and obesity, they can only indirectly measure adiposity or excess body fat (Goran, 1998). BMI is a widely used indirect measure and has been correlated with DXA body fat measurements in children and adolescents (Glasser, Zellner, & Kromeyer-Hauschild, 2011; Flegal, et al., 2010; Ochiai, et al., 2010; Pietrobelli , Faith, Gallagher, Chiumello, & Heymsfield, 1998). Although the correlation between BMI and body fat is generally strong, it is better seen in prepubertal children than pubertal adolescents. Studies have shown that BMI increases in adolescents are due to increases in lean mass as opposed to fat mass (Maynard, Wisemandle, Roche, Chumlea, Guo, & Siervogel, 2001;

Daniels, Khoury, & Morrison, 1997; Bigornia, LaValley, Benfield, Ness, & Newby, 2013). Despite this, BMI often expressed as a percentile or *z*-score, is used in obesity definitions such as the 2000 CDC, 2007 WHO, and 2000 IOTF growth curves due to its practicality and accessibility to screen overweight and obesity in children and adolescents and the lack of references to interpret more direct measures of body fat (Rodriguez, et al., 2004).

1.2 Depression

Obese children and adolescents tend to have more mental health challenges including low self-esteem, increased peer conflicts, anxiety, and depression (Pitrou, Shojaei, Wazana, Gilbert, & Kovess-Masfety, 2010; Lawlor, Mamun, O'Callaghan, Bor, Williams, & Najman, 2005; Lumeng, Gannon, Cabral, Frank, & Zuckerman, 2003; ter Bogt, van Dorsselaer, Monshouwer, Verdurmen, Engels, & Vollebergh, 2006; Vila, et al., 2004). The prevalence of depression in children and adolescents has been reported to range from 2.7% to 7.8% in population-based studies (Fleming, Offord, & Boyle, 1989; Cheung & Dewa, 2006; Affifi, Enns, Cox, & Martens, 2005).

1.2.1 Classifying Depression

Depression can be categorized into multiple classes – including major depressive disorder (MDD), dysthymia, and postpartum depression – with MDD being the most common (Parikh, Lam, & CANMAT Depression Work Group, 2001). Depression is usually defined by one of two classification systems: The 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) or 10th revision of the

International Classification of Diseases (ICD-10). Both came into use in 1994 where the American Psychiatric Association (APA) developed the DSM-IV and the WHO developed the ICD-10. While the developers of these two classification systems worked together to create more congruence, there still remain many differences (American Psychiatric Association, 2012). Both systems classify depression severity based on the number of criteria symptoms satisfied and have comparable diagnoses of moderate to severe/major depressive episodes but ICD-10 may be more sensitive to the mild range of depressive episodes than the DSM-IV (Saito, et al., 2010; Zuckerbrot, Cheung, Jensen, Stein, Laraque, & GLAD-PC Steering Group, 2007). The DSM-IV or the updated version, DSM-V, is commonly used in North America while the ICD-10 is more popular in Europe.

Diagnosis of depression in children and adolescents is difficult as depression may manifest differently in children than in adults. These symptoms include mood lability, irritability, low frustration tolerance, temper tantrums, somatic complaints, and/or social withdrawal, rather than the verbalization of depressive feelings (Bujoreanu, Benhayon, & Szigethy, 2011). Children also tend to show fewer depressive symptoms and suicide attempts than their adult counterparts and so depression is often unrecognized in children and youth due to symptoms that may be misinterpreted as typical mood swings seen in child and adolescent development (Zuckerbrot, Cheung, Jensen, Stein, Laraque, & GLAD-PC Steering Group, 2007; Bujoreanu, Benhayon, & Szigethy, 2011). While both the DSM-IV and ICD-10 systems are used to define depression in children and adolescents, only the DSM-IV has provided youth specific criteria (Figure 1).

Criteria for Major Depressive Episode in Adults, Children, and Adolescents

Adults	*Children and adolescents*
A. Five (or more) of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is (1) depressed mood or (2) loss of interest or pleasure.	
(1) Depressed mood most of the day, nearly every day, as indicated by subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful)	Mood can be depressed or irritable. Children with immature cognitive-linguistic development may not be able to describe inner mood states and therefore may present with vague physical complaints, sad facial expression, or poor eye contact. Irritable mood may appear as "acting out"; reckless behavior; or hostile, angry interactions. Adult-like mood disturbance may occur in older adolescents.
(2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by subjective account or observation made by others)	Loss of interest can be in peer play or school activities.
(3) Significant weight loss when not dieting, or weight gain (e.g., a change of more than 5 percent of body weight in a month), or decrease or increase in appetite nearly every day	Children may fail to make expected weight gain rather than losing weight.
(4) Insomnia or hypersomnia nearly every day	Similar to adults
(5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feeling of restlessness or being slowed down)	Concomitant with mood change, hyperactive behavior may be observed.
(6) Fatigue or loss of energy nearly every day	Disengagement from peer play, school refusal, or frequent school absences may be symptoms of fatigue.
(7) Feeling of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)	Child may present with self-depreciation (e.g., "I'm stupid," "I'm a retard"). Delusional guilt usually is not present.
(8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (by subjective account or as observed by others)	Problems with attention and concentration may be apparent as behavioral difficulties or poor performance in school.
(9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide	There may be additional nonverbal cues for potentially suicidal behavior, such as giving away a favorite collection of music or stamps.
B. Symptoms do not meet the criteria for mixed bipolar disorder.	Same as adults
C. Symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.	Clinically significant impairment of social or school functioning is present. Adolescents also may have occupational dysfunction.
D. Symptoms are not caused by the direct physiologic effects of a substance (e.g., drug of abuse, medication) or a general medical condition (e.g., hypothyroidism).	Similar to adults
E. Symptoms are not caused by bereavement—i.e., after the loss of a loved one, the symptoms persist for longer than two months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.	Psychotic symptoms in severe major depression, if present, are more often auditory hallucinations (usually criticizing the patient) than delusions.

Adapted with permission from American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR. 4th ed. rev. Washington, D.C.: American Psychiatric Association, 2000:356, with additional information from references 21 through 24.

Figure 1: DSM-IV criteria for depressive disorders in adults and children.
The DSM-IV criteria for a major depressive episode in adults and youth differs in certain areas. Children and adolescents tend to display less obvious symptoms than adults and thus, require an altered criteria to diagnose depressive disorders (Bhatia & Bhatia, 2007).

1.2.2 Assessment Tools for Depression in Children and Youth

While there are a number of assessment tools available to measure depression and its symptoms in children and adolescents, they fall into one of two categories: depression screening tools or diagnostic interviews. While screening tools usually measure self-reported depressive symptoms by youth or by parents if the child is too young or incapable, diagnostic interviews provide a clinical diagnosis of depression based on one of the two classification systems. There are a number of validated screening tools available for children and adolescents including the Children's Depression Inventory (CDI), the Beck Depression Inventory-Youth (BDI-Y), and the Center for Epidemiological Studies-Depression Scale for Children (CES-DC).

When selecting an assessment tool, multiple factors must be considered including characteristics of the population, psychometric properties of the instrument, time to complete and score the questionnaire, ease of use, and cost. Even though the majority of available assessment tools do not diagnose depression, they provide an indication of the degree of depressive symptoms and often provide a cut-off point where people should be tested for clinical depression (Barkmann, Erhart, Schulte-Markwort, & BELLA Study Group, 2008; Sharp & Lipsky, 2002).

1.2.3 Determinants of Depression

There are multiple factors that may contribute to depression in children and adolescents. Increased prevalence of depression in adolescents has been associated with puberty, as well as an increased risk of depression in females than in males (Twenge & Nolen-Hoeksema, 2002; Wade, Cairney, & Pevalin, 2002). Angold *et al.* (1998) found

that it was only after mid-puberty, defined as Tanner stage III and above, that a higher proportion of girls were found to be depressed than boys regardless of age. However, others have argued that social changes in adolescence such as transitions into high schools, body image, self-esteem, and rejection may contribute to this disparity (Nolan, Flynn, & Garber, 2003; Calles, 2007).

Children with a family history of depression are also particularly vulnerable to developing depression (Williamson, et al., 1995; Weissman, Leckman, Merikangas, Gammon, & Prusoff, 1984), and it has been recommended that when diagnosing depression clinicians consider family history as a risk indicator (Bhatia & Bhatia, 2007). Other factors such as parental education, household income, SES, ethnicity, and adverse childhood events may also contribute to the risk of developing depression in childhood and adolescence (Bhatia & Bhatia, 2007; Cheung & Dewa, 2006; Twenge & Nolen-Hoeksema, 2002).

1.3 Depression & Obesity

Many parallels have been made between depression and obesity, and both disorders are associated with an increased risk of mortality, coronary heart disease, hypertension and diabetes (Olszanecka-Glinianowicz, et al., 2009). Studies have shown that obesity can increase the risk of developing depression and vice versa (Goodman & Whitaker, 2002; Richardson, Garrison, Drangsholt, Manci, & LeResche, 2006; Pine, Goldstein, Wolk, & Weissman, 2001). However, the association between obesity and depression is more strongly reported in the adult population particularly in women than in the pediatric population.

Children and youth with obesity have lower self-esteem and higher rates of depression compared to their normal weight counterparts (Goodman & Must, 2011; Goldfield, Moore , Henderson, Buchholz, Obeid, & Flament, 2010). Cortese *et al.* (2009) studied the cross-sectional association between BMI *z*-scores and depression in a sample of 678 adolescents aged 11 to 14 years using Italian national norms and the CDI. He found a U-shaped association between CDI and BMI *z*-scores, which suggested an increase in depressive symptoms with the extremes of body size. Consistent with Revah-Levy *et al.* (2011), Cortese *et al.* found BMI z-scores and depressive symptoms were non-linearly associated in girls and boys.

However, population- and clinic-based studies have found conflicting results over the association between depression and obesity in children and adolescents (Van Vlierberghe, Braet, Goossens, & Mels, 2009). Furthermore, the prevalence of depression in obese youth have varied due to a number of methodological differences such as depression and obesity definitions and sample populations as discussed in the following sections.

1.3.1 Prevalence of Depression in Obese Youth in Population-based Studies

The majority of community-based studies have demonstrated depression prevalence rates from 8% to 9% among obese adolescents, however rates up to 26.7% have also been reported (Goodman & Must, 2011; McIntyre, Konarski, Wilkins, Soczynska, & Kennedy, 2006; Sjoberg, Nilsson, & Leppert, 2005). Using the adult version of the CES-DC validated in adolescents, obese Americans younger than 20 years of age had a depression prevalence of 8.2% (Goodman & Whitaker, 2002). Although the

Canadian Community Health Survey (CCHS) provides prevalence rates of depression in adolescents and young adults, no Canadian study has evaluated the prevalence of depression in obese children and adolescents thus far. Appendix D, Table 1 (pg. 106) provides more prevalence studies among community-dwelling obese adolescents.

1.3.2 Prevalence of Depression in Obese Youth in Clinic-based Studies

Similar to population-based studies, clinic-based studies report varied rates of depression in obese children and adolescents ranging from 4% to 62.5% (Petty, Davis, Tkacz, Young-Hyman, & Waller, 2009; Zeller, Reiter-Purtill, Ratcliff, Inge, & Noll, 2011). This variability may be the result of methodological differences in depression measures. Zeller and Modi (2006) found 11% of 166 obese youth aged 8 to 18 years had significant depressive symptoms using a conservative cutoff score of 20 for the CDI, however using the recommended cutoff score of 12, a prevalence of 34% was found in their sample (Kovacs, 1992). Also within clinic-based studies, the prevalence has varied between lifestyle intervention and bariatric studies with bariatric surgical studies reporting depression rates in the higher range from 30% to 62.5% in small samples of obese adolescents (Zeller, Modi, Noll, Long JD, & Inge, 2009; Holterman, et al., 2007) (for more information, see Appendix D, Table 2, pg. 108). Therefore, a number of factors including variations in depression and obesity measures, sample populations, and weight changes seen in adolescent development as well as confounding factors must be considered when assessing prevalence of depression in this population (Revah-Levy, et al., 2011).

1.3.3 Determinants of Depression and Obesity

1.3.3.1 Socio-demographic links

Age, sex, and puberty influence depression in the general population and evidence indicates this is also true in children and adolescents with obesity (Anderson, Cohen, Naumova, Jacques, & Must, 2007; Mustillo, Worthman, Erkanli, Keeler, Angold, & Costello, 2003). Puberty may be a significant contributor to the association between obesity and depression, where girls who are in the later stages of puberty and have high depressive symptoms are more likely to be obese while this is evident in earlier puberty in boys (Richardson, Garrison, Drangsholt, Manci, & LeResche, 2006). However, the status of obesity, not overweight, may also mediate depression in obese children and youth (Boutelle, Hannan, Fulkerson, Crow, & Stice, 2010).

Parental factors such as SES and marital status influence the association of depression and obesity in youth where lower SES, parental unemployment, and children with separated parents have an increased risk of both depression and obesity (Cortese, et al., 2009).

It can be seen that the relationship of depression and obesity in children and adolescents is complex and many factors may influence this association. However, few studies have examined the impact of multiple factors such as age, sex, puberty, and family demographics simultaneously on depression in obese children and adolescents.

1.3.3.2 Biological Links

In addition to social and demographic factors, inflammation may also impact the association between obesity and depression. Inflammation is the principal reaction to an

injury invoked by the immune system and involves the recruitment and regulation of various types of cells and inflammatory markers such as cytokines and chemokines (Hotamisligil, 2006). It is classified into two categories: acute or chronic, with acute inflammation occurring rapidly with a sudden increase in immune activation in response to tissue injury, while chronic inflammation is reported to be prolonged with a lower elevation of inflammatory markers (Hotamisligil, 2006). Depression and obesity are both considered to be chronic inflammatory states and changes in cytokines are particularly interesting in these conditions (Soczynska, et al., 2011). Cytokines and chemokines such as tumor necrosis factor-α (TNFα), interferon-α (IFNα), interleukin-1 (IL-1), interleukin-6 (IL-6), C-reactive protein (CRP), are soluble immune proteins that are involved in inflammation. These molecules are involved in initiating and maintaining immune activation by recruiting cells and stimulating the production of other inflammatory markers.

Induction of 'sickness behaviour', a syndrome phenotypically similar to depressive symptoms, can be reliably produced in animals and humans by administration of cytokines, TNFα, IL-6, IL-1, and IL-2 or by administering agents such as endotoxins that induce production of pro-inflammatory cytokines (Reichenberg, Kraus, Haack, Schuld, Pollmacher, & Yirmiya, 2002; Spath-Schwalbe, et al., 1998). Although cytokines are too large to pass freely from the periphery to the brain through the blood-brain barrier (BBB), leaky regions in the BBB allow cytokine signals to access the brain (Konsman, Parnet, & Dantzer, 2002). This is illustrated in several studies that have found increased peripheral and cerebrospinal fluid (CSF) levels of pro-inflammatory cytokines, IL-1, IL-

6, CRP, TNFα, in healthy depressed individuals (Benson, et al., 2008; Maes, 1999; Raison, et al., 2009).

Obesity has also been strongly associated with inflammation. Clinical studies have reported higher circulating levels of IL-6, TNFα, and CRP in obese children and youth than their normal weight counterparts, (Waters, et al., 2007; Yeste, et al., 2007; Martos-Moreno, Barrios, Martinez, Hawkins, & Argente, 2010) and adipose tissue not only produces both IL-6 and TNFα, it also expresses receptors specific to these markers (Feve, 2005). While the direction of causality still remains to be determined, given the association between inflammatory cytokines in both depression and obesity, it appears these soluble markers may be significant determinants of depression in obese children and adolescents. Although this relationship has not been well studied, the following sections describe biomarkers that are produced by adipose tissue or related to adiposity and have been reported to be involved in obesity and depression.

1.3.3.3 Cytokines

1.3.3.3a C-Reactive Protein (CRP)

Known as an acute phase reactant, CRP has a number of different roles but its main function is to provide the first line of defense against a pathogen (Du Clos, 2000; Ansar & Ghosh, 2013). There is strong evidence that CRP is mainly regulated by IL-6 and is primarily synthesized in liver hepatocytes, although expression has been reported in a number of tissues and cells including the respiratory tract and kidneys (Gould & Weiser, 2001; Jabs, et al., 2003). While the signaling mechanism of CRP still remains elusive due to its myriad roles in disease, trauma, and infection, CRP levels in sera and

plasma are widely used as an indicator for diagnosis, risk assessment, and prognosis for many diseases such as cardiovascular disease (Ansar & Ghosh, 2013).

As a marker for inflammation, high-sensitivity CRP (hs-CRP) is used to detect risk of cardiovascular disease in adult patients where levels <1mg/L, 1-3mg/L, and >3mg/L indicate low, intermediate, or high risk groups, respectively (Yeh & Willerson, 2003). In children and adolescents however, these risk groups may not apply. Using NHANES 1999-2000 data of 3348 healthy children and youth aged 3 to 19 years, Ford *et al.* (2003) found a median CRP concentration of 0.4mg/L, while British children aged 11 years (n=699) had a concentration of 0.15mg/L (Cook, et al., 2000; Ford, Giles, Myers, Rifai, Ridker, & Mannino, 2003). However, in obese children and adolescents, reported mean levels of CRP range from 2.3mg/L to 3.7mg/L (Utsal, et al., 2012; Stoppa-Vaucher, et al., 2012; Many, et al., 2013; Maffeis, et al., 2008).

CRP has also been associated with depression in children and adolescents (Chaiton, O'Loughlin, Karp, & Lambert, 2010; Copeland, Shanahan, Worthman, Angold, & Costello, 2012; Miller & Cole, 2012), where depressed youth have been reported to have higher levels of CRP ranging from 0.8mg/L to 2.9mg/L than their normal counterparts (Danner, Kasl, Abramson, & Vaccarino, 2003; Elovainio, et al., 2006; Manco, Morandi, Marigliano, Rigotti, Manfredi, & Maffeis, 2013; Vikram, et al., 2003).

1.3.3.3b Interleukin-6 (IL-6)

Although IL-6 is known as an inflammatory cytokine, it has a number of roles in the regulation of metabolic, regenerative, and neural processes (Scheller & Rose-John, 2006). It is produced by a variety of cell types including adipocytes and myocytes during

infection, trauma, and immunological challenge, and increased levels have been found in a number of diseases (Guillen, Blanes, Gomez-Lechon, & Castell, 1995; Hack, et al., 1989; Hermann, Fleischer, Mayet, Poralla, & Meyer zum Buschenfelde, 1989). IL-6 has been described as both a pro- and anti-inflammatory protein and carries out these roles through the binding of different forms of the IL-6 receptor (Carey & Febbraio, 2004; Scheller & Rose-John, 2006). While it can promote induction of acute phase reactants such as CRP in hepatocytes, it also has a protective role during disease and counteracts certain inflammatory responses by stimulating the production of IL-10 (Jones, Horiuchi, Topley, Yamamoto, & Fuller, 2001).

Circulating concentrations of IL-6 are low in healthy subjects generally <10pg/mL (Hoene & Weigert, 2008). Systemic IL-6 levels can range between 1.1pg/mL to 8.5pg/mL in obese, as well as depressed children and adolescents (Hood, et al., 2012; Gabbay, et al., 2009; Gherlan, et al., 2012; Manco, Morandi, Marigliano, Rigotti, Manfredi, & Maffeis, 2013; Utsal, et al., 2012). Adipose tissue can contribute 10-35% of circulating plasma IL-6 in healthy resting humans (Mohamed-Ali, et al., 1997; Fain, Madan, Hiler, Cheema, & Bahouth, 2004). Along with increased IL-6, elevated levels of other markers such as TNFα, IL-1, and an infiltration of macrophages into adipose tissue are also seen in obesity (Kern, Ranganathan, Li, Wood, & Ranganathan, 2001; Trayhurn & Wood, 2004).

1.3.3.3c Tumor Necrosis Factor-alpha (TNFα)

TNFα is a potent inflammatory cytokine that exerts pleiotropic effects on a variety of cell types. It is produced in response to infection, inflammatory and other stimuli, primarily by immune cells such as macrophages and T and B lymphocytes, as well as

other cell types including endothelial cells, mast cells, and neuronal tissues (Apostolaki, Armaka, Victoratos, & Kollias, 2010). There are two TNF receptors: TNFR1 is responsible for pro-inflammatory, cytotoxic, and apoptotic responses whereas TNFR2 is preferentially expressed in hematopoietic cells (Chen & Goeddel, 2002; Grell, et al., 1995; Wajant, Pfizenmaier, & Scheurich, 2003). TNF receptors can be released in soluble forms from the cell surface, but it is suggested that these forms neutralize the action of TNFα.

The secretion of TNFα is mainly by cells of the stromal-vascular and matrix fractions including macrophages of adipose tissue and levels have been reported to be higher in subcutaneous than visceral adipose tissue (Fain, Bahouth, & Madan, 2004; Weisberg, McCann, Desai, Rosenbaum, Leibel, & Ferrante, 2003). With TNFα levels of 1.03pg/mL in normal weight children, several studies have found that obese youth have higher TNFα concentrations ranging from 3.18pg/mL to 7.2pg/mL (Gherlan, et al., 2012; Manco, Morandi, Marigliano, Rigotti, Manfredi, & Maffeis, 2013; Utsal, et al., 2012; Aerberli, Molinari, Spinas, Lehmann, I'Allemand, & Zimmermann, 2006). In depressed children and adolescents, significantly higher levels ranging from 18.1pg/mL to 30.9pg/mL have been reported (Gabbay, et al., 2009; Brambilla, Monteleone, & Maj, 2004) whereas levels of TNFα as well as other inflammatory markers have yet to be reported in depressed youth with obesity.

1.3.3.3d Interleukin-10 (IL-10)

IL-10 can be expressed in a variety of cells usually in response to an activation stimulus (Powell, Thompson, Tone, Waldmann, & Tone, 2000). Known as an anti-

inflammatory cytokine, IL-10 inhibits many activated macrophage/monocyte functions, as well as production of cytokines including IL-6 and TNFα. The inhibitory effects of IL-10 on IL-1 and TNFα production are crucial because these cytokines often have synergistic activities on inflammatory pathways and processes (de Waal Malefyt, Abrams, Bennett, Figdor, & de Vries, 1991; Fiorentino, Zlotnik, Mosmann, Howard, & O'Garra, 1991). IL-10 not only inhibits production of these effectors, but it also enhances the expression of their natural antagonists such as interleukin-1 receptor antagonist and the soluble forms of TNFR (Dickensheets, Freeman, Smith, & Donnelly, 1997; Hart, Hunt, Bonder, Watson, & Finlay-Jones, 1996; Joyce & Steer, 1996).

As adipose tissue volume increases, circulating levels of TNFα and IL-6 also increase and in turn, stimulate CRP production and a disruption in the IL-6/IL-10 pathway causes a decrease in IL-10 (Moore, de Waal Malefyt, Coffman, & O'Garra, 2001). While the majority of studies have shown a decreased concentration of IL-10 in depressed and obese children and adults (Dhabhar, et al., 2009; Huang & Lee, 2007; Stoppa-Vaucher, et al., 2012; Tam, et al., 2010), others have reported conflicting observations (Benson, et al., 2008; Henje Blom, Lekander, Ingvar, Asberg, Mobarrez, & Serlachius, 2012). In obese children and adolescents, IL-10 concentration levels tend to be low, ranging from 0.3pg/mL to 3.2pg/mL (Manco, Morandi, Marigliano, Rigotti, Manfredi, & Maffeis, 2013; Mager, Yap, Rodriguez-Dimitrescu, Mazurak, Ball, & Gilmour, 2013; Utsal, et al., 2012) whereas IL-10 levels have not been measured in depressed youth very often (Henje Blom, Lekander, Ingvar, Asberg, Mobarrez, & Serlachius, 2012).

1.3.3.4 Inflammation in Depression and Obesity

Given that chronic inflammation is linked to both depression and obesity, perhaps inflammation acts as a mediator between these two conditions (Miller, Carney, Freedland, & Banks, 2002; Miller, Freedland, Carney, Stetler, & Banks, 2003). Depression and inflammation in obese individuals have higher CRP, TNFα, and IL-6 levels in depressed obese groups compared to their non-depressed counterparts (Dixon, et al., 2008; Hamer, Molloy, de Olveira, & Demakakos, 2009; Miller, Carney, Freedland, & Banks, 2002; Hiles, Baker, de Malmanche, & Attia, 2012). However, these findings are not consistent and other studies have reported no differences in inflammatory markers (Benson, et al., 2008; Olszanecka-Glinianowicz, et al., 2009). Although evidence shows that depressed obese patients have an abnormal functioning of the inflammatory response system, to our knowledge, this has only been studied in adults (Ortiz-Dominguez, et al., 2007).

Anti-inflammatory markers have not been as extensively studied as pro-inflammatory markers in depression. Animal studies have indicated there may be a relationship between IL-10 and depressive behaviour (Toth & Opp, 2001; Mesquita, et al., 2009) and a meta-analysis by Hiles *et al.* (2012) reported that overall levels of IL-10 were not significantly different in depressed humans compared to their non-depressed counterparts. However in an overweight/obese subgroup, depressed subjects had significantly lower IL-10 levels than non-depressed overweight/obese subjects. Since IL-10 is able to inhibit pro-inflammatory cytokines implicated in depression and obesity, it is necessary to understand whether an imbalance in the inflammatory milieu is involved in the association of adiposity and depression.

However, childhood and adolescence is a critical period to assess this association because of the constant change in physical growth, emotional development, and brain plasticity during this time. Evidence supports that intense acute or chronic stress during these periods may also have long-term and irreversible effects on emotion, behaviour, growth, metabolism, reproductive, immune, and cardiovascular function (Charmandari, Kino, Souvatzoglou, & Chrousos, 2003). However to our knowledge, no study has examined potential pathways by which inflammation could influence depression in the obese pediatric population.

1.3.3.4a Inflammation infiltrating the brain

A number of potential mechanisms linking inflammation in depression and obesity come to mind – one in which systemic inflammation directly influences the brain. Since inflammatory markers are normally too large to cross the BBB, they can influence the peripheral afferent nerve (vagus nerve) that travels between the periphery and the brain (Konsman, Parnet, & Dantzer, 2002). Additionally, peripheral inflammatory markers can also increase inflammation in the brain through leaky regions in the BBB and the choroid plexus – a structure in the brain that produces CSF (Konsman, Parnet, & Dantzer, 2002). Through these entryways, inflammatory markers can activate microglia – the brain's immune cells – and thereby increase brain cytokine production. This would in turn stimulate production of indoleamine 2,3-dioxygenase (IDO) – an enzyme that catalyzes tryptophan, the precursor to serotonin, to kynurenic acid – that could lead to greater neurotoxicity that has been associated with depression (Delgado, Charney, Price, Aghajanian, Landis, & Heninger, 1990; Mellor & Munn, 1999; Capuron, et al., 2003).

1.3.3.4b The Hypothalamic-Pituitary-Adrenal (HPA) Axis

Another mechanism by which inflammation could influence depression and obesity is via the hypothalamic-pituitary-adrenal (HPA) axis. Pro-inflammatory markers are able to stimulate the HPA axis resulting in the activation of a cascade of hormones and ultimately increased secretion of cortisol (Dunn, 2000; Muller, Myint, & Schwarz, 2011). Cortisol is a steroid hormone responsible for alleviating stress in the body by increasing blood sugar and fat metabolism, and suppressing the immune system among other functions. However, activation of the HPA axis can also result in 'sickness behaviour' – symptoms that are very similar to symptoms seen in depression. While some studies have reported increased cortisol levels in obese and depressed patients (Bornstein, Schuppenies, Wong, & Licinio, 2006; Strickland, Deakin, Percival, Dixon, Gater, & Goldberg, 2002; Dockray, Susman, & Dorn, 2009), others have shown no association of HPA axis activation with depression and obesity. This indicates that the HPA axis may play a role in some subgroups or may only relate to depression and obesity during acute stress situations (van Reedt Dortland, et al., 2013; Veen, Giltay, DeRijk, van Vliet, van Pelt, & Zitman, 2009). The association between depression and obesity is supported by common abnormalities in HPA axis function including increased IL-6 in obese and depressed individuals, while animal studies have shown higher glucocorticoid levels to be associated with weight gain, insulin resistance, and increased anxiety and depression (Bornstein, Schuppenies, Wong, & Licinio, 2006; Coste, Murray, & Stenzel-Poore, 2001). However, other theories explaining the relationship of depression and obesity have been posed.

1.3.3.4c Brain-Derived Neurotrophic Factor (BDNF)

BDNF is a secreted protein of the neurotrophin family that is responsible for neuronal survival, development, and function (Reichardt, 2006). During development, it is synthesized at low levels in the central nervous system and increases during the postnatal period (Maisonpierre, et al., 1990; Leibrock, et al., 1989). In the human brain, BDNF is the most abundant and widespread neurotrophin, with the highest levels of mRNA and protein located in the hippocampus, amygdala, cerebral cortex, and hypothalamus (Kolbeck, Bartke, Eberle, & Barde, 1999; Tang, Machallani, & Waters, 2010; Webster, Herman, Kleinman, & Shannon Weickert, 2006). The first indication of a role in appetite came from the finding that intracerebroventricular delivery of BDNF reduced food intake and body weight in rats (Pelleymounter, Cullen, & Wellman, 1995; Lapchak & Hefti, 1992). In addition to expression in the brain, BDNF is also present in peripheral tissues important for energy homeostasis such as adipose tissue, skeletal and smooth muscle, and liver (Noble, Billington, Kotz, & Wang, 2011; Ukropec, Ukropcova, Kurdiova, Gasperikova, & Klimes, 2008).

An inverse association between peripheral BDNF concentration and obesity in children and adults has been reported (Krabbe, et al., 2007; Lommatzsch, et al., 2005). Human genetic studies have found that mutations in the *Bdnf* gene or its receptor, trkB, exhibit obesity (Yeo, et al., 2004; Gray, et al., 2006), while *Bdnf* gene variants are associated with increased obesity risk in children and adults (Skledar , Nikolac, Dodig-Curkovic, Curkovic, Borovecki, & Pivac, 2012; Speliotes, et al., 2010; Wu , et al., 2010). However, levels of systemic BDNF in obese children and adolescents compared to normal weight counterparts have been inconsistent (El-Gharbawy, Mirch, Theim,

Ranzenhofer, Tanofsky-Kraff, & Yanovski, 2006; Corripio, et al., 2012; Roth, Elfers, Gabhardt, Muller, & Reinehr, 2013).

BDNF has important roles in neural development and synaptic plasticity, but recently it has been suggested to be involved in the pathophysiology of depression (Greenberg, Xu, Lu, & Hempstead, 2009; Lu B. , 2003; Martinowich, Manji, & Lu, 2007). Specifically, studies have reported that a substitution of valine-to-methionine at codon 66 (Val66Met) in the prodomain of BDNF is associated with higher depressive symptoms in adolescents (Caldwell, et al., 2013; Buchmann, et al., 2013; Chen, Li, & McGue, 2013). In addition, lower BDNF levels in serum and plasma have also been associated with depression and obesity in both children and adults (Corripio, et al., 2012; Terracciano, et al., 2011).

A decrease in BDNF can also be seen after infiltration of inflammatory markers in the brain, thereby decreasing neurogenesis and neuronal plasticity potentially leading to depression (Terracciano, et al., 2011). In an animal model, Schmidt & Duman (2010) reported that systemic administration of BDNF increased hippocampal neurogenesis and antidepressant-like behaviours whereas in humans, increased peripheral BDNF levels after antidepressant treatment has been reported (Bocchio-Chiavetto, et al., 2010; Piccinni, et al., 2008).

1.3.3.5 Leptin

In addition to inflammation, leptin is commonly studied in obesity and more recently in depression. Leptin is a 16kDa adipokine that was discovered in 1994 in an obese mouse model (Zhang, Proenca, Maffei, Barone, Leopold, & Friedman, 1994), and

is secreted from adipose tissue where its roles include regulation of food intake and energy expenditure via actions in the hypothalamus (Brennan & Mantzoros, 2006). Leptin levels have a strong direct correlation with adiposity measured in percent body fat as well as BMI in both children and adults (Blum, Englaro, Heiman, Attanasio, Kiess, & Rascher, 1997; Considine, et al., 1996; Maffeis, et al., 1995). Under normal conditions, an increase in leptin promotes a decrease in body weight through the action of energy regulation. However in obese individuals, although leptin levels are higher, a reduction in body weight is not seen due to a phenomenon called leptin resistance where an excess amount of leptin is present but the body does not effectively respond to its higher levels (Considine, et al., 1996; Frederich, Hamann, Anderson, Lollmann, Lowell, & Flier, 1995). It has been posed that leptin resistance occurs due to impairments in the leptin signaling pathway to the brain and/or defective leptin receptors. This is evident in obese individuals that have a decreased ratio of CSF to plasma leptin and defective leptin receptor signaling (Myers, Heymsfield, Haft, Kahn, Laughlin, & Leibel, 2012).

Apart from its actions on physiological processes such as appetite and energy expenditure, leptin has also been associated with depression although studies in adults have been conflicting (Kraus, Haack, Schuld, Hinze-Selch, & Pollmacher, 2001; Morris, et al., 2012; Yang, et al., 2007; Taylor & Macqueen, 2010). Few studies have examined the link between leptin and depression in children and adolescents, however Hood *et al.* (2012) measured leptin levels in Type 1 and 2 diabetic youth under the age of 20 and found significantly higher leptin levels in the moderate to severe depressive group compared to those with no or minimal depressive symptoms.

When examining leptin and depression in the obese population, some have reported higher circulating leptin levels in depressed individuals than non-depressed obese counterparts whereas others find that adiposity may mediate the association between depression and leptin (Morris, et al., 2012; Milaneschi, Simonsick, Vogelzangs, Strotmeyer, Yaffe, & Harris, 2012; Milaneschi, et al., 2014). While human studies examining leptin in depression and obesity report conflicting results, animal studies have shown more conclusive findings. The lack of leptin in obese *ob/ob* mice or its receptor in obese *db/db* mice has been associated with increased behavioural despair in tests evaluating depression in animals (Sharma, Elased, Garrett, & Lucot, 2010; Yamada, Katsuura, Ochi, Ebihara, Kusakabe, & Hosoda, 2011). In addition, systemic or central leptin administration in normal mice have shown antidepressant effects measured by various tests for depression such as the forced swim task (FST) and tail suspension test but the same is not evident in obese mice (Liu, Garza, Bronner, Kim, Zhang, & Lu, 2010; Yamada, Katsuura, Ochi, Ebihara, Kusakabe, & Hosoda, 2011).

1.3.3.5a Leptin in Depression and Obesity

Leptin is negatively correlated with cortisol in humans (Komorowski, Jankiewicz-Wika, & Stepien, 2000) and in leptin deficient *ob/ob* mice, leptin replacement causes elevated cortisol levels to decline (Arvaniti, Huang, & Richard, 2001; Huang , Rivest, & Richard , 1998). Chronic stress in rats has led to depressive behaviours and is associated with HPA activation and decreases in serum leptin levels (Ge, Qi, & Zhuo, 2013; Taylor & Macqueen, 2010). However, cortisol has been shown to stimulate leptin production in

normal conditions (Williams, et al., 2000), suggesting that a dysregulation of the HPA axis occurs causing depression in these obese animals.

Beyond HPA dysfunction, leptin administration into the hippocampus, an area in the brain involved in depression, has been associated with antidepressant effects in animals deficient in leptin (Asakawa, Inui, Inui, Katsuura, Fujino, & Kasuga, 2003; Liu, Garza, Bronner, Kim, Zhang, & Lu, 2010; Lu, Kim, Frazer, & Zhang, 2006). A loss of the leptin receptor, LepRb, which is highly expressed in the hippocampus and involved in depression, has elicited depressive-like behaviour (Guo, Huang, Garza, Chua, & Lu, 2013; Guo, Lu, Garza, LiY, Chua, & Zhang, 2012) suggesting defective leptin signaling to cause depression. Leptin resistance in obesity could also partly explain the increased risk of depression. Yamada *et al.* (2011) found that in normal mice fed a control diet, systemic administration of leptin had antidepressant effects whereas in diet-induced obese (DIO) mice, this effect was not seen suggesting that DIO resulted in leptin resistance that in turn affected depressive symptoms.

Leptin is also related to inflammation in particular IL-6 and CRP (Hukshorn, van Dielen, Buurman, Westerterp-Plantenga, Campfield, & Saris, 2002; Hukshorn, et al., 2004; Mackintosh & Hirsch, 2001; Shamsuzzaman, et al., 2004), and therefore, this relationship could ultimately influence inflammatory mechanisms previously discussed in the brain and lead to depression.

There is evidence that the relationship of depression and adiposity may be influenced by inflammation, adipokines and/or neurotrophins. With this in mind, based on previous literature a proposed model was developed to explain the potential mechanistic

pathways of this relationship. The biological factors – IL-6, TNFα, IL-10, CRP, BDNF, leptin – were chosen for this thesis project because they are produced in adipocytes or related to adiposity and have been reported to be involved in obesity and depression. Figure 2 shows the proposed model of this thesis project.

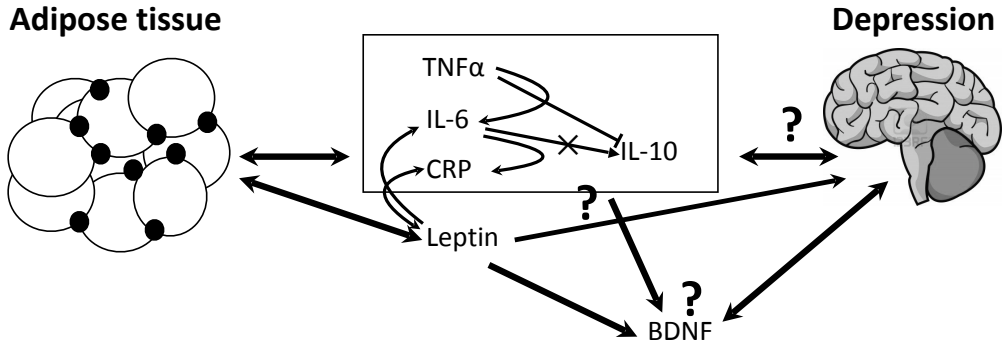

Figure 2: Proposed model for thesis examining the influence of inflammatory markers, leptin, and BDNF to depression in obese children and adolescents.
It has been reported that there is an association between adiposity and depression. However, recent studies have linked these two conditions with inflammation. Both depression and obesity have been associated with an increase in circulating levels of leptin, TNFα, IL-6, CRP, and decrease in IL-10 levels. Interactions between these biomarkers have also been reported where Reichenberg *et al.* (2002) reported that after an injection of endotoxin, TNFα rapidly increased while IL-6 started to rise after one hour post-injection, suggesting that TNFα may induce the production of IL-6 (Reichenberg, Kraus, Haack, Schuld, Pollmacher, & Yirmiya, 2002). CRP production in the liver is mainly regulated by IL-6 (Spath-Schwalbe, et al., 1998) and under normal circumstances, IL-6 acts to increase IL-10 production to restore balance whereas TNFα inhibits IL-10 (Meisel, Vogt, Platzer, Randow, Liebenthal, & Volk, 1996). However, a disruption in the IL-6/IL-10 pathway has been proposed to explain the decreased IL-10 levels seen in obese and depressed individuals (Dhabhar, et al., 2009; Mesquita, et al., 2009). Therefore, inflammation is one mechanistic pathway that obesity and depression are linked. However in obesity, leptin is increased and has shown to have a direct influence on depression as well as influence IL-6 and CRP levels (Chen K. , et al., 2006; Yamada, Katsuura, Ochi, Ebihara, Kusakabe, & Hosoda, 2011; Trujillo, Sullivan, Harten, Schneider, Greenberg, & Fried, 2004). As a result, leptin could be involved in the obesity-depression association either directly or via inflammation. Lastly, inflammatory markers and leptin also influence BDNF, which has been associated with depression (Yamada, Katsuura, Ochi, Ebihara, Kusakabe, & Hosoda, 2011; You , et al., 2011).

CHAPTER 2: STUDY RATIONALE

The relationship between obesity and depression is a relatively new area of research in pediatric populations. Even though there is increased recognition of this association, clinic-based and population-based studies have not been consistent in reporting a relationship between obesity and depression. Depressive disorders are more prevalent in treatment-seeking youth than those in the general obese population (Britz, et al., 2000; Van Vlierberghe, Braet, Goossens, & Mels, 2009) and given the relatively high prevalence of depression among obese youth in clinical studies, identifying the determinants of depressive symptoms may assist clinicians in recognizing "at risk" youth. While it has been suggested that depression among obese youth increases with age, pubertal development, lower SES and extent of obesity, these determinants have not been examined simultaneously. In addition, the influence of inflammatory markers, leptin, and BDNF on depression in children and adolescents with obesity has not been studied. Furthermore, studying depression and obesity in the pediatric age group allows the evaluation of potential determinants of depression in its early stages.

CHAPTER 3: OBJECTIVES & HYPOTHESES

The main objective of this thesis project was to examine family, social, anthropometric and biological determinants of depressive symptoms among obese children and adolescents at the time of entry into a weight management program. We hypothesized that older children who have undergone or are in the later stages of puberty and have a lower SES would have a larger contribution to depressive symptoms than other measured determinants. We also hypothesized that higher inflammation would be

related to depressive symptoms independent of socio-demographic factors or physical measures suggesting that inflammation acts a potential mediator between depression and adiposity in obese children and adolescents entering into a weight management program. Lastly, we hypothesized that BDNF but not leptin would have a relationship with depressive symptoms independent of socio-demographic factors or physical measures but inflammation would mediate this relationship suggesting that through BDNF, inflammation is influencing depressive symptoms.

Data collected in the Determinants of Change in Childhood Obesity (DECCO) study were used to: 1) examine potential determinants of depression (age, sex, pubertal development, extent of obesity, household income, family history of depression) in obese children and youth presenting for a weight management program, 2) compare inflammatory markers – IL-6, TNFα, CRP, IL-10 – leptin, and BDNF in obese youth with high depressive symptoms to those without, and 3) examine the contribution of low grade inflammation, leptin, and BDNF to depressive symptoms in obese children and youth.

CHAPTER 4: METHODS

4.1 The DECCO Study

The DECCO study was a prospective, longitudinal study examining determinants of health in children and adolescents entering a weight management program and in follow-up. However, this thesis project only considered the baseline visit and therefore is cross-sectional in design. The treatment program was delivered independent of the research study. Informed written consent was provided by the legal guardian and the child

provided signed assent. The study was approved by the institutional review board at the Hamilton Health Sciences Corporation (Hamilton, ON, Canada).

4.2 Study Population

Children and adolescents from the Children's Exercise and Nutrition Centre (CENC) weight management program were asked to take part in the DECCO study. The CENC is a multidisciplinary, outpatient clinic that provides consultation, education, medical care, and prescription of physical activity, nutrition, and lifestyle alterations for patients and their families. To be eligible for the DECCO study, participants had to be aged 5 to 17 years entering a weight management program, with no untreated endocrine disorder and willingness to participate. However, due to age limitations for the mental health questionnaire, only participants aged 8 to 17 years were included in this thesis project. Therefore, a total of 244 children and adolescents participated in this study (Figure 3).

In their baseline visit, participants were asked to fast overnight and drink lots of water the night before and the day of the visit. After consent was obtained, all study visit testing was conducted. This included: ascertainment of participant and parental demographic characteristics, anthropometric evaluation, physical measures, completion of mental health questionnaires, and a 2h oral glucose tolerance test. Questionnaires pertaining to mental health, pubertal development, and use of tobacco products and alcohol were completed by the participants in privacy.

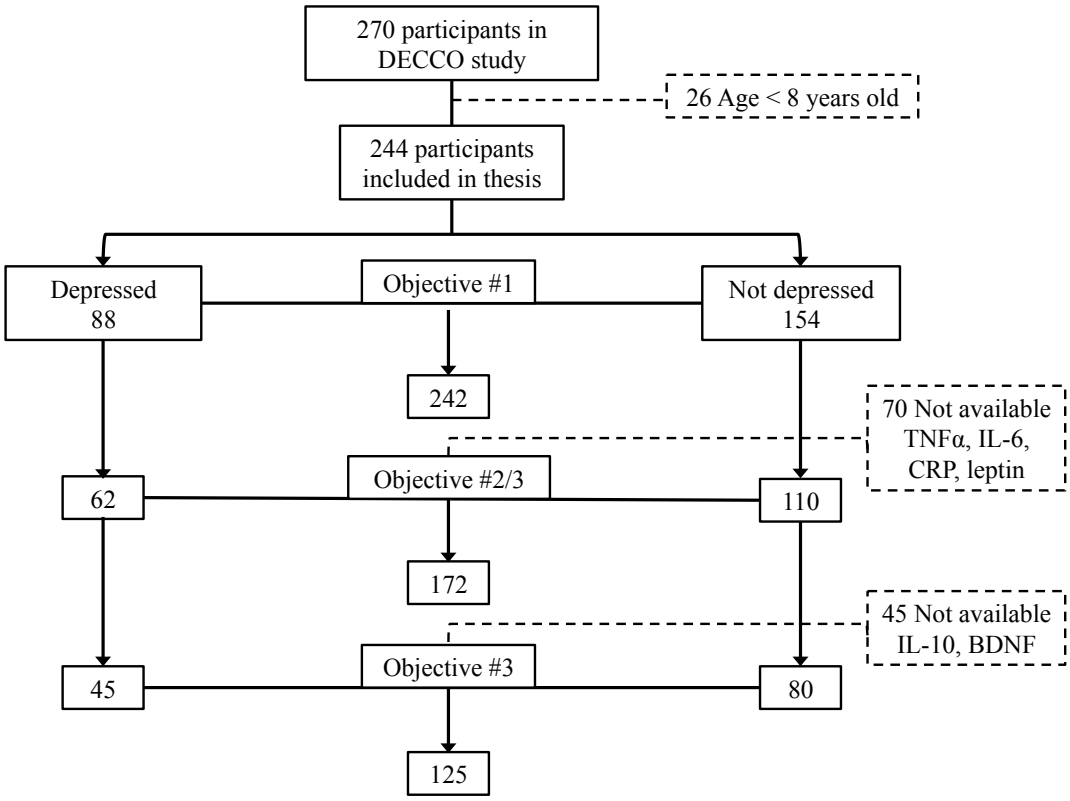

Figure 3: Flow chart of included participants for each thesis objective.
A total of 270 participants took part in the baseline visit of the DECCO study. However, only 244 of these participants were included for this thesis project as the CES-DC questionnaire is validated in 8 to 17 year-olds. Two participants did not complete the CES-DC questionnaire but completed other parts of the study. A total of 242 participants were included for the analyses of objective 1 while 172 and 125 were included for objectives 2 and 3.

4.3 Outcome and Measures

Depressive symptoms were the primary outcome of interest. Other health measures included potential determinants of depressive symptoms: socio-demographic variables (age, sex, income, family history of depression), physical measures (puberty, adiposity), and adipose-related biomarkers that may be related to depression (IL-6, TNFα, IL-10, CRP, BDNF, leptin).

4.3.1 Depressive Symptoms

Overview: Depressive symptoms were evaluated using the Center of Epidemiological Studies Depression Scale for Children (CES-DC) questionnaire. The CES-DC is a 20-item self-report depression inventory with possible scores ranging from 0 to 60. Higher scores indicate increased levels of depressive symptoms and each response to an item is scored by: 0 = "Not at all"; 1 = "A little"; 2 = "Some"; or 3 = "A lot". A score of 15 or greater has been suggestive of high depressive symptoms in children and adolescents (Faulstich, Carey, Ruggiero, Enyart, & Gresham, 1986). The CES-DC takes an average of 5 minutes to complete and was adapted from an instrument widely used to measure depressive symptoms in adults, the Centre for Epidemiological Studies Depression Scale (CES-D) (Fendrich, Weissman, & Warner, 1990). In this thesis, a participant was classified as having high depressive symptoms if the CES-DC score ≥ 15 or if the participant was taking antidepressant medication.

Rationale for use: The CES-DC has been validated in children and adolescents aged 8 to 17 years, and it is able to differentiate between psychiatric diagnoses according to DSM-III criteria. A disadvantage of this questionnaire is that it does not perform well when distinguishing different sub-types of depressive disorders especially using DSM-IV criteria (Fendrich, Weissman, & Warner, 1990; Olsson & von Knorring, 1997; Barkmann, Erhart, Schulte-Markwort, & BELLA Study Group, 2008). However, as this project focused on differentiating those with high depressive symptoms and those without, rather than distinguishing sub-types of depression, the CES-DC was an appropriate tool for this study.

4.4 Potential Determinants of Depressive Symptoms

4.4.1 Socio-demographic

Age was calculated from the date of birth to the date of the baseline study visit while sex was self-identified by the participants.

Total current annual income of all household members was measured by the parents' best estimate of household income for the past 12 months before taxes and deductions. Parents were asked to choose one of six categories: $0 – 14,999; $15,000-29,999; $30,000-49,999; $50,000-69,999; $70,000-99,999; or $100,000 and above.

Family history of depression was collected in a standardized manner from the clinical chart and included history of the parents, siblings, aunt/uncle, and grandparents of the participant.

4.4.2 Physical Measures

Pubertal development was self-assessed using Tanner stages where participants were asked to choose the schematic drawings most representative of them – stages of breast development for females and stages of pubic hair and genital development for males (Brooks-Gunn, Warren, Rosso, & Gargiulo, 1987; Neinstein, 1982).

Adiposity was evaluated using BMI z-scores and body fat. Standing height was measured using a Harpenden Stadiometer (London, UK) and weight was measured using a GE Lunar Prodigy Advance DXA scanner (Model #8743). DXA determines bone density, fat-free mass, and fat mass by utilizing two x-ray energies to measure the amount of x-rays absorbed by the bones and tissues of an individual (Pietrobelli, Formica, Wang, & Heymsfield, 1996). BMI (calculated as weight (kg)/height (m^2)) and BMI z-scores

were calculated based on CDC normative data, using NUTSTAT – a component of the Epi Info Program – while percent (%) body fat was measured using DXA.

4.4.3 Biomarkers – Inflammatory Markers, Leptin, and BDNF

IL-6, TNFα, and leptin were quantified by the McMaster Core Lab using Meso Scale Discovery Multi-Array technology (Gaithersburg MD, USA) on the MSD SECTOR 6000 Imager. This sandwich immunoassay system utilizes electrochemiluminescent detection to measure levels of these biomarkers. A sample with a solution containing detection antibodies attached with electrochemiluminescent labels is placed into a plate pre-coated with capture antibodies. Using a buffer to create the appropriate chemical environment for electrochemiluminescence, the plate is loaded into the MSD SECTOR 6000 Imager where a voltage is applied causing the captured labels to emit light. The imager measures the intensity of emitted light providing a quantitative measure of the biomarkers in the sample. Of the 244 participants, IL-6, TNFα, and leptin were quantified from stored fasting serum samples from 173 participants. Samples were run in duplicates and the limit of detection of this multiplex assay was 2.4pg/mL for IL-6, TNFα, and leptin.

High sensitivity CRP was quantified in 173 fasting serum samples using the Beckman Coulter Unicel DxC600 Synchron Clinical System and Beckman reagents (Beckman Coulter Inc, Brea CA, USA) by the McMaster Core Lab. An anti-CRP antibody coated particle binds to CRP in the sample resulting in the formation of insoluble aggregates causing turbidity. The system monitors the change in absorbance at 940nm and this change in absorbance is proportional to the concentration of CRP in the

sample. The system provides a quantitative measure of CRP concentration based on single-point adjusted, pre-determined calibration curve. The limit of detection for this assay was 0.20mg/L and samples were run in duplicate.

High sensitivity IL-10 was measured using eBioscience IL-10 High Sensitivity ELISA kits (eBioscience, San Diego, CA, USA, Catalog #: BMS215HS) in 126 serum samples according to manufacturer's instructions with the exception that samples were run undiluted as the 1:2 dilution suggested resulted in a number of samples below the limit of detection of 0.39pg/mL. IL-10 present in the samples was bound to the immobilized antibody specific for IL-10 pre-coated on the microplate. A biotin-conjugated anti-human IL-10 antibody was then added creating a complex with the immobilized antibody-IL-10. Streptavidin-HRP was added to bind to the biotin-conjugated anti-human IL-10 antibody followed by amplification. Lastly, a substrate solution was added to produce a colour change in proportion to the amount of bound IL-10. Optical density was determined by subtracting readings at wavelengths 450nm and 620nm to correct for optical imperfections in the plate. A 4-parameter logistic curve was fitted and IL-10 concentration in unknown samples was determined by interpolation from the standard curve. The intra-assay coefficient of variation (CV) for each duplicate was <25%; mean intra-assay CV was 11.54% whereas the mean inter-assay CV was 19.81%.

BDNF was measured in 123 serum samples using the R&D Systems Quantikine ELISA kits (R&D Systems, Minneapolis, MN, USA, Catalog #: DBD00) according to manufacturer's instructions. This assay employed a sandwich enzyme immunoassay technique to quantify the amount of BDNF in samples. Any BDNF present in the samples

bound to the immobilized antibody specific for BDNF pre-coated on the microplate. A detection antibody was then added to create a sandwich with the immobilized antibody-BDNF complex. Lastly, a substrate solution was added to produce a colour change in proportion to the amount of bound BDNF. Serum samples run in duplicate and were diluted 1:20 for this assay and so final results were multiplied by a 20 dilution factor. Optical density was determined by subtracting readings at wavelengths 540nm and 450nm to correct for optical imperfections in the plate. A 4-parameter logistic curve was fitted and BDNF concentration in unknown samples was determined by interpolation from the standard curve. The lower limit of detection for this ELISA assay was 62.5pg/mL. The intra-assay CV for each duplicate was <16% with a mean of 7.78% and mean inter-assay CV was 5.39%.

4.5 Statistical Analysis

Statistical analysis was performed using SPSS (version 20 for Mac). Data were tested for normality and equal variance.

4.5.1 Objective #1

To examine potential determinants of depression (age, sex, pubertal development, extent of obesity, parental education, household income, family history of depression) in obese children and youth presenting for a weight management program.

Univariate analyses were used to compare those with and without depression in regards to sex, age, extent of obesity, and family history of depression. Independent *t*-tests were performed for continuous variables (age, BMI z-score, % body fat) and χ^2 tests for discrete variables (sex, family history). Mann-Whitney U tests were used to compare

Tanner pubertal stage and income between groups, as these variables were ordinal variables. Partial correlation analyses were used to assess the univariate relationship of socio-demographic factors and physical measure to the CES-DC score adjusting for age and sex. Multivariate logistic regression was conducted to examine the most important determinants that influence depression classification (outcome). Significance of all statistical tests was defined as $p<0.05$.

4.5.2 Objective #2

To compare inflammatory markers – IL-6, TNFα, hsCRP, IL-10 – leptin, and BDNF in obese youth with high depressive symptoms to those without.

Independent t-tests were used to compare those with and without depression in regards to IL-6, TNFα, hsCRP, IL-10, leptin, and BDNF. With the exception of BDNF, all biomarkers were not normally distributed and therefore, were logarithmically transformed before statistical group comparison. Values that fell below the limit of detection (LOD) were substituted by half the LOD.

Rationale for use: Substituting half the LOD has been used in previous studies to provide an estimate of the true value of these undetectable values (Marques-Vidal, et al., 2011; Gimeno, et al., 2009). Hornung & Reed (1990) reported that when comparing different simple substitution methods – substituting half of LOD or dividing the LOD by the square root of two – substitution by half the LOD produced better results with highly skewed data and when approximately 50% of the values were undetectable (Hornung & Reed, 1990). Hewett & Ganser (2007) provided further evidence that when the proportion of undetectable values ranged from 50% to 80%, substituting half of the LOD faired

better than substituting the LOD divided by the square root of two (Hewett & Ganser, 2007). Thus, we chose this method (53.8% below LOD).

4.5.2.1 Sample size calculations for objective 2

IL-10 levels have not been measured in obese youth with depression. However, Dhabhar et al. (2009) examined IL-10 levels in serum samples of adults suffering from major depressive disorder. They identified that depressed adults (0.34pg/mL) had lower IL-10 concentrations than their healthy counterparts (0.83pg/mL) (Dhabhar, et al., 2009). We used information from this study to determine the required sample size to examine differences in IL-10 levels between depressed and non-depressed obese youth. With a minimum sample size of 17 depressed and 17 non-depressed obese youth, we have adequate statistical power (>90%) to identify effect sizes (Cohen's d) of -0.99.

4.5.3 Objective #3

To examine the contribution of low-grade inflammation, leptin, and BDNF to depressive symptoms in obese children and youth.

Partial correlation analyses were used to assess the univariate relationship of socio-demographic, physical measures, and biomarkers to the CES-DC score adjusting for age and sex. Potential determinants of depressive symptoms were then analyzed using a multivariate hierarchical linear regression analysis. Potential determinants included: socio-demographic predictors (age, sex, household income, family history), physical measures (pubertal development, % body fat), and biological factors (IL-6, TNFα, CRP, IL-10, BDNF, leptin). The CES-DC score was the dependent (outcome) variable. In this

type of regression analysis, the order of entry of predictor variables is determined *a priori* as shown in Table 1a-b.

In multiple regression models, multicollinearity can pose as a problem between predictors with a strong correlation. If predictors that are collinear are included in the models, it becomes impossible to distinguish which of these predictors is acting on the outcome variable. Therefore to identify multicollinearity, tolerance and variance inflation factor (VIF) values were calculated. The VIF calculates whether a predictor has a strong linear relationship with other predictors while tolerance is the reciprocal of VIF (Field, 2009). According to Myers (1990), values indicating potential problems of multicollinearity include VIF values of 10 or more, or tolerance values of 0.10 or less. Appendix B, Table 3 (pg. 92) shows the VIF and tolerance values of the multivariate logistic regression model of potential socio-demographic and physical measure determinants of depressive symptoms analyzed in Objective 1 while Appendix B, Table 4 (pg. 93) show VIF and tolerance values of multivariate model of potential biological determinants of depressive symptoms analyzed in Objective 3.

Rationale for order of entry: Further multivariate analyses of leptin (Table 1a) and TNFα (Table 1b) were conducted to identify independent influences on depressive symptoms because univariate correlation analyses revealed these biomarkers to be significantly related to adiposity and/or the CES-DC score. There were also significant interactions between TNFα, IL-6, CRP, and IL-10 and therefore, we tested whether these inflammatory markers were independently related to the CES-DC score (Appendix B, Table 6a, pg. 95).

Table 1a: Order of entry of predictors for hierarchical multivariate linear regression in Objective 3 (leptin).

Model 1	Model 2	Model 3
Age	Age	Age
Sex	Sex	Sex
Pubertal stage	Pubertal stage	Pubertal stage
Household income	Household income	Household income
Family history	Family history	Family history
--	% body fat	% body fat
--	--	Leptin

Table 1b: Order of entry of predictors for hierarchical multivariate linear regression in Objective 3 (TNFα).

Model 1	Model 2	Model 3
Age	Age	Age
Sex	Sex	Sex
Pubertal stage	Pubertal stage	Pubertal stage
Household income	Household income	Household income
Family history	Family history	Family history
--	% body fat	% body fat
--	--	TNFα

4.5.3.1 Sample size calculation for objective 3

A common rule of thumb for sample size calculation for multivariate regression is 10 cases per predictor in the model (Field, 2009). Models to examine the contribution of TNFα and leptin to depressive symptoms had seven predictors (Table 1a,b), and therefore a minimum sample size of 70 participants is required. The last model to examine whether inflammatory markers were independently related to depressive symptoms, there were 10 predictors (Appendix B, Table 6a, pg. 95), and therefore a minimum of 100 participants is required to carry out this multivariate analysis. There were 153 participants included in the analysis of models in Table 1a and 1b, and a sample size of 111 participants included to analyze model in Appendix B, Table 6a (pg. 95).

CHAPTER 5: RESULTS

5.1 Sample Characteristics

Demographic characteristics, anthropometric values, and CES-DC scores were summarized using means, standard deviations, and frequencies. Descriptive characteristics of the study population at baseline (n=244) are presented in Table 2. There were 125 girls and 119 boys with a mean age of 12.19 (2.314) years that participated and 77.6% of these had entered puberty. This group was markedly overweight with a mean BMI z-score of 2.21 (0.366) and 40.9% (4.97) body fat. The mean CES-DC score was 13.15 (9.176). Of the 242 who completed the CES-DC, 87 (36.0%) had a score ≥ 15 and 8 participants were on antidepressants. Together, 88 (36.4%) participants were classified as depressed. Only 1 of the 8 participants on antidepressants had a CES-DC score < 15.

Table 2: Baseline characteristics of sample population.

Characteristic	Sample Population	
	N	Statistic
Participants, n	244	--
Age in years, mean (SD)	244	12.19 (2.314)
Sex, n (%)	244	
Male		119 (48.8)
Female		125 (51.2)
Pubertal Development, n (%)	228	
Tanner I		51 (22.4)
Tanner II		72 (31.6)
Tanner III		50 (21.9)
Tanner IV		27 (11.8)
Tanner V		28 (12.3)
Household Income, n (%)	234	
$0 – 14,999		12 (5.1)
$15,000 – 29,999		29 (12.4)
$30,000 – 49,999		37 (15.8)
$50,000 – 69,999		43 (18.4)
$70,000 – 99,999		49 (20.9)
$100,000 and above		64 (27.4)
Family History of Depression, n (%)	244	
Yes		51 (20.9)
No		193 (79.1)
Weight in kilograms, mean (SD)	244	77.13 (21.401)
Height in centimeters, mean (SD)	244	156.51 (11.817)
BMI in kg/m^2, mean (SD)	244	30.97 (5.466)
BMI z-score, mean (SD)	244	2.21 (0.366)
Percent body fat, mean (SD)	242	40.91 (4.968)
CES-DC score, mean (SD)	242	13.15 (9.176)
Antidepressant medication use, n (%)	244	
Yes		8 (3.3)
No		236 (96.7)

5.2 Objective #1

To examine potential determinants (age, sex, pubertal development, extent of obesity, parental education, household income, family history of depression) of depression and depressive symptoms in obese children and youth presenting for a weight management program.

Age, sex and pubertal development were comparable between both the depressed and non-depressed participant groups (Table 3). No differences in extent of obesity, measured as either BMI z-score or % body fat, were apparent between those with and without depression. However, household income was lower in the children and youth with depression ($p = 0.01$). Family history of depression was common in both groups (20.5% in depressed, 20.8% in non-depressed). Missing data is presented in Appendix B, Table 1 (pg. 92). In general, there was very little missing data. The most common missing variables were pubertal development (6.6%) and household income (4.1%).

After adjusting for age and sex and using univariate correlation analyses, the correlation between % body fat and the CES-DC depression score neared significance ($r=0.129$, $p=0.059$) whereas BMI z-score was not significantly related (Table 4).

Table 3: Baseline characteristics of obese children and adolescents categorized by depressed versus not depressed.

N = 242	**Not depressed**		**Depressed**		**p-value**
	N	**Statistic**	**N**	**Statistic**	*p<0.05
Participants, n	154		88		--
Age in years, mean (SD)	154	12.31 (2.236)	88	12.06 (2.424)	0.42
Female	82	53.2%	42	47.7%	0.43
Pubertal Development (stage ≥ 2)	120	81.6%	57	70.4%	0.08
Household income ≥ $50K	***107***	***72.8%***	***48***	***56.5%***	***0.01****
Family history of depression	32	20.8%	18	20.5%	>0.99
CES-DC score, mean (SD)	***154***	***7.59 (4.034)***	***88***	***22.88 (7.367)***	***<0.001****
Weight in kilograms, mean (SD)	154	77.33 (20.336)	88	76.95 (23.242)	0.89
Height in centimeters, mean (SD)	154	157.02 (11.730)	88	155.63 (11.803)	0.38
BMI in kg/m^2, mean (SD)	154	30.87 (5.062)	88	31.22 (6.158)	0.64
BMI z-score, mean (SD)	154	2.21 (0.334)	88	2.22 (0.422)	0.86
Percent body fat, mean (SD)	154	40.56 (4.920)	86	41.62 (5.037)	0.11

Table 4: Correlation coefficients for sample population adjusted for age and sex.

		Income	Pubertal stage	Weight	Height	BMI	% body fat	BMI z-score	CES-DC	Family history
Income	**r**		-.062	-.002	.121	-.117	-.041	-.081	-.128	.060
	p		.368	.978	.077	.087	.545	.240	.061	.383
Pubertal stage	**r**			***.148***	.111	.093	-.063	.108	-.034	-.020
	p			***.031****	.105	.175	.361	.113	.615	.775
Weight	**r**				***.546***	***.842***	***.507***	***.748***	.060	-.100
	p				***.000****	***.000****	***.000****	***.000****	.380	.145
Height	**r**					.034	-.014	-.046	-.037	.037
	p					.615	.836	.505	.592	.585
BMI	**r**						***.633***	***.935***	.090	***-.146***
	p						***.000****	***.000****	.187	***.032****
% body fat	**r**							***.580***	.129	-.038
	p							***.000****	.059	.577
BMI z-score	**r**								.071	***-.145***
	p								.301	***.034****
CES-DC	**r**									-.028
	p									.688
Family history	**r**									
	p									

df = 213; r = correlation coefficient; p = p-value; *p<0.05

BMI z-score and % body fat, as well as pubertal stage and age were moderately correlated to each other and therefore, the potential of multicollinearity could occur. However, multicollinearity was not a concern in these multivariate regression analyses as the highest VIF value was 2.427 and the lowest tolerance value was 0.412 (Appendix B, Table 3, pg. 92). Therefore, BMI z-score and % body fat, as well as pubertal stage and age were included in the same regression model.

Using multivariate logistic regression, increased household income was associated with lower risk of depression (OR 0.77 [95%CI 0.637, 0.929]; p=0.007). In addition, extent of obesity measured by % body fat but not BMI z-score, was weakly associated with increased risk of depression (OR 1.08 [95%CI 0.999, 1.169]; p=0.05). The other variables did not have a significant association with depression (Table 5). The results from this objective have been recently published (Morrison, Shin, Tarnopolsky, & Taylor, 2015).

Table 5: Multivariate Logistic Regression for predictors of depression.

N = 217	**Odds Ratio (OR)**	**95% CI of OR**		**p-value**
		Lower	**Upper**	
Age	1.012	0.838	1.224	0.898
Sex	0.821	0.433	1.560	0.548
Pubertal Development	0.813	0.570	1.158	0.251
Household income	***0.769***	***0.637***	***0.929***	***0.007****
BMI z-score	0.658	0.218	1.984	0.457
Percent body fat	***1.080***	***0.999***	***1.169***	***0.054****
Family history of depression	0.912	0.440	1.892	0.805

Analyses were re-run excluding those taking antidepressants because these medications can affect physical measures such as extent of obesity. While those taking antidepressant medication tended to be older with a mean age of 14.5 (1.82) years than

those not taking antidepressants, univariate analysis revealed a significant difference in pubertal development in those not depressed and depressed excluding antidepressants (p=0.035, Appendix C, Table 1, pg. 98). In multivariate regression analysis, household income continued to be a significant predictor of depression but % body fat became insignificant (p=0.062; Appendix C, Table 4, pg. 101).

5.3 Objective #2

To compare inflammatory markers – IL-6, TNFα, CRP, IL-10 – leptin, and BDNF in obese youth with high depressive symptoms to those without.

A total of 173 participants had biomarkers evaluated (Table 6). Appendix B, Table 2 (pg. 92) shows the participants with missing biomarker data and those whose levels were below the limit of detection. No differences were found between those with high depressive symptoms and those without in any of the measured biological markers (Table 7).

When analyses were re-run excluding participants taking antidepressants, no significant differences were found between the non-depressed and depressed groups excluding those on antidepressants (Appendix C, Table 2, pg. 99).

Table 6: Baseline characteristics of participants measured for biomarkers.

Characteristic	Sample Population	
	N	Statistic
Participants, n	173	--
Age in years, mean (SD)	173	12.23 (2.286)
Sex, n (%)	173	
Male		86 (49.7)
Female		87 (50.3)
Pubertal Development, n (%)	160	
Tanner I		32 (20.0)
Tanner II		57 (35.6)
Tanner III		35 (21.9)
Tanner IV		18 (11.3)
Tanner V		18 (11.3)
Household Income, n (%)	165	
$0 – 14,999		7 (4.2)
$15,000 – 29,999		18 (10.9)
$30,000 – 49,999		28 (17.0)
$50,000 – 69,999		30 (18.2)
$70,000 – 99,999		33 (20.0)
$100,000 and above		49 (29.7)
Family History of Depression, n (%)	173	
Yes		32 (18.5)
No		141 (81.5)
Weight in kilograms, mean (SD)	173	75.96 (20.910)
Height in centimeters, mean (SD)	173	156.35 (11.427)
BMI in kg/m^2, mean (SD)	173	30.60 (5.433)
BMI z-score, mean (SD)	173	2.17 (0.386)
Percent body fat, mean (SD)	173	40.55 (5.051)
CES-DC score, mean (SD)	172	13.24 (9.223)
Antidepressant medication use, n (%)	173	
Yes		5 (2.9)
No		168 (97.1)
TNFα in pg/mL, median (IQR)	173	11.3 (3.1)
IL-6 in pg/mL, median (IQR)	173	1.2 (1.9)
CRP in mg/L, median (IQR)	173	1.91 (2.815)
IL-10 in pg/mL, median (IQR)	126	0.92 (0.955)
Leptin in ng/mL, median (IQR)	173	36.46 (35.641)
BDNF in ng/mL, mean (SD)	123	23.79 (8.564)

IQR = interquartile range

Table 7: Comparison of participants measured for biomarkers categorized by depressed versus not depressed.

	Not depressed	Depressed	p-value
Participants, n	110	62	--
TNFα in pg/mL, median (IQR)	11.4 (3.1)	11.1 (3.3)	0.45
IL-6 in pg/mL, median (IQR)	1.2 (1.93)	2.4 (1.8)	0.52
CRP in mg/L, median (IQR)	1.84 (2.568)	1.91 (4.168)	0.17
IL-10 in pg/mL, median (IQR)	1.04 (1.086)	0.74 (0.744)	0.24
Leptin in ng/mL, median (IQR)	34.50 (34.143)	40.98 (37.075)	0.13
BDNF in ng/mL, mean (SD)	23.53 (9.177)	24.11 (7.501)	0.72

IQR = interquartile range; *p<0.05

5.4 Objective #3

To examine the contribution of low-grade inflammation, leptin, and BDNF to depressive symptoms in obese children and youth.

Univariate correlation analysis revealed significant correlations between inflammatory markers, IL-6 and IL-10 (r=0.209, p=0.031), IL-6 and CRP (r=0.329, p<0.001), and CRP and IL-10 (r=0.240, p=0.013). Furthermore, adiposity was significantly related to IL-6, CRP, and leptin (Table 8). Only leptin was significantly related to CES-DC (r=0.238, p=0.014) while TNFα neared significance (p=0.057). An inverse relationship was found between BDNF and CRP (r=-0.205, p=0.035) but no other biomarkers. We did not find a relationship between leptin and any of the other measured biomarkers.

Table 8: Correlation coefficients of participants measured for biomarkers adjusted for age and sex.

		Income	Pubertal stage	% body fat	BMI z-score	CES-DC	Family history	TNFα	IL-6	CRP	IL-10	Leptin	BDNF
Income	**r**		-.155	-.129	-.096	-.127	*.214*	.125	-.070	-.050	.099	*-.194*	.156
	p		.112	.187	.328	.195	*.028**	.200	.474	.612	.313	*.046**	.111
Pubertal stage	**r**			-.035	.128	.109	-.085	*-.290*	-.046	.116	.020	-.076	-.072
	p			.723	.193	.265	.385	*.003**	.640	.235	.838	.441	.464
% body fat	**r**				*.426*	*.197*	-.142	-.043	*.204*	*.312*	.039	*.422*	-.161
	p				*.000**	*.043**	.147	.664	*.036**	*.001**	.692	*.000**	.100
BMI z-score	**r**					.165	*-.196*	-.086	.038	*.227*	.133	*.417*	-.150
	p					.090	*.045**	.382	.702	*.019**	.175	*.000**	.125
CES-DC	**r**						-.056	-.185	.132	.080	-.034	*.238*	-.023
	p						.571	.057	.177	.414	.727	*.014**	.814
Family history	**r**							-.062	-.186	-.152	.038	*-.263*	*.253*
	p							.527	.056	.120	.701	*.007**	*.009**
TNFα	**r**								.181	-.101	.087	-.029	.190
	p								.063	.304	.377	.771	.051
IL-6	**r**									*.329*	*.209*	.089	.063
	p									*.001**	*.031**	.367	.524
CRP	**r**										*.240*	.013	*-.205*
	p										*.013**	.893	*.035**
IL-10	**r**											.136	-.087
	p											.163	.373
Leptin	**r**												-.081
	p												.408

Log-transformed CRP, IL-6, TNFα, IL-10, leptin. df = 104; r = Pearson correlation coefficient; p = p-value; *p<0.05

Based on findings in univariate analysis, TNFα and leptin were the only measured biomarkers that were related to depressive symptoms. Therefore, we tested whether both of these would be independently related to depressive symptoms measured by the CES-DC following the order of entry of predictors listed in Table 1a. Multicollinearity was not a concern in these multivariate regression analyses (VIF < 2.8; tolerance > 0.36; Appendix B, Table 4, pg. 93). We found that although age was significant (p=0.045) in Model 1, it became insignificant once % body fat was added (p=0.064). Once leptin was added to the model, it had a significant influence on CES-DC score where with every unit increase in leptin, there was a 0.072 unit increase in CES-DC score (p=0.030; Table 9a) and this was independent of body fat (Appendix B, Table 5, pg. 94). However, TNFα was not significantly related to CES-DC score independent of socio-demographic factors or physical measures (p=0.277, Table 9b). Although inflammatory markers – IL-6, CRP, IL-10 – were not significantly related to depressive symptoms, they did have significant interactions with each other and with TNFα. Therefore, we tested whether TNFα, IL-6, CRP, and IL-10 were independently related to the CES-DC score but none of the inflammatory markers were independently related to depressive symptoms (Appendix B, Table 6b, pg. 96).

When excluding those taking antidepressant medication, the correlation between TNFα and CES-DC became significant (Appendix C, Table 3, pg. 100) but in multivariate regression analyses leptin was still significantly related to depressive symptoms whereas TNFα was not (Appendix C, Table 5a-d, pg. 102-105).

Table 9a: Multivariate analysis of leptin on depressive symptoms in obese children and adolescents.

	N	Unstd β	SE	Std β	95% CI		Adj R^2	ΔR^2	p-value
					Lower	Upper			
Model 1	153						0.029		0.098
Constant		27.456	5.133		17.313	37.599			0.000
Age*		***-1.003***	***0.496***	***-0.248***	***-1.982***	***-0.023***			***0.045****
Sex		0.142	1.590	0.008	-3.000	3.285			0.929
Puberty		0.579	0.947	0.079	-1.293	2.451			0.542
Income		-0.902	0.496	-0.150	-1.881	0.077			0.071
Family history		-0.805	1.901	-0.034	-4.563	2.952			0.672
Model 2	153						0.046	0.023	0.057
Constant		14.781	8.346		-1.714	31.276			0.079
Age		-0.921	0.493	-0.228	-1.895	0.053			0.064
Sex		-0.572	1.619	-0.031	-3.773	2.628			0.724
Puberty		0.621	0.939	0.084	-1.234	2.477			0.509
Income		-0.886	0.491	-0.148	-1.857	0.084			0.073
Family history		-0.595	1.887	-0.025	-4.325	3.136			0.753
% body fat		0.290	0.152	0.158	-0.009	0.590			0.057
Model 3	153						0.070	0.029	***0.030***
Constant		21.064	8.726		3.818	38.309			0.017
Age*		***-1.022***	***0.489***	***-0.253***	***-1.988***	***-0.056***			***0.038****
Sex		-0.611	1.599	-0.033	-3.771	2.549			0.703
Puberty		0.534	0.928	0.072	-1.300	2.368			0.566
Income		-0.728	0.490	-0.121	-1.697	0.241			0.140
Family history		-0.441	1.865	-0.019	-4.126	3.245			0.814
% body fat		0.081	0.178	0.044	-0.270	0.432			0.648
Leptin*		***0.072***	***0.033***	***0.209***	***0.007***	***0.136***			***0.030****

Table 9b: Multivariate analysis of the influence of TNFα on depressive symptoms in obese children and adolescents.

	N	Unstd β	SE	Std β	95% CI		Adj R^2	ΔR^2	p-value
					Lower	Upper			
Model 1	153						0.029		0.098
Constant		27.456	5.133		17.313	37.599			0.000
Age*		***-1.003***	***0.496***	***-0.248***	***-1.982***	***-0.023***			***0.045****
Sex		0.142	1.590	0.008	-3.000	3.285			0.929
Puberty		0.579	0.947	0.079	-1.293	2.451			0.542
Income		-0.902	0.496	-0.150	-1.881	0.077			0.071
Family history		-0.805	1.901	-0.034	-4.563	2.952			0.672
Model 2	153						0.046	0.023	0.057
Constant		14.781	8.346		-1.714	31.276			0.079
Age		-0.921	0.493	-0.228	-1.895	0.053			0.064
Sex		-0.572	1.619	-0.031	-3.773	2.628			0.724
Puberty		0.621	0.939	0.084	-1.234	2.477			0.509
Income		-0.886	0.491	-0.148	-1.857	0.084			0.073
Family history		-0.595	1.887	-0.025	-4.325	3.136			0.753
% body fat		0.290	0.152	0.158	-0.009	0.590			0.057
Model 3	153						0.047	0.007	0.277
Constant		18.251	8.925		0.610	35.892			0.043
Age		-0.870	0.495	-0.215	-1.848	0.108			0.081
Sex		-0.616	1.619	-0.034	-3.815	2.584			0.704
Puberty		0.386	0.963	0.052	-1.517	2.289			0.689
Income		-0.870	0.491	-0.145	-1.841	0.100			0.078
Family history		-0.809	1.896	-0.034	-4.557	2.939			0.670
% body fat		0.293	0.151	0.160	-0.006	0.593			0.055
TNFα		-0.306	0.280	-0.091	-0.860	0.248			0.277

CHAPTER 6: DISCUSSION

Given the relatively high prevalence of depressive disorders in treatment-seeking youth than in the general obese population (Britz, et al., 2000), it is important to identify determinants of depressive symptoms in obese children and adolescents. While a number of socio-demographic factors have been associated with depression, the influence of these factors along with potential biological determinants has not been studied. To our knowledge, we have for the first time, identified potential determinants of depressive symptoms in children and adolescents entering into a weight management program.

6.1 Objective #1

Population-based studies have reported the prevalence of depression in obese youth to range from 8% to 10% (Goodman & Must, 2011; Goodman & Whitaker, 2002). However in our study, we found a prevalence of 36.1% similar to that reported in clinic-based studies (Zeller & Modi, 2006; Zeller, Modi, Noll, Long JD, & Inge, 2009). These studies tend to have higher prevalence rates of depressive symptoms than population-based studies due to methodological differences (Britz, et al., 2000) but also because children and adolescents referred to weight management clinics report more externalizing and internalizing problems than their non-referred obese counterparts (Erermis, Cetin, Tamar, Bukusoglu, Akdeniz, & Goksen, 2004). However, rates of high depressive symptoms have varied even within the clinic population with reported ranges from 4% to 33% (Erermis, Cetin, Tamar, Bukusoglu, Akdeniz, & Goksen, 2004; Van Vlierberghe, Braet, Goossens, & Mels, 2009). In a clinic population, Zeller and Modi (2006) found a prevalence of 11% in 166 obese youth aged 8 to 18 years using a conservative cutoff CDI

score of 20 typically recommended for population data. However, when using the recommended cutoff for clinic samples, a prevalence of 34% was found in their sample (Kovacs, 1992). This study illustrates the challenge of comparing studies that use different measures of depressive symptoms and cutoffs. This partly explains the wide range of depression rates in clinic obese youth that report prevalence rates using the CES-DC ranging from 12.1% to 53% but study populations mainly include large adolescent communities or intervention studies for adolescents mothers (supplementary information found in Appendix D, Table 3, pg. 111) (Brown, Harris, Woods, Buman, & Cox, 2012; Bettge, Wille, Barkmann, Schulte-Markwort, Ravens-Sieberer, & BELLA study group, 2008; Hudson, Elek, & Campbell-Grossman, 2000; Olsson G. , Nordstrom, Arinell, & von Knorring, 1999). Nevertheless, although there is a wide range of rates of depression in obese youth, our rate of 36.1% is similar to what has been reported in other clinic-based studies.

When examining potential socio-demographic and physical measure determinants of depression, we showed that % body fat and household income were the most important socio-demographic predictors of depressive symptoms. Whereas previous studies have reported an association between depressive symptoms and BMI and/or BMI z-scores (Goodman & Whitaker, 2002; Pine, Goldstein, Wolk, & Weissman, 2001; Richardson, Garrison, Drangsholt, Manci, & LeResche, 2006), we found that body fat related more closely to depressive symptoms than BMI. One other paper has examined body composition and depression in youth. In a cohort of 11 to 17 year-olds, Hillman *et al.* (2010) found an association between depressive symptoms and body fat but not with BMI

z-scores. Unlike other studies (Goodman & Whitaker, 2002; Richardson, Garrison, Drangsholt, Manci, & LeResche, 2006), we used measured height and weight as opposed to self-reported measures to calculate BMI and we used a validated depression screening tool to quantify depressive symptoms. As our population evaluated obese children and adolescents, a narrower range of BMI z-scores may have contributed to the lack of association to depressive symptoms (Riazi, Shakoor, Dundas, Eiser, & McKenzie, 2010) but it should also be noted that BMI fails to distinguish between fat mass and lean mass. This may become problematic because the contributions of fat and lean mass to body weight vary depending on age, sex, and puberty among other factors (Weber, Moore, Leonard, & Zemel, 2013). Comorbidities associated with obesity such as cardiovascular disease are related to the excess amount of fat rather than body weight (Dencker, Wollmer, Karlsson, Linden, Andersen, & Thorsson, 2012) and therefore, the lack of association between BMI and depressive symptoms may indicate that it is not necessarily body size but the degree of adiposity that predicts depressive symptoms in these children and adolescents.

Our findings confirmed that household income is an important predictor of depressive symptoms in our population. SES has been associated with depression where individuals living in poorer neighbourhoods have an increased risk of depression than those living in wealthier communities (Lorant, Deliege, Eaton, Robert, Philippot, & Ansseau, 2003). A lack of family support and social achievement or stressful life events in lower income families could affect the mental development during childhood and through adolescence and therefore, contribute to the higher risk of depression in this

population (Page, et al., 2014; Luby, et al., 2013). Studies have also shown that children from lower income backgrounds have smaller hippocampal grey matter while poverty has been associated with smaller hippocampal and amygdala volumes (Luby, et al., 2013; Hanson, Chandra, Wolfe, & Pollak, 2011). These brain regions have been associated with depression and go through developmental changes during adolescence (Yurgelun-Todd, Killgore, & Cintron, 2003; Rosso, Cintron, Steingard, Renshaw, Young, & Yurgelun-Todd, 2005). Therefore, the environment in which children from lower income families develop in may predispose them to a higher risk of depression. Our study and others emphasize that socio-demographic factors such as SES, be included as potential determinants of depression (Yackobovitch-Gavan, Meshy-Tamir, Nagelberg, Phillip, & Meyerovitch, 2014).

In contrast to previous studies, we identified no association between depression and sex, age, or pubertal status. In population-based studies, rates of depression tend to be similar in girls and boys before adolescence but after the onset of puberty, the prevalence of depression shifts to 2:1 girls to boys ratio (Cyranowski, Frank, Young, & Shear, 2000; Kessler, 2003; Brooks, Harris, Thrall, & Woods, 2002). This indicates that puberty may have a role in the risk of depression but whether this is linked to hormonal changes or morphological changes related to puberty is unclear (Angold, Costello, Erkanli, & Worthman, 1999; Lokuge, Frey, Foster, Soares, & Steiner, 2011; Joinson, et al., 2012). It is also possible that in obese children, males are not as protected as in lean males and therefore, sex or puberty were not identified as determinants of depression in our sample. However, very few studies have assessed multiple predictors simultaneously and their

association with depressive symptoms but when examining them simultaneously, sex, age, or pubertal status may not be as important predictors as body fat and household income in the obese adolescent population.

6.2 Objective #2

Although several studies have measured inflammatory markers in obese and depressed youth, to our knowledge, no study has measured inflammatory markers in obese children and adolescents and its relationship with depressive symptoms. The levels of inflammatory markers found in our study were comparable to those reported in previous studies. We report TNFα levels of 11.1pg/mL that were comparable to previously reported levels amongst depressed and obese children and adolescents (Brambilla, Monteleone, & Maj, 2004; Gabbay, et al., 2009; Henje Blom, Lekander, Ingvar, Asberg, Mobarrez, & Serlachius, 2012). Similarly, IL-6 levels were found to be within the range seen in previous literature ranging from 1.3 to 2.1pg/mL (Gabbay, et al., 2009; Henje Blom, Lekander, Ingvar, Asberg, Mobarrez, & Serlachius, 2012). However, CRP levels of 1.91mg/L were higher in our study than Hood *et al.* (2012) who reported levels ranging between 0.3 and 0.5 mg/L in depressed children and adolescents with diabetes but slightly lower than levels reported in studies in obese children and adolescents (Stoppa-Vaucher, et al., 2012; Utsal, et al., 2012; Martos-Moreno, Barrios, Martinez, Hawkins, & Argente, 2010; Many, et al., 2013). In addition, we found a median of 0.74pg/mL of IL-10 levels that were on the lower range of previous findings reporting ranges from 0.6pg/mL to 11.4pg/mL in obese children and adolescents (Calcaterra , et al., 2009; Chang, et al., 2013; Tam, et al., 2010; Schipper, et al., 2012). Very few studies

have measured IL-10 levels as well as other 'anti-inflammatory' markers in obese depressed children and adolescents. However, Henje Blom *et al.* (2012) reported mean IL-10 levels of 1.4pg/mL in adolescent girls diagnosed with an anxiety disorder or major depressive disorder.

Inflammation in obese children and adolescents with depression has not been studied but reports have identified that youth suffering from depression or obesity have higher circulating levels of TNFα, IL-6, and CRP and lower IL-10 levels than their non-depressed and lean counterparts (Henje Blom, Lekander, Ingvar, Asberg, Mobarrez, & Serlachius, 2012; Stoppa-Vaucher, et al., 2012). However, we did not find significant median differences of any of these inflammatory markers between depressed and non-depressed groups in our study. Several studies have found similar findings as ours suggesting that differences in methodologies such as immunoassays as well as depression measures may contribute to conflicting findings (Benson, et al., 2008; Olszanecka-Glinianowicz, et al., 2009). In depressed obese adults, some studies have found higher inflammatory markers (or lower in the case of IL-10) than their non-depressed obese counterparts while others have not (Vetter, et al., 2013; Schmidt, et al., 2014). While potential confounders or other determinants could mask the effects of inflammatory markers on depressive symptoms which was further examined in objective 3, a narrower range of body fat could lessen the impact of inflammation on depressive symptoms. Furthermore, the heightened inflammation reported in the depressed obese may not manifest until adulthood explaining no differences found in our pediatric population.

Few studies have focused on circulating levels of BDNF in children and adolescents; two studies have reported a wide range of circulating levels from 57.7ng/mL to 39.8 ng/dl in obese youth (El-Gharbawy, Mirch, Theim, Ranzenhofer, Tanofsky-Kraff, & Yanovski, 2006; Corripio, et al., 2012). Our levels aligned more so with mean BDNF levels reported by Roth *et al.* (2013) of 19.0ng/mL. Levels of circulating BDNF have not been consistent in children and adolescents with obesity compared to their normal weight counterparts and so to infer whether our results are within normal ranges of current literature is premature and further studies reporting levels in both depressed and obese youth are needed.

6.3 Objective #3

Our third objective was to examine the relationship of low-grade inflammation, leptin, and BDNF to depressive symptoms in obese children and adolescents. We found that leptin was an important correlate of depression in our sample where for every unit increase in leptin, there was a 0.072 unit increase in CES-DC score.

Prior to statistical analysis, we proposed a model to explain the relationship of adiposity and depression. We also proposed potential pathways in which inflammation, leptin and BDNF could be mediating the association (Figure 2). Through correlation analyses, we confirmed there was a direct relationship between adiposity and depressive symptoms. IL-6 was related to adiposity but more so with % body fat than BMI z-score while CRP and leptin were related to both % body fat and BMI z-score. Unexpectedly, only leptin had a significant direct relationship with depressive symptoms while TNFα was weakly related. Surprisingly, no relation of BDNF to adiposity or depressive

symptoms was identified although previous reports suggested that BDNF was involved in depression in adults (Terracciano, et al., 2011; Bocchio-Chiavetto, et al., 2010; Piccinni, et al., 2008). Therefore in our population, univariate correlation analyses showed that although inflammatory markers and leptin were directly related to adiposity, only leptin and possibly TNFα could potentially directly mediate the relationship of depressive symptoms and obesity.

The direct relationship proposed in our model of IL-6 with CRP was confirmed but the relationship of TNFα and other inflammatory markers was not evident. Under normal conditions, IL-6 acts to increase IL-10 production to restore balance, but we proposed that a disruption in this pathway occurs to explain the lower levels of IL-10 reported in obese and depressed individuals (Meisel, Vogt, Platzer, Randow, Liebenthal, & Volk, 1996; Mesquita, et al., 2009; Dhabhar, et al., 2009). However, we found that there was a significant direct relationship between IL-6 and IL-10, suggesting that there is no disruption in the IL-6/IL-10 pathway. Furthermore, we did find a significant inverse relationship of BDNF with CRP confirming that BDNF levels are inversely related to inflammation.

We did not find significant relationships of inflammatory markers and depressive symptoms in univariate or multivariate analyses. In a systematic review of inflammation and depression in youth, Kim *et al.* (2014) found that while some studies reported an association between inflammation and depression, others did not and therefore, further studies are warranted. Our findings extend this literature by demonstrating no relationship between inflammatory markers and depressive symptoms in obese children and youth.

Although studies in depressed adults have reported elevated inflammatory markers measured in our study to be associated with depressed individuals (Hafner, et al., 2008; Miller, Carney, Freedland, & Banks, 2002; Eller, Vasar, Shlik, & Maron, 2008), others have not (Miller, Freedland, Carney, Stetler, & Banks, 2003; Chaiton, O'Loughlin, Karp, & Lambert, 2010). The association of inflammatory markers and depressive symptoms has been most consistently reported in animal studies where systemic or central administration of cytokines or cytokine-induced agents such as LPS in rodents has induced depressive-like behaviours (Capuron, et al., 2003; Reichenberg, Kraus, Haack, Schuld, Pollmacher, & Yirmiya, 2002; Dinel, et al., 2014). Although administration of cytokines and cytokine-induced agents has been reproduced in humans (Spath-Schwalbe, et al., 1998; Reichenberg, Kraus, Haack, Schuld, Pollmacher, & Yirmiya, 2002), other factors such as psychosocial factors not readily present in animals can also affect this association. However, the fact that we did not observe any significant relationships between inflammatory markers and depressive symptoms in obese youth suggests that this relationship has not manifested yet and may only be detected in older populations or this association is not seen in a narrower range of body fat. The role of inflammation in depression continues to be elucidated and therefore, further studies that examine inflammation and other psychosocial or socio-demographic factors are warranted to fully understand its role in depression and obesity.

Leptin was the most important determinant of depressive symptoms in our sample. It was also related to depressive symptoms independently of body fat signifying that leptin could be mediating the association between adiposity and depression similar to

previous studies (Pasco, et al., 2008; Lawson, et al., 2012) but not others (Milaneschi, Simonsick, Vogelzangs, Strotmeyer, Yaffe, & Harris, 2012).

Our findings are supported by animal studies. Several tests such as the forced swim test (FST) and tail suspension test have been devised and validated to model depressive symptoms in animals. Both of these tests subject animals to a stressful situation and consequently they develop a characteristic immobile posture, which is believed to mimic behavioural despair, an animal equivalent symptom of depression (Cyran, Mombereau, & Vassout, 2005). Mice that lack leptin (*ob/ob* mice) or its receptor (*db/db* mice) had increased behavioural despair in the FST (Sharma, Elased, Garrett, & Lucot, 2010; Yamada, Katsuura, Ochi, Ebihara, Kusakabe, & Hosoda, 2011) and systemic or central administration of leptin in normal mice has antidepressant effects measured by the tail suspension test, FST, and social interaction test. This is not seen, however in obese mice (Liu, Garza, Bronner, Kim, Zhang, & Lu, 2010; Yamada, Katsuura, Ochi, Ebihara, Kusakabe, & Hosoda, 2011). This could be explained by the theory of leptin resistance whereby high circulating leptin levels do not seem to affect food intake or energy expenditure in obese individuals. Yamada *et al.* (2011) show that impaired leptin action centrally could explain the association of high leptin levels with higher depressive symptoms in obese individuals.

However, human studies have reported conflicting findings. Several studies have shown that MDD patients have lower plasma leptin levels than healthy controls with similar BMIs, while other studies report increased leptin levels or no difference (Atmaca, Kuloglu, Tezcan, & Ustundag, 2008; Esel, Ozsoy, Tutus, Sofuoglu, Kartalci, & Bayram ,

2005; Jow, Yang, & Chen, 2006). However, many of these studies did not take adiposity into account in data analysis or were examined in normal weight individuals mainly measured by BMI and therefore, future research should account for adiposity.

In our model for this thesis, we proposed three different potential pathways that may help explain the relationship of adiposity and depression. Firstly, an imbalanced inflammatory milieu would contribute to adiposity and depression. Second, we proposed that leptin could potentially influence the association between depression and adiposity either directly or via inflammation or BDNF. Lastly, due to its suspected involvement with depression, it was proposed that BDNF would contribute to adiposity and depression through the actions of inflammation, leptin, or directly. Analyses did not find that an imbalanced inflammatory milieu or BDNF influenced depressive symptoms in obese youth entering into a weight management program. However, it may be leptin that has a direct influence on the relationship of adiposity and depression and is mediating this association independent of body fat (Figure 4). Therefore, when examining several socio-demographic and biological determinants of depression, leptin stands out as one of the important biological determinants to explain the relationship of adiposity and depression in children and adolescents.

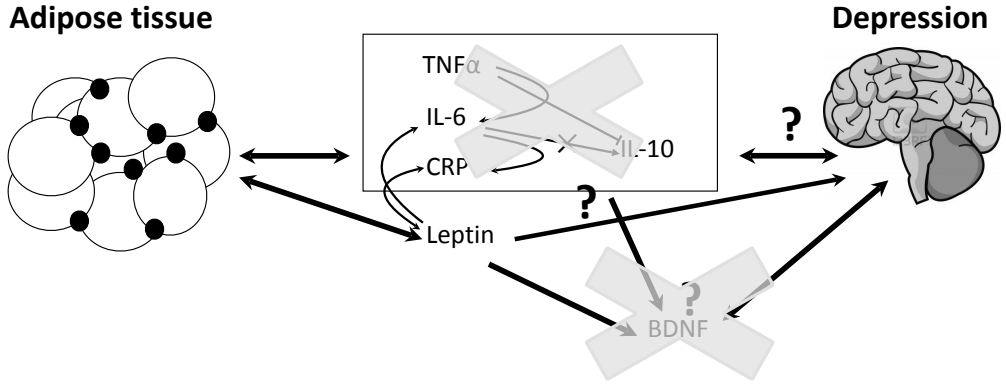

Figure 4: Results of proposed model based on statistical analyses.
It was found that an imbalanced inflammatory milieu nor BDNF contributed to adiposity and depression but leptin, independent of body fat, mediates the association between adiposity and depression in children and adolescents entering into a weight management program.

6.4 Limitations

The cross-sectional analysis of this project does not allow us to determine causality of depression in this population and any significant factors found are only potential determinants of depression. However, as the DECCO study is a longitudinal study, we will be able to evaluate the influence of these factors in future analyses. In addition, the study population is from the clinical population of children and adolescents seeking obesity treatment. Therefore, we cannot extend these results to the general population of children and youth with obesity or even a wider range of BMI or % body fat but these youth tend to have more behavioural problems than obese youth in the community. Lastly, our classification of high depressive symptoms used a depression screening tool, the CES-DC questionnaire. The CES-DC can only assess depressive

symptoms and is not a diagnostic tool for clinical depression but it is able to identify children and adolescents at risk of clinical depression.

6.5 Conclusions and Future Directions

This study demonstrated that a higher prevalence of depression is seen in obese youth compared to population-based studies. Household income and body fat were important determinants of depressive symptoms in this population while leptin was also a significant predictor even after consideration of other potential predictors. This finding is very exciting as it suggests that leptin may mediate the relationship of adiposity and depression although future studies are required to understand its implications.

In the future, longitudinal analysis of these determinants in the DECCO study is needed to examine if the identified predictors found in this thesis are able to predict depressive symptoms in follow-up visits. This analysis will ultimately identify factors that will help to improve depressive symptoms in obese children and adolescents. However, tracking these determinants over a longer period of time from childhood to adulthood would provide information about potential changes in determinants of depression in the obese population. Although this thesis provided insight into elucidating the relationship of depression and adiposity in the pediatric population, a more thorough understanding of this relationship is needed in order to identify determinants of depression that may assist clinicians in recognizing “at risk” youth.

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APPENDIX A: OBESITY DEFINITIONS

2007 WHO Growth References	2000 IOTF Reference Curves	2000 CDC Growth Curves
- 2006: WHO Child Growth Standards for preschool children based on multicentre study from 1997-2003 in Brazil, Ghana, India, Norway Oman, USA - 2007: Reconstructed historical datasets from NHES II (6-11y) and III (12-17y) and NHANES I (1-24y) to produce growth curves for school-aged children that closely align with WHO Child Growth Standards and adult cutoffs for overweight and obesity at 19y (BMI of 25 and 30, respectively) - Statistical methods and data from WHO Child Growth Standards used to smooth transition at age 5y - Result: percentile and z-score curves and tables ranging from 1^{st} to 99^{th} percentile and -3 to +3 SD by age and sex - Obese: BMI > 2SD or 97.7^{th} percentile - Overweight: 1SD or 84^{th} percentile <BMI<2SD or 97.7^{th} percentile	- 6 large nationally representative cross-sectional growth surveys from Brazil, Great Britain, Hong Kong, Netherlands, Singapore, USA - Curve-smoothing statistical techniques used to construct centile curves that pass through adult BMI cut-points for overweight and obesity ($25kg/m^2$, $30kg/m^2$, respectively) at age 18	- Cross-sectional survey data from 1963 to 1995 of US children and adolescents aged 2 to 20yo - As child approaches adolescence, percentiles approach BMI levels used for adult cut-points for overweight and obesity - 2007: obesity cutoff changed - Obese: BMI $\geq 95^{th}$ percentile for age and gender - Overweight: $85^{th} \leq$BMI$< 95^{th}$ percentile

APPENDIX B: RESULTS OF MISSING DATA & MULTIVARIATE ANALYSIS

Table 1: Missing data in sample population.

Variable	Total N	N missing (%)
Participants	244	--
Age	244	0 (0)
Gender	244	0 (0)
Pubertal development	228	16 (6.6)
Income	234	10 (4.1)
Weight	244	0 (0)
Height	244	0 (0)
BMI	244	0 (0)
BMI z-score	244	0 (0)
Percent body fat	242	2 (0.8)
Antidepressant use	244	0 (0)
Family history of depression	244	0 (0)
CES-DC score	242	2 (0.8)
Depression classification	242	2 (0.8)

Table 2: Missing data of biological markers.

Variable	Total N	N missing (%)	N undetectable (%)
Participants	173	--	--
TNFα	173	0 (0)	0 (0)
IL-6	173	0 (0)	93 (53.8)
CRP	173	0 (0)	8 (4.6)
Leptin	173	0 (0)	0 (0)
IL-10	126	47 (27.2)	24 (19.0)
BDNF	123	50 (28.9)	0 (0)

Table 3: Multicollinearity analysis for multivariate logistic regression in Objective 1.

N = 217	Tolerance	VIF
Age	0.450	2.220
Sex	0.832	1.201
Pubertal Development	0.412	2.427
Household income	0.982	1.018
BMI z-score	0.591	1.691
Percent body fat	0.604	1.655
Family history of depression	0.971	1.030

Appendix B, Table 4: Multicollinearity analysis for multivariate regression model in Objective 3.

Multivariate regression model of Leptin on Depressive symptoms			**Multivariate regression model of TNFα on Depressive symptoms**		
	Tolerance	**VIF**		**Tolerance**	**VIF**
Model 1			**Model 1**		
Age	0.425	2.354	Age	0.425	2.354
Sex	0.853	1.172	Sex	0.853	1.172
Puberty	0.387	2.585	Puberty	0.387	2.585
Income	0.937	1.067	Income	0.937	1.067
Family history	0.971	1.030	Family history	0.971	1.030
Model 2			**Model 2**		
Age	0.422	2.372	Age	0.422	2.372
Sex	0.808	1.238	Sex	0.808	1.238
Puberty	0.387	2.586	Puberty	0.387	2.586
Income	0.937	1.067	Income	0.937	1.067
Family history	0.968	1.033	Family history	0.968	1.033
% body fat	0.921	1.086	% body fat	0.921	1.086
Model 3			**Model 3**		
Age*	0.418	2.393	Age	0.418	2.394
Sex	0.808	1.238	Sex	0.807	1.238
Puberty	0.386	2.591	Puberty	0.367	2.722
Income	0.917	1.091	Income	0.936	1.068
Family history	0.966	1.035	Family history	0.957	1.044
% body fat	0.654	1.529	% body fat	0.921	1.086
Leptin	0.672	1.489	TNFα	0.911	1.097

Appendix B, Table 5: Multivariate analysis of leptin on depressive symptoms in obese children and adolescents independent of body fat.

	N	Unstd β	SE	Std β	95% CI		Adj R^2	ΔR^2	Tolerance	VIF	p-value
					Lower	Upper					
Model 1	153						0.029				0.098
Constant		27.456	5.133		17.313	37.599					0.000
Age*		***-1.003***	***0.496***	***-0.248***	***-1.982***	***-0.023***			0.425	2.354	***0.045****
Sex		0.142	1.590	0.008	-3.000	3.285			0.853	1.172	0.929
Puberty		0.579	0.947	0.079	-1.293	2.451			0.387	2.585	0.542
Income		-0.902	0.496	-0.150	-1.881	0.077			0.937	1.067	0.071
Family history		-0.805	1.901	-0.034	-4.563	2.952			0.971	1.030	0.672
Model 2	153						0.075	0.051			***0.004****
Constant		24.285	5.126		14.153	34.417					0.000
Age*		***-1.049***	***0.484***	***-0.260***	***-2.005***	***-0.093***			0.424	2.357	***0.032****
Sex		-0.474	1.566	-0.026	-3.568	2.621			0.838	1.194	0.763
Puberty		0.516	0.925	0.070	-1.311	2.343			0.387	2.586	0.578
Income		-0.713	0.488	-0.119	-1.677	0.251			0.921	1.086	0.146
Family history		-0.465	1.859	-0.020	-4.139	3.209			0.967	1.034	0.803
Leptin*		*0.080*	*0.027*	*0.232*	*0.025*	*0.134*			0.946	1.057	*0.004*
Model 3	153						0.070	0.001			0.648
Constant		21.064	8.726		3.818	38.309					0.017
Age*		***-1.022***	***0.489***	***-0.253***	***-1.988***	***-0.056***			0.418	2.393	***0.038****
Sex		-0.611	1.599	-0.033	-3.771	2.549			0.808	1.238	0.703
Puberty		0.534	0.928	0.072	-1.300	2.368			0.386	2.591	0.566
Income		-0.728	0.490	-0.121	-1.697	0.241			0.917	1.091	0.140
Family history		-0.441	1.865	-0.019	-4.126	3.245			0.966	1.035	0.814
Leptin*		***0.072***	***0.033***	***0.209***	***0.007***	***0.136***			0.672	1.489	***0.030****
% body fat		0.081	0.178	0.044	-0.270	0.432			0.654	1.529	0.648

Appendix B, Table 6a: Order of entry of predictors for hierarchical multivariate linear regression

Model 1	**Model 2**	**Model 3**
Age	Age	Age
Sex	Sex	Sex
Household income	Household income	Household income
Family history	Family history	Family history
Pubertal stage	Pubertal stage	Pubertal stage
--	% body fat	% body fat
--	--	TNFα IL-6 CRP IL-10

Appendix B, Table 6b: Multivariate analysis of inflammatory markers on depressive symptoms in obese youth.

	N	Unstd β	SE	Std β	95% CI		Adj R^2	ΔR^2	Tolerance	VIF	p-value
					Lower	Upper					
Model 1	111						0.020				0.216
Constant		27.897	6.393		15.220	40.573					0.000
Age*		***-1.287***	***0.601***	***-0.304***	***-2.479***	***-0.096***			0.441	2.265	***0.035****
Sex		1.108	1.951	0.057	-2.761	4.977			0.870	1.150	0.571
Puberty		1.184	1.156	0.151	-1.108	3.475			0.412	2.427	0.308
Income		-0.653	0.610	-0.106	-1.863	0.557			0.903	1.108	0.287
Family history		-0.764	2.463	-0.030	-5.648	4.119			0.924	1.082	0.757
Model 2	111						0.052	0.040			***0.034****
Constant		8.037	11.182		-14.137	30.211					0.474
Age		-1.114	0.596	-0.263	-2.297	0.069			0.433	2.308	0.065
Sex		-0.091	1.998	-0.005	-4.053	3.872			0.802	1.247	0.964
Puberty		1.367	1.140	0.174	-0.892	3.627			0.410	2.441	0.233
Income		-0.529	0.603	-0.086	-1.724	0.667			0.894	1.118	0.382
Family history		0.036	2.450	0.001	-4.823	4.895			0.903	1.108	0.988
% body fat*		***0.425***	***0.198***	***0.217***	***0.033***	***0.818***			0.846	1.182	***0.034****
Model 3	111						0.054	0.036			0.381
Constant		14.892	11.986		-8.887	38.671					0.217
Age		-1.071	0.606	-0.253	-2.274	0.132			0.418	2.390	0.080
Sex		0.188	2.033	0.010	-3.845	4.222			0.773	1.294	0.926
Puberty		1.141	1.193	0.145	-1.227	3.508			0.373	2.682	0.341
Income		-0.463	0.608	-0.075	-1.669	0.743			0.877	1.140	0.448
Family history		0.116	2.480	0.005	-4.803	5.036			0.879	1.137	0.963
% body fat		0.361	0.203	0.184	-0.042	0.764			0.802	1.246	0.079
TNFα		-0.554	0.339	-0.164	-1.226	0.118			0.852	1.174	0.105
IL-6		1.421	0.971	0.162	-0.506	3.349			0.703	1.422	0.147
CRP		-0.213	0.285	-0.078	-0.778	0.353			0.792	1.262	0.457
IL-10		-0.288	0.516	-0.055	-1.310	0.735			0.899	1.113	0.578

APPENDIX C: RESULTS OF ANTIDEPRESSANT MEDICATION DATA

Sample Characteristics: Analyses were re-run excluding those taking antidepressants because these medications can affect physical measures such as extent of obesity. Those that were taking antidepressant medication tended to be older with a mean age of 14.5 (1.82) years than those not taking antidepressants.

Objective 1: In addition to the significant difference in household income, when excluding participants on antidepressants, we found a significant difference in pubertal development in those not depressed and depressed excluding antidepressants (p=0.035, Appendix C, Table 1, pg. 75). Correlation analysis revealed that BMI z-score was significantly correlated with CES-DC (r=0.193; p=0.049) whereas other significant correlations found including all participants did not change (Appendix C, Table 3, pg. 77). In multivariate logistic regression analysis, household income continued to be a significant predictor of depression but % body fat became insignificant (p=0.062; Appendix C, Table 4, pg. 78).

Objective 2: No significant differences of biomarkers were found between the non-depressed and depressed groups much like when all participants were included in the analysis (Appendix C, Table 2, pg. 76).

Objective 3: When excluding those taking antidepressant medication, correlation analyses showed a significant correlation between TNFα and CES-DC (r = -0.193; p = 0.048) whereas BMI z-score and CRP as well as income and leptin became not significant (p=0.056; 0.052, respectively) (Appendix C, Table 3, pg. 77). Multivariate regression models showed that income in addition to age was significantly related to depressive symptoms (p=0.042) but became non-significant once leptin was added into the model (Appendix C, Table 5a,b, pg. 79-80). This was also seen when examining TNFα in the model but much like when analyzing all the data, TNFα did not independently predict depressive symptoms (Appendix C, Table 5c, pg. 81). Inflammatory markers – TNFα, IL-6, CRP, IL-10 – still did not significantly predict depressive symptoms even when excluding participants on antidepressants (Appendix C, Table 5d, pg. 82).

Appendix C, Table 1: Characteristics of obese youth categorized by depression classification and antidepressant medication use.

	All	Not Depressed[#]	Depressed		p-value
			Including antidepressants	Excluding antidepressants[#]	
Participants, n	244	154	88	80	--
Age in years, mean (SD)	*12.19 (2.314)*	12.31 (2.236)	12.06 (2.424)	11.82 (2.352)	0.117
Female, n (%)	125 (51.2%)	82 (53.2%)	42 (47.7%)	36 (45.0%)	0.271
Pubertal Development (stage ≥ 2), n (%)	177 (77.6%)	***120 (81.6%)***	57 (70.4%)	***52 (69.3%)***	***0.035****
Household income ≥ $50K, n (%)	156 (66.7%)	***107 (72.8%)***	48 (56.5%)	***44 (57.1%)***	***0.009****
Family history of depression, n (%)	51 (20.9%)	32 (20.8%)	18 (20.5%)	17 (21.3%)	>0.99
CES-DC score, mean (SD)	13.2 (9.18)	***7.59 (4.034)***	22.88 (7.367)	***23.26 (7.219)***	***<0.001****
Weight in kg, mean (SD)	77.13 (21.401)	77.33 (20.336)	76.95 (23.242)	75.83 (21.588)	0.601
Height in cm, mean (SD)	156.51 (11.817)	157.02 (11.730)	155.63 (11.803)	155.07 (11.629)	0.227
BMI in kg/m^2, mean (SD)	30.97 (5.466)	30.87 (5.062)	31.22 (6.158)	31.04 (5.773)	0.821
BMI z-score, mean (SD)	2.21 (0.366)	2.21 (0.334)	2.22 (0.422)	2.24 (0.385)	0.558
% body fat, mean (SD)	40.9 (4.968)	40.56 (4.920)	41.62 (5.037)	41.83 (4.835)	0.064

*$p<0.05$; [#]statistical tests were conducted between the Not Depressed and Depressed-Excluding Antidepressants groups.

Appendix C, Table 2: Comparison of obese children and adolescents with high depressive symptoms to those with consideration of participants taking antidepressant medication.

	All	Not Depressed	Depressed		p-value
			Including antidepressants	Excluding antidepressants	
Participants, n	173	110	62	57	--
TNFα in pg/mL	11.3 (3.1)	11.4 (3.1)	11.1 (3.3)	11.2 (3.2)	0.497
IL-6 in pg/mL	1.2 (1.9)	1.2 (1.925)	2.4 (1.8)	2.5 (1.85)	0.322
CRP in mg/L	1.91 (2.815)	1.84 (2.568)	1.91 (4.168)	1.92 (4.100)	0.125
IL-10 in pg/mL	0.92 (0.955)	1.04 (1.086)	0.74 (0.744)	0.74 (0.603)	0.312
Leptin in ng/mL	36.46 (35.641)	34.50 (34.143)	40.98 (37.075)	42.76 (31.356)	0.089
BDNF in ng/mL, mean (SD)	23.79 (8.564)	23.53 (9.177)	24.11 (7.501)	24.05 (7.491)	0.758

Data represented as median (IQR) unless otherwise indicated. *$p<0.05$; p-value represents the comparison of not depressed and depressed-excluding antidepressants groups.

Appendix C, Table 3: Correlation coefficients of obese youth excluding antidepressant medication adjusted for age and sex.

		Income	Pubertal stage	% body fat	BMI z-score	CES-DC	Family history	TNFα	IL-6	CRP	IL-10	Leptin	BDNF
Income	**r**		-.141	-.119	-.072	-.138	***.223***	.118	-.064	-.027	.095	-.190	.151
	p		.151	.225	.463	.159	***.022****	.230	.515	.783	.338	.052	.125
Pubertal stage	**r**			-.050	.097	.125	-.096	***-.283***	-.055	.088	.027	-.084	-.065
	p			.610	.327	.206	.332	***.003****	.574	.372	.782	.397	.512
% body fat	**r**				***.417***	***.208***	-.149	-.036	***.200***	***.299***	.044	***.420***	-.156
	p				***.000****	***.033****	.130	.718	***.041****	***.002****	.658	***.000****	.112
BMI z-score	**r**					***.193***	***-.216***	-.070	.025	.187	.148	***.419***	-.141
	p					***.049****	***.027****	.475	.804	.056	.132	***.000****	.151
CES-DC	**r**						-.050	***-.193***	.138	.102	-.039	***.243***	-.028
	p						.610	***.048****	.160	.302	.695	***.012****	.776
Family history	**r**							-.058	-.190	-.169	.041	***-.266***	***.273***
	p							.559	.052	.085	.680	***.006****	***.008****
TNFα	**r**								.186	-.087	.084	-.025	.186
	p								.057	.376	.397	.798	.057
IL-6	**r**									***.325***	***.212***	.086	.066
	p									***.001****	***.030****	.383	.504
CRP	**r**										***.256***	.004	***-.198***
	p										***.008****	.971	***.043****
IL-10	**r**											.139	-.090
	p											.158	.360
Leptin	**r**												-.079
	p												.424

Log-transformed CRP, IL-6, TNFα, IL-10, leptin. df = 103; r = Pearson correlation coefficient; p = p-value; *p<0.05. Shaded areas indicate changes in significance compared to analysis including all participants.

Appendix C, Table 4: Multivariate Logistic Regression for predictors of depression excluding participants on antidepressant medication.

N = 211	Odds Ratio (OR)	95% CI of OR		p-value
		Lower	Upper	
Age	0.974	0.802	1.184	0.792
Sex	0.760	0.390	1.483	0.421
Pubertal Development	0.820	0.568	1.185	0.291
Household income	**0.785**	**0.647**	**0.952**	**0.014***
BMI z-score	0.688	0.221	2.139	0.518
Percent body fat	1.080	0.996	1.171	0.062
Family history of depression	0.956	0.452	2.022	0.906

Shaded areas indicate changes in significance compared to analysis including all participants.

Appendix C, Table 5a: Multivariate analysis of leptin on depressive symptoms in participants not taking antidepressant medication. Shaded areas indicate changes in significance compared to analysis including all participants.

	N	Unstd β	SE	Std β	95% CI		Adj R^2	ΔR^2	p-value
					Lower	Upper			
Model 1	150						0.037		0.064
Constant		28.040	5.133		17.895	38.186			0.000
Age*		***-1.021***	***0.497***	***-0.252***	*-2.002*	*-0.039*			***0.042****
Sex		0.312	1.607	0.017	-2.865	3.489			0.847
Puberty		0.572	0.953	0.077	-1.312	2.456			0.550
Income*		***-1.021***	***0.497***	***-0.170***	***-2.004***	***-0.039***			***0.042****
Family history		-0.686	1.894	-0.030	-4.430	3.058			0.718
Model 2	150						0.050	0.019	0.086
Constant		16.473	8.413		-0.158	33.103			0.052
Age		-0.963	0.494	-0.238	-1.941	0.014			0.053
Sex		-0.459	1.657	-0.025	-3.735	2.817			0.782
Puberty		0.659	0.948	0.089	-1.215	2.534			0.488
Income*		***-1.002***	***0.494***	***-0.167***	***-1.978***	***-0.025***			***0.044****
Family history		-0.469	1.885	-0.020	-4.196	3.258			0.804
% body fat		0.267	0.155	0.145	-0.038	0.573			0.086
Model 3	150						0.072	0.027	***0.038***
Constant		22.194	8.754		4.890	39.498			0.012
Age*		***-1.061***	***0.491***	***-0.262***	***-2.031***	***-0.091***			***0.032****
Sex		-0.574	1.639	-0.031	-3.815	2.666			0.726
Puberty		0.607	0.937	0.082	-1.246	2.460			0.518
Income		-0.849	0.494	-0.141	-1.825	0.127			0.088
Family history		-0.319	1.865	-0.014	-4.006	3.367			0.864
% body fat		0.074	0.179	0.040	-0.280	0.427			0.680
Leptin*		***0.069***	***0.033***	***0.199***	***0.004***	***0.134***			***0.038****

Appendix C, Table 5b: Multivariate analysis of the influence of leptin on depressive symptoms independent of body fat in participants not taking antidepressants. Shaded areas indicate changes in significance compared to analysis including all participants.

	N	Unstd β	SE	Std β	95% CI		R^2	ΔR^2	p-value
					Lower	Upper			
Model 1	150						0.037		0.064
Constant		28.040	5.133		17.895	38.186			0.000
Age*		***-1.021***	***0.497***	***-0.252***	***-2.002***	***-0.039***			***0.042****
Sex		0.312	1.607	0.017	-2.865	3.489			0.847
Puberty		0.572	0.953	0.077	-1.312	2.456			0.550
Income*		***-1.021***	***0.497***	***-0.170***	***-2.004***	***-0.039***			***0.042****
Family history		-0.686	1.894	-0.030	-4.430	3.058			0.718
Model 2	150						0.077	0.045	***0.008***
Constant		25.115	5.139		14.956	35.273			0.000
Age*		***-1.082***	***0.487***	***-0.267***	***-2.044***	***-0.121***			***0.028****
Sex		-0.431	1.597	-0.024	-3.588	2.726			0.788
Puberty		0.584	0.933	0.079	-1.260	2.429			0.532
Income		-0.837	0.491	-0.139	-1.809	0.134			0.091
Family history		-0.348	1.858	-0.015	-4.021	3.325			0.852
Leptin*		***0.076***	***0.028***	***0.219***	***0.020***	***0.131***			***0.008****
Model 3	150						0.072	0.001	0.680
Constant		22.194	8.754		4.890	39.498			0.012
Age*		***-1.061***	***0.491***	***-0.262***	***-2.031***	***-0.091***			***0.032****
Sex		-0.574	1.639	-0.031	-3.815	2.666			0.726
Puberty		0.607	0.937	0.082	-1.246	2.460			0.518
Income		-0.849	0.494	-0.141	-1.825	0.127			0.088
Family history		-0.319	1.865	-0.014	-4.006	3.367			0.864
Leptin*		***0.069***	***0.033***	***0.199***	***0.004***	***0.134***			***0.038****
% body fat		0.074	0.179	0.040	-0.280	0.427			0.680

Appendix C, Table 5c: Multivariate analysis of the influence of TNFα on depressive symptoms in participants not taking antidepressant medication.

	N	Unstd β	SE	Std β	95% CI		Adj R^2	ΔR^2	p-value
					Lower	Upper			
Model 1	150						0.037		0.064
Constant		28.040	5.133		17.895	38.186			0.000
Age*		***-1.021***	***0.497***	***-0.252***	***-2.002***	***-0.039***			***0.042****
Sex		0.312	1.607	0.017	-2.865	3.489			0.847
Puberty		0.572	0.953	0.077	-1.312	2.456			0.550
Income*		***-1.021***	***0.497***	***-0.170***	***-2.004***	***-0.039***			***0.042****
Family history		-0.686	1.894	-0.030	-4.430	3.058			0.718
Model 2	150						0.050	0.019	0.086
Constant		16.473	8.413		-0.158	33.103			0.052
Age		-0.963	0.494	-0.238	-1.941	0.014			0.053
Sex		-0.459	1.657	-0.025	-3.735	2.817			0.782
Puberty		0.659	0.948	0.089	-1.215	2.534			0.488
Income*		***-1.002***	***0.494***	***-0.167***	***-1.978***	***-0.025***			***0.044****
Family history		-0.469	1.885	-0.020	-4.196	3.258			0.804
% body fat		0.267	0.155	0.145	-0.038	0.573			0.086
Model 3	150						0.052	0.009	0.248
Constant		20.143	8.980		2.392	37.894			0.026
Age		-0.907	0.496	-0.224	-1.888	0.074			0.070
Sex		-0.510	1.656	-0.028	-3.784	2.763			0.758
Puberty		0.417	0.970	0.056	-1.499	2.334			0.667
Income*		***-0.991***	***0.493***	***-0.165***	***-1.966***	***-0.015***			***0.047****
Family history		-0.700	1.894	-0.030	-4.443	3.044			0.712
% body fat		0.271	0.155	0.147	-0.035	0.576			0.082
TNFα		-0.324	0.280	-0.097	-0.878	0.229			0.248

Appendix C, Table 5d: Multivariate analysis of inflammatory markers on depressive symptoms in participants not on antidep.

	N	Unstd β	SE	Std β	95% CI		R^2	ΔR^2	p-value
					Lower	Upper			
Model 1	109						0.029		0.158
Constant		29.071	6.431		16.317	41.825			0.000
Age*		***-1.385***	***0.604***	***-0.325***	***-2.583***	***-0.186***			***0.024****
Sex		1.039	1.980	0.054	-2.888	4.967			0.601
Puberty		1.207	1.171	0.152	-1.116	3.530			0.305
Income		-0.715	0.612	-0.116	-1.929	0.499			0.246
Family history		-0.479	2.466	-0.019	-5.370	4.412			0.846
Model 2	109						0.061	0.039	***0.036****
Constant		8.984	11.352		-13.533	31.500			0.431
Age*		***-1.224***	***0.599***	***-0.287***	***-2.412***	***-0.036***			***0.044****
Sex		-0.350	2.053	-0.018	-4.423	3.723			0.865
Puberty		1.492	1.159	0.188	-0.808	3.791			0.201
Income		-0.608	0.604	-0.099	-1.806	0.589			0.316
Family history		0.375	2.458	0.015	-4.500	5.250			0.879
% body fat*		***0.432***	***0.203***	***0.220***	***0.030***	***0.835***			***0.036****
Model 3	109						0.064	0.038	0.366
Constant		15.464	12.100		-8.549	39.476			0.204
Age		-1.183	0.608	-0.278	-2.391	0.024			0.055
Sex		-0.104	2.083	-0.005	-4.237	4.029			0.960
Puberty		1.303	1.211	0.164	-1.100	3.707			0.284
Income		-0.549	0.608	-0.089	-1.756	0.659			0.369
Family history		0.524	2.488	0.021	-4.414	5.461			0.834
% body fat		0.371	0.207	0.189	-0.040	0.782			0.077
TNFα		-0.553	0.338	-0.164	-1.223	0.118			0.105
IL-6		1.496	0.971	0.171	-0.430	3.423			0.126
CRP		-0.203	0.284	-0.075	-0.767	0.360			0.476
IL-10		-0.280	0.515	-0.053	-1.303	0.742			0.587

APPENDIX D: ADDITIONAL INFORMATION

Table 1: Prevalence rates of depression in population-based studies

Citation	Methods	Age	Sample size	Prevalence of Depression
(Goodman & Whitaker, 2002)	***Participants:*** Add Health (USA) ***Depression:*** CES-D; cutoff = 24 (females); 22 (males) ***Obesity:*** Self-report BMI% and z-scores (2000 CDC)	< 20y	9374	→ 8.2% (obese) → 8.9% (non-obese)
(McIntyre, Konarski, Wilkins, Soczynska, & Kennedy, 2006)	***Participants:*** 2002 CCHS 1.2 (Canada) ***Depression:*** World Mental Health Composite International Diagnostic Interview (WMH-CIDI) – "Mood Disorder (lifetime prevalence)" ***Obesity:*** Self-report BMI (WHO guidelines)	≥ 15y	36,984	→ 9.2% (15-29y; obese class I-III)
(Goodman & Must, 2011)	***Participants:*** 2001-2002 school-based longitudinal cohort study ***Depression:*** CES-D; cutoff = 24 (females); 22 (males) ***Obesity:*** Measured BMI% and z-scores (2000 CDC)	12.8-18.7y	102 (51 severely obese)	→ 9.8% (severely obese) → 9.8% (normal weight)
(Sjoberg, Nilsson, & Leppert, 2005)	***Participants:*** SALVe-2004 data (survey regularly distributed by County Council of Vestmanland to monitor psychosocial health of adolescent population of county) ***Depression:*** Depression Self-Rating Scales (DSRS); cutoff ≥ 5 symptoms ***Obesity:*** Self-report BMI (IOTF guidelines)	15-17y	4703 (131 obese)	→ 26.7% (obese) → 17.5% (normal weight)
(Erermis, Cetin, Tamar, Bukusoglu, Akdeniz, & Goksen, 2004)	***Participants:*** Recruited from high school in Izmir ***Depression:*** CDI; cutoff ≥ 19 ***Obesity:*** Measured BMI (CDC)	12-16y	30	→ 20%

(Van Vlierberghe, Braet, Goossens, & Mels, 2009)	***Participants:*** Large-scale school mailings and healthcare magazine advertisements ***Depression:*** Structured Clinical Interview for DSM-IV Childhood version (KID-SCID) – "Major Depressive Disorder" ***Obesity:*** Measured BMI z-scores (2000 CDC)	8-18y	73	→ 4.11%
(Britz, et al., 2000)	***Participants:*** Lived in greater Munich area. Recently published representative study (Wittchen 1998) ***Depression:*** Munich-Composite International Diagnostic Interview (M-CIDI) – "Major Depressive Disorder-lifetime" - modified version of WHO CIDI, computer-assisted personal interview ***Obesity:*** Self-reported BMI	14-24y	47	→ 8.5%

Appendix D, Table 2: Prevalence rates of depression in clinic-based studies

Citation	Methods	Age	Sample size	Prevalence of Depression
(Zeller & Modi, 2006)	***Inclusion Criteria:*** Hospital-based pediatric weight management program. BMI ≥ 95th percentile and excludes youth with genetic syndromes associated with obesity and developmental disabilities. ***Depression:*** CDI; cutoff ≥ 20 (conservative); ≥ 12 (recommended) ***Obesity:*** Measured BMI% and z-score (CDC)	8-18y	166	→ 11% (conservative) → 34% (recommended)
(Pott, Albayrak, Hebebrang, & Pauli-Pott, 2010)	***Inclusion Criteria:*** Outpatient, family-based weight-reduction. BMI > 97th age- and gender-related percentile of the German reference data or BMI above the 90th percentile but with the presence of further risk factors (e.g., hypertension, dyslipidemia, orthopedic problems). program. ***Depression:*** CDI (German version); cutoff ≥18 ***Obesity:*** Measured BMI-SDS based on German reference data	7-16y	116	→ 18%
(Petty, Davis, Tkacz, Young-Hyman, & Waller, 2009)	***Inclusion Criteria:*** 7–11 years old, overweight (≥85th percentile BMI), did not participate in a regular physical activity program more than 1 h per week, had no medical condition that would affect study results or limit physical activity, attended a school included in the study, and provided a blood sample. ***Depression:*** Reynolds Child Depression Scale (RCDS); cutoff=74 (scores range 30-121) ***Obesity:*** Measured BMI% and z-scores (CDC)	7-11y	204	→ 4%
(Daley, Copeland, Wright, Roalfe, &	***Inclusion Criteria:*** Referral or community ad. Adolescents with a BMI > 98th percentile for age	11-16y	81	→ 30.3%

Wales, 2006)	and gender, according to 1990 United Kingdom reference data, were defined as obese and were eligible. ***Depression:*** CDI; cutoff ≥ 13 ***Obesity:*** Measured BMI z-scores (UK reference data)			
(Erermis, Cetin, Tamar, Bukusoglu, Akdeniz, & Goksen, 2004)	***Inclusion Criteria:*** Adolescents seeking treatment from pediatric endocrinology outpatient clinic ***Depression:*** CDI; cutoff ≥ 19 ***Obesity:*** Measured BMI (CDC)	12-16y	30	→ 33.3%
(Benson, Williams, & Novick, 2013)	***Inclusion Criteria:*** Penn State Multi-disciplinary Weight Loss Program. New patients to the program between August 2007 and July 2008, were 7 to 17 years old, and were referred by their primary care provider. ***Depression:*** CDI; cutoff ≥ 13 ***Obesity:*** Measured BMI z-score (CDC)	12.4 (2.89) y	117	→ 26.5%
(Van Vlierberghe, Braet, Goossens, & Mels, 2009)	***Inclusion Criteria:*** youngsters were recruited via an obesity treatment centre. ***Depression:*** Structured Clinical Interview for DSM-IV Childhood version (KID-SCID) – "Major Depressive Disorder" - semi-structured diagnostic interview ***Obesity:*** Measured BMI z-scores (2000 CDC)	8-18y	115	→ 4.46%
(Britz, et al., 2000)	***Inclusion Criteria:*** Obesity Treatment Center INSULA in Berchtesgaden, Germany. Patients treated between Sept 1996-Apr 1997 aged 15 yrs and above with BMI > 95th age-centile upon admission. ***Depression:*** Munich-Composite International Diagnostic Interview (M-CIDI) – "Major	15-21y	47	→ 23.4% (clinic pts) → 10.3% (pop'n controls; N=1608)

	Depressive Disorder" - modified version of WHO CIDI, computer-assisted personal interview ***Obesity:*** No measurement reported			
(Zeller, Modi, Noll, Long JD, & Inge, 2009)	***Inclusion Criteria:*** longitudinal study documenting the psychosocial outcomes of adolescent RYGBP. 13–17 years of age and have no physical impairments unrelated to obesity (e.g., spinal anomaly), or developmental disability, BMI ≥ 95th percentile for age and gender. ***Depression:*** BDI-II; cutoff ≥ 17 ***Obesity:*** Measured BMI% (Barlow 2007)	16.4 (1.4)y	31	→ 38.7%
(Zeller, Reiter-Purtill, Ratcliff, Inge, & Noll, 2011)	***Inclusion Criteria:*** 14–17 years old with no developmental disability owing to the study's high reading demand. ***Depression:*** BDI-II; cutoff ≥ 17 ***Obesity:*** Measured BMI	16.2 (1.4)y	16	→ 62.5%
(Holterman, et al., 2007)	***Inclusion Criteria:*** Ongoing participation in the New Hope Pediatric and Adolescent Weight Management Program, Clearance by the New Hope team for behavioral and emotional readiness for the study, BMI ≥ 40 or BMI≥35 with associated comorbidities,14 ≤ age <18 yrs at time of enrollment, Tanner stage ≥4 or achievement of skeletal maturity as determined by bone age. ***Depression:*** BDI-II; cutoff ≥ 16 ***Obesity:*** Measured BMI	15-17y	10 (all girls)	→ 30%

Appendix D, Table 3: Prevalence rates of depression in studies using the CES-DC screening questionnaire

Citation	Methods	Age	Sample size	Prevalence of Depression
(Brown, Kim Harris, Woods, Buman, & Cox, 2012)	***Participants:*** First time adolescent mothers age 18 years or younger at enrollment in the teen tot clinic who received clinic services between January 2002 and January 2005. ***Depression:*** CES-DC; cutoff ≥ 16	17.4 (1.3) yrs	120	→ 53% (baseline)
(Bettge, Wille, Barkmann, Schulte-Markwort, Ravens-Sieberer, & BELLA study group, Depressive symptoms of children and adolescents in a German representative sample: results of the BELLA study, 2008)	***Participants:*** BELLA study assesses the prevalence and persistence of mental health problems in a representative sample of children and adolescents aged 7–17 years in Germany. A random selection of 4,199 families from the KiGGS sample with children aged 7–17 were asked to participate in the BELLA study. ***Depression:*** CES-DC; cutoff ≥ 15 (parent-report and self-report) - self-report only completed by 11-17 yr-olds	7-17 yrs	2860	→ 10.9% (parent-report) → 12.3% (self-report, boys) → 21.2% (self-report, girls)
(Berganza & Aguilar, 1992)	***Participants:*** 15 yr-old adolescents from coeducational lay schools not supported by foreign resources ***Depression:*** CES-DC; cutoff ≥ 21 (own validation study)	15 yrs	339	→ 56% (w/ cutoff ≥ 15) → 35.1% (w/ cutoff ≥ 21)
(Cox, Buman, Valenzuela, Pierre Joseph, Mitchell, & Woods, 2008)	***Participants:*** Enrolled in a parenting program that provided comprehensive multidisciplinary medical care to teens and their children, intensive social and mental health services, and psychosocial parenting groups, < 19 yrs old at time of enrollment, recruited between Jan 2002-Jan 2005. ***Depression:*** CES-DC; cutoff ≥ 15	17.6 (1.2) yrs	168	→ 53.6%

(Hudson, Elek, & Campbell-Grossman, Depression, self-esteem, loneliness, and social support among adolescent mothers participating in the new parents project, 2000)	***Participants:*** Recruited from 3 primary health care practices in different medium-sized Mid-western cities. Between ages 15 and 19 yrs, expecting their first child, access to telephone in their home, could read English at 8th-grade level, expecting to reside in the city for duration of the study. ***Depression:*** CES-DC; cutoff ≥ 15	18 (1.14) yrs; (16-19 yrs)	21	→ 53%
(Olsson G. , Nordstrom, Arinell, & von Knorring, 1999)	***Participants:*** Adolescents (16-17 yr-olds) in all high schools, students in the first grade in Uppsala, A university town of 180,000 habitants in centre of Sweden, those of the same age in vocational training or those not yet qualified for high school also invited. ***Depression:*** CES-DC, cutoff ≥ 30 and/or BDI, cutoff ≥ 16	16-17 yrs	2465	→ 13.1%