THE IMPACT OF OBESITY ON TREATMENT FOR DEPRESSION IN YOUTH

APPROVED BY SUPERVISORY COMMITTEE

Betsy Kennard, Psy.D.

Graham Emslie, M.D.

Julie Germann, Ph.D.

Carroll Hughes, Ph.D.

Deborah Wiebe, Ph.D.

# DEDICATION

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# THE IMPACT OF OBESITY ON TREATMENT FOR DEPRESSION IN YOUTH

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HAYLEY EVANS FOURNIER

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HAYLEY EVANS FOURNIER, B.A.

The University of Texas Southwestern Medical Center, 2013

BETH DOHONEY KENNARD, PSY. D.

The relationship between weight status and depression in children and adolescents was examined through an analysis of pooled data from three studies of Major Depressive Disorder in youth. Participants included 434 youth, ages 8 to 17. During the acute phase of treatment (0 to 12 weeks), youth received open treatment with fluoxetine. Participants were divided into three groups: normal weight, overweight, and obese. This study examined the association between weight status and various baseline characteristics of depression. The associations of weight status with depression severity (as measured by the Children's Depression Rating Scale-Revised), remission status (defined as a score of ≤ 28 on the Children's Depression Rating Scale-Revised and a Clinical Global Impressions-Improvement score of 1 or 2 following 12 weeks of acute treatment with fluoxetine), and time to remission were examined. Weight status was associated with ethnicity, such that African American participants were more highly

represented in the obese group than in normal and overweight groups. Additionally, obesity status (obese, not obese) was associated with ethnicity, such that Caucasians were more highly represented in the non-obese group than in the obese group. Obesity status was also found to be significantly associated with a family history of depression, such that those with a positive family history of depression were more likely to be categorized as obese. Change in depressive symptoms over time and time to remission were not found to be associated with weight status as hypothesized. Remission status was found to be associated with weight status, age, and family history of depression. Results suggest that youth with normal weight may have a better response to depression treatment. Further research is needed in the area of obesity and depression in youth as it relates to outcomes for depression treatment to better understand this complex relationship.

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LIST OF ABBREVIATIONS

BMI – Body Mass Index

CBT – Cognitive Behavioral Therapy

CDRS-R – Children's Depression Rating Scale-Revised

CGAS – The Children's Global Assessment Scale

CGI – Clinical Global Impressions

CMC – Children's Medical Center

DSM-IV – Diagnostic and Statistical Manual of Mental Disorders

FDA – Food and Drug Administration

IE – Independent Evaluator

K-SADS-PL – Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version

MDD – Major Depressive Disorder

NIMH – National Institute of Mental Health

RP – Relapse Prevention

RR – Remission and Relapse

SES – Socioeconomic Status

SSRI – Selective Serotonin Reuptake Inhibitor

STS – Pediatric MDD: Sequential Treatment with Fluoxetine and Relapse Prevention CBT

TADS – Treatment for Adolescents with Depression Study

TORDIA – The Treatment of Resistant Depression in Adolescents

WHO – World Health Organization

# CHAPTER ONE
# Introduction

## BACKGROUND OF THE STUDY

### Major Depressive Disorder (MDD)

Depression impacts a significant percentage of children and adolescents. With prevalence rates of 2% in children and 4% to 8% in adolescents, the illness causes significant impairment in the academic, familial, and social functioning of youth (Birmaher et al., 1996). Further, depression negatively impacts the development of children and adolescents, which can lead to enduring impairment and increased risk for psychopathology over the lifespan. Current research on the treatment of depression in youth has shown that anti-depressant medication and cognitive behavioral therapy (CBT) are effective in reducing depressive symptoms and preventing relapse (Birmaher, Brent, & AACAP Work Group, 2007).

### Association between Obesity and Depression

The association between obesity and depression has been repeatedly examined and confirmed (de Wit, van Straten, van Herten, Penninx, & Cuijpers, 2009; Faith, Matz, & Jorge, 2002; Scott, Bruffaerts, & Simon, 2008; Scott, McGee, Wells, & Oakley Browne, 2008). In a comprehensive meta-analysis examining the bidirectional association of obesity and depression, researchers showed that adults with obesity had a 55% increased risk of developing depression, and that those with depression had a 58% increased risk of become obese (Luppino et al., 2010).

#### *Obesity and Clinical Characteristics of Depression*

In adults, the relationship between obesity and depression has been associated with several demographic characteristics, including female gender, younger age, and higher SES (Fabricatore &

Wadden, 2004; Moore, Stunkard, & Srole, 1962; Ross, 1994; Scott et al., 2007). Obesity has also been associated with clinical characteristics of depression, including over-eating, weight gain, hopelessness, hypersomnia, suicidal ideation, greater number of depressive episodes, and longer duration of depressive episode, among others (Murphy et al., 2009). These data suggest that the nature of depression among those with obesity may be more chronic and severe than among those with normal weight.

In youth, the relationship between obesity and depression has been shown to be stronger in female gender, white, non-hispanic youth, and high SES (Wardle, Williamson, Johnson, & Edwards, 2006). Regarding depressive symptomatology, obese youth were more likely to report anhedonia, negative self-esteem, and overall severity of depressive symptoms (Goldfield, Cerimoore, Bucholz, Obeid, & Flamont, 2010).

*Studies Examining the Impact of Obesity on Treatment Outcome in MDD*

The impact of overweight and obesity on response to depression treatment has been explored among adults. Researchers found that obese outpatients with bipolar I disorder experienced a shorter time to recurrence during maintenance treatment than their non-obese counterparts (Fagiolini, Kupfer, Houck, Novick, & Frank, 2003). Similarly, in a study exploring the association between relative body weight and obesity and clinical response to depression treatment with pharmacotherapy, investigators found that greater body weight (continuous BMI) predicted non-response to treatment with fluoxetine. However, they found that obesity status (dichotomous) did not predict non-response (Papakostas et al., 2004). This finding is consistent with previous studies exploring the relationship between obesity and treatment response. Carpenter, Hasin, Allison, and Faith (2000) identified a link between greater relative body weight and MDD, but not between obesity and MDD. This data may suggest that defining obesity as a

continuous construct, rather than as a minimum BMI may be better suited for studying the effects of excess weight on depression.

## STATEMENT OF THE PROBLEM

The relationship between obesity and depression has been well studied among adults. The bidirectional association between obesity and depression has been repeatedly examined and confirmed. Additionally, several causal pathways linking obesity and depression have been elucidated. Recently, researchers have begun to examine the effects of obesity on depression treatment outcome in adults. Less is known about the relationship between obesity and depression in youth. Although a bidirectional relationship has been suggested, pathways linking obesity and depression are not fully understood. In addition, there have been no studies examining the impact of obesity on depression treatment outcomes in youth, to our knowledge.

## PURPOSE OF THE STUDY

This study examines the relationship between obesity and clinical characteristics in the presentation of major depressive disorder in children and adolescents. Variables that may be associated with obesity include female gender, high SES, white, non-Hispanic race, and overall severity of depressive symptoms. This study attempts to contribute to the current gap in the literature concerning explanatory factors in the obesity-depression relationship in youth.

## STUDY AIMS

This study examines the association between weight status and various demographic and clinical characteristics of depression at baseline. These include gender, age, ethnicity, SES, and certain clinical characteristics of depression, such as age of onset and duration of depressive illness, age of onset and duration of current depressive episode, severity of depressive illness, family history of depression, and presence of comorbid psychiatric disorders. Further, we examine the association between weight status and severity of depression across time, including remission after 12 weeks of acute treatment with fluoxetine and time to remission. Additionally, this study examines the association between sleep disturbance and obesity status at baseline.

## IMPORTANCE OF THE STUDY

This study may provide a better understanding of the role that overweight and obesity play in the treatment of depression. Findings from this study may help clinicians better determine the type and intensity of treatment for youth with depression. In 2008, the National Institute of Mental Health (NIMH) outlined strategic objectives calling for research to examine "individual patterns of intervention response" due to the "considerable individual variation in treatment response depending on a range of biological and psychosocial factors." This study aims to contribute to this much-needed area of research.

# CHAPTER TWO
# Review of the Literature

## MAJOR DEPRESSIVE DISORDER

### Characteristics

Major Depressive Disorder (MDD) is defined as having one or more episodes of depressive symptoms that cause significant impairment in social, academic, or other important areas of functioning, for at least 2 weeks. Specifically, an individual must experience depressed mood and/or anhedonia, defined as the loss of interest or pleasure in nearly all activities, as well as at least five of the following symptoms: appetite disturbance, sleep disturbance, psychomotor agitation or retardation, fatigue, poor concentration or inattention, feelings of worthlessness or guilt, and thoughts of death or suicide. In the current diagnostic manual, the criteria for youth differs slightly, as children and adolescents may present with irritable, rather than depressed, mood (APA, 2000).

Although the clinical presentation of MDD is largely similar across the lifespan, developmental differences may cause children and adolescents to experience depression differently than adults. Primarily, children may be less adept at verbalizing their experience of sadness and depression and, as a result, may present more often with irritability, labile mood, low frustration tolerance, temper tantrums, social withdrawal, and physical complaints. The most common symptoms reported by children and adolescents presenting for treatment of depression include depressed or irritable mood, difficulty concentrating, sleep disturbance, and changes in appetite or weight. On the other hand, children tend to have fewer melancholic symptoms, suicide attempts, and delusions than adults (Birmaher et al., 2007). Clinicians should be cautious of the unique clinical presentation of children and adolescents with depression in order to appropriately diagnose and treat depression in youth.

**Prevalence and Course**

Major depressive disorder in youth presents a substantial public health concern. The prevalence of MDD is approximately 2% in children and ranges from 4% to 8% in adolescents (Birmaher, Arbelaez, & Brent, 2002). Prevalence rates increase after puberty by a factor of 2 to 4, particularly in females (Angold, Costello, & Worthman, 1998). Rates are similar among males and females during childhood, but the male-to-female ratio increases in adolescence to 1:2 (Birmaher et al., 1996). By age 18, the cumulative incidence of MDD in community samples is 20% (Lewinsohn, Rohde, & Seeley, 1998).

The median duration of MDD ranges from 1 to 2 months in community samples to 8 months in clinical samples. The majority of youth recover from their first depressive episode. However, longitudinal studies have found a 20% to 60% probability of recurrence by 1 to 2 years following remission, and a 70% probability of recurrence by 5 years following remission (Birmaher et al., 2002; Costello et al., 2002). Further, a significant proportion of youth with MDD will experience MDD as adults (Birmaher et al., 2007). These data suggest that MDD affects a substantial number of youth throughout both childhood and adolescence, and for some, may persist throughout the lifespan.

**Complications**

If left untreated, depression may impede emotional, cognitive, and social development, as well as, interfere with family functioning (Birmaher et al., 1996; Birmaher et al., 2002; Lewinsohn, Klein, Durbin, Seeley, & Rohde, 2003a). Suicidal ideation and behavior are among the most substantial and damaging consequences of depression, due to the associated morbidity. Approximately 60% of youth with MDD

report suicidal ideation and an estimated 30% report an actual suicide attempt (Brent, Baugher, Bridge, Chen, & Chiappetta, 1999; Gould et al., 1998). Several factors, such as a history of suicide attempts, a positive family history for suicidality, comorbid psychiatric disorders, aggression, impulsivity, access to lethal agents, and exposure to negative events increases the risk of suicide (Beautrais, 2000; Brent et al., 1988; Gould et al., 1998).

In addition to increased suicide rates, youth with depression are at an increased risk for substance abuse, legal involvement, exposure to negative life events, medical comorbidities, pregnancy, academic problems, and poor psychosocial functioning. Although psychosocial functioning has been shown to improve gradually following a depressive episode, a substantial proportion of youth will continue to experience impaired psychosocial functioning after remission of the depressive episode (Fergusson & Woodward, 2002; Hammen, Shih, Altman, & Brennan, 2003; Hammen, Brennan, & Shih, 2004; Lewinsohn, Rohde, Seeley, Klein, & Gotlib, 2003b). It is not only the depressive episode that interferes with psychosocial functioning, but also the associated factors of depression, such as comorbid psychopathology, medical illness, impaired family functioning, and low socioeconomic status, that affect psychosocial functioning in depressed youth (Birmaher et al., 1996; Fergusson & Woodward, 2002; Lewinsohn et al., 1998, 2003b).

**Evidence-based Treatment of MDD**

A recent practice parameter on the assessment and treatment of depressive disorders in youth sets forth recommended treatment guidelines based on the existent scientific evidence and current clinical practice. Authors discuss acute, continuation, and maintenance treatment of depression. They highlight

the importance of continuation and maintenance phase treatment to support treatment response acquired during the acute phase and to prevent relapse (Birmaher et al., 2007).

*Psychopharmacology*

The effectiveness of SSRI's in the acute treatment of MDD has been replicated in several randomized clinical trials (Cheung, Emslie, & Mayes, 2005; Emslie & Mayes, 2001). Until 2009, fluoxetine remained the only FDA approved medication for the treatment of depression in children and adolescents. Escitalopram recently gained approval by the FDA, despite criticism that substantial research on the efficacy and safety of this drug for treating depression in youth is lacking. Fluoxetine has consistently been shown to produce a more favorable response than other antidepressants on the market, when compared to placebo (Birmaher et al., 2007). However, despite its apparent efficacy, a large proportion of youth fail to adequately respond to first-line treatment. Those youth who do not improve following initial treatment with an SSRI often benefit from a medication change (either to a different SSRI or venlafaxine) paired with the addition of CBT (Brent et al., 2008). These data suggest that although research supports the efficacy and safety of the use of SSRI's, particularly fluoxetine, in treating depression in youth, many will fail to improve with first-line medication treatment and may benefit from alternative treatment modalities or a combination of treatment modalities.

*Psychotherapy*

The literature on the efficacy of psychotherapy presents mixed findings. In general, the effects of psychotherapy for the treatment of depression in youth have been shown as modest (effect size=0.34) according to a recent meta-analysis of randomized controlled trials (Weisz, McCarty, & Valeri, 2006). No difference was found between the effect sizes of various types of therapy, including CBT, family

therapy, interpersonal therapy, and social skills training. However, authors found a large effect (some effect sizes higher than 1.0) when CBT was compared to a control group. Authors also note that CBT and interpersonal therapy have been established as efficacious in the treatment of adolescents. McCarty and Weisz (2007) reviewed the relevant components of psychotherapy that are important in treating depression. These include psychoeducation, treatment orientation, promoting competence, enhancing relationship skills, teaching problem solving, cognitive restructuring, and behavioral activation.

In a randomized clinical trial comparing cognitive behavioral therapy, systemic behavioral family therapy, and nondirective supportive therapy, researchers discovered that CBT led to faster and greater relief of depressive symptoms. Additionally, these researchers found higher remission rates by the end of acute treatment among patients receiving CBT, over other forms of psychotherapy (Brent et al., 1997). However, these differences may fade over time. In another study comparing the effectiveness of different psychotherapies, researchers found that, after two years, most patients had remitted regardless of the type of psychotherapy received (Birmaher et al., 2009).

Several factors have been found to be associated with poor response to psychotherapy. These include comorbid anxiety disorders, higher levels of cognitive distortion and hopelessness, psychosocial adversity, and a history of sexual abuse (Brent et al., 1998; Barbe, Bridge, Birmaher, Kolko, & Brent, 2004; Curry et al., 2006; Jayson, Wood, Kroll, Fraser, & Harrington, 1998). Additionally, certain clinical and demographic characteristics may limit the effectiveness of psychotherapy, such as lower SES and higher levels of depression severity (Curry et al., 2006). Given the mixed findings on the effectiveness of psychotherapy, due to the previously mentioned factors associated with poor response, additional

treatment may be needed. One such treatment is the combination of pharmacotherapy and psychotherapy, outlined below.

*Combination Treatment*

Recently, randomized clinical trials comparing treatments for depressed youth have demonstrated evidence for the efficacy of combination treatment with pharmacotherapy and psychotherapy (Brent et al., 2008; TADS Team, 2004). In the Treatment for Adolescents with Depression Study (TADS), an NIMH-sponsored, multisite, randomized clinical trial, researchers studied the efficacy of treatment with fluoxetine, CBT, their combination, and placebo. Following acute treatment, combination treatment resulted in the highest response rates (71%), followed by fluoxetine (61%), CBT (43%), and placebo (35%). Combination treatment and fluoxetine alone were more effective than placebo, while CBT was not (TADS Team, 2004). These results support the efficacy of combination treatment among adolescents with depression.

The Treatment of Resistant Depression in Adolescents (TORDIA) provides further support for the efficacy of combination treatment in treating adolescents with depression. TORDIA was a randomized clinical trial that examined the efficacy of treatments for adolescents who failed to respond to initial treatment with an SSRI. Participants were randomized to either a medication switch or a combination of a medication switch with the addition of CBT. Higher response rates were found with the combination treatment (55%) as compared to a medication switch alone (41%) (Brent et al., 2008).

Combination treatment has been indicated as an efficacious treatment in high-risk populations of depressed adolescents, as well. In a study examining the effectiveness of treatment among adolescent

suicide attempters, combination treatment of an SSRI plus CBT was found to produce similar rates of response among suicidal and non-suicidal teens (Vitiello et al., 2009). This evidence supports the efficacy of combination treatment in depressed youth who present with more complex or difficult-to-treat cases. Overall, few studies examining the efficacy of combination treatment have been performed to date. However, these studies suggest the superiority of combination treatment to pharmacotherapy or psychotherapy alone.

*Continuation Treatment*

Though the majority of depression treatment studies among youth have focused on response to acute treatment, recent support of continuation treatment has increased. Studies including an analysis of lasting effects consistently indicate that remission rates are low following the acute phase of treatment. Specifically, remission rates among adolescents were found to be 23% across various treatment types and 37% among those treated with combination treatment (fluoxetine plus CBT) (Kennard et al., 2006). When full remission is not reached in acute treatment, residual symptoms may be present, increasing the likelihood of relapse. To consolidate the benefits of treatment and prevent relapse in youth with depression, recent support for continued treatment has increased. In a study examining remission rates among treatment with fluoxetine, CBT, or their combination, researchers found a two-fold increase in remission rates among adolescents who received continued treatment beyond the acute phase. Approximately 60% of adolescents reached remission by week 36 of treatment (Kennard et al., 2009).

In considering the low remission rates among youth treated for depression, researchers outlined treatment strategies that would increase benefit to youths. Continuation of antidepressant treatment following the acute phase may be associated with relapse prevention (Birmaher et al., 2007; Emslie et al.,

2008; Emslie, Mayes & Ruberu, 2005). Rather than discontinuing medication after an adequate response is achieved, research supports continuation of medication treatment. Similar results have been found when examining the long-term benefit of psychotherapy treatment. Short-term psychotherapy administered acutely does not show lasting effects, thus indicating the need for continuation treatment (Weisz et al., 2006). Preliminary results indicate that the addition of CBT during the continuation phase of treatment may further reduce the risk for relapse when compared with responders maintained on antidepressant treatment alone (Kennard et al., 2008). Research examining the treatment of child and adolescent depression clearly indicates the need for continued treatment that combines the use of antidepressants and psychotherapy.

## OBESITY

### Definition of Obesity

The most commonly-used measure of overweight and obesity is body mass index (BMI), or the weight in kilograms divided by the height in meters squared (kg/m2). Overweight and obesity can be measured using several different methods, including densitometry, in which a tomography scan or magnetic resonance imaging is used to create a single-cut image of the abdomen, and dual energy X-ray absorptiometry. Though BMI is a more crude measure of overweight and obesity, its low cost and simplicity make it the most widely-used measurement available (Nguyen & El-Serag, 2010).

The World Health Organization (2008) defines overweight and obesity as abnormal or excessive fat accumulation that presents health risks. The World Health Organization (WHO) further defines overweight as having a body mass index between 25.0 and 29.9 $kg/m^2$ and defines obesity as having a

BMI greater than 30.0 $kg/m^2$. BMI in adults remains relatively stable over time, whereas BMI in youth changes as individuals mature and growth patterns vary by gender. For this reason, BMI in youth is classified using thresholds that are calculated from a reference population, or a child growth reference, that accounts for age and gender. There are several child growth references, including the WHO 2007 growth reference. This growth reference defines overweight as having a BMI between 1 and 2 standard deviations above the mean and obese as greater than 2 standard deviations above the mean (Dinsdale, Ridler, & Ells, 2011).

**Obesity Trends in Adults and Children**

In 2008, the WHO estimated that over 1.4 billion adults, ages 20 and older, were overweight. Of those classified as overweight, approximately 200 million men and 300 million women were considered obese. This data suggests that over 10% of the world's population were classified as obese in 2008.

According to the National Health and Nutrition Examination Survey (NHANES), a cross-sectional, nationally representative series of surveys conducted by the US Centers for Disease Control and Prevention, 66.2% of US adults, ages 20 to 74 years old, were classified as overweight or obese (33.4% and 32.9%, respectively) in the 2003-2004 survey. Although obesity prevalence rates more than doubled from 15% in 1980 to 34% in 2006, there were no significant changes in obesity prevalence rates in the 2005-2006 survey, suggesting a possible stabilization in the obesity epidemic (Ogden, Carroll, McDowell, & Flegal, 2007; Ogden, Yanovski, Carroll, & Flegal, 2007).

NHANES data show that overweight and obesity prevalence rates in children show a slightly different trend than rates in adults. Data from the 2009-2010 survey indicate that 31.8% of youth ages 2 to

19 years old were classified as either overweight or obese (BMI ≥ 85th percentile) and 16.3% were classified as obese (BMI ≥ 95th percentile). Approximately 12.3% of youth had a BMI above the highest cutoff for BMI (≥ 97th percentile) (Ogden, Carroll, Kit, & Flegal, 2012). Significant increases were seen in obesity prevalence rates among children and adolescents during the 1980s and 1990s. However, between 1999-2000 and 2007-2008, increases were seen only among 6- through 19-year-old males that were classified at the highest cut point of BMI (≥ 97th percentile).

Several demographic variables, including age, SES status, gender, race and ethnicity, and geographic location, are associated with overweight and obesity. For example, older age and lower socioeconomic status are associated with overweight and obesity (Ogden et al., 2006; Paeratakul, Lovejoy, Ryan, & Bray, 2002). In regards to gender, men are overweight more often than women (Hedley et al., 2004). However, extreme obesity is more commonly associated with women than men (Poulose et al., 2005). In addition, individuals that live in certain areas of the country, such as the South and the Midwest, tend to show higher rates of obesity than those from other regions (Nguyen & El-Serag, 2010).

Large ethnic differences in the prevalence of obesity exist. Based on data from NHANES 2003–2004, African Americans had the highest prevalence of obesity (45% of those between 20 and 74 years of age), as compared to 36.8% of Mexican Americans and 30.6% of Caucasians (Ogden et al., 2007). These differences exist in children, as well. Certain racial and ethnic minority populations, such as African American, Hispanic, and American Indian groups, are at particular risk for the development of overweight and obesity (Crocker & Yanovski, 2011).

**Potential Causes of Obesity**

Obesity develops from a complex interaction of environmental, genetic, and behavioral factors. One environmental factor involved in obesity has been shown to be a positive imbalance between energy intake and energy expenditure (Nguyen & El-Serag, 2010). In a study by Kant and Graubard (2006), dietary data from four studies consisting of 39,094 US adults was used to show that the increase in prevalence of obesity coincides with the temporal increase of the quantity and energy density of foods consumed. Similar trends exist in regards to decreased energy expenditure (Kant & Graubard, 2006). Dietz and Gortmaker (1985) showed that each additional hour of television viewed by study subjects paralleled a 2% increase in obesity. Other environmental factors may play a role in the obesity epidemic, including the relative price and availability between high-caloric density food and healthier options, such as fruits and vegetables, and the affect of the quality of local parks on physical activity levels (Holsten, 2008; Kipke et al., 2007).

**Obesity as a Risk Factor for Psychiatric Disorders in Adults**

The association between obesity and psychiatric disorders is well-established in the literature in both clinical and non-clinical samples (Noppa & Hallstrom, 1981; Roberts, Strawbridge, Deleger, & Kaplan, 2002; Kasen, Cohen, Chen, & Must, 2008; Scott et al., 2008a, 2008b). In a study by Carpiniello et al. (2009), the lifetime prevalence of obese patients presenting for obesity treatment having an Axis I disorder was 58%, with an increased prevalence in females (61%) over males (50%). Anxiety disorders were found to have the highest lifetime prevalence (approximately 35%). Mood disorders had the next highest prevalence rate (30%), followed by personality disorders (28%), and eating disorders (18%) (Carpiniello et al., 2009). This was confirmed more recently in a review and meta-analysis by Gariepy, Wang, Lesage, and Schultz (2010), who found that obesity and anxiety disorders were positively associated.

This relationship has also been shown in non-clinical samples. Results of the National Comorbidity Survey – Replication Study (NCS-R) provided evidence that obesity increased the risk of lifetime or past-year anxiety disorders (Simon et al., 2006). This finding was replicated in a large, nationally representative study by Petry, Barry, Pietrzak, and Wagner (2008). In this study, BMI, used as both a continuous and categorical variable, was found to be associated with the odds of having a variety of DSM-IV anxiety disorders. Specifically, obesity status was related to increased odds of having GAD, panic disorder with and without agoraphobia, social phobia, and specific phobia. This association was also significant in moderately overweight individuals, as well, but to a lesser degree, and only in GAD, panic disorder without agoraphobia, and specific phobia. In contrast, obesity has been found to be significantly inversely related to substance use disorders (Petry et al., 2008; Simon et al., 2006; Rosen-Reynoso, Alegria, Chen, Laderman, & Roberts, 2011).

In addition to an association with anxiety disorders, obesity has also been linked to mood disorders. Simon et al. (2006) showed that obesity was significantly associated with increased rates of major depressive disorder, dysthymia, manic episode, and hypomanic episode among obese individuals compared to their normal-weight counterparts. This finding was consistent across genders and other demographic variables (Simon et al., 2006).

**Association between Obesity and Depression in Adults**

Bidirectional associations between depression and obesity have been repeatedly examined and confirmed at the cross-sectional level (de Wit et al., 2009; Faith at al., 2002; Scott et al., 2008a, 2008b). A recent meta-analysis of 17 cross-sectional, community-based studies among adults found a positive

association between depression and obesity (deWit, Luppino, van Straten & Cuijpers, In Press). Similarly, deWit et al. (2009) confirmed that depression in adults is associated with an 18% increased risk of obesity (overall odds ratio of 1.18). However, this relationship was only present in women. Though this evidence is informative, cross-sectional studies fail to provide information on the specific mechanisms that may link depression and obesity.

Until recently, the literature on the relationship between depression and overweight and obesity has consisted largely of cross-sectional studies. To address the gap in the literature, Luppino et al. (2010) performed a meta-analysis examining longitudinally whether overweight and obesity are risk factors for depression and whether depression is a risk factor for overweight and obesity. These researchers found bidirectional associations between obesity and depression. Specifically, they found that those with obesity had a 55% increased risk of developing depression over time, and that those with depression had a 58% increased risk of become obese. The association between depression and obesity was stronger than the association between depression and overweight. Additionally, Luppino et al. (2010) confirmed a reciprocal relationship between depression and obesity, regardless of gender. Interestingly, results of this meta-analysis found a larger effect size (ORs between 1.20 and 1.58) than the OR of 1.18 found in the cross-sectional meta-analysis by de Wit et al. (2009). These data suggest that time may play a role in the relationship between obesity and depression.

## Potential Mechanisms in the Association between Depression and Obesity in Adults

### *Biological Pathways*

Evidence of a biological link between overweight, obesity, and depression is complex and not fully understood. The most current biological explanations of the relationship between obesity exposure

and depression outcome involve inflammatory pathways, increased rates of chronic disease, medication side effects, dysregulation of the hypothalamic-pituitary-adrenal axis (HPA axis), and insulin resistance. Obesity may be viewed as an inflammatory state, as evidence has shown that weight gain activates inflammatory pathways, and inflammation, in turn, has been linked to depression (Emery et al., 2007; Shoelson, Herrero, & Naaz, 2007; Vaccarino et al., 2007; Bremmer et al., 2008; Milaneschi et al., 2009). This suggests that inflammation could mediate the association between depression and obesity. Another potential mechanism linking obesity to depression may involve the functional impairment resulting from chronic diseases, such as cardiovascular disease and diabetes, often associated with obesity. In a sample of mostly obese, Type 2 diabetics, the extent to which diabetes interfered with daily functioning predicted depressive symptoms (Talbot, Nouwen, Gingras, Belanger, & Audet, 1999). Similar findings have been shown in individuals with rheumatoid arthritis and cancer (Devins et al., 1993; Neugebauer, Katz, & Pasch, 2003; Williamson & Schulz, 1995). The hypothalamic-pituitary-adrenal axis (HPA axis) has also been suggested as playing a role in the association among obesity and depression. Obesity may play a role in HPA-axis dysregulation, which has long been associated with depression. Therefore, obesity may cause depression through the dysregulation of the HPA-axis (Belanoff, Kalehzan, Sund, Fleming Ficek, & Schatzberg, 2001; Holsboer, 2000). Another biological mechanism thought to play a role in the depression-obesity relationship is insulin resistance. Obesity is associated with an increased risk of diabetes mellitus and increased insulin resistance, which, in turn, could cause alterations in the brain that may increase the risk of depression (Atlantis & Ball, 2008; Derenne & Beresin, 2006).

Current explanations of the relationship between depression exposure and obesity outcome include the HPA-axis, neuroendocrine disturbance, and medication side effects. Bjorntorp (1996, 2001) posited that depression causes long-term HPA-axis activation, which leads to increased weight over time.

When insulin is present, cortisol impedes lipid-mobilizing enzymes, a process facilitated by glucocorticoid receptors found in fat deposits (Bjorntorp 1996, 2001). Possible side effects from medications used to treat chronic illness and obesity may also cause depression (Vaidya, Ramirez, Ichimura, Bobadilla, & Bonventre, 2006).

*Psychological Pathways*

Several psychological mechanisms have been suggested as playing a role in the association between obesity exposure and depression outcome. Thinness is currently considered a beauty ideal in the United States. This factor, as well as social acceptance and sociocultural factors, may cause those classified as obese to have increased body dissatisfaction and diminished self-esteem, which are risk factors for depression (Hoek et al., 2005). Another potential mechanism involves perceived health. Evidence suggests that obese individuals have poorer perceived health, which may lead to other related depressogenic beliefs regarding activities or having a long and fulfilling life (Markowitz, Friedman, & Arent, 2008). In addition, poor self-rated health is associated with decreased behavioral functioning, which can lead to depressed feelings.

Several factors have been identified as contributing to the relationship between depression exposure and obesity. Negative cognitions have been identified as a potential mechanism in the association between depression exposure and obesity outcome. According to Markowitz et al. (2008), depressed individuals may hold negative beliefs about their ability to lose weight, which may hinder any weight loss attempts.

The association between depression exposure and obesity outcome has also been explained by unhealthy lifestyle. Depression may cause the adoption of an unhealthy lifestyle, such as insufficient physical activity and poor dietary choices, which may lead to overweight or obesity (Luppino et al., 2010). Finally, antidepressant use, which is known to potentially cause weight gain, has been identified as contributing to the association between depression and obesity (Stunkard, Faith, & Allison, 2003). For example, weight gain has been shown to be a side effect of tricyclic antidepressants and SSRI's (Luppino et al., 2010).

*Behavioral Pathways*

Several behavioral factors have been named as mechanisms in the association between obesity exposure and depression. Certain consequences of obesity, such as repeated dieting or weight cycling, have been shown to be associated with increased rates of depression. This association is especially strong with repeated diet failure and weight cycling, which is thought to cause individuals to feel like failures, activating negative self-schemas leading to depression (Markowitz et al., 2008). Evidence of the relationship between dieting and depression and obesity was shown in a 1994 study by Ross. In a large, nationwide sample of men and women, obesity was found to be related to increased dieting, and dieting was related to symptoms of depression, measured by CES-D scores. Additionally, research shows that the experience of being on a diet itself causes a worsening of mood. Laederach-Hofmann, Kupferschmid, and Mussgay (2002) showed that a very low calorie diet is associated with irritability. Smith, Williams, and Cowen (2000) found that obese women on diets showed a disrupted regulation of brain serotonin function.

Behavioral factors have also been shown to be involved in the relationship between depression exposure and obesity. Adopting an unhealthy lifestyle with a poor diet and insufficient physical activity

may be a factor in the relationship between depression and obesity (Luppino et al., 2010). Using food as a coping strategy is another potential mechanism. There is evidence that suggests that negative mood may lead to binge eating episodes among obese women with binge eating disorder (BED), and that emotional overeating is related to depression among overweight patients presenting for treatment of BED (Arnow, Kenardy, & Agras, 1995; Masheb & Grilo, 2006). Dysregulatory eating, binge eating, and BED have been implicated as possible risk factors for obesity and depression, as well (Fabricatore & Wadden, 2004; Faith, Calamaro, Dolan, & Pietrobelli, 2004; Faith et al., 2002; Friedman & Brownell, 1995; Stunkard et al., 2003). In a study by Telch and Agras (1994), among a sample of obese females diagnosed with BED, binge-eating severity was positively correlated with severity of depression. Finally, poor adherence to weight loss programs may mediate the association between depression and obesity. Evidence has shown depression to predict discontinuation from weight loss programs, suggesting that individuals with obesity and depression may have greater difficulty losing weight (Clark, Niaura, King, & Pera, 1996).

*Social Pathways*

Several social mechanisms have been identified as playing a role in the association between obesity and depression. One factor involves weight-related stigma and discrimination. Existing evidence shows that individuals with obesity endure discrimination and mistreatment on a regular basis (Carr & Friedman, 2005; Puhl & Brownell, 2003) and that repeated discrimination and mistreatment lead to lower self-esteem, negative affect, and heightened depressive symptoms, regardless of the role of perception (Kessler, Mickelson, & Williams, 1999). Another factor involves body image dissatisfaction (BID). Researchers have found that individuals with obesity are more likely to experience dissatisfaction about their body size and shape, causing them to experience lower self-esteem, which is related to depression (Friedman & Brownell, 1995). In a study by Friedman, Reichman, Constanzo, and Musante (2002), BID

was found to be associated with depressive symptoms and low-self esteem, and degree of obesity was associated with BID in treatment seeking individuals. Further, degree of obesity was found to be associated with depressive symptoms and self-esteem, and BID was found to mediate the relationship between BMI and depressive symptoms and self-esteem (Friedman et al., 2002).

Social factors have been also been found to be involved in the relationship between depression exposure and obesity onset. Reduced familial and social support has been named as one such factor. According to Markowitz et al. (2008), individuals with depression are likely to have reduced social support, which can interfere with adherence to weight loss programs. Depression has been found to cause strain on family functioning and social support (Coyne, 1976; Keitner & Miller, 1990), which in turn, has been found to be associated with weight loss (Black, Gleser, & Kooyers, 1990; McLean, Griffin, Toney, & Hardeman, 2003).

**Relationship of Obesity to Characteristics of Depression in Adults**

Obesity has been associated with several demographic characteristics, including female gender, younger age, and higher SES. Certain clinical characteristics of depression, including over-eating, weight gain, hopelessness, hypersomnia, greater number of depressive episodes, and longer duration of depressive episodes are associated with the obesity-depression relationship. Support for the relationships between obesity and these demographic and clinical characteristics are outlined below.

*Demographic Characteristics*

The association between depression and obesity has repeatedly been found in women, but not in men. In studies by Istvan, Zavela, and Weidner (1992) and Fabricatore and Wadden (2004), prevalence

rates suggest that obese women in the general population are 37% and 38% more likely, respectively, to be depressed than their normal-weight peers. No relationship between depression and obesity was found in men in this study, which is consistent with recent findings in the literature (Fabricatore & Wadden, 2004). The reasons behind this gender difference in the obesity-depression relationship are unclear. One line of reasoning presented in the literature involves varying societal expectations regarding thinness among women. Further, women report increased levels of weight-related teasing and body dissatisfaction than men. However, these theories have yet to be empirically studied (Faith et al., 2011).

Age may play a role in the relationship between obesity and depression. In a prospective study of obesity and mood disorders, Pine, Cohen, Brook, and Coplan (1997) found a positive relationship between depression in youth and overweight in early adulthood (among females). However, Carpenter et al. (2000) failed to find an association between depression in late adulthood and obesity in later adulthood, suggesting that depression may predict obesity among younger individuals only. In a recent meta-analysis by Luppino et al. (2010), subgroup analyses revealed that overweight status at baseline was associated with depression in subjects, age 20 or older, but not in younger subjects. Due to the contradictory findings in the literature, the relationship between age and the obesity-depression association warrants further study.

*Clinical Characteristics*

In a study entitled, the Stirling County Study, researchers investigated obesity in relation to depressive symptoms and qualities of depressive episodes among a representative community sample of adult men and women. A primary aim of this study was to explore whether depressed, obese participants were more likely than depressed, non-obese participants to report over-eating that led to weight gain

during a major depressive episode. Researchers found that those with obesity were 5 times more likely to experience weight gain while depressed than non-obese participants. Additionally, depressed, obese participants reported increased levels of hopelessness and hypersomnia (Murphy et al., 2009). In the same study, investigators found that obese participants were more likely than non-obese participants to report a history of a major depressive episode that persisted for over 1 year. Additionally, obese participants were more likely than non-obese participants to report a history of multiple depressive episodes. These findings, when taken with the fact that depressed, obese subjects were found to be more vulnerable to thoughts about death, including suicidal ideation, than depressed, non-obese subjects, indicate that the nature of depression among those with obesity may be more chronic and severe than among those with normal weight.

**Obesity as a Risk Factor for Psychiatric Disorders in Youth**

Early studies on the relationship between obesity and psychological functioning in youth often failed to find significant differences among obese and normal weight participants. For example, in a study examining the impact of obesity status on measures of social skills, self-esteem, and internalizing and externalizing symptoms, Renman, Engstrom, Silfverdal, and Aman (1999) found no significant differences among obese and normal weight youth. These findings were confirmed in two previous studies examining this relationship (Quaade, 1955; Sallade, 1973; Vila, et al., 2004). However, these early studies have been criticized for lacking standardized evaluation or control group methods. Subsequent studies using more standardized methods have since shown substantial evidence for an increased prevalence of DSM-IV disorders among obese adolescents, (Buddeberg-Fischer, Klaghofer, & Reed, 1999). Researchers have also found increased depressive symptoms and decreased self-esteem among obese youth when compared to their non-obese counterparts (Hammar, et al., 1972; Strauss, Smith,

Frame, & Forehand, 1985; Isnard-Mugnier et al., 1995; Vila et al., 2004).

In a study of youth presenting for obesity treatment, Vila et al., (2004) found that prevalence rates for DSM-IV disorders were significantly higher than community prevalence rates. The rate of mental disorders, measured by standardized methods (K-SADS-R, a clinician-rated interview, and questionnaire screening technique), ranged from 50 – 64%, while epidemiological data based on a community sample of school-aged children, indicated a prevalence rate of only 5%. Anxiety disorders were found to be the most prevalent of the disorders found in the sample and included separation anxiety and social phobia most often. Other studies have reported increased rates of psychological disorders in obese youth, especially in females. For example, Buddeburg-Fisher et al. (1999) found increased rates of somatoform, mood, pain, and anxiety disorders in overweight adolescent females.

**Association between Obesity and Depression in Youth**

Existing data point to a bidirectional relationship between depression and obesity, though there is far less evidence of this association in the pediatric literature, as compared to the adult literature (Pitrou, Shojaei, Wazana, Gilbert, & Kovess-Masfety, 2010; Drukker, Wojciechowski, Feron, Mengelers, & Von Os, 2009; Vila et al., 2004; Lamertz, Jacobi, Yassouridis, Arnold, & Henkel, 2002; Pine, Goldstein, Wolk, & Weissman, 2001; Csabi, Tenyi, & Molnar, 2000). This relationship has been examined at both the cross-sectional and longitudinal levels.

Depression in youth has been shown to be associated with an increased risk of developing obesity at the cross-sectional level. Csabi, et al. (2000) compared depressive symptoms in obese and normal-weight children. Obese children showed a significantly increased rate of depression, as measured by the

Montgomery-Asberg Depression Rating Scale, than the normal-weight controls. In a study by Richardson, Garrison, Drangsholt, Manel, and LeResche (2006), examining the relationship between depressive symptoms and obesity with pubertal development, researchers found that youth with high depressive symptoms were twice as likely to be obese, regardless of age or stage of pubertal development (male OR=1.95; female OR=2.17). Strauss (2000) prospectively studied changes in the self-esteem of 9- and 10-year-old obese and non-obese children. This author found that obese children had worse ratings of self-esteem over the 4-year follow-up period than non-obese children. The decline in self-esteem was found to be associated with increased feelings of sadness in early adolescence.

Depression as a risk factor for obesity among youth has also been explored longitudinally. In a large, nationally- representative sample of children and adolescents, those with depressed mood at baseline were more likely to be classified as obese one year later. Further, among those who were already obese at baseline, depressed mood was associated with a two-fold increase in severity of obesity one year later. However, this latter association was believed by the authors to be moderated by low self-esteem (Goodman & Whitaker, 2002).

## Potential Mechanisms in the Association between Depression and Obesity in Youth

### *Biological Pathways*

Similar to adults, the obesity-depression association in children may be explained by dysregulation of the HPA axis. Evidence suggests that body fat regulation and depression share genetic factors and common neurotransmitters (Hasler, Pine, & Kleinbaum, 2005). Chronic stress leads to repeated activation of the HPA axis, causing an increase in cortisol release. In turn, high cortisol levels have been found to be associated with abdominal obesity. In a study exploring the association between depressive symptoms and BMI in 8- to 13-year-olds, cortisol reactivity was identified as a mediating

factor in girls only (Dockray, Susman, Dorn 2009). However, in a similar study by Roemmich, Smith, Epstein, and Lambiase (2007), researchers found that changes in stress and heart-rate reactivity was independently associated with body fat. In regards to the relationship between depression exposure on obesity, the weight-gain side effects of medications used to treat depression have been identified as a mediator in the child literature as it has in the adult literature.

*Psychological Pathways*

Potential psychological mechanisms that may help explain the depression-obesity association in youth include social isolation, stigmatization from peers, low self-esteem, and body dissatisfaction. Overweight youth have been shown to experience social isolation and stigmatization from peers (Strauss & Pollack, 2003; Neumark-Sztainer et al., 2002). While overweight males are more likely to be verbally teased or experience physical aggression by peers, overweight females are more likely to experience relational victimization, which involves exclusion from social activities or friendships. These experiences may lead to poor peer relationships and a perceived lack of control, factors which may influence the development of depression (Faith et al., 2002; Pearce, Boergers, & Prinstein, 2002; Thompson, Coovert, Richards, & Johnson, 1995). The impact of social isolation and stigmatization was confirmed in a study examining the mediating and moderating effects of perceived peer isolation and social support availability. These researchers also found that the perception of peer relations and social support is an important factor in the obesity-depression relationship (Xie et al., 2005).

Low self-esteem has also been suggested in the literature to mediate the relationship between obesity and depression. Low self-esteem may be related to overeating and weight gain in youth (Martyn-Nemeth, Penckofer, Gulanick, Velsor-Friedrich, & Bryant, 2009). This is seen in a longitudinal study of

9- to 10-year-old children exploring the relationship between obesity and self-esteem. Researchers found that changes in global self-esteem during adolescence were strongly associated with obesity. Further, researchers found that children with decreased self-esteem experienced more sadness, loneliness, and anxiety, and showed levels of risk-taking behaviors, such as smoking and drinking alcohol (Strauss, 2000). Age, gender, and sampling techniques may play roles in the relationship between self-esteem and obesity and depression. The association between self-esteem and obesity has been shown to be stronger among girls than among boys and strengthens from pre-adolescence to young adulthood (Walker & Hill, 2009). Lower self-esteem is found among clinical samples of obese youth when compared to community samples (Hill, 2005; Flodmark, 2005). Wardle and Cooke (2005) posit that this finding may be due to an increase in psychological complications of obesity in treatment-seeking samples, as they may feel less able to control their weight.

Another potential mechanism involves body dissatisfaction. Research suggests that sociocultural attitudes and norms regarding appearance contribute to the obesity-depression association. However, body dissatisfaction is not inevitable in obese children, as the link between weight and body dissatisfaction has not been confirmed in the child literature (Wardle & Cooke, 2005). Ali, Fang, and Rizzo (2010) recently found a strong negative association between perceived weight and mental health, which was stronger in females and unaffected by actual weight. Similar conclusions were also found in a study of Australian adolescents (Allen, Byrne, Blair, & Davis, 2006).

Psychological mechanisms contributing to the depression-obesity relationship in the child literature are similar to the adult literature. The primary psychological mechanism linking depression exposure to obesity involves the barrier that negative cognitions pose on weight loss attempts (Markowitz

et al., 2008).

*Behavioral Pathways*

Several behavioral mechanisms contribute to the obesity-depression relationship in children. One such mechanism involves low physical activity levels and poor diet. Meriaux, Berg, and Hellstrom (2010) found that insufficient physical activity and unhealthy diet, which are associated with obesity, have been shown to be risk factors for mental health disorders in youth. Eating behavior has also been shown to be associated with obesity and depression. Loss of control eating has been suggested as being associated with increased anxiety and depressive symptoms and decreased body satisfaction (Cornette, 2008). The effect of stress on energy levels may be an important factor in the depression-obesity relationship. In a study by Lawson (2003), researchers concluded that depression leads to fatigue, which in turn may hinder a child's likelihood to engage in exercise.

*Social Pathways*

Several social factors are involved in the obesity-depression relationship. Children with obesity experience increased social rejection, discrimination, and negative stereotyping (Eisenberg, Neumark-Sztainer, & Story, 2003). According to Eisenberg et al. (2003), nearly a third of teens report being a victim of weight-related teasing, with obese girls experiencing the highest level of teasing. Further, weight-based teasing in youth has been shown to predict disordered eating, such as binge eating.

**Relationship of Obesity to Characteristics of Depression in Youth**

*Demographic Characteristics*

The majority of the literature on the relationship between obesity and depression in adults

suggests that this relationship is stronger in women and this has been confirmed in the literature for youth as well. Studies indicate that depressed young women may have an increased risk for developing obesity than young men. Results from two longitudinal studies showed boys to have a lesser risk or no risk for developing obesity, despite being depressed (Richardson et al., 2003; Barefoot et al., 1998). In a study by Reeves, Postolache, and Snitker (2008), gender modified the relationship between depression and weight. Depression was found to be associated with lower childhood BMI in males, whereas depression was related to higher childhood BMI in females. In the same study, depression was found to be associated with higher weight gain over time in females, while depression was not significantly related to weight change in males. In a recent meta-analysis of longitudinal studies, Blaine (2008) showed that subjects with depression were more likely to be obese at follow-up and that this relationship was stronger in adolescent females, with depressed, adolescent women being over twice as likely to be obese than adolescent women without depression. The stronger obesity-depression association in females is thought to be related to sociocultural norms regarding weight gain being applied more strictly to girls (Achenbach & Edelbrock, 1981).

Non-Hispanic, white youth may be particularly vulnerable to the effects of obesity and depression. In a study examining the association between severe obesity and depressive symptoms in adolescents followed over three years, researchers found that the association between weight status and depressive symptoms was moderated by race. Post-hoc analyses revealed that scores on a depression symptom inventory were significantly higher for white adolescents with severe obesity compared with their non-obese peers (Goodman & Must, 2011).

Obesity may have a greater impact on those from a higher SES background. High SES has been

consistently linked with an increased concern with meeting appearance standards, which may translate to a greater emotional impact on obese children and adolescents from a higher SES background (Wardle et al., 2006). In a study by Wardle, Volz, and Golding (1995), children from schools with a higher average SES were more likely to negatively stigmatize obese youth than children from lower SES schools.

The association between obesity and depression has been found to be stronger in adolescents than in children (Shin & Shin, 2008). Two population-based studies failed to find a significant relationship between obesity and depression in children as they found in adolescents (Brewis, 2005; Eisenberg et al., 2003). The literature on this topic states that these differential results may be due to heightened concern about others' appraisal of appearance among adolescents as compared to children (Shin & Shin, 2008).

*Clinical Characteristics*

In addition to demographic characteristics, obesity has also been shown to be associated with important clinical characteristics of depression, including depression severity. Depression severity has been shown to be higher in children and adolescents with obesity. In a study comparing depressive symptoms in obese and normal-weight children, Csabi et al. (2000) found that obese children showed a significantly increased rate of depression than the normal-weight controls. In a study by Richardson, Garrison, Drangsholt, Manel, and LeResche (2006), examining the relationship between depressive symptoms and obesity with pubertal development, researchers found that youth with high depressive symptoms were twice as likely to be obese, regardless of age or stage of pubertal development. Finally, in a study by Goldfield et al. (2010), obese youth were more likely to report greater overall severity of depressive symptoms.

## PREDICTORS OF TREATMENT OUTCOME IN MDD

Several clinical and baseline characteristics have been shown to affect treatment response for depression. Severity of depression and duration of episode have been repeatedly identified as strong predictors of poor response to treatment (Asarnow et al., 2009; Curry et al., 2006). Results from the Treatment of Adolescents with Depression Study (TADS), a large multi-site study that examined treatment for depressed adolescents, showed that increased age, chronicity, melancholic features, hopelessness, suicidal ideation, comorbid diagnoses (particularly anxiety disorders), and poor treatment expectations were related to poorer acute treatment response (Curry et al., 2006). In a study examining treatment response among youth who failed an SSRI trial, several treatment moderators and predictors were identified. Researchers found higher baseline depression severity, greater impairment in functioning, increased rates of suicidal ideation, hopelessness, self-injurious behaviors, and family discord to be associated with non-response to subsequent treatment following the failed SSRI trial (Asarnow et al., 2009). Among the most robust predictors of treatment response in depressed youth are initial depression severity, suicidal ideation, and length of depressive illness.

### Obesity Affects Treatment Outcome

*Studies in Adults*

Only a few studies to date have explored the impact of overweight and obesity on response to depression treatment in adults. In a study by Fagiolini et al. (2003), researchers found that obese outpatients with bipolar I disorder experienced a shorter time to recurrence during maintenance treatment than their non-obese counterparts. Similarly, in a study exploring the association between relative body

weight and obesity and clinical response to depression treatment with pharmacotherapy, Papakostas et al. (2004) found that greater body weight (continuous BMI) predicted non-response to treatment with fluoxetine. However, they found that obesity status (dichotomous) did not predict non-response. This finding is consistent with previous studies exploring the relationship between obesity and treatment response. Carpenter et al. (2000) identified a link between greater relative body weight and MDD, but not between obesity and MDD. This data may suggest that defining obesity as a continuous construct, rather than as a minimum BMI may be better suited for studying the effects of excess weight on depression.

*Studies in Youth*

In a study by Mansoor et al. (in press), the bidirectional relationships between BMI and treatment response were examined in adolescents with treatment resistant major depression. Specifically, authors examined the impact of baseline BMI as a predictor and moderator of treatment response over 24 weeks of treatment with an SSRI (paroxetine, citalopram, or fluoxetine) or SNRI (venlafaxine) with or without the addition of cognitive behavioral therapy. Authors also examined changes in participants' BMI as a function of treatment assignment response. BMI was not found to be a predictor nor a moderator of treatment outcome following 24 weeks of treatment. Additionally, authors did not find a differential change in BMI by treatment assignment or response. However, authors did find a significant differential increase in BMI in the overweight subgroup treated by an SSRI (as opposed to an SNRI). Post-hoc analyses revealed that paroxetine and citalopram resulted in significantly greater increase in BMI than fluoxetine. Authors concluded that overweight individuals treated with an SSRI, especially paroxetine or citalopram, may be particularly vulnerable to increases in BMI than normal individuals treated with fluoxetine and venlafaxine.

## WEIGHT STATUS AND SLEEP DISTURBANCE

### Sleep Disturbance and MDD

Patients with both sleep disturbance and depression represent a more impaired and difficult to treat subgroup. Approximately 75% of depressed youth with report sleep disturbance in the form of insomnia (Ivanenko et al. 2004). Having insomnia and depression concurrently is related to increased severity of illness, increased psychosocial difficulties, and an increased risk for suicidal behavior (Sunderajan et al. 2010; O'Brien et al. 2011; Fawcett et al. 1990; Agargun et al. 1997; Goldstein et al. 2008). In adults, studies have shown that insomnia leads to poorer response to treatment (Buysse et al. 1997; Thase et al. 1997). In two subsequent studies by Fawcett et al. 1990 and Ohayon and Roth (2003), youth with co-occurring depression and sleep disturbance had an increased risk of relapse or recurrence. For example, in at trial by Emslie et al. 2001 examining sleep polysomnography in youth with depression, children and adolescents who relapsed by one year were more likely to have delayed sleep onset and decreased quality of sleep than those who did not relapse by one year. Further analyses on a subset of this sample showed that those with sleep electroencephalography rhythms with more impaired temporal coherence were less likely to remit after one year. Of those who remitted, youth with more impaired temporal coherence experienced faster rates of recurrence (Armitage et al. 2002).

### Sleep Disturbance and Obesity

The past few decades have seen a significant increase in obesity, to the point that it is now referred to as a global epidemic. At the same time, there has been a reduction in sleep time among both youth and adults (Cappuccio et al., 2008). In a large US survey, researchers found a significant decline in

self-reported sleep duration over the past 50 years. Specifically, it was found that the amount of sleep that Americans receive per night is now 1.5 to 2 hours less than before (National Sleep Foundation, 2005). A recent meta-analysis examining the relationship between sleep disturbance and obesity across the lifespan shows a consistent pattern of a 60 to 80% increased likelihood of having shortened sleep duration among obese adolescents and adults. A pooled regression analysis suggests that for every one-hour reduction in sleep there is an associated 0.35 kg/m2 increase in BMI (Carppuccio et al., 2008).

## HYPOTHESES

### Weight Status and Baseline Characteristics of Depression

1a. First, this study aims to examine whether weight status is associated with certain demographic variables, including age, gender, SES, and ethnicity in depressed youth. Obese individuals will be more likely to be adolescent, female, high SES, and Caucasian.

1b. Next, this study aims to examine whether weight status is associated with several baseline clinical characteristics of depression, including severity of depression at baseline. Obese individuals will have increased depression severity scores than their non-obese counterparts.

### Weight Status and Acute Treatment

2a. This study aims to examine the relationship between weight status and depressive symptoms across time among youth during acute treatment with fluoxetine. Children and adolescents who are obese will show differences in their symptoms of depression when compared to non-obese children and adolescents. Specifically, obese youth will exhibit greater depressive symptoms across time.

2b. This study aims to examine the relationship between weight status and the odds of achieving remission after adequate treatment with fluoxetine in the acute phase of treatment. Odds of achieving remission will be greater for non-obese patients.

2c. This study aims to examine the time to remission during acute treatment with fluoxetine, considering the impact of weight status. Obese youth will experience a longer time to remission than non-obese youth.

**Relationship of Weight Status and Sleep Disturbance**

3a. This study aims to examine the relationship between sleep disturbance and the odds of obesity at baseline. Odds of obesity will be greater for patients with sleep disturbance.

# CHAPTER THREE
# Methodology

## DESIGN

### Overview

The current study is a secondary analysis of pooled data from three studies of Major Depressive Disorder (MDD) in youth: Remission and Relapse (RR; PI: Graham J. Emslie; n=168), Relapse Prevention CBT (RP; PI: Beth D. Kennard; n=66), and an ongoing NIMH-funded study, Pediatric MDD: Sequential Treatment with Fluoxetine and Relapse Prevention CBT (STS; PIs: Graham J. Emslie and Beth D. Kennard, n=200). All three studies involved an acute phase of treatment, in which subjects received open treatment with fluoxetine, and a randomization phase consisting of continuation treatment. All three studies aimed to explore the effects of continuation of fluoxetine and/or augmentation with a relapse-prevention-specific cognitive behavioral therapy (RP-CBT) on relapse rates for MDD.

### Acute Phase

Participants include children and adolescents, ages 8 to 17, who presented for outpatient treatment of MDD, as defined by the Diagnostic and Statistic Manual, 4$^{th}$ ed. *(*APA, 2000). During acute phase treatment, participants were treated openly with fluoxetine. Acute treatment lasted 12 weeks in RR and RP and six weeks in STS. In RR and RP, participants received weekly evaluations for the first four weeks of treatment and bi-weekly evaluations for the duration of acute treatment. In STS, participants received weekly evaluations throughout the full six weeks of acute treatment. In the case that additional visits were needed during acute phase treatment, participants were allowed two visits beyond their scheduled evaluations. Participants initially received 10 mg of fluoxetine and, if well tolerated, the medication was increased to 20 mg after one week. Treating psychiatrists further increased the medication dosing to 30 or 40 mg dependent on response after week 4 (STS) or week 6 (RR, RP).

**Continuation Phase**

Following acute treatment, participants who responded to fluoxetine were randomized to continuation treatment for an additional 24 weeks, which consisted of bi-weekly medication-management visits through week 18 and monthly medication-management visits for the duration of the continuation phase. Response to treatment was defined as a 50% reduction in depressive symptoms measured by the Children's Depression Rating Scale Revised (CDRS-R) and a score of 1 (very much improved) or 2 (much improved) on the Clinical Global Impressions-Improvement (CGI-I) scale. In the RR study, participants were randomized to receive placebo or continued medication management on fluoxetine. In RP and STS, participants were randomized to receive continued medication management (MM) on fluoxetine or a combination of medication management and relapse-prevention cognitive behavioral therapy (MM + CBT).

**Study Visits**

At each visit throughout the studies, psychiatrists completed depression severity (CDRS-R), global improvement (CGI-I), and suicidality measures. Clinicians also closely monitored and documented adverse events and reported all serious adverse events to the Institutional Review Board (IRB). Participants and their parents completed self-report and parent-report measures that assessed depression severity, cognitive, social, and family functioning, and medication compliance. In RR, medication assignment was double-blind during continuation treatment so the treating psychiatrist's ratings served as the primary outcome. In RP and STS, an independent evaluator (IE) who remained blind to treatment assignment (RP-CBT vs no CBT) evaluated participants at baseline and every six weeks until study exit.

# PARTICIPANTS

## Recruitment

Participants were children and adolescents (ages 8 to 17) with a primary diagnosis of MDD, based on DSM-IV criteria. Participants were recruited from clinical referrals and through advertisements to the child and adolescent outpatient clinic at Children's Medical Center at Dallas.

## Inclusion Criteria

Children and adolescents, ages 8 to 17, who presented for outpatient treatment of MDD, were considered for inclusion in the studies. Specifically, participants were required to have a primary DSM-IV diagnosis of non-psychotic major depressive disorder for at least four weeks, as well as a CDRS score ≥40 and a CGI-severity (CGI-S) score of ≥4 for depression. Participants were required to be in good general medical health and of normal intelligence (IQ>80).

## Exclusion Criteria

Several comorbid mental health diagnoses were considered exclusionary in all three studies. In RR and RP, exclusionary diagnoses included a lifetime diagnosis of a psychotic disorder, lifetime diagnosis of bipolar disorder, anorexia nervosa, bulimia, severe suicidal ideation, previous history of a serious suicide attempt, and alcohol or substance abuse within the six months prior to entry. STS considered the same diagnoses exclusionary with the exception of substance abuse. Additionally, only those diagnosed with bulimia or anorexia within the prior year and those with a previous history of a serious suicide attempt that required more intense treatment were excluded. In all three studies,

participants with a parent or sibling diagnosed with Bipolar I disorder, those who have medically unstable chronic illnesses, those who have failed an adequate trial of fluoxetine (≥4 weeks of at least 40 mg), and female participants who were pregnant, lactating, or sexually active, but not using medically acceptable contraception, were excluded. In RR and RP, participants taking psychotropic medication were also excluded, with the exception of a stimulant for ADHD. STS allowed psychotropic medication if used to treat a medically stable illness, comorbid ADHD, or adjunct treatment for insomnia (i.e. melatonin or Benadryl, but not other antidepressants or atypical anti-psychotics). Participants who required additional treatment strategies were exited from the study and provided with recommendations for additional treatment.

## ASSESSMENT

### Initial Evaluation

*Consent*

Research coordinators assessed referrals for general suitability for the study via phone screen. Suitable participants were scheduled for an initial evaluation visit. Research coordinators were responsible for providing consent and assent to participants and parents. Informed consent included education about the study, a discussion of risks and benefits of participation, and answering any questions. Consent forms and protocols for all studies were approved by the IRB of UT Southwestern prior to patient participation. A parent or guardian provided written consent, and the participant provided written assent. A copy of the signed consent form was provided to the family, as well as to medical records at Children's Medical Center (CMC).

*Screening*

Once written consent and assent was obtained, a trained evaluator and a psychiatrist or psychologist separately evaluated participants to determine study eligibility, including diagnosis and severity of depression, presence of comorbid mental health disorders, and consideration of medical, psychiatric, and family history. Clinical judgment and information gathered from standardized administration of the Kiddie Schedule for Affective Disorders and Schizophrenia- Present and Lifetime Version (Kaufman, Birmaher, Brent, Rao, & Ryan, 1996; K-SADS-PL) were used to determine whether participants met criteria for a primary DSM-IV diagnosis of MDD. The Children's Depressive Rating Scale – Revised (Poznanski & Mokros, 1996; CDRS-R) and the Clinical Global Impressions scale (Guy, 1976; CGI) were used to assess depression severity. Parents and patients were interviewed separately in accordance with administration guidelines for the K-SADS-PL and CDRS-R and to ensure that all relevant information was gathered. Labs were conducted during the screening period if requested by the study physician.

*Consensus*

Eligible participants returned for a follow up evaluation one week after the initial visit to verify the persistence of depression. Rater reliability among the evaluator and psychiatrist or psychologist was assessed by a consensus committee, which included the principle investigator(s).

*Participant Characteristics*

Demographic information and clinical characteristics, such as age, gender, ethnicity, socioeconomic status, family psychiatric history, comorbid mental health diagnoses, number of

depressive episodes, and age of onset of current episode and length of current episode were collected at the baseline visit. Participants and parents also completed self-report and parent-report measures assessing cognitive, social, and family functioning, as well as psychosocial characteristics.

## MEASURES

### Diagnostic Measure

*Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (K-SADS-PL)*

The K-SADS-PL (Kaufman et al., 1997) is a semi-structured diagnostic interview based on DSM-IV criteria. The K-SADS-PL is designed to assess present and lifetime psychiatric history in youth, ages 7 to 17. Parents and patients are interviewed separately by clinicians. Responses are then combined to obtain a summary score for each item. According to Kaufman et al. (1997), adequate inter-rater and test-retest reliability have been established. In addition to the screening form, the Affective Disorders Supplement was administered to all participants at baseline in order to ascertain additional information regarding symptoms of depression and mania.

### Depression Rating Scales

*Children's Depressive Rating Scale-Revised (CDRS-R)*

The Children's Depressive Rating Scale-Revised (CDRS-R; Poznanski & Mokros, 1996) is a 17-item clinician-rated interview designed to assess severity of depressive symptoms in youth (ages 6-18). This measure was modeled after the Hamilton Depression Rating Scale for adults. Items are rated on a scale ranging from 1 to 5 or 1 to 7, with 1 indicating an absence of the symptom. Total scores range from 17 to 113, with a score of 40 or greater indicating depression. Research on the CDRS-R has established

adequate inter-rater reliability, internal consistency, and test-retest reliability. Additionally, the CDRS-R has good research support as an outcome measure of adolescent depression (TADS, 2004). Presence and severity of depression were assessed with the CDRS-R, which was completed by the clinician at each study visit and by the independent evaluator at baseline and follow-up visits.

*Clinical Global Impressions (CGI)*

The Clinical Global Impressions scale (Guy, 1976; CGI) measures clinical severity of psychiatric illness and global improvement based on a 7-point scale (lower values indicate less severity and greater improvement). Clinical severity (CGI-S) is measured at the initial assessment and subsequent visits, while global improvement (from the initial assessment) (CGI-I) is measured at follow-up visits. The CGI is a standard measure used to measure response to treatment and has been widely used in psychopharmacology research. A clinical severity rating of ≤ 3 and a global improvement rating of 1 (very much improved) or 2 (much improved) are considered acceptable responses to treatment. The CGI-I has been shown to have adequate reliability and internal consistency (Guy, 1976).

**Global Functioning**

*The Children's Global Assessment Scale (CGAS)*

The Children's Global Assessment Scale (Shaffer, 1985; CGAS) is the children's version of the Global Assessment Scale for adults. The CGAS is a clinician-rated tool that measures overall functioning of subjects. Ratings are a single number (0-100), which is equal to the subject's most impaired level of general functioning over the assessment period. This measure is intended for use in youth ages 4-18.

## Obesity-related Measures

*Body Mass Index*

Height in centimeters and weight in kilograms were collected by a trained nurse or technician at baseline and each subsequent visit. BMI was then calculated by weight in kilograms divided by the square of height in meters. Using the youth's BMI at assessment and national BMI norms according to age, gender, and ethnicity, BMI z -scores were computed (Rosner, 1998). For the purposes of this study, overweight is defined as having a BMI between 1 and 2 standard deviations above the mean. Obesity is defined as 2 or more standard deviations above the mean. These definitions are in accordance with guidelines set forth by WHO in 2007.

## Medication Compliance

Because of the developmental age of the majority of the sample, parents were usually responsible for dispensing their child's study medication. Through psychoeducation, research coordinators emphasized the importance of compliance. Coordinators collected medication bottles from families at each visit and calculated the percentage of compliance. In addition, parents and participants completed a measure at each visit in which they were asked to indicate the patient's medication compliance since last visit and who administered the medication. Patients considered non-compliant were withdrawn from the study.

# DATA ANALYSIS

## Data Collection and Cleaning

All data was contained in locked filing cabinets, which were housed in locked offices to protect patient confidentiality and data. The Statistical Package for the Social Sciences (SPSS) program, Version 20, was utilized to enter and analyze data. In order to avoid human error in the data entry process and maintain accuracy, data was double entered by different research assistants. Microsoft *Excel* was utilized to compare databases, according to guidelines set forth by Elliott, Hynan, Reisch, and Smith (2006). Inconsistencies in the database were resolved and corrected. Only clean data were used for analysis.

## Data Analysis Procedures

To prevent the effects of attrition and potential biases, we conducted intent-to-treat analyses. We set the level of significance for all tests at $\alpha = .05$ (two-tailed). Because the proposed analyses utilized data from three different studies, we examined whether study participation caused any significant differences. We also examined dosing schedules of fluoxetine among the three studies, given that STS had a much shorter acute phase. Other potential covariates examined were examined, including the number of participants classified as obese, baseline severity, and other clinical and demographic variables. All significant differences found were included as covariates in the analyses described below. Weight status was classified as normal, overweight, or obese as there were no participants classified as underweight in the three studies. For a consort diagram of the three studies, see *Figure 1*.

### *Demographics and Clinical Characteristics*

1a. Baseline characteristics of participants that entered the acute phase of treatment were examined to assess the relationship of weight status to demographic variables (gender, age, SES, and ethnicity). Chi-square tests were utilized to determine whether weight-status differs across these variables. Non-parametric tests were substituted as appropriate.

1b. Baseline characteristics of participants that entered the acute phase of treatment were examined to assess the relationship of weight status to baseline clinical characteristics of depression (primary diagnosis, family history of depression, number of depressive episodes, number of comorbid psychiatric disorders, depression severity, global functioning, age of onset of current depressive episode, duration of current depressive episode, age of onset of depressive illness, and duration of depressive illness. Chi-square tests were utilized to determine whether weight-status differs across primary diagnosis, family history of depression, number of depressive episodes, and number of comorbid psychiatric disorders. One-way analyses of variance (ANOVA) were computed to determine whether weight status (normal weight, overweight, and obese) differs across continuous measures.

*Weight Status and Acute Treatment*

2a. The change over time (weeks 1, 2, 3, 4, 6, 8, 10, 12) in depressive symptoms (CDRS-R total score) was compared between levels of weight status (normal weight, overweight, obese) using a linear mixed model analysis of repeated measures. The fixed effects in the model were weight status (normal weight, overweight, obese), time period (Weeks 1, 2, 3, 4, 6, 8, 10, 12), and the interaction of weight status by time period. Study involvement (RR, RP) was included in the model as a random effect. Baseline covariates that

were included in the model were age, gender, ethnicity, CDRS-R total score, duration of depressive episode (in months), and family history of depression.

2b. A logistic regression was utilized in order to examine whether weight status was associated with remission following acute treatment with fluoxetine over a 12-week period. An odds ratio indicated the likelihood of remission status based on weight status. Weight status was treated as a multinomial variable including three groups (normal weight, overweight, and obese, with normal weight as the reference group). Remission status was treated as a binary (remitted or not-remitted) outcome variable. We defined remission as a CDRS-R total score $\leq 28$ and CGI-Improvement score of 1 or 2. We included age, gender, ethnicity, baseline depression severity (CDRS-R total score), duration of depressive illness, and family history of depression as covariates.

2c. To examine the relationship between weight status and time to remission while adjusting for the effects of other covariates, such as age, gender, ethnicity, family history of depression, baseline severity of depression (CDRS-R), and length of depressive illness, a Cox regression survival analysis was performed. Hazard ratios were examined to determine whether weight status was associated with time to achieve remission during 12 weeks of acute treatment with fluoxetine.

3a. A logistic regression was utilized in order to examine whether baseline sleep disturbance was associated with obesity status at baseline. An odds ratio indicated the likelihood of obesity status based on sleep disturbance. Sleep disturbance was treated as a binary variable including two groups (no sleep disturbance, sleep disturbance, with no sleep disturbance as the reference group). Obesity status was treated as a binary (not obese, obese) outcome variable. We defined sleep disturbance as a CDRS-R sleep

item ≥4. We included age, gender, ethnicity, baseline depression severity (CDRS-R total score), duration of depressive illness, and family history of depression as covariates.

# CHAPTER FOUR
# Results

## DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

### Summary of Pooled Sample

*Demographics*

The pooled sample consists of 434 children and adolescents (ages 7-18) from three studies examining depression in youth (RR, *N* = 168; RP, *N* =66; STS, *N* = 200). The sample is comprised of 128 children (ages 7-11) and 306 adolescents (ages 12-18). The mean age of the sample is 13.15. Gender was equally distributed in the sample, with 221 (50.9%) male participants and 213 (49.1%) female participants. The sample consists of 275 (63.4%) White, non-Hispanic participants, 87(20.0%) Hispanic participants, 53 (12.2%) African American participants, and 19 (4.4%) other ethnicity. Socio-economic status was assessed by highest parental education level. Over half of the youth (50.1%) had at least one parent who graduated college or obtained graduate training. See Table 1 for a summary of sample demographic characteristics.

*Clinical Characteristics*

At baseline, 338 youth (77.9%) were experiencing their first major depressive episode, while 96 (22.1%) were experiencing a recurrent episode. The mean baseline severity of depression (CGI-S) placed most participants in the moderately to markedly ill range, *M* = 5.04 (0.68); CDRS-R, *M* = 58.36 (8.37). During the youth's initial interview, independent evaluators assessed the presence of comorbid psychiatric diagnoses; 71.4% of participants met criteria for one or more comorbid diagnoses at the baseline visit. A high number of youth were found to have a family history of depression, as 61.5% of the sample had a first-degree relative with a history of depression. Additional clinical characteristics of the sample are found in Table 2.

*Weight-Related Characteristics*

A total of 430 youth were included in analyses related to weight, as 4 participants did not have their height and weight assessed at baseline. A high number of youth in this sample were classified as overweight or obese, with the breakdown by weight classification as follows: 258 youth (59.4%) were classified as normal weight ($-2 \leq SD < 1$), 87 youth (20.0%) were classified as overweight ($1 \leq SD < 2$), and 85 youth (19.6%) were classified as obese ($SD \geq 2$). Additional weight-related characteristics, including a breakdown of baseline BMI by age category and national and state norms, are further outlined in Table 3.

**Evaluation of Study Differences**

*Demographic Characteristics by Study Involvement*

Differences in demographic and clinical characteristics of depression among the participants in the three studies were examined prior to completing further analyses. There were no significant differences among studies in gender and parental education. A significant difference in age was found among the studies $F(2, 434) = 46.42$, $p < .001$, with a significantly higher proportion of children in RR than the other two studies. A significant difference was found in ethnicity among the studies $F(6, 433) = 28.38$, $p < .001$, with a significantly lower proportion of White participants and a significantly higher proportion of Hispanic participants in STS than the other two studies. Additional demographic characteristics by study involvement, including chi-square and significance values, may be found in Table 4.

*Clinical Characteristics by Study Involvement*

Study participation was not significantly associated with baseline depression severity (CDRS-R), number of comorbid diagnoses, age of onset of current MDD episode, age of onset of first MDD episode, or BMI at baseline. Additional clinical characteristics by study involvement, including relevant statistical tests and *p*-values, may be found in Table 5.

*Depression Severity by Study Involvement*

Though severity of depression, measured by the CDRS-R, was consistent across studies, severity of depression, measured by the CGI-S was not. Because data was ordinal in nature and normality was questionable, a Kruskal-Wallis test was performed to assess differences in CGI-S, and was found to be significant. *Post hoc* tests were performed by computing individual Mann-Whitney U tests among each study pair. Baseline CGI-S severity ratings were significantly higher in STS than the other two studies. Additionally, global assessment of functioning, as measured by the CGAS, was found to be significantly different among the studies, with lower scores of functioning in STS than in the other two studies. Overall, youth in STS were more likely to be experiencing a more severe episode of depression and worse functioning than youth in RR and RP.

*Current Depressive Episode by Study Involvement*

An association between primary diagnosis and study involvement was found to be significant, as participants in STS were more likely to be experiencing their first depressive episode, while participants in RR and RP were more likely to be experiencing a recurrent episode. An association between length of current depressive episode and study involvement was also found to be significant. Examination of cell

frequencies showed that youth in STS exhibit a longer duration of current depressive episode than those in RR and RP. Overall, youth in STS were significantly more likely to be experiencing a longer and more severe first depressive episode.

## DOSING SCHEDULE

### Dosing Schedule by Study Involvement

*Three Studies Across 6-week Acute Phase*

Because of the differing lengths of acute phase treatment among studies, we examined the mean prescribed dose of fluoxetine at each study visit. A repeated measures ANOVA was performed to compare dosing schedule among the three studies across the first 5 visits of the acute phase of treatment: baseline visit and 1, 2, 3, and 4-week post-baseline visits (visit 4 was the last clinician visit prior to the week 6 observation for two of the three studies). A significant within-subject effect for dose across acute treatment was found, $\Lambda = .028$, $F(4,368) = 3146.08$, $p < 0.001$. Mean dose increased from baseline to visit 1, but remained level through visit 4 for the majority of youth. The interaction of study involvement by dose across acute treatment was also found to be significant, $\Lambda = .728$, $F(8, 736) = 15.81$, $p < 0.001$. A significant difference in dose at visit 4 was found between STS and the other two studies. Clinicians in STS may have been more likely to increase fluoxetine dose at visit 4 as the acute phase was only 6 weeks, rather than 12 weeks in RR and RP. In addition, the univariate between-subjects effect for study involvement on dose was significant, $F(2,371) = 29.74$, $p < 0.001$. Pairwise comparisons were conducted using the Bonferroni method. At the 0.05 level, there was a significant dose by study effect between STS [$M = 19.14$ (.12)] and the other two studies (RR [$M = 17.96$ (.12)] and RP [$M = 17.78$ (.23)]). However, no significant differences in mean fluoxetine dose between RR and RP across the first 6 weeks of acute

treatment were found. A graphical representation of mean fluoxetine dose over acute treatment across the three studies is found in Figure 2.

*Two Studies across 12-week Acute Phase*

We also examined the dosing schedule across the 12-week acute phase in RR and RP by computing an ANOVA. We found a significant within-subject effect for fluoxetine dose across 12 weeks of acute treatment $\Lambda = .035$, $F(7, 168) = 624.58$, $p < 0.001$. In contrast to our examination of study involvement by fluoxetine dose among all three studies, there was not a significant interaction between study involvement and fluoxetine dose among the two studies over 12 weeks of acute treatment $\Lambda = .927$, $F(7, 168) = 1.78$, $p = .095$. Further, we found that the between-subjects effect for study involvement on overall mean fluoxetine dose was not significant, $F(1, 168) = 3.21$, $p = .075$. A graphical representation of mean fluoxetine dose over acute treatment across the two studies is found in Figure 3. In conclusion, these results confirm our assumption that the dose schedule in RR and RP are equivalent.

**Dosing by Weight Status Group**

We examined the mg/kg dose equivalent of fluoxetine across 12 weeks of acute treatment among weight status groups (normal, overweight, obese) in the RR and RP studies by computing an ANOVA. We found a significant within-subject effect for mg/kg dose equivalent of fluoxetine across 12 weeks of acute treatment $\Lambda = .158$, $F(7, 117) = 89.066$, $p < 0.001$. There was also a significant interaction between weight status and mg/kg dose equivalent of fluoxetine over 12 weeks of acute treatment $\Lambda = .768$, $F(14, 234) = 2.359$, $p < .01$. Further, we found that the between-subjects effect for weight status on overall mean mg/kg dose equivalent of fluoxetine was significant, $F(1, 126) = 15.379$, $p = < .001$, such that the obese group had significantly lower mean mg/kg dose equivalents of fluoxetine across the 12 weeks of

acute treatment. These findings remained significant when the mg/kg dose equivalents of fluoxetine among weight status groups were examined by age group (child, adolescent). A graphical representation of mean mg/kg dose equivalents of fluoxetine across acute treatment in the two studies is found in Figure 4. These findings support the inclusion of mg/kg dose equivalent of fluoxetine as a covariate in the following analyses.

## AIM I

### Demographic Characteristics by Weight Status

We examined baseline participant characteristics to determine whether weight status (normal weight, overweight, obese) had an impact on demographic characteristics prior to acute phase treatment with fluoxetine. Chi-square tests (for categorical variables) and one-way ANOVAS (for continuous variables) were performed to test the association between weight status and baseline demographic characteristics. Because highest parent education was ordinal in nature and exhibited questionable normality, a non-parametric test was used. Weight status was not found to be significantly associated with gender, age, or highest parent education. However, weight status, was found to be significantly associated with ethnicity. An additional analysis was performed to examine the relationship between baseline demographic characteristics and baseline BMI z-score (continuous variable). Baseline BMI z-score was not found to be significantly associated with gender, age, or highest parent education. However, ethnicity was found to be significantly associated with baseline BMI z-score, $F(3, 430) = 4.06$, $p < .01$. Additional demographic characteristics by weight status, including relevant statistical tests and *p*-values, may be found in Table 6.

*Ethnicity by Weight Status*

Weight status was found to be significantly associated with ethnicity, $X^2(6, 430) = 22.23$, $p < .001$. The Bonferroni method was used to perform pairwise comparisons following a significant overall test result. Examination of the cell frequencies showed that 23.5% (20 out of 85) of obese participants were African American while only 9.7% (25 out of 258) and 8% (7 out of 87) of normal and overweight participants, respectively, were African American.

**Demographic Characteristics by Obesity Status**

We examined baseline participant characteristics to determine whether obesity status (not obese, obese) had an impact on demographic characteristics prior to acute phase treatment with fluoxetine. Chi-square tests (for categorical variables) and one-way ANOVAS (for continuous variables) were performed to test the association between obesity status and baseline demographic characteristics. Because highest parent education was ordinal in nature and exhibited questionable normality, a non-parametric test was used. Obesity status was not found to be significantly associated with gender, age, or highest parent education. However, obesity status was found to be significantly associated with ethnicity. Additional demographic characteristics by obesity status, including relevant statistical tests and *p*-values, may be found in Table 7.

*Ethnicity by Obesity Status*

Obesity status was found to be significantly associated with ethnicity, $X^2(3, 430) = 15.62$, $p < .01$. The Bonferroni method was used to perform pairwise comparisons following a significant overall test result. Examination of the cell frequencies showed that 23.5% (20 out of 85) of obese participants were African American compared to 9.3% (32 out of 345) of participants who were not obese. Examination of

cell frequencies also showed that 54.1% of those who were obese were Caucasian, while 66.1% of those who were not obese were Caucasian.

**Clinical Characteristics by Weight Status**

We also examined baseline clinical characteristics of depression to determine whether weight status (normal weight, overweight, obese) had an impact on clinical characteristics of depression prior to acute phase treatment with fluoxetine. Chi-square tests (for categorical variables) and one-way ANOVAS (for continuous variables) were performed to test the association between weight status and baseline demographic characteristics. ANCOVAS were performed to test the association between weight status and age of onset of current episode and age of onset of depressive illness while controlling for current age. Because data was ordinal in nature and normality was questionable, a Kruskal-Wallis test was performed to assess differences in the CGI-S. Weight status was not found to be significantly associated with primary diagnosis, family history, number of MDD episodes, or number of comorbid diagnoses. Additionally, depression severity, as measured by the CDRS-R and CGI-S, global functioning, as measured by the CGAS, duration of current episode, age of onset of current episode, age of onset of current depressive illness, and length of current depressive illness were equivalent between the weight status groups. An additional analysis was performed to examine the relationship between baseline clinical characteristics and baseline BMI z-score (continuous variable). Baseline BMI z-score was not found to be significantly associated with baseline clinical characteristics. See Table 8 for relevant statistical data on the baseline clinical characteristics of depression by weight status.

**Clinical Characteristics by Obesity Status**

We also examined baseline clinical characteristics of depression to determine whether obesity status (not obese, obese) had an impact on clinical characteristics of depression prior to acute phase treatment with fluoxetine. Chi-square tests (for categorical variables) and one-way ANOVAS (for continuous variables) were performed to test the association between obesity status and baseline demographic characteristics. ANCOVAS were performed to test the association between obesity status and age of onset of current episode and age of onset of depressive illness while controlling for current age. Because data was ordinal in nature and normality was questionable, a Kruskal-Wallis test was performed to assess differences in the CGI-S. Obesity status was not found to be significantly associated with primary diagnosis, number of MDD episodes, or number of comorbid diagnoses. Additionally, depression severity, as measured by the CDRS-R and CGI-S, global functioning, as measured by the CGAS, duration of current episode, age of onset of current episode, age of onset of current depressive illness, and length of current depressive illness were equivalent between the obesity status groups. However, obesity status was found to be significantly associated with a family history of depression. See Table 9 for relevant statistical data on the baseline clinical characteristics of depression by obesity status.

*Family History by Obesity Status*

Obesity status was found to be significantly associated with family history, $X^2$ (1, 425) = 4.42, $p <$ .05. The Bonferroni method was used to perform pairwise comparisons following a significant overall test result. Examination of the cell frequencies showed that 71.4% (60 out of 85) of obese participants had a positive family history of depression, compared to 59.2% (202 of 345) of participants who were not obese.

# AIM II

## Rationale for STS Exclusion

There are several differences in the methodology among STS and the other two studies, RR and RP. STS has a shorter acute phase (6 weeks) than RR and RP (12 weeks). Additionally, as outlined previously, we found a significant difference in fluoxetine dosing schedules and in baseline clinical characteristics among STS and the other two studies, including severity on the CGI-S, primary diagnosis, and length of current episode. Due to these differences, the three studies cannot be assumed to accurately represent the larger sample. Therefore, remaining analyses will be conducted on the smaller sample of RR and RP, excluding youth in STS. Furthermore, by excluding STS, we will be able to investigate response throughout the longer 12-week acute phase. Demographic information on the pooled sample including RR and RP (N = 234) are listed in Table 10.

## Factors Associated with Acute Outcome

Prior to completing further analyses, we examined demographic and clinical characteristics to determine whether any differences were associated with outcome, as measured by remission at week 12. There were no significant differences in gender, ethnicity, or highest parent education among responders and non-responders. A significant difference in age among responders and non-responders was found, as expected, such that children were more likely experience response than adolescents $X^2 (1, 180) = 6.24$, $p < .05$. In regard to baseline clinical characteristics, family history of depression was found to be significantly associated with remission status at week 12, such that youth with a positive family history were more likely to remit than youth with no family history of depression. Additionally, normal weight in

adolescents was found to be associated with remission. See Table 11 and Table 12 for relevant statistical values on the demographic and clinical characteristics associated with acute outcome.

**Weight Status on Depressive Symptoms across Acute Treatment**

Data from a total of 226 subjects in RR and RP were included in the following analysis. The change over time (Weeks 1, 2, 3, 4, 6, 8, 10, 12) in depressive symptoms (CDRS-R total score) was compared between levels of weight status (normal weight, overweight, obese) using a linear mixed model analysis of repeated measures. The fixed effects in the model were weight status (normal weight, overweight, obese), time period (Weeks 1, 2, 3, 4, 6, 8, 10, 12), and the interaction of weight status by time period. Study involvement (RR, RP) was included in the model as a random effect. Baseline covariates that were included in the model were age, gender, ethnicity, CDRS-R total score, duration of depressive episode (in months), and family history of depression. Restricted maximum likelihood estimation and Type 3 tests of fixed effects were used. Simple weight status group effects at each time period were also examined.

A significant overall improvement in depressive symptoms was observed across the 12 weeks of fluoxetine treatment (time effect, $p < .0001$). The main effect of weight status and the interaction effect of weight status by time period on depressive symptoms were not significant. Overall, across the entire 12 weeks, there were no differences between weight status (normal weight, overweight, and obese) on the omnibus least squares mean CDRS-R total scores [35.23 (SE=0.598) vs. 33.908 (SE=1.057) vs. 36.763 (SE=1.048)], respectively, $F(2, 203) = 1.85$, $p = 0.160$]. The weight status by time interaction effect also was not significant, $F(14, 196) = 0.87$, $p=.595$. A significant (post-hoc) simple weight status group effect was found on adjusted CDRS-R total scores at Week 10 ($p < .05$). See Table 13 for best-fitted model. See

Figure 5 for plot of adjusted least-squared means for CDRS-R total score across 12-week acute phase for each weight status group.

**Obesity Status on Depressive Symptoms across Acute Treatment**

A linear mixed model of analysis of repeated measures was computed to assess whether the change over time (weeks 1, 2, 3, 4, 6, 8, 10, 12) in depressive symptoms (CDRS-R total score) was associated with levels of obesity status (obese, not obese). The fixed effects in the model were obesity status (obese, not obese), time period (weeks 1, 2, 3, 4, 6, 8, 10, 12), and the interaction of obesity status by time period. Study involvement (RR, RP) was included in the model as a random effect. Baseline covariates that were included in the model were age, gender, ethnicity, CDRS-R total score, duration of depressive episode (in months), and family history of depression. Restricted maximum likelihood estimation and Type 3 tests of fixed effects were used. Simple obesity status group effects at each time period were also examined.

A significant overall improvement in depressive symptoms was observed across the 12 weeks of fluoxetine treatment (time effect, $p < .0001$). The main effect of obesity status and the interaction effect of obesity status by time period on depressive symptoms were not significant. Overall, across the entire 12 weeks, there were no differences between obesity status (obese, not obese) on the omnibus least squares mean CDRS-R total scores [36.773 (SE=1.048) vs. 34.905 (SE=0.519)], respectively, $F(1, 206) = 2.536$, $p = 0.113$]. The obesity status by time interaction effect also was not significant, $F(7, 198) = 1.313$, $p=.246$. A significant (*post-hoc*) simple obesity status group effect was found on adjusted CDRS-R total scores at Week 10 ($p < .05$). See Table 14 for best-fitted model. See Figure 6 for plot of adjusted least-squared means for CDRS-R total score across 12-week acute phase for each obesity status group.

**Weight Status on Remission Status**

To assess prediction of remission status at week 12, a logistic regression was performed with weight status group (normal weight, overweight, obese) as the predictor variable. We defined remission as a CDRS-R total score ≤ 28 and CGI-Improvement score of 1 or 2. Weight status was not found to be a significant predictor of remission status at week 12, $X^2$ (2, $N$ =178) = 1.344, $P$ = 0.511.

An additional logistic regression analysis was performed to examine the effect of weight status on remission status at week 12, while accounting for the effect of various demographic and clinical characteristics. We included age, gender, ethnicity, baseline depression severity (CDRS-R total score), duration of depressive illness, and family history of depression. The test of the full model was found to be significant $\chi^2$ (10, $N$ = 177) = 22.840, $p < 0.05$, indicating that, when taken together, the predictors reliably distinguished between remitters and non-remitters at week 12. When tested alone, age remained a significant predictor of remission status at week 12, $\chi^2$ (1, $N$ = 180) = 5.879, $p < 0.05$, indicating that younger age subjects are more likely to remit after 12 weeks of acute treatment. When tested alone, family history of depression also remained a significant predictor of remission status at week 12, $\chi^2$ (1, $N$ = 179) = 13.412, $p < 0.001$, indicating that those with a positive family history for depression are more likely to remit. Gender, ethnicity, baseline depression severity, and duration of depressive illness were removed from the full model because they did not have a significant effect on remission status. A test of the reduced model with age, family history of depression, and weight status was significant, $\chi^2$ (4, $N$ = 177) = 16.367, $p < 0.05$, indicating that the predictors as a set reliably distinguished between remitters and non-remitters at week 12. The overall classification rate was 75.7%, with a rate of 97.7% for remitted and 16.7% for not remitted. Weight status was again not a significant predictor of remission status. Age no longer remained a significant predictor of remission status in the reduced model. In the reduced model,

only family history of depression reliably predicted remission status at week 12. The odds of remission after 12 weeks of acute treatment with fluoxetine are 3.12 times greater in children and adolescents with a positive family history of depression. See Table 15 for relevant regression coefficients, chi-square tests of selected variables, odds ratios, and the 95% confidence intervals around them, for each model.

An additional regression was performed (post hoc) to better understand the relationship between age, weight status, and remission. The predictor variable was the interaction of weight status group and age category (child, adolescent). Family history of depression was also included in the model. The interaction of weight status and age category was found to be a significant predictor of remission status at week 12, $X^2$ (3, $N$ =222) = 12.484, $P < 0.01$. Family history of depression remained a significant predictor of remission.

**Obesity Status on Remission Status**

To assess prediction of remission status at week 12, a logistic regression was performed with obesity status group (obese, not obese) as the predictor variable. We defined remission as a CDRS-R total score $\leq 28$ and CGI-Improvement score of 1 or 2. Obesity status was not found to be a significant predictor of remission status at week 12, $X^2$ (1, $N$ =178) = .965, $P = 0.326$.

An additional logistic regression analysis was performed to examine the effect of weight status on remission status at week 12, while accounting for the effect of age and family history. The test of the full model was found to be significant $\chi^2$ (3, $N$ = 177) = 15.936, $p < 0.01$, indicating that, when taken together, the predictors reliably distinguished between remitters and non-remitters at week 12. See Table

16 for relevant regression coefficients, chi-square tests of selected variables, odds ratios, and the 95% confidence intervals around them, for each model.

### Impact of Weight Status on Time to Remission

To explore the relationship between weight status and time to remission while adjusting for the effects of other covariates, such as age, gender, ethnicity, family history of depression, baseline severity of depression (CDRS-R), and length of depressive illness, a Cox regression survival analysis was performed. A total of 222 cases were included in the analysis, 12 were lost due to missing values. The set of covariates predicted survival time fairly well, $\chi^2$ (10, $N$ =222) = 25.185, $p$ = < 0.01. Table 17 shows regression coefficients, degrees of freedom, $p$ values, and hazard ratios for covariates. After adjusting for covariates, weight status (normal weight, overweight, obese) did not have a statistically significant effect on survival time, $\chi^2$ (4, $N$ =222) = 21.819, $p$ = .505. Figure 7 provides an illustration of cumulative survival proportions by weight status. Age was found to be a reliable predictor of survival time ($p < .05$). Each year in age of youth decreased the likelihood of remission (hazard ratio = 0.900). In conclusion, shorter time to remission is related to younger age. However, shorter time to remission is not related to gender, ethnicity, baseline severity of depression (CDRS-R), length of depressive illness, family history of depression, or weight status (normal weight, overweight, obese).

## EXPLORATORY ANALYSES

### Sleep Disturbance and Obesity

To assess baseline obesity status in relation to sleep disturbance, a logistic regression was performed with sleep disturbance (no sleep disturbance, sleep disturbance) as the predictor variable and

obesity status (not obese, obese) as a binary outcome variable. A total of 141 (60.3%) of the sample had sleep disturbance. We defined sleep disturbance as a CDRS-R sleep item score ≥ 4. Sleep disturbance was not found to be a significant predictor of obesity status at baseline, $X^2$ (1, *N =234*) = .432, *p* = 0.511.

An additional step-wise logistic regression analysis was performed to examine the effect of sleep disturbance on baseline obesity, while accounting for the effect of various demographic and clinical characteristics. We included age, gender, baseline depression severity (CDRS-R total score), duration of depressive illness, and family history of depression. The test of the full model was not found to be significant $\chi^2$ (9, *N* = 234) = 9.477, *p* =.394, indicating that, when taken together, the predictors did not reliably distinguish between obese and non-obese participants at baseline. See Table 18 for relevant regression coefficients, chi-square tests of selected variables, odds ratios, and the 95% confidence intervals around them, for each model.

# CHAPTER FIVE

## Conclusions and Recommendations

## WEIGHT STATUS AND DEPRESSION

### Baseline Demographic Characteristics

Youth were categorized based on weight status (normal, overweight, obese) at baseline. In accordance with guidelines set forth by WHO in 2007, overweight was defined as having a BMI between 1 and 2 standard deviations above the mean and obesity was defined as 2 or more standard deviations above the mean. Weight status was not found to be associated with gender, age, or SES, but was found to be significantly associated with ethnicity.

No gender differences were found among obese children and adolescents, contrary to our hypotheses and other studies of weight status in youth (Blaine, 2008). Sex differences have been repeatedly found among overweight and obese youth with depression. The rational for such differences may involve differences in the endocrine system among males and females, gender role socialization, and psychosocial factors, such as sociocultural norms and expectations regarding weight gain in females (Dockray, 2009). The differences in findings may be a result of several differences in design among the present study and past studies of the depression-obesity relationship, including the diagnosis of depression by standard psychiatric interview and standardized measurement of height and weight (Goodman, 2002).

Age was not found to be associated with levels of weight status in the current study. Age has been found to play a role in the relationship between obesity and depression in numerous studies (Pine et al., 1997; Luppino et al. 2010). However, these findings contradict a large number of studies that did not find

an effect of age in the obesity-depression relationship (Carpenter et al., 2000). Due to the contradictory findings in the literature, the relationship between age and the obesity-depression association warrants further study.

Socio-economic status, as measured by highest parental education, was not found to be associated with weight status in the current study. Specifically, we predicted that high SES would be associated with obesity, but no relationship was found among these variables. This finding is in contrast to the existing literature on the obesity-depression association in youth. Higher SES has been consistently linked to greater appearance-related concerns and stigma associated with overweight and obesity, suggesting that obesity may have a greater emotional impact on youth from higher SES backgrounds (Dockray, 2009).

In the current study, weight status was found to be associated with ethnicity, such that African American participants were more highly represented in the obese group than in normal and overweight groups. Obesity status (not obese, obese) was also associated with ethnicity, such that African American participants were more highly represented in the obese group than in the non-obese group. Additionally, Caucasians were more highly represented in the non-obese group than in the obese group. This finding is in contrast to the existing literature regarding increased obesity-depression associations among white youth due to an increase in appearance-related concern and impact of weight-related stigma among white youth. Further, ethnic differences in weight perception have been observed in several US studies, with white adults being more likely to view themselves as overweight than African American or Hispanic adults, suggesting that overweight and obesity may have a greater emotional effect or impact on mood in white adults. Overall, African American adults have been shown to have the least amount of weight-

related stigma among all ethnic groups. Our contrasting findings may be due to insufficient numbers of ethnic minorities when compared with numbers of non-Hispanic white participants.

**Baseline Clinical Characteristics**

Weight status was not found to be associated with primary diagnosis, family history of depression, number of MDD episodes, number of comorbid diagnoses, global functioning as measured by the CGAS, duration of current episode, age of onset of current episode, age of onset of current depressive illness, and length of current depressive illness.

Depression severity, as measured by the CDRS-R and CGI-S, was not found to be associated with weight status, contrary to our hypothesis and the existing literature. Past studies have shown that obese youth were more likely to report anhedonia, negative self-esteem, and overall severity of depressive symptoms (Goldfield, Cerimoore, Bucholz, Obeid, & Flamont, 2010).

Obesity status was found to be significantly associated with a family history of depression, such that those with a positive family history of depression were more likely to be categorized as obese. This finding supports previous studies examining the obesity-depression association in youth. A potential rationale for this finding may involve the relationship between parental depression and reduced familial support. Parental depression has been associated with more withdrawn, less reactive, and more emotionally negative behavior toward children, which has been found to contribute to positive depression-obesity associations in youth (Lovejoy, Graczyk, O'Hare, & Neuman, 2000; Xie et al., 2005). Further research is needed in this area to better understand the relationship between obesity and depression and family history of depression.

**Defining BMI**

In the present study, the relationship between obesity and depression was examined using BMI as both a dichotomous and a continuous construct. This was done in response to contradictory findings in the literature on the association between obesity and depression. In a study exploring the association between relative body weight and obesity and clinical response to depression treatment with pharmacotherapy, investigators found that greater body weight (continuous BMI) predicted non-response to treatment with fluoxetine. However, they found that obesity status (dichotomous) did not predict non-response (Papakostas et al., 2004). This finding is consistent with previous studies exploring the relationship between obesity and treatment response. Carpenter, Hasin, Allison, and Faith (2000) identified a link between greater relative body weight and MDD, but not between obesity and MDD. This data suggests that defining obesity as a continuous construct, rather than as a minimum BMI may be better suited for studying the effects of excess weight on depression. In the present study, defining BMI as both a continuous and categorical construct also produced contrasting findings, consistent with the literature.

## WEIGHT STATUS AND ACUTE TREATMENT

A significant overall improvement in depressive symptoms was observed across the 12 weeks of fluoxetine treatment. We hypothesized that obese children and adolescents would show less improvement in depressive symptoms over acute treatment. However, contrary to our hypothesis, there were no overall differences between weight status groups on depressive symptoms. We did find a significant post-hoc simple weight status group effect on depression symptoms at week 10.

Our hypothesis that weight status would impact remission rates following acute treatment with fluoxetine in youth with MDD was partially supported. When comparing remission rates among weight status groups, we found that adolescents of normal weight more frequently remitted than overweight and obese adolescents. When examining predictive factors of remission, we found a positive interaction between age (children, adolescents) and weight status (normal weight, overweight, obese), such that normal weight children, as opposed to normal weight adolescents, were more likely to remit following 12 weeks of acute treatment. It is hard to be certain how age plays a role in the relationship between weight status and depression treatment outcomes. However, the present study consistently found that normal weight is prognostic indicator of positive outcome for depression.

In a study by Papakostas et al. (2004), greater body weight predicted non-response to treatment with fluoxetine. Therefore, our findings are supportive of previous adult studies examining the relationship between weight status and outcomes in the treatment of MDD. However, our findings were inconsistent with a recent study examining bidirectional relationships between BMI and treatment response in youth.

In a study by Mansoor et al. (in press), the bidirectional relationships between BMI and treatment response were examined in adolescents with treatment resistant major depression. Specifically, authors examined the impact of baseline BMI as a predictor and moderator of treatment response over 24 weeks of treatment with an SSRI (paroxetine, citalopram, or fluoxetine) or SNRI (venlafaxine) with or without the addition of cognitive behavioral therapy. Authors also examined changes in participants' BMI as a function of treatment assignment response. BMI was not found to be a predictor nor a moderator of treatment outcome following 24 weeks of treatment. Additionally, authors did not find a differential

change in BMI by treatment assignment or response. However, authors did find a significant differential increase in BMI in the overweight subgroup treated by an SSRI (as opposed to an SNRI). Post-hoc analyses revealed that paroxetine and citalopram resulted in significantly greater increase in BMI than fluoxetine. Authors concluded that overweight individuals treated with an SSRI, especially paroxetine or citalopram, may be particularly vulnerable to increases in BMI than normal individuals treated with fluoxetine and venlafaxine.

Having a positive family history of depression was the most robust predictor of remission following 12 weeks of acute treatment with fluoxetine and remained a significant predictor even after controlling for demographic and clinical characteristics. The odds of remission following 12 weeks of acute treatment with fluoxetine are more than 3 times greater in children and adolescents with a positive family history of depression. This finding was also reported in a study by Tao et al., 2009 using the RR sample, one of the three studies pooled in the present study. Authors postulated that youth with a positive family history for depression may have more of a "biologic depression" than youth without a family history of depression. They suggested that a "biologic depression" responds more favorably to treatment with medication, as opposed to individuals who have a different etiology, such as environmental stressors, that may respond less favorably to antidepressant medication. Youth with less of a "biologic depression" may respond more favorably to other forms of treatment, like psychotherapy aimed at helping youth develop coping and problem solving skills.

Our hypothesis that time to remission following 12 weeks of acute treatment with fluoxetine would be longer in obese or overweight participants was not supported. Weight status, obesity status, and

BMI as a continuous variable did not have an effect on time to remission. However, age was associated with a quicker time to achieve remission, such that shorter time to remission is related to younger age.

Our hypothesis that sleep disturbance would be associated with a higher likelihood of being obese was not supported. Sleep disturbance, as measured by a CDRS-R sleep item score ≥ 4, was not found to be a significant predictor of obesity status at baseline. This negative finding remained after controlling for the effect of various demographic and clinical characteristics. Future studies should consider using a different measurement for sleep disturbance and consider inter-rater reliability, rather than using one item from the CDRS-R.

## LIMITATIONS OF STUDY

Several limitations of this study should be considered in the above discussion. Because the present study was a secondary analysis of pooled data, no modifications to the methods or study procedures were made. Primary analyses involved evaluating the effectiveness of continuation treatment with pharmacotherapy or CBT on treatment or relapse prevention for MDD in youth. The sample size of the present study was adequate to assess the primary hypotheses, but may have been too small for adequate examination of secondary analyses since the studies were not initially designed to assess the impact of weight status on the nature of depressive episode or response to treatment. Therefore, the number of participants classified as obese was relatively small, which may have caused the level of significance in some of our analyses to reflect a lack of power to detect differences. This may be especially true in instances that required groups to be further differentiated by age, gender, and other various baseline characteristics. Further, the present study only included data from the 12-week acute

treatment phase of the study. It is possible that by only looking at this relatively short period, remission rates may be artificially inflated (72% in this study versus 30-40% reported in previous double-blind, placebo-controlled, pediatric antidepressant trials) (Cheung et al., 2005; March et al., 2004). Had the present study followed patients over a longer period of time, remission rates may have been lower.

A related limitation involves the definition of obesity used in this study. A very strict definition of obesity (BMI $\geq 97^{th}$ percentile) was applied to study participants in order to form weight status groups. Although the proportion of participants within the obesity and overweight groups were significantly greater than the proportion of obese and overweight youth in the general population, the use of this strict definition may have caused sample sizes within weight status groups to be too small for adequate power.

Another limitation of this study may be the use of Major Depressive Disorder as the only definition of depression. There may be an association among weight status and depression, but these associations may not exist in the most extreme form of depression. For example, previous studies on the impact of weight status on depression have defined depression as depressed mood or dysthymia, rather than MDD.

An additional limitation pertains to the exploratory aim involving the relationship between sleep disturbance and obesity. These findings are limited by the fact that this study was not originally designed to investigate this aim. This study defined sleep disturbance as a CDRS-R sleep item score $\geq 4$. The CDRS-R is a clinician-rated screening measure of depression. Future studies should use more sleep-specific measures, such as a sleep diary, actigraphy, or polysomnography. In conclusion, the negative findings of the exploratory aims of this study may have been limited by methodology. Due to contradictory findings in the literature, the relationship between sleep and obesity warrants further study.

## CLINICAL IMPLICATIONS

Though bidirectional associations among depression and obesity have been repeatedly examined and confirmed in the adult literature, this relationship remains less clear in youth. Our hypotheses that weight status would impact baseline characteristics of depression and outcome of treatment for depression in youth were partially supported.

In 2008, a primary objective outlined by the NIMH called for an enhanced understanding of individual variability in treatment response based on demographic and clinical factors. An understanding of how a patient's weight status may impact their depressive presentation can aid in a clinician's consideration of their treatment. The present study indicates that obese youth with depression differ from normal weight youth in regards to ethnicity and family history of depression. Additionally, the present study indicates that normal weight youth may have better outcomes when receiving acute fluoxetine treatment for depression. Further exploration is needed to fully understand the implications of the impact of these variables on a patient's depressive presentation and treatment outcomes. The present study also confirmed the finding by Tao et al., 2009 that a positive family history of depression reliably predicts remission following 12 weeks of acute treatment with fluoxetine, which may further aid clinicians in their understanding variability in treatment response.

The present study also compared the effect of assessing the depression-obesity relationship with BMI as both a categorical variable and a continuous variable. To our knowledge, this is the first study that

has used both definitions of excess weight in assessing the obesity-depression relationship in youth. In the adult literature, relative body weight (continuous BMI) was found to be associated with MDD and to predict non-response. However, categorical BMI was not found to be associated with MDD nor was it found to predict non-response (Papakostas et al., 2004; Carpenter et al., 2000). Therefore, the way BMI is defined is important and may contribute to the variation in the literature. Our findings suggest that the decision to define BMI as a continuous or a dichotomous variable does have a significant impact on studying the obesity-depression association, which is consistent with the adult literature.

In conclusion, excess weight is a large public health concern as data shows more and more children and adolescents being classified overweight or obese. Clearly, this has health implications , including mental health implications, as normal weight children and adolescents may have a better response to depression treatment. Normal weight may be a protective factor in youth as it is associated with remission from depression.

**FIGURES**

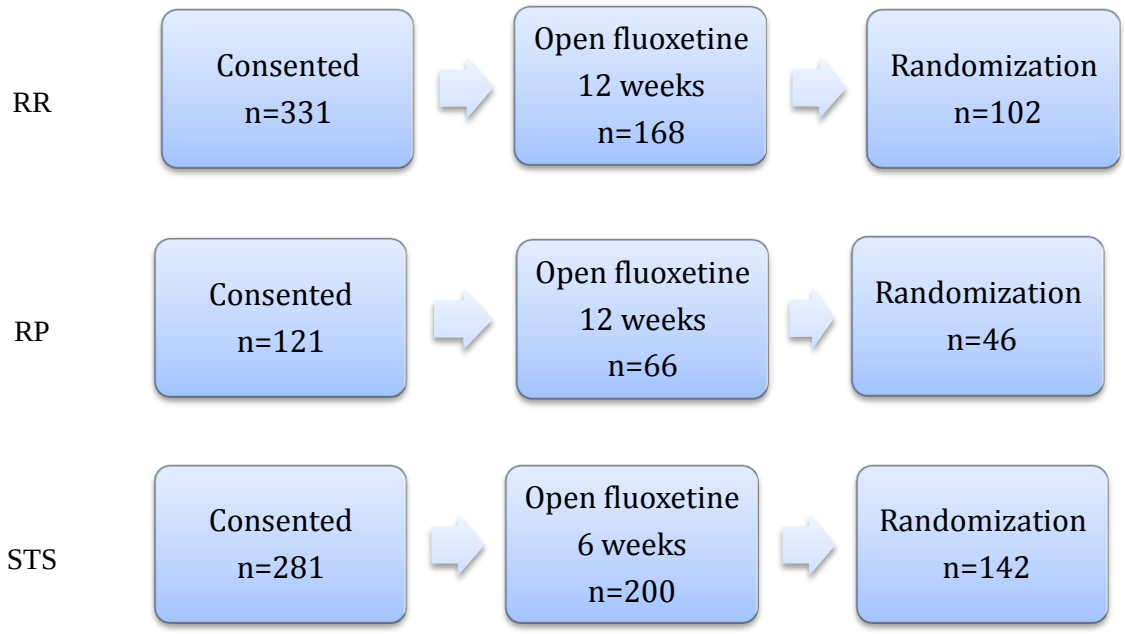


*Figure 1*. Participant flow chart in three studies of depression in youth.
*Note*. RR: PI = G. Emslie; RP: PI = B. Kennard; STS: PIs = G. Emslie and B. Kennard.

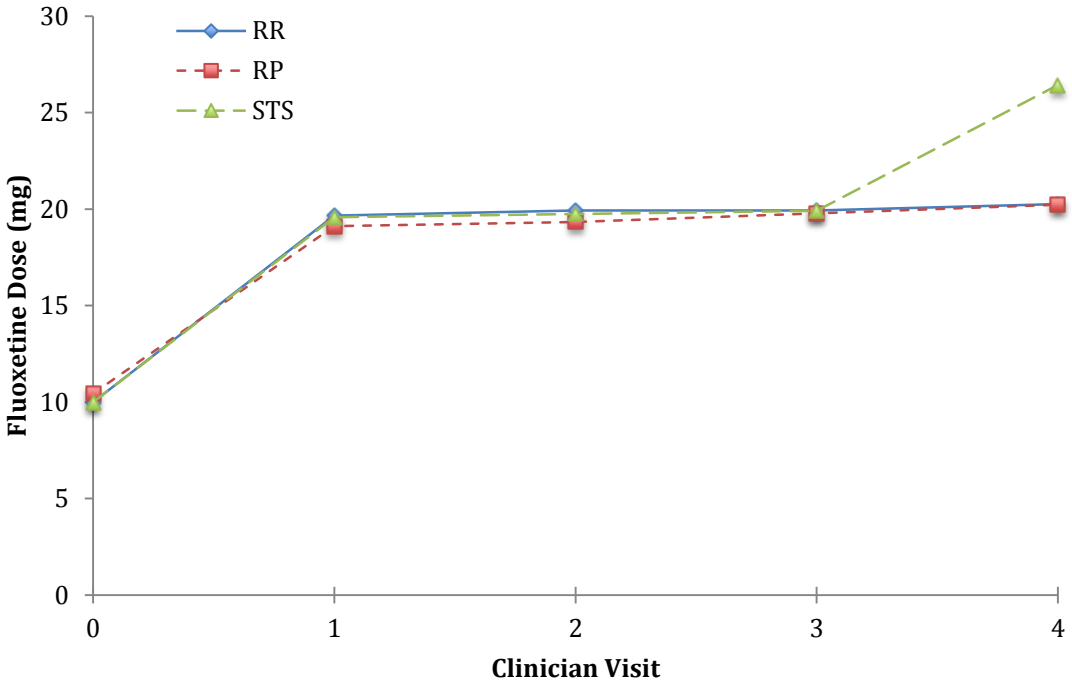


*Figure 2.* Plot of mean fluoxetine dose by study participation (RR, RP, STS) across first 6 weeks of acute treatment.

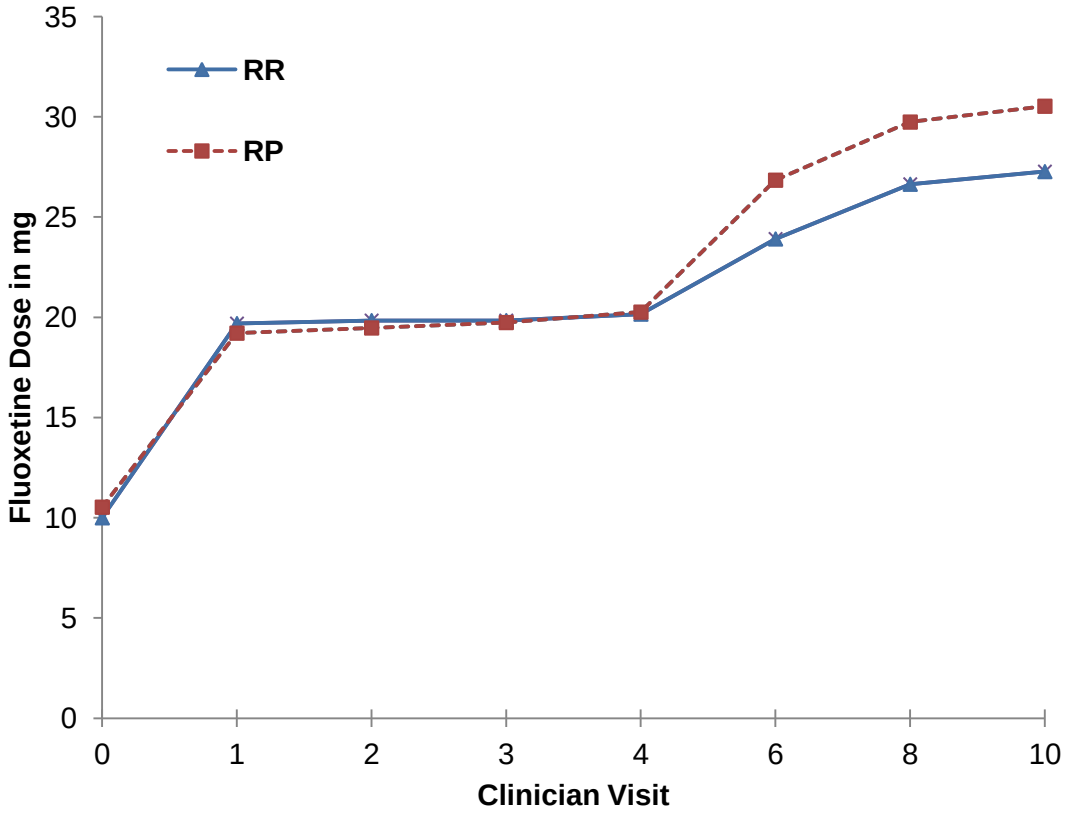


*Figure 3.* Plot of mean fluoxetine dose across 12-week acute phase in RR and RP

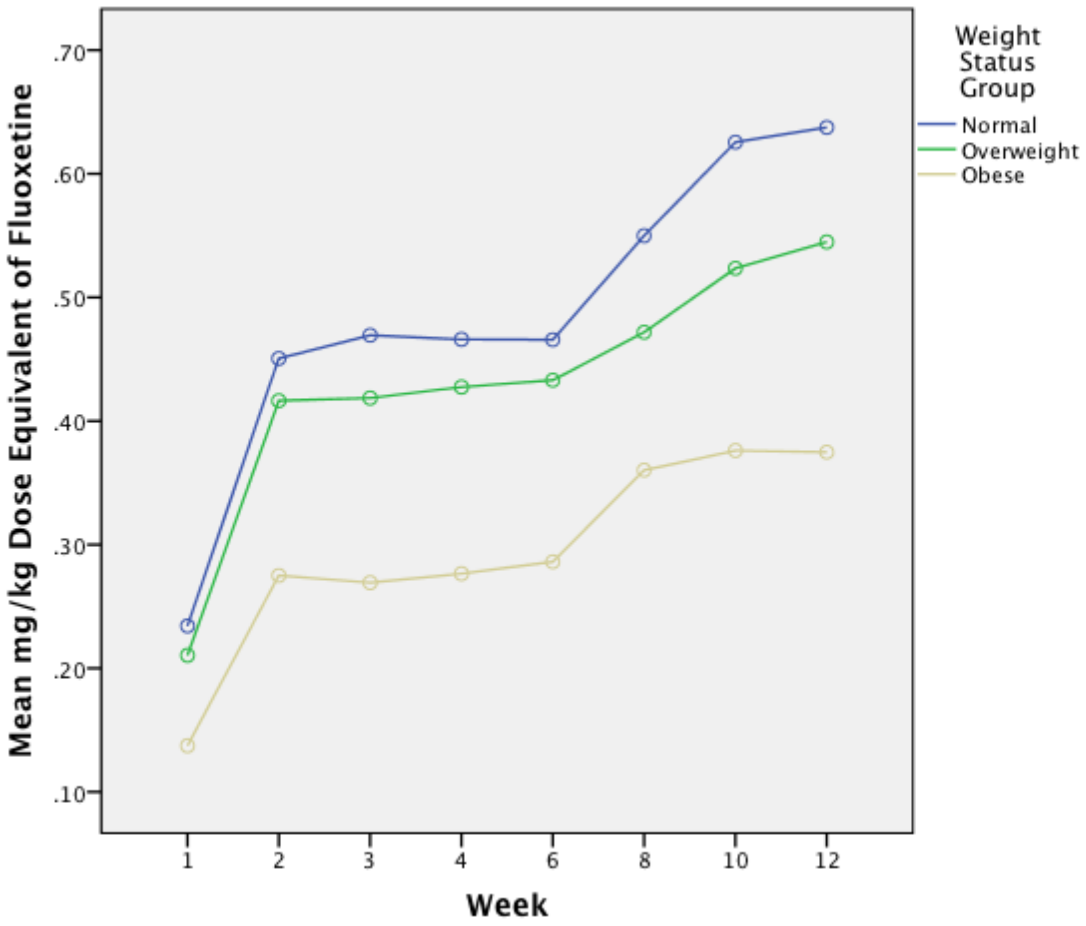


*Figure 4.* Plot of mean mg/kg dose equivalent of fluoxetine across 12-week acute phase in RR and RP.

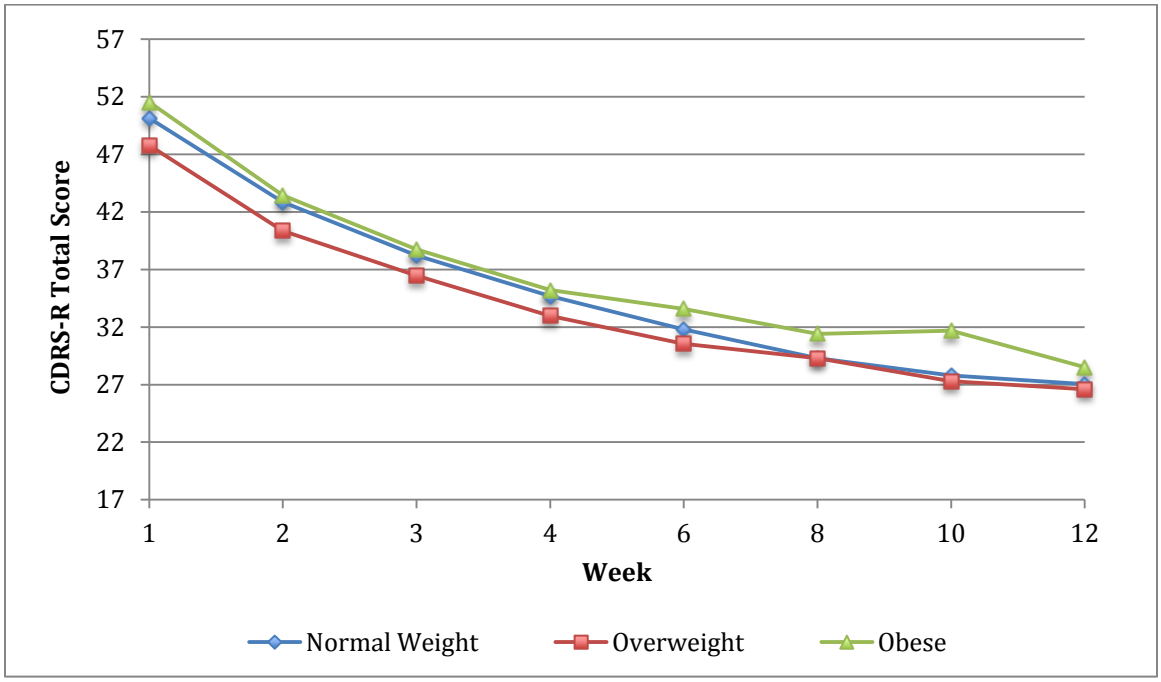


*Figure 5.* Plot of adjusted LS Means for CDRS-R total score across 12-week acute phase for each weight status group

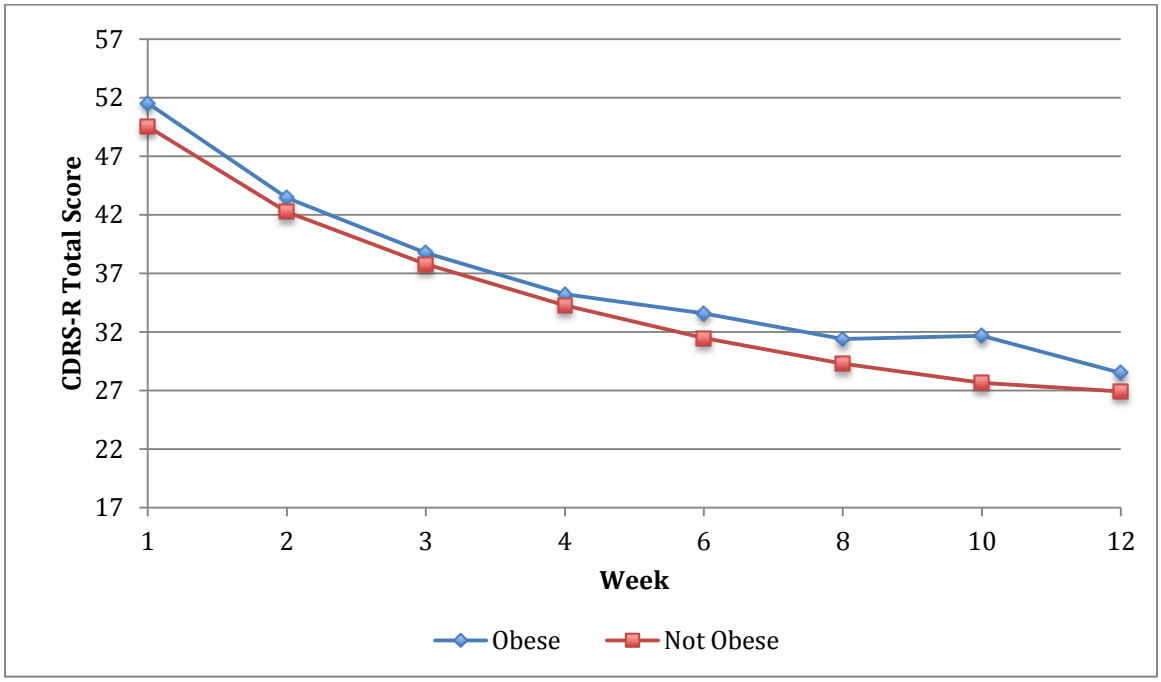


*Figure 6.* Plot of adjusted LS Means for CDRS-R total score across 12-week acute phase for each obesity status group

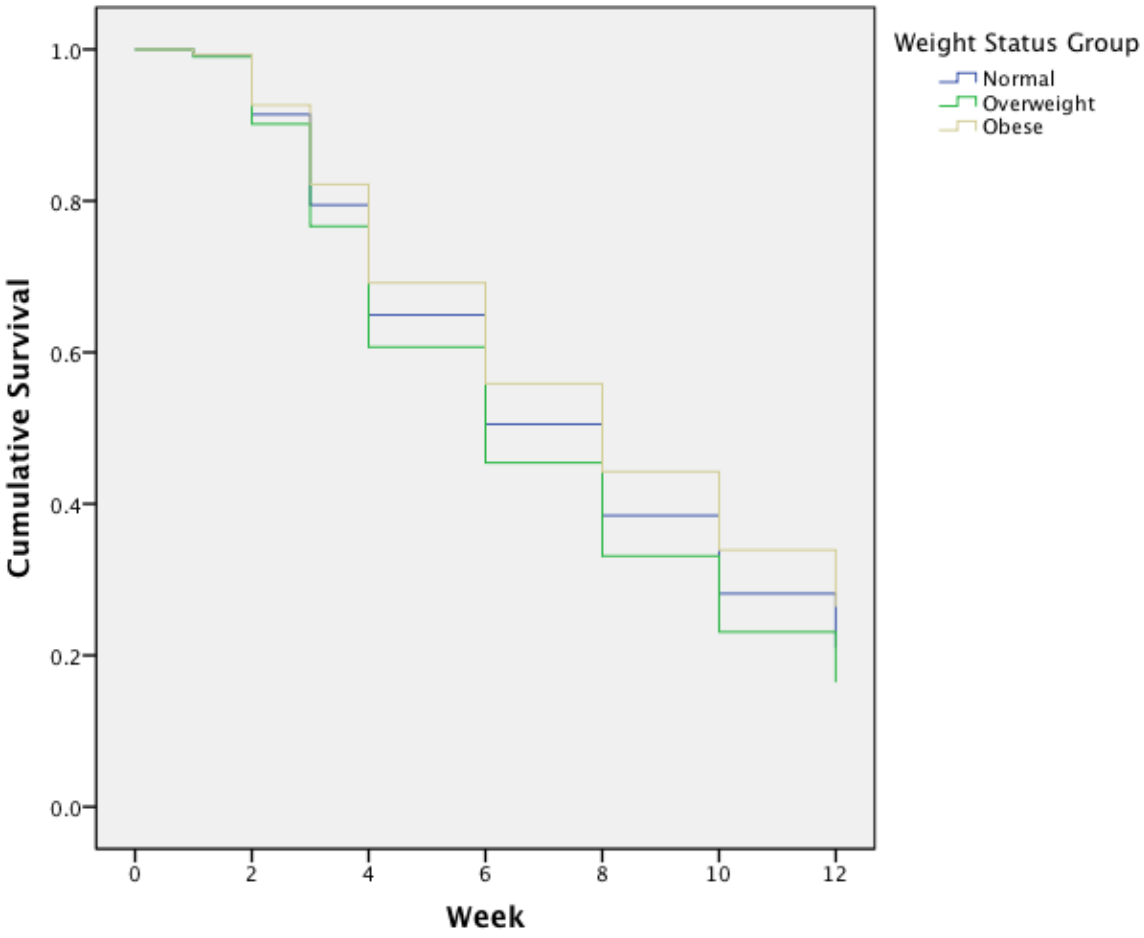


*Figure 7.* Survival Curve across 12 weeks acute treatment by Weight Status

## TABLES

Table 1

*Baseline Demographic Characteristics of Pooled Sample (n = 434)*

| Characteristic | *n* (%) | *M (SD)* |
|---|---|---|
| Gender | | |
| Male | 221 (50.9%) | |
| Female | 213 (49.1%) | |
| Age | | 13.15 (2.79) |
| Age Group | | |
| Child | 128 (29.5%) | |
| Adolescent | 306 (70.5%) | |
| Ethnicity | | |
| White | 275 (63.4%) | |
| Hispanic | 87 (20.0%) | |
| African American | 53 (12.2%) | |
| Other | 19 (4.4%) | |
| Highest Parent Education | | |
| Less than HS | 20 (5.0%) | |
| HS Graduate | 59 (14.8%) | |
| Partial College | 120 (30.1%) | |
| College Graduate | 125 (31.3%) | |
| Graduate Training | 75 (18.8%) | |

*Note.* HS=High School.

Table 2

*Baseline Clinical Characteristics of Pooled Sample (n = 434)*

| Characteristic | *n* (%) | *M (SD)* |
|---|---|---|
| Primary Diagnosis | | |
| Single Episode | 338 (77.9%) | |
| Recurrent | 96 (22.1%) | |
| Family History | | |
| Depression | 264 (61.5%) | |
| No depression | 165 (38.5%) | |
| Comorbid Diagnoses | | |
| 0 | 124 (28.6%) | |
| 1 | 174 (40.1%) | |
| 2 | 100 (23.0%) | |
| 3 or 4 | 36 (8.3%) | |
| Severity (CDRS-R) | | 58.36 (8.37) |
| Functioning (CGAS) | | 50.29 (6.20) |
| CE Duration (wk) | | 33.25 (31.57) |
| CE Age of Onset | | 12.52 (2.76) |
| Age of Onset of MDD | | 11.94 (2.84) |
| Length of Illness (mo) | | 12.94 (14.95) |
| Severity (CGI-S) | | 5.04 (0.68) |

*Note*. CE=Current Episode.

Table 3

*Weight-related Characteristics of Pooled Sample (n = 430)*

| Characteristic | *n* (%) | M (SD) | US Prevalence[a] | Texas Prevalence |
|---|---|---|---|---|
| Baseline BMI | | 1.30 (1.45)[d] | | |
| Underweight | 0 (0.0%) | | | |
| Normal | 258 (59.4%) | | | |
| Overweight | 87 (20.0%)[b,c] | | 15.0% | 15.6% |
| Obese | 85 (19.6%)[b,c] | | 13.0% | 13.6% |
| Child Baseline BMI | | 1.41 (1.46)[d] | | |
| Underweight | 0 (0.0%) | | | |
| Normal | 72 (56.7%) | | | |
| Overweight | 25 (19.7%) | | 14.6% | |
| Obese | 30 (23.6%)[b] | | 13.0% | |
| Adolescent Baseline BMI | | 1.25 (1.45)[d] | | |
| Underweight | 0 (0.0%) | | | |
| Normal | 186 (61.4%) | | | |
| Overweight | 62 (20.5%)[b] | | 15.2% | |
| Obese | 55 (18.2%)[b] | | 13.0% | |

*Note*. [a]US Prevalence based on percentiles from the Centers for Disease Control and Prevention's 2000 BMI-for-age growth charts. Overweight is defined as ≥85$^{th}$ percentile. Obesity is defined as ≥97$^{th}$ percentile.

[b]Sample prevalence is significantly greater than US Prevalence at $\alpha = .05$.

[c]Sample prevalence is significantly greater than TX Prevalence $\alpha = .05$.

[d]Mean of BMI z-score.

Table 4

*Demographic Characteristics of Patients by Study Involvement*

| | *n* (% within study) | | | |
|---|---|---|---|---|
| Characteristic | RR (*n* = 168) | RP (*n* = 66) | STS (*n* = 200) | $\chi^2$ |
| Gender | | | | 5.50 |
| Male | 97 (57.7%) | 33 (50.0%) | 91 (45.5%) | |
| Female | 71 (42.3%) | 33 (50.0%) | 109 (54.5%) | |
| Age Group | | | | 46.42*** |
| Child | 80 (47.6%)[a] | 6 (9.1%)[b] | 42 (21.0%)[b] | |
| Adolescent | 88 (52.4%)[a] | 60 (90.9%)[b] | 158 (79.0%)[b] | |
| Ethnicity | | | | 28.38*** |
| African American | 18 (10.7%)[a] | 3 (4.5%)[a] | 32 (16.0%)[a] | |
| White | 126 (75.0%)[a] | 47 (71.2%)[a] | 102 (51.0%)[b] | |
| Hispanic | 18 (10.7%)[a] | 14 (21.2%)[a,b] | 55 (27.5%)[b] | |
| Other | 6 (3.6%)[a] | 2 (3.0%)[a] | 11 (5.5%)[a] | |
| Highest Parent Education | | | | 1.75[c] |
| Less than HS | 4 (2.5%) | 3 (5.9%) | 13 (6.6%) | |
| HS Graduate | 33 (21.4%) | 4 (7.8%) | 22 (11.3%) | |
| Partial College | 46 (29.9%) | 15 (29.4%) | 59 (30.4%) | |
| College Graduate | 44 (28.6%) | 21 (41.2%) | 60 (30.9%) | |
| Graduate Training | 27 (17.5%) | 8 (15.7%) | 40 (20.6%) | |

*Note.* [a,b] Subsets sharing a common superscript are not statistically different at $\alpha = .05$. [c] represents results of chi-square statistic computed via Kruskal-Wallis method due to data being ordinal in nature.

***$p < .001$

Table 5

*Clinical Characteristics of Patients by Study Involvement*

| | *n* (% within study) | | | |
|---|---|---|---|---|
| Characteristic | RR (*n* = 168) | RP (*n* = 66) | STS (*n* = 200) | $\chi^2$ |
| Primary Diagnosis | | | | 26.52*** |
| Single Episode | 116 (69.0%)[a] | 44 (66.7%)[a] | 178 (89.0%)[b] | |
| Recurrent | 52 (31.0%)[a] | 22 (33.3%)[a] | 22 (11.0%)[b] | |
| Family History | | | | 8.96* |
| No depression | 49 (29.9%) | 25 (38.5%) | 91 (45.5%) | |
| Depression | 115 (70.1%) | 40 (61.5%) | 109 (54.5%) | |
| Comorbid Diagnoses | | | | 7.44 |
| 0 | 43 (25.6%) | 23 (34.8%) | 58 (29.0%) | |
| 1 | 71 (42.3%) | 29 (43.9%) | 74 (37.0%) | |
| 2 | 38 (22.6%) | 12 (18.2%) | 50 (25.0%) | |
| 3 or 4 | 16 (9.5%) | 2 (3.0%) | 18 (9.0%) | |
| Baseline BMI | | | | 0.09[c] |
| Underweight | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | |
| Normal Weight | 100 (59.9%) | 40 (61.5%) | 118 (59.6%) | |
| Overweight | 33 (19.8%) | 13 (20.0%) | 41(20.7%) | |
| Obese | 34 (20.4%) | 12 (18.5%) | 39 (19.7%) | |
| Child Baseline BMI | | | | |
| Underweight | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1.74[c] |
| Normal Weight | 43 (53.8%) | 2 (33.3%) | 27 (65.9%) | |
| Overweight | 17 (21.2%) | 1 (16.7%) | 7 (17.1%) | |
| Obese | 20 (25.0%) | 3 (50.0%) | 7 (17.1%) | |
| Adolescent Baseline BMI | | | | 3.64[c] |
| Underweight | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | |
| Normal Weight | 57 (65.5%) | 38 (64.4%) | 91 (58.0%) | |
| Overweight | 16 (18.4%) | 12 (20.3%) | 34 (21.7%) | |
| Obese | 14 (16.1%) | 9 (15.3%) | 32 (20.4%) | |
| | | *M (SD)* | | *F* |
| Severity (CDRS-R) | 57.60 (7.30) | 58.08 (9.71) | 58.10 (8.72) | 1.52 |
| Functioning (CGAS) | 52.01 (6.04)[a] | 51.20 (5.39)[a] | 48.55 (6.14)[b] | 16.08*** |
| CE Duration (wk) | 25.30 (21.10)[a] | 26.11 (22.68)[a] | 42.28 (38.39)[b] | 16.26*** |
| CE Age of Onset | 12.66 (0.80) | 12.44 (0.78) | 12.43 (0.78) | 0.57[d] |
| Age of Onset of MDD | 11.75 (2.46)[a] | 11.63 (3.83)[a] | 12.21 (2.17)[b] | 6.20[d]** |
| Length of Illness (mo) | 14.64 (17.63) | 9.04 (9.13) | 12.80 (13.80) | 3.38* |
| Baseline BMI z-score | 1.24 (1.25) | 1.34 (1.55) | 1.30 (1.58) | 0.29 |
| | | *M (SD)* | | $\chi^2$ |
| Severity (CGI-S) | 4.83 (0.64)[a] | 4.94 (0.78)[a] | 5.23 (0.72)[b] | 29.89*** |

*Note*. CE = Current Episode.

[a,b] Subsets sharing a common superscript are not statistically different at $\alpha = .05$.

[c] represents results of chi-square statistic computed via Kruskal-Wallis method due to data being ordinal in nature.

[d]*F* value represents results of analysis of covariance, controlling for participants' current age.
* $p < .05$, ** $p < .01$, *** $p < .001$.

Table 6

*Differences in Demographic Characteristics of Patients by Weight Status*

| Characteristic | *n* (% within study) | | | |
|---|---|---|---|---|
| | Normal (*n* = 258) | Overweight (*n* = 87) | Obese (*n* = 85) | $\chi^2$ |
| Gender | | | | 1.09 |
| Male | 135 (52.3%) | 45 (51.7%) | 39 (45.9%) | |
| Female | 123 (47.7%) | 42 (48.3%) | 46 (54.1%) | |
| Age Group | | | | 1.71 |
| Child | 72 (27.9%) | 25 (28.7%) | 30 (35.3%) | |
| Adolescent | 186 (72.1%) | 62 (71.3%) | 55 (64.7%) | |
| Ethnicity | | | | 22.23*** |
| African American | 25 (9.7%)[a] | 7 (8.0%)[a] | 20 (23.5%)[b] | |
| White | 174 (67.4%)[a] | 54 (62.1%)[a] | 46 (54.1%)[a] | |
| Hispanic | 43 (16.7%)[a] | 24 (27.6%)[a] | 18 (21.2%)[a] | |
| Other | 16 (6.2%)[a] | 2 (2.3%)[a] | 1 (1.2%)[a] | |
| Highest Parent Education | | | | 8.75[c] |
| Less than HS | 10 (4.1%) | 4 (5.0%) | 6 (7.7%) | |
| HS Graduate | 28 (11.9%) | 16 (20.0%) | 15 (19.0%) | |
| Partial College | 72 (30.5%) | 24 (30.0%) | 24 (30.4%) | |
| College Graduate | 76 (32.2%) | 25 (31.2%) | 20 (25.3%) | |
| Graduate Training | 50 (21.2%) | 11 (13.8%) | 14 (17.7%) | |

*Note*. [a,b] Subsets sharing a common superscript are not statistically different at $\alpha = .05$.
[c] value represents results of chi-square statistic computed via Kruskal-Wallis method due to data being ordinal in nature.
***$p < .001$

Table 7

*Differences in Demographic Characteristics of Patients by Obesity Status*

| | *n* (% within obesity status group) | | |
|---|---|---|---|
| Characteristic | Not Obese (*n* = 345) | Obese (*n* = 85) | $\chi^2$ |
| Gender | | | 1.08 |
| Male | 180 (52.2%) | 39 (45.9%) | |
| Female | 165 (47.8%) | 46 (54.1%) | |
| Age Group | | | 1.69 |
| Child | 97 (28.1%) | 30 (35.3%) | |
| Adolescent | 248 (71.9%) | 55 (64.7%) | |
| Ethnicity | | | 15.62** |
| African American | 32 (9.3%)[a] | 20 (23.5%)[b] | |
| White | 228 (66.1%)[a] | 46 (54.1%)[b] | |
| Hispanic | 67 (19.4%)[a] | 18 (21.2%)[a] | |
| Other | 18 (5.2%)[a] | 1 (1.2%)[a] | |
| Highest Parent Education | | | 2.09[c] |
| Less than HS | 10 (4.1%) | 4 (5.0%) | |
| HS Graduate | 28 (11.9%) | 16 (20.0%) | |
| Partial College | 72 (30.5%) | 24 (30.0%) | |
| College Graduate | 76 (32.2%) | 25 (31.2%) | |
| Graduate Training | 50 (21.2%) | 11 (13.8%) | |

*Note.* [a,b] Subsets sharing a common superscript are not statistically different at $\alpha = .05$.
[c] value represents results of chi-square statistic computed via Kruskal-Wallis method due to data being ordinal in nature.
**$p < .01$

Table 8

*Baseline Clinical Characteristics of Depression by Weight Status*

| | *n* (% within weight status group) | | | |
|---|---|---|---|---|
| Characteristic | Normal (*n* = 258) | Overweight (*n* = 87) | Obese (*n* = 85) | $\chi^2$ |
| Primary Diagnosis | | | | 1.49 |
| Single Episode | 198 (76.7%) | 72 (82.8%) | 65 (76.5%) | |
| Recurrent | 60 (23.3%) | 15 (17.2%) | 20 (23.5%) | |
| Family History | | | | 4.36 |
| No Depression | 103 (40.2%) | 36 (42.4%) | 24 (28.6%) | |
| Depression | 153 (59.8%) | 49 (57.6%) | 60 (71.4%) | |
| Number of Episodes | | | | 1.04 |
| 1 | 201 (77.9%) | 72 (82.8%) | 65 (76.5%) | |
| 2 | 48 (18.6%) | 11 (12.6%) | 16 (18.8%) | |
| 3 or 4 | 9 (3.5%) | 4 (4.5%) | 4 (4.7 %) | |
| Comorbid Diagnoses | | | | 0.02 |
| 0 | 73 (28.3%) | 28 (32.2%) | 21 (24.7%) | |
| 1 | 105 (40.7%) | 27 (31.0%) | 40 (47.1%) | |
| 2 | 54 (20.9%) | 26 (29.9%) | 20 (23.5%) | |
| 3 or 4 | 26 (10.1%) | 6 (6.9%) | 4 (4.8%) | |
| | | *M (SD)* | | *F* |
| Severity (CDRS-R) | 57.37 (8.53) | 58.06 (8.30) | 58.81 (8.13) | 0.18 |
| Functioning (CGAS) | 50.49 (6.39) | 50.23 (6.15) | 49.66 (6.72) | 1.04 |
| CE Duration (wk) | 31.06 (24.30) | 36.07 (41.05) | 37.95 (39.18) | 1.90 |
| CE Age of Onset | 12.57 (2.75) | 12.66 (2.89) | 12.21 (2.67) | 0.03[a] |
| Age of Onset of MDD | 12.00 (2.79) | 12.06 (3.11) | 11.64 (2.76) | 1.87[a] |
| Length of Illness (mo) | 12.71 (13.99) | 12.93 (16.13) | 14.07 (16.76) | 0.26 |
| | | *M (SD)* | | $\chi^2$ |
| Severity (CGI-S) | 5.05 (0.73) | 5.01 (0.71) | 4.98 (0.74) | 0.69 |

*Note*. CE = Current Episode.

[a]*F* value represents results of analysis of covariance, controlling for participants' current age.

Table 9

*Baseline Clinical Characteristics of Depression by Obesity Status*

| | *n* (% within obesity status group) | | |
|---|---|---|---|
| Characteristic | Not Obese (*n* = 345) | Obese (*n* = 85) | $\chi^2$ |
| Primary Diagnosis | | | 0.13 |
| Single Episode | 270 (78.3%) | 65 (76.5%) | |
| Recurrent | 75 (21.7%) | 20 (23.5%) | |
| Family History | | | 4.24* |
| No Depression | 139 (40.8%)[a] | 24 (28.6.%)[b] | |
| Depression | 202 (59.2%)[a] | 60 (71.4%)[b] | |
| Number of Episodes | | | 2.15 |
| 1 | 273 (79.1%) | 65 (76.5%) | |
| 2 | 59 (17.1%) | 16 (18.8%) | |
| 3 or 4 | 13 (3.8%) | 4 (4.7%) | |
| Comorbid Diagnoses | | | 4.77 |
| 0 | 101 (29.3%) | 21 (24.7%) | |
| 1 | 132 (38.3%) | 40 (47.1%) | |
| 2 | 80 (23.2%) | 20 (23.5%) | |
| 3 or 4 | 32 (9.2%) | 4 (4.8%) | |
| | *M (SD)* | | *F* |
| Severity (CDRS-R) | 58.29 (8.46) | 58.81 (8.13) | 0.26 |
| Functioning (CGAS) | 51.82 (5.93) | 51.17 (6.49) | 0.42 |
| CE Duration (wk) | 32.32 (29.45) | 37.95 (39.18) | 2.17 |
| CE Age of Onset | 12.01 (2.75) | 11.63 (2.89) | 0.65[c] |
| Age of Onset of MDD | 12.59 (2.79) | 12.21 (2.67) | 0.07[c] |
| Length of Illness (mo) | 12.77 (14.53) | 14.07 (16.75) | 0.51 |
| | *M (SD)* | | $\chi^2$ |
| Severity (CGI-S) | 5.04 (0.72) | 4.98 (0.74) | 0.45 |

*Note*. CE = Current Episode.

[a,b] Subsets sharing a common superscript are not statistically different at $\alpha = .05$.

[c] F value represents results of analysis of covariance, controlling for participants' current age.

* $p < .05$

Table 10

*Demographic and Clinical Characteristics of Two Studies, RR and RP (n = 234)*

| Demographic Characteristics | | Clinical Characteristics | |
|---|---|---|---|
| | *n* (%) | | *n* (%) |
| Gender | | Baseline BMI | |
| Male | 130 (55.6%) | Underweight | 0 (0.0%) |
| Female | 104 (44.4%) | Normal Weight | 140 (59.8%) |
| Age Group | | Overweight | 46 (19.7%) |
| Child | 86 (36.8%) | Obese | 46 (19.7%) |
| Adolescent | 148 (63.2%) | Child Baseline BMI | |
| Ethnicity | | Underweight | 0 (0.0%) |
| African American | 21 (9.0%) | Normal Weight | 45 (52.3%) |
| White | 173 (73.9%) | Overweight | 18 (20.9%) |
| Hispanic | 32 (13.7%) | Obese | 23 (26.7%) |
| Other | 8 (3.4%) | Adolescent Baseline BMI | |
| Highest Parent | | Underweight | 0 (0.0%) |
| Education | | Normal Weight | 95 (64.2%) |
| Less than HS | 7 (2.9%) | Overweight | 28 (18.9%) |
| HS Graduate | 37 (15.8%) | Obese | 23 (15.5%) |
| Partial College | 61 (26.1%) | Primary Diagnosis | |
| College Graduate | 65 (27.8%) | Single Episode | 160 (68.4%) |
| Graduate Training | 35 (15.0%) | Recurrent | 74 (31.6%) |
| | | Family History | |
| | | Depression | 74 (31.6%) |
| | | No depression | 155 (67.7%) |
| | | Comorbid Diagnoses | |
| | | 0 | 66 (28.2%) |
| | | 1 | 100 (42.7%) |
| | | 2 | 50 (21.4%) |
| | | 3 or 4 | 18 (7.7%) |
| | *M (SD)* | | *M (SD)* |
| Age | 12.59 (2.86) | Severity (CDRS-R) | 57.73 (8.03) |
| | | Functioning (CGAS) | 51.73 (6.05) |
| | | CE Duration (wk) | 25.53 (21.51) |
| | | CE Age of Onset | 12.06 (2.75) |
| | | Age of Onset of MDD | 11.23 (2.78) |
| | | Length of Illness (mo) | 13.06 (15.89) |
| | | Severity (CGI-S) | 4.86 (0.68) |
| | | Baseline BMI z-score | 1.27 (1.34) |

*Note*. CE = current episode. HS = high school.

Table 11

*Demographic Characteristics Associated with Remission at Week 12*

| | *n* (% within characteristic) | | |
|---|---|---|---|
| Characteristic | Not Remitted (*n* = 51) | Remitted (*n* = 129) | $\chi^2$ |
| Age | | | 6.24* |
| Child | 13 (18.1%)[a] | 59 (81.9%)[b] | |
| Adolescent | 38 (35.2%)[a] | 70 (64.8%)[b] | |
| Gender | | | 0.53 |
| Male | 27 (26.2%) | 76 (73.8%) | |
| Female | 24 (31.2%) | 53 (68.8%) | |
| Ethnicity | | | 1.04 |
| White | 39 (30.0%) | 91 (70.0%) | |
| Hispanic | 5 (20.0%) | 20 (80.0%) | |
| African American | 5 (27.8%) | 13 (72.2%) | |
| Other | 2 (28.6%) | 5 (71.4%) | |
| Highest Parent Education | | | |
| Less than HS | 2 (28.6%) | 5 (71.4%) | 0.01[c] |
| HS Graduate | 10 (33.3%) | 20 (66.7%) | |
| Partial College | 11 (22.9%) | 37 (77.1%) | |
| College Graduate | 14 (25.9%) | 40 (74.1%) | |
| Graduate Training | 9 (33.3%) | 18 (66.7%) | |

*Note*. CE = Current Episode.

[a,b] Subsets sharing a common superscript are not statistically different at $\alpha = .05$.

[c] value represents results of chi-square statistic computed via Kruskal-Wallis method due to data being ordinal in nature.

* $p < .05$

Table 12

*Baseline Clinical Characteristics of Depression Associated with Remission at Week 12*

| | *n* (% within characteristic) | | |
|---|---|---|---|
| Characteristic | Not Remitted (*n* = 51) | Remitted (*n* = 129) | $\chi^2$ |
| Primary Diagnosis | | | 0.10 |
| Single Episode | 36 (27.2%) | 94 (72.3%) | |
| Recurrent | 15 (30.0%) | 35 (70.0%) | |
| Family History | | | 13.90*** |
| No Depression | 27 (45.8%)[a] | 32 (54.2%)[b] | |
| Depression | 23 (19.2%)[a] | 97 (80.8%)[b] | |
| Number of Episodes | | | 0.36 |
| 1 | 36 (27.7%) | 94 (72.3%) | |
| 2 | 12 (28.6%) | 30 (71.4%) | |
| 3 or 4 | 3 (37.5%) | 5 (62.5%) | |
| Comorbid Diagnoses | | | 5.74 |
| 0 | 16 (32.7%) | 33 (67.3%) | |
| 1 | 19 (26.4%%) | 53 (73.6%) | |
| 2 | 9 (20.0%) | 36 (80.0%) | |
| 3 or 4 | 7 (50.0%) | 7 (50.0%) | |
| Baseline BMI | | | 1.34[c] |
| Underweight | 0 (0.0%) | 0 (0.0%) | |
| Normal Weight | 26 (24.5%) | 80 (75.5%) | |
| Overweight | 11 (29.7%) | 26 (70.3%) | |
| Obese | 12 (34.3%) | 23 (65.7%) | |
| Child Baseline BMI | | | 0.03[c] |
| Underweight | 0 (0.0%) | 0 (0.0%) | |
| Normal Weight | 8 (21.6%) | 29 (79.4%) | |
| Overweight | 0 (0.0%) | 15 (100.0%) | |
| Obese | 5 (25.0%) | 15(75.0%) | |
| Adolescent Baseline BMI | | | 4.98[c]* |
| Underweight | 0 (0.0%)[a] | 0 (0.0%)[a] | |
| Normal Weight | 18 (26.1%)[a] | 51 (73.9%)[b] | |
| Overweight | 11 (50.0%)[a] | 11 (50.0%)[a] | |
| Obese | 7 (46.7%)[a] | 8 (53.3%)[a] | |
| | *M (SD)* | | *F* |
| Severity (CDRS-R) | 58.45 (9.18) | 57.76 (7.13) | 0.19 |
| Functioning (CGAS) | 52.45 (6.00) | 51.57 (4.67) | 0.71 |
| CE Duration (wk) | 29.53 (25.34) | 25.54 (20.43) | 0.79 |
| CE Age of Onset | 12.57 (2.75) | 11.58 (2.74) | 1.37[d] |
| Age of Onset of MDD | 11.90 (2.71) | 10.90 (2.83) | 2.96[d] |
| Length of Illness (mo) | 11.63 (9.61) | 13.91 (16.19) | 0.63 |
| Baseline BMI z-score | 1.35 (1.51) | 1.24 (1.27) | 0.29 |
| | *M (SD)* | | $\chi^2$ |
| Severity (CGI-S) | 4.93 (0.67) | 4.81 (0.68) | 0.12 |

*Note*. CE = Current Episode.
[a,b] Subsets sharing a common superscript are not statistically different at α = .05.
[c] value represents results of chi-square statistic computed via Kruskal-Wallis method due to data being ordinal in nature.
[d] *F* value represents results of analysis of covariance, controlling for participants' current age.
* $p < .05$, *** $p < .001$

Table 13

*Linear Mixed Model Repeated Measures Analysis by Weight Status*

| Fixed Effects | Num df | Den df | *F*-value | *p* |
|---|---|---|---|---|
| Weight Status | 2 | 203 | 1.847 | 0.160 |
| Time (CDRS-R) | 7 | 195 | 114.552 | <.0001 |
| Weight Status*Time | 14 | 195 | 0.868 | 0.595 |
| Age | 1 | 204 | 17.330 | <.0001 |
| Gender | 1 | 210 | 0.157 | 0.693 |
| Ethnicity | 1 | 206 | 0.016 | 0.899 |
| Baseline Severity (CDRS-R) | 1 | 216 | 152.233 | <.0001 |
| Length of Illness (mo) | 1 | 215 | 3.121 | 0.079 |
| Family History of Depression | 1 | 210 | 1.451 | 0.230 |

Table 14

*Linear Mixed Model Repeated Measures Analysis by Obesity Status*

| Fixed Effects | Num df | Den df | *F*-value | *p* |
|---|---|---|---|---|
| Obesity Status | 1 | 206 | 2.536 | 0.113 |
| Time (CDRS-R) | 7 | 198 | 100.132 | <.0001 |
| Weight Status*Time | 7 | 198 | 1.313 | 0.246 |
| Age | 1 | 204 | 17.524 | <.0001 |
| Gender | 1 | 210 | 0.249 | 0.618 |
| Ethnicity | 1 | 206 | 0.018 | 0.892 |
| Baseline Severity (CDRS-R) | 1 | 216 | 150.703 | <.0001 |
| Length of Illness (mo) | 1 | 215 | 2.689 | 0.103 |
| Family History of Depression | 1 | 210 | 1.635 | 0.202 |

Table 15

*Logistic Regression Analysis of Remission Status at Week 12 as a Function of Baseline Characteristics and Weight Status*

| | | | | | | | | | 95% CI | |
|---|---|---|---|---|---|---|---|---|---|---|
| Variables | Model $\chi^2$ | *p* | *B* | *S.E.* | *Wald* | df | *p* | Exp (*B*) | Lower | Upper |
| Weight Status | 1.344 | 0.511 | | | 1.359 | 2 | 0.507 | | | |
| Overweight | | | -0.264 | 0.425 | 0.386 | 1 | 0.535 | 0.768 | 0.334 | 1.766 |
| Obese | | | -0.473 | 0.422 | 1.260 | 1 | 0.262 | 0.623 | 0.273 | 1.423 |
| Full Model | 22.840 | 0.011 | | | | | | | | |
| Age | | | -0.133 | 0.068 | 3.845 | 1 | 0.050 | 0.875 | 0.766 | 1.000 |
| Gender | | | -0.231 | 0.379 | 0.373 | 1 | 0.541 | 0.793 | 0.378 | 1.667 |
| Ethnicity | | | | | 3.415 | 3 | 0.332 | | | |
| African American | | | 1.192 | 1.171 | 1.036 | 1 | 0.309 | 3.292 | 0.332 | 32.647 |
| Caucasian | | | 0.356 | 0.958 | 0.138 | 1 | 0.710 | 1.427 | 0.218 | 9.323 |
| Hispanic | | | 1.261 | 1.119 | 1.270 | 1 | 0.260 | 3.531 | 0.394 | 31.667 |
| Baseline CDRS-R Total Score | | | -0.013 | 0.025 | 0.285 | 1 | 0.593 | 0.987 | 0.940 | 1.036 |
| Length of Depressive Illness | | | 0.022 | 0.016 | 1.847 | 1 | 0.174 | 1.022 | 0.990 | 1.054 |
| Family Hx of Depression | | | 1.060 | 0.388 | 7.471 | 1 | 0.006 | 2.886 | 1.350 | 6.170 |
| Weight Status | | | | | 2.757 | 2 | 0.252 | | | |
| Overweight | | | -0.261 | 0.474 | 0.304 | 1 | 0.581 | 0.770 | 0.304 | 1.949 |
| Obese | | | -0.778 | 0.469 | 2.752 | 1 | 0.097 | 0.459 | 0.183 | 1.394 |
| Demographic | 5.879 | 0.015 | | | | | | | | |
| Age | | | -0.141 | 0.059 | 5.660 | 1 | 0.017 | 0.868 | 0.773 | 0.975 |
| Clinical | 13.412 | <.001 | | | | | | | | |
| Family History of Depression | | | 1.269 | 0.349 | 13.198 | 1 | <.001 | 3.558 | 1.794 | 7.058 |
| Reduced Model | 16.367 | 0.003 | | | | | | | | |
| Weight Status | | | | | 2.758 | 2 | 0.252 | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Overweight | -0.303 | 0.458 | 0.438 | 1 | 0.508 | 0.739 | 0.301 | 1.812 |
| Obese | -0.745 | 0.452 | 2.721 | 1 | 0.099 | 0.475 | 0.196 | 1.150 |
| Age | -0.103 | 0.063 | 2.637 | 1 | 0.104 | 0.902 | 0.796 | 1.022 |
| Family History | 1.137 | 0.371 | 9.403 | 1 | 0.002 | 3.117 | 1.507 | 6.446 |

Table 16

*Logistic Regression Analysis of Remission Status at Week 12 as a Function of Demographic, Clinical Characteristics and Obesity Status*

| Variables | Model $\chi^2$ | *p* | *B* | *S.E.* | *Wald* | df | *p* | Exp (*B)* | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|---|---|---|---|---|
| Simple Model | 0.965 | 0.326 | | | | | | | | |
| Obesity Status | | | -0.402 | 0.404 | 0.989 | 1 | 0.320 | 0.669 | 0.303 | 1.477 |
| Full Model | 15.936 | 0.001 | | | | | | | | |
| Age | | | -0.103 | 0.064 | 2.628 | 1 | 0.105 | 0.902 | 0.797 | 1.022 |
| Family Hx of Depression | | | 1.115 | 0.368 | 9.158 | 1 | 0.002 | 3.050 | 1.481 | 6.279 |
| Obesity Status | | | -0.663 | 0.432 | 2.358 | 1 | 0.125 | 0.515 | 0.221 | 1.201 |

Table 17

*Cox Regression Analysis of Weight Status and Covariates on Time to Remission*

| | | | | | | | 95% CI for Exp(*B*) | |
|---|---|---|---|---|---|---|---|---|
| Covariate | *B* | *S.E.* | *Wald* $\chi^2$ | df | *p* | Hazard Ratio | Lower | Upper |
| Age | -0.106 | 0.031 | 11.314 | 1 | < 0.01 | 0.900 | 0.846 | 0.947 |
| Gender | 0.037 | 0.172 | 0.047 | 1 | 0.828 | 1.038 | 0.741 | 1.454 |
| Ethnicity | | | 0.149 | 3 | 0.985 | | | |
| Family History of Depression | 0.373 | 0.193 | 3.741 | 1 | 0.053 | 1.452 | 0.995 | 2.118 |
| Baseline Severity | -0.017 | 0.011 | 2.537 | 1 | 0.111 | 0.983 | 0.963 | 1.004 |
| Length of Illness | 0.004 | 0.006 | 0.501 | 1 | 0.479 | 1.004 | 0.993 | 1.016 |
| Weight Status | | | 0.093 | 2 | 0.954 | | | |

Table 18

*Logistic Regression Analysis of Baseline Obesity Status as a Function of Demographic, Clinical Characteristics and Sleep Disturbance*

| | | | | | | | | | 95% CI | |
|---|---|---|---|---|---|---|---|---|---|---|
| Variables | Model $\chi^2$ | *p* | *B* | *S.E.* | *Wald* | df | *p* | Exp (*B)* | Lower | Upper |
| Sleep Disturbance | 0.155 | 0.694 | -0.133 | 0.338 | 0.155 | 1 | 0.693 | 0.875 | 0.451 | 1.697 |
| Full Model | 22.840 | 0.011 | | | | | | | | |
| Age | | | -0.108 | 0.066 | 2.682 | 1 | 0.101 | 0.897 | 0.788 | 1.022 |
| Gender | | | 0.331 | 0.352 | 0.884 | 1 | 0.347 | 1.392 | 0.698 | 2.776 |
| Baseline CDRS-R Total Score | | | 0.010 | 0.022 | 0.207 | 1 | 0.649 | 1.010 | 0.968 | 1.054 |
| Length of Depressive Illness | | | 0.007 | 0.011 | 0.434 | 1 | 0.510 | 1.007 | 0.986 | 1.028 |
| Family Hx of Depression | | | 0.344 | 0.398 | 0.748 | 1 | 0.387 | 1.411 | 0.647 | 3.078 |
| Sleep Disturbance | | | -0.074 | 0.364 | 0.041 | 1 | 0.839 | 0.929 | 0.455 | 1.897 |

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