

**OBESITY, BODY COMPOSITION AND INSULIN RESISTANCE IN WOMEN WITH
AND WITHOUT BIPOLAR DISORDER**

by

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University of Pittsburgh, 2006

Obesity and cardiovascular disease is common in bipolar disorder, both of which are associated with insulin resistance. Insulin resistance is also associated with distribution of body fat, specifically abdominal visceral fat and fat accumulation in skeletal muscle. Furthermore, reduced capacity to utilize fat has been linked with obesity, type 2 diabetes and insulin resistance.

PURPOSE: To compare insulin sensitivity, body composition and resting substrate utilization between obese and normal weight patients with bipolar 1 disorder and race, age and BMI matched controls. **METHODS:** Participants underwent dual energy X-ray absorptiometry (DEXA) to measure fat mass (FM) and fat-free mass (FFM), computed tomography (CT) to measure cross-sectional abdominal adipose tissue and indirect calorimetry to measure resting substrate oxidation. Free- living energy expenditure was measured for 5 days using BodyMedia SenseWear Pro Armband and the food frequency questionnaire estimated the usual consumption of 79 main food items over the preceding 12 months. Insulin sensitivity was measured from fasting insulin and glucose measurements and defined by the homeostatic model assessment of insulin resistance (HOMA IR). **RESULTS:** Eighteen patients with bipolar 1 disorder and 17 controls participated in this study. There were no differences observed in insulin resistance between obese ($BMI > 30 \text{ kg/m}^2$) patients and controls (56.8 ± 17.2 vs. 51.8 ± 11.1 ; $P = 0.842$) or normal weight ($BMI < 25 \text{ kg/m}^2$) patients and controls (30.5 ± 6.3 vs. 27.0 ± 5.7 $P = 0.691$). CT revealed a difference in total abdominal fat (718.1 ± 33.6 vs. $607.4 \pm 38.6 \text{ cm}^2$; $P = 0.04$), a trend in visceral abdominal fat ($P =$

0.06) though no difference in subcutaneous abdominal fat between obese patients and controls. Indirect calorimetry revealed a trend ($P=0.06$) in reduced fat oxidation in normal weight patients compared to controls and when combining obese and normal weight patients. **CONCLUSION:** Patients with bipolar 1 disorder do not appear to be more insulin resistant than controls after accounting for their obesity. However, a reduced fat oxidation in normal weight patients may be an underlying factor predisposing them for future weight gain and concomitant increased risk for type 2 diabetes.

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PREFACE

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"A true friend is someone who thinks that you are a good egg even though he knows that you are slightly cracked"

—Bernard Meltzer

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1.0 INTRODUCTION

Insulin resistance has been linked to diabetes, hypertension, dyslipidemia and cardiovascular disease. Obesity is a common thread among metabolic disorders (Reilly and Rader 2003) as well as cardiovascular disease (Haffner 1997; Lempiainen, Mykkanen et al. 1999) and is associated with insulin resistance.(Goodpaster, Thaete et al. 1997) In addition to generalized obesity by either body fat or body mass index (BMI) criteria, insulin resistance is also associated with the distribution of body fat, including abdominal visceral fat (Goodpaster, Thaete et al. 1997) and fat accumulation within skeletal muscle.(Goodpaster, Thaete et al. 2000) There is also increasing evidence that impaired capacity for fat oxidation in obesity and type 2 diabetes is related to insulin resistance.(Kelley, Goodpaster et al. 1999) Thus, the metabolic disturbances of insulin resistance and type 2 diabetes appear to be more global to include dysregulated fat metabolism as well as impaired glucose metabolism.

1.1 OBESITY

The alarming increase in obesity in the U.S. (Mokdad, Ford et al. 2003) and around the world (Hernandez, Cardonnet et al. 1987; al-Isa 1995; Hodge, Dowse et al. 1995; Flegal, Carroll et al. 1998; Arroyo, Loria et al. 2000) is a paramount public health concern affecting children, middle-aged and older men and women across a variety of ethnic and racial groups. The

increase in obesity has led to a marked increase in the metabolic syndrome (Ford, Giles et al. 2002) creating additional risks for type II diabetes and cardiovascular disease. Data from the Framingham study have established an increased incidence of cardiovascular events with increasing weight (Hubert, Feinleib et al. 1983; Colditz, Willett et al. 1995) and weight gain was a significant risk factor for development of diabetes. The association of obesity with the insulin resistance syndrome is not only related to the degree of obesity but is dependent on body fat distribution. Thus, individuals with greater degrees of central adiposity develop this syndrome more frequently than do those with a peripheral body fat distribution.(Kissebah and Krakower 1994)

1.2 BIPOLAR DISORDER

Patients with bipolar disorder present pleomorphic signs and symptoms that include recurring manic, hypomanic and depressive states. To complicate matters further, individuals suffering from bipolar disorder have been particularly afflicted by the rampant increase in obesity. Indeed, these patients have a higher prevalence of obesity (Fagiolini, Frank et al. 2002; Fagiolini, Kupfer et al. 2003; McElroy, Kotwal et al. 2004), diabetes (Russell and Johnson 1981; Cassidy, Ahearn et al. 1999; Regenold, Thapar et al. 2002), dyslipidemia (Yates and Wallace 1987; Atmaca, Kuloglu et al. 2002), hypertension (Elmslie, Silverstone et al. 2000), and cardiovascular disease (Elmslie, Silverstone et al. 2000; 2001; Lakka, Laaksonen et al. 2002) than the general population. For instance, Elmsie et al (2000) evaluated the prevalence of overweight, obesity, and central adiposity in euthymic bipolar patients and reference subjects, matched for age and sex.(Elmslie, Silverstone et al. 2000) Female patients were more often

overweight and obese than female reference subjects. In males, the frequency of being overweight was similar in patients and reference subjects although male patients were more likely to be obese. Additionally, this study revealed that patients were more centrally obese than the general population and patients treated with antipsychotic drugs were more obese than patients not receiving these drugs. This was later supported by Fagiolini et al (2005) who found a 30% prevalence of obesity in bipolar patients taking part in the Pittsburgh Study of Maintenance Therapies in Bipolar Disorder.(Fagiolini, Frank et al. 2002)

Whilst the etiology of obesity and these associated metabolic disorders in patients is certainly complex, likely involving a combination of genetic, lifestyle and medication influences, it is not known whether these patients are more insulin resistant than would be expected for their level of generalized obesity. Moreover, it is not known whether patients with bipolar disorder can be characterized by the sub-clinical correlates of insulin resistance, namely abdominal fat accumulation and an impaired capacity for fat oxidation.

1.2.1 Primary Specific Aims

Insulin resistance or metabolic syndrome is thought to be a unifying feature of diabetes, hypertension, dyslipidemia and cardiovascular disease. Therefore, identifying and treating insulin resistance has immense preventative potential. The overall goal of this pilot study was to determine whether insulin resistance, as well as sub-clinical features of insulin resistance, namely patterns of regional fat distribution and lower post-absorptive fat oxidation, distinguishes obese and normal weight patients with diagnosed bipolar 1 disorder from obese and normal weight controls.

Two primary specific aims and one secondary aim were addressed (See Table 1).

AIM 1: To compare insulin resistance in women with bipolar 1 disorder to race, age and BMI matched controls.

Hypothesis: Insulin resistance, defined by the homeostatic model assessment of insulin resistance (HOMA IR) derived from fasting insulin and glucose, would be more severe in obese and normal weight women with bipolar 1 disorder compared to obese and normal weight controls.

AIM 2: To compare visceral and subcutaneous abdominal as well as lower extremity (mid-thigh) adipose tissue in women with bipolar 1 disorder to controls.

Hypothesis: Obese and normal weight women with bipolar 1 disorder would have more visceral and subcutaneous abdominal adipose tissue, but less mid-thigh subcutaneous adipose tissue compared to obese and normal weight controls, respectively.

Secondary Aim To compare resting metabolic rate, rates of post-absorptive fat oxidation, energy expenditure and nutritional habits in patients with bipolar 1 disorder and controls.

Hypothesis: Obese and normal weight women with bipolar 1 disorder would be characterized by: a) similar absolute resting metabolic rates and b) lower rates of post-absorptive fat oxidation c) lower energy expenditure and d) higher caloric intake compared to obese and normal weight controls.

Table 1 Primary and Secondary Aims

	Obese		Normal Weight	
	Patients	Controls	Patients	Controls
Insulin Resistance	↑↑	↑	↑	—
Visceral Adiposity	↑↑	↑	↑	—
Body Composition	↑↑	↑	↑	—
Resting Metabolic Rate	—	—	—	—
Carbohydrate oxidation	↑↑	↑	↑	—
Fat oxidation	↓↓	↓	↓	—
Energy Expenditure	↓↓	↓	↓	—
Caloric Intake	↑↑	↑	↑	—

— Is similar; ↑↑ is highest; ↑ is higher; ↓ is lower

2.0 SECOND CHAPTER

2.1 LITERATURE REVIEW

2.1.1 BACKGROUND

A key feature of metabolic syndrome is insulin resistance, also a characteristic of virtually all individuals with type 2 diabetes. Obesity and cardiovascular disease is common in bipolar disorder, both of which are associated with insulin resistance. Insulin resistance is also associated with distribution of body fat, specifically abdominal visceral fat and fat accumulation in skeletal muscle. Furthermore, reduced capacity to utilize fat has been linked with obesity, type 2 diabetes and insulin resistance. However, it is unclear whether patients with bipolar disorder are more insulin resistant than could be expected on the basis of their body weight or generalized obesity.

2.2 BIPOLAR DISORDER

Bipolar disorder, also known as manic-depressive illness, is a brain psychiatric disorder that causes abnormal variations in a person's mood, energy, and ability to function. It can present a recurrent or chronic course and it is characterized by the presence of recurrent

depressive episodes, often very severe, and at least one episode of mania, hypomania or mixed state. Each single episode is defined by specific criteria in terms of quality, intensity and duration of symptoms (Diagnostic and statistical manual, APA 2000). Bipolar 1 disorder involves at least one or more episodes of mania and depression and has a lifetime prevalence of 0.4 to 1.6%(Robins 1991; Kessler, McGonagle et al. 1994; Angst 1998) Bipolar II Disorder however, never develops into severe mania but instead the individual experiences milder episodes of hypomania that alternate with depression. Bipolar spectrum includes attenuated forms of the disorder, such as cyclothymic disorder, bipolar disorder not otherwise specified (NOS) is characterized by episodes of hypomania and depression that do not fulfill either duration criteria or number of symptoms. When factoring in these forms of bipolar disorder, lifetime prevalence rates increase to 2-7%.(Angst 1998) Rapid-cycling occurs when four or more episodes of illness occur within a 12-month period and is more common later in the course of illness.

Albeit the prevalence of the more severe form of the disorder is not extremely high, especially if compared to other forms of mood disorders such as Major Depressive Disorder, bipolar disorder ranks as the sixth cause of disability worldwide (Wyatt and Henter 1995), configuring a major economic burden in terms of direct and indirect costs. The course of illness is typically described as episodic, with euthymic inter-episodic periods of variable length; nevertheless up to 30% of individuals with bipolar disorder experience residual symptoms and psychosocial impairment even during the “recovery” phase, regardless of treatment.(Judd, Schettler et al. 2002; Judd and Akiskal 2003) According to Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), approximately 5% of patients who met criteria for recovery relapsed each month. In most cases depression overrides mania and patients tend to

spend three times as much time in depression than in mania, regardless of number and polarity of episodes.(Judd, Schettler et al. 2002; Judd and Akiskal 2003) Furthermore, 80% of the patients that relapsed in STEP-BD were due to depression. Bipolar disorder is often under diagnosed or misdiagnosed as unipolar depression and it is not infrequent that a lapse of several years occurs between the onset of symptoms and the prescription of a mood stabilizer.(Dunner 2003) Evidence suggests that the number of previous untreated episodes may negatively affect treatment response.(Post 1992)

Bipolar disorder is commonly treated with mood stabilizers for extended periods of time. Due to its effects in controlling mania and preventing recurrence of both episodes, the most common mood stabilizer today is lithium. Anticonvulsant medications such as valproate have recently been shown to be useful in treating bipolar episodes although medications may be combined for maximum effects. More recently, the U.S. Food and Drug Administration have approved the atypical antipsychotics olanzapine, risperdone, quetiapine, ziprasidone and aripiprazole for the treatment of bipolar mania. In fact, combination therapy with a mood stabilizer and an antipsychotic is becoming a common therapy (90%) for patients with mania.(Miller, Yatham et al. 2001; Yatham, Kennedy et al. 2003) Specific risks have been associated with atypical antipsychotic treatment such as obesity, diabetes, glucose intolerance, thirst and nausea.(Fagiolini, Frank et al. 2002; Regenold, Thapar et al. 2002; McElroy, Kotwal et al. 2004)

2.3 METABOLIC SYNDROME

The dramatic increase in obesity in the United States has led to a marked increase in metabolic syndrome, a clustering of cardiovascular disease risk factors characterized by visceral adiposity, insulin resistance, low HDL cholesterol and systemic inflammatory states.(Ford, Giles et al. 2002) The Adult Treatment Panel III (appears most often used in the literature (Kahn, Buse et al. 2005) proposed guidelines for diagnosis highlighting the key features of this syndrome. The definition is based on having 3 of the 5 criteria (central obesity, insulin resistance, dyslipidemia, hyperglycemia, and hypertension) though not all persons manifest the full syndrome. The diagnosis of metabolic syndrome identifies substantial additional risks for type II diabetes and cardiovascular disease. Therefore, diagnosis of metabolic syndrome may be an imperative tool for identification of high-risk patients. Recently, much attention has been focused on the increased rate of metabolic syndrome components among psychiatric patients, including glucose intolerance, hyperglycemia, diabetes mellitus, hyperlipidemia, hypertension, and weight gain.

2.3.1 Metabolic Syndrome in Bipolar Disorder

Risk factors for cardiovascular disease such as obesity and hypertension have been examined in patients with bipolar disorder for the past several years, although recently researchers have focused their attention on metabolic syndrome. The prevalence of two components of metabolic syndrome, obesity and diabetes, is markedly increasing in patients with bipolar disorder.(Fagiolini, Frank et al. 2002; Regenold, Thapar et al. 2002; Kessing, Nilsson et al. 2004; McElroy, Kotwal et al. 2004) Metabolic syndrome is relatively (23.7%) prevalent in

the general population (Ford, Giles et al. 2002) though few investigational studies have examined metabolic abnormalities in bipolar disorder. An epidemiological pilot study conducted by Basu et al (2004) investigated metabolic syndrome in Schizoaffective Disorder Bipolar Subtype.(Basu, Brar et al. 2004) They recruited patients currently partaking in a double-blind study of topiramate or placebo as adjunctive treatment. Subjects had to receive either lithium and/or valproate for at least 2 weeks and could also receive one antipsychotic agent but not an antidepressant. Basu and associates describe a 42% prevalence rate and those with the metabolic syndrome were significantly heavier and primarily in the obese range.

Similarly, Fagiolini et al (2005) examined individuals diagnosed with bipolar disorder taking part in the Bipolar Disorder Center for Pennsylvanians Study (BDCCP) which is a multi-center randomized controlled study involving bipolar I, bipolar II and bipolar not otherwise specified (NOS) and schizoaffective bipolar subtype.(Fagiolini, Frank et al. 2002) This study included 173 adults from November 2003 to August 2004 and reported that 30% of patients were diagnosed with metabolic syndrome in addition to 74% being either obese (45%) or overweight (29%). Interestingly, almost half of the participants met criterion for abdominal obesity and hypertriglyceridemia whereas approximately 30% met criterion for abnormal HDL cholesterol and hypertension.

2.4 INSULIN RESISTANCE

Insulin enhances overall energy stores by restricting the release of fuel substrates from the tissues into circulation resulting in an increase in cellular uptake of glucose and amino acids. In healthy controls, increases in insulin usually occur after meals when exogenous fuels are

available. Insulin also promotes glucose as the preferred oxidative substrate instead of sparing amino acids and fatty acids for protein and triglyceride synthesis. The predominant site of postprandial glucose disposal is skeletal muscle whereby insulin controls glucose uptake and stimulates the oxidation of glucose in addition to glycogen storage. Overall, insulin orchestrates the disposal of carbohydrates after a meal by stimulating glucose uptake and oxidation or storage of blood glucose while simultaneously inhibiting endogenous glucose production. When the body does not respond well to insulin, this is known as insulin resistance and often develops into hyperglycemia.

Hyperglycemia represents a spectrum of disorders ranging from glucose intolerance to type 2 diabetes. When measured on at least 2 separate occasions, fasting glucose levels between 110 and 126mg/dL are classified as glucose intolerant and fasting levels \geq 126mg/dL and random glucose levels \geq 200mg/dL are diagnostic of diabetes. The World Health Organization (WHO) reports that the prevalence of diabetes will be more than double by the year 2025 and the prevalence to date has increased to approximately 30%.(Kabinoff, Toalson et al. 2003)

Insulin resistance is progressed by obesity, inactivity, illnesses, and age and may additionally be a prime mechanism in causing dyslipidemia.(Abbott, Lillioja et al. 1987; Garg, Helderman et al. 1988; Laakso, Sarlund et al. 1990) Insulin resistance in respect to glucose and fat metabolism has become exceedingly common in obesity especially in upper-body or visceral obesity. Theoretically, this would act to make more lipid fuel available and reduce glucose oxidation resulting in excessive adipose lipolysis in addition to increased free fatty acids to the liver, although a recent study has shown quite the opposite. Kelley et al (2000) has shown under basal conditions increased, rather than decreased, glucose oxidation as well as impaired fat oxidation. During insulin stimulated conditions these authors report a decreased glucose

oxidation in addition to impaired fat oxidation was observed creating a state of “metabolic inflexibility.” (Kelley, Goodpaster et al. 1999)

2.4.1 Insulin Resistance in Bipolar Disorder

Research has shown that type 2 diabetes is more prevalent in bipolar disorder than the general population.(Lilliker 1980; Cassidy, Ahearn et al. 1999; Regenold, Thapar et al. 2002) Though insulin resistance has not been examined directly in bipolar disorder, one of the primary defects of type 2 diabetes is insulin resistance, one can hypothesize that individuals diagnosed with bipolar disorder also have an increased prevalence of insulin resistance.

2.5 OBESITY

National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) estimated that obesity is becoming a worldwide emergency with over 280,000 deaths directly attributed to obesity related morbidity. Major problems linked with obesity include hypertension, cardiovascular disease, dyslipidemia, diabetes mellitus, gallbladder disease, osteoarthritis, gallstones, musculoskeletal problems, and some cancers. Furthermore, it is estimated that approximately \$68 billion per year is spent on economic costs of illnesses associated with obesity.(Wolf 1998)

Obesity is one of the central components of metabolic syndrome (Matsuzawa, Funahashi et al. 1999; Montague and O'Rahilly 2000) but the mechanistic role of obesity has not been fully elucidated. Adipocytes produce a variety of active molecules such as adipocytokines, including

plasminogen activator inhibitor-1 (PAI-1), tumor necrosis factor- α (TNF- α), resistin, leptin and adiponectin. Any irregularities in these molecules have been associated with the pathophysiology of obesity related metabolic syndrome. An accumulation of fat has been reported to increase PAI-1 and TNF- α , contributing to the development of insulin resistance. In contrast, decreases in adiponectin have been shown to be causative of insulin resistance; however, the exact mechanism by which fat accumulation contributes to irregularities in molecules is unknown. Furukawa et al (2004) investigated whether oxidative stress in accumulated fat may in part be the underlying cause of abnormalities in adipocytokines and therefore the development of metabolic syndrome.(Furukawa, Fujita et al. 2004) They report that fat accumulation is correlated with oxidative stress in humans and mice. Specifically, elevated levels of fatty acids increased oxidative stress in turn causing dysregulation of adipocytokines including adiponectin and PAI-1. Furthermore, Furukawa and colleagues reported that treatment with NADPH attenuated dysregulation of adipocytokines, improved diabetes and hyperlipidemia.

2.5.1 Obesity in Bipolar Disorder

Individuals diagnosed with bipolar disorder have an increased prevalence of obesity (Elmslie, Silverstone et al. 2000; Fagiolini, Frank et al. 2002; McElroy, Frye et al. 2002; Keck and McElroy 2003) most of which appears to be abdominally stored.(Elmslie, Silverstone et al. 2000; McElroy, Kotwal et al. 2004) (Fagiolini, Frank et al. 2002) Treatment of obesity has become important to physicians today since obesity has been correlated with a poorer outcome (Fagiolini, Kupfer et al. 2003) and discontinuation of therapy.(Tardieu, Micallef et al. 2003) Furthermore, the number of previous depressive episodes contributes to obesity (Fagiolini, Frank

et al. 2002) and bipolar patients seeking to lose weight have higher rates of depression.(McElroy, Kotwal et al. 2004)

Since most patients spend their time suffering from depressive symptoms or depressive episodes, bipolar disorder itself may be an underlying risk of obesity and other related morbidity and mortality.(Judd, Schettler et al. 2002; Judd and Akiskal 2003; Nolen, Luckenbaugh et al. 2004) Risk factors such as co-morbid binge-eating disorder, number of depressive episodes, and treatment with medications associated with weight gain, excessive carbohydrate consumption and low rates of exercise have also been shown to increase the risk of obesity in these patients. (Fagiolini, Kupfer et al. 2003), (Kruger, Shugar et al. 1996), (Graham, Perkins et al. 2005), (Deshmukh and Franco 2003)

2.5.2 Causes of Obesity in Bipolar Disorder

Obesity appears to be a proxy for medical burden in patients with mood disorders and may be multifaceted, consisting of environmental, genetic and medication factors. They may be independent conditions with completely separate patho-physiological pathways or they may co-occur by causal association, though the exact mechanism is unknown.

Bipolar disorder itself: 1) Some peculiar features in the biology of mood disorders may also play a role in the development of a high BMI. Hyperactivity of Hypothalamic Pituitary Adrenal (HPA) axis is one of the most consistent biological findings in mood disorders,(Holsboer and Barden 1996) and it may persist after clinical remission of symptoms.(Rybakowski and Twardowska 1999) Furthermore, there is also evidence that the HPA axis may precede mood episode,(Heuser, Schweiger et al. 1996) and is a risk factor for

relapse when there is no normalization after treatment.(Zobel, Yassouridis et al. 1999) Animal studies have consistently shown interaction between HPA axis and the serotonin system, and HPA axis dysregulation seems to be related to serotonergic system abnormalities.(Porter, Gallagher et al. 2004) Nevertheless, long before the extensive use of psychotropic medications, Kretschmer (1921) described a somatic typology (pyknic body type) that was characterized by an abdominal fat pattern, and that was associated with “cycloid temperament” and predisposition to manic-depressive psychosis.

2) More recent prospective studies have established that depression is a risk factor for weight gain and obesity and child or adolescent depression predicts greater BMI in adulthood.(Pine, Cohen et al. 1997) In cross-sectional analyses, depression, but not mania, seems to be a correlate for obesity in bipolar disorder.(Fagiolini, Kupfer et al. 2003) Bipolar depression often portrays atypical symptoms (Akiskal, Walker et al. 1983; Mitchell, Wilhelm et al. 2001) that are associated with hyperphagia, binge eating and weight gain.(Angst, Gamma et al. 2002) Binge eating is a common eating pattern in obese subjects.(Bulik, Sullivan et al. 2002; Yanovski 2003) and it is frequently reported by patients with bipolar disorder.(Kruger, Shugar et al. 1996) McElroy and colleagues reported that 13.5% of obese patients with bipolar disorder and 50% of extremely obese patients with bipolar disorder had current or lifetime history of binge eating, compared to 4.9% of normal weight bipolar subjects,(McElroy, Frye et al. 2002) suggesting that the engagement in abnormal eating behavior may be a pathway to obesity for patients with bipolar disorder. On the other hand, high prevalence of mood disorder is reported for treatment-seeking obese binge eaters (Bulik, Sullivan et al. 2002; Yanovski 2003) and binge eating is associated with increased medical comorbidity independent from BMI.(Bulik, Sullivan et al. 2002)

Medication Induced Obesity: The most relevant question regarding obesity and bipolar disorder is whether obesity is increased independent of medication. Additionally, if medication does induce obesity, to what extent do you see an increased rate of medication induced obesity? This current project is not intended to address the relationship between medications and obesity although it is intended to serve as a segway into future projects to examine this issue more closely. 1) One hypothesis is that the current medications used to treat bipolar disorder increase energy intake.(Elmslie, Mann et al. 2001) Current evidence suggests that increased energy intake seems to begin with afferent signals (i.e. leptin, ghrelin etc) alerting the hypothalamus to the state of the body's environment. This mechanism may either stimulate appetite (food intake) or decrease appetite to maintain adipose mass.(Kennedy 1953; Kennedy 1966) Although neither leptin nor ghrelin have been shown to be a causal factor in the development of obesity in the healthy population (Baptista and Beaulieu 2002) they have not been examined in patients with bipolar disorder. 2) Most medications currently used as maintenance treatment can cause weight gain and some are thought to directly affect glucose and lipid metabolism.(Bergman and Ader 2005; Newcomer 2005) Atypical antipsychotics, common today in treating bipolar disorder, have been shown to promote serotonin antagonism at the 5-HT_{2c} receptors and dopamine antagonism eliciting increased caloric intake. Furthermore, metabolic ailment with some antipsychotics may contribute in unwanted energy storage promoted by a reduced oxidation of fat.(Graham, Perkins et al. 2005)

Common Biological Diathesis: 1) Both obesity (Haslam and James 2005) and bipolar disorder (Mathews and Reus 2003; Tsuang, Taylor et al. 2004; Mansour, Monk et al. 2005) seem to have a complex genetic pattern, with multiple genetic variants. One hypothesis is that there may be a common genetic vulnerability for obesity and bipolar disorder that include

serotonergic, dopaminergic and noradrenergic systems, involved either in mood regulation or in food intake. For example, two variants with functional impact in the promoter region of the Serotonin (5HT) Transporter (5HTT) have been identified. Briefly, these two variants represent a short allele (S) and a long allele (L). The presence of the S allele has been associated with lower selective serotonin reuptake inhibitor (SSRI) response in depression (Pollock, Ferrell et al. 2000) and Bulimia Nervosa (Monteleone, Santonastaso et al. 2005) homozygosity SS has been associated with bipolar disorder and recurrent depression (Collier, Arranz et al. 1996). This data suggest that there may be an overlap in the pathogenesis of affective disorders and disordered eating (possibly via affect instability and impulsivity) and that the functional correlate of this genetic marker may be dimensional, rather than sequential.

2) Mesolimbic dopaminergic pathways may also be involved in the regulation of affect and eating (Balleine 2005). A variant of the dopamine receptor gene DRD4 has been associated with binge eating and higher lifetime BMI in women with Seasonal Affective Disorder (SAD) (Levitan, Masellis et al. 2004). Furthermore, functional neuroimaging studies show a substantial overlap between neural circuits involved in affect regulation and neural circuits involved in food-related stimuli (Price 1999; Killgore, Young et al. 2003). There is a speculation that a predisposition to obesity may involve areas of the brain that control complex aspects of eating behavior including anticipation and reward, chemosensory perception, and autonomic control of digestion, enteroception and learning memory (del Parigi A; Chen K, 2004).

2.5.3 Central Obesity

Central obesity is associated with hypercortisolemia in the general population (Bjorntorp and Rosmond 2000) and the functional correlates of cortisol levels in patients with mood

disorders has been poorly investigated. Hypercortisolemia has been proposed to be the major cause of visceral fat deposition in patients with mood disorder, but there is only one study addressing this issue. Weber-Hamann et al. compared 22 postmenopausal depressed women to 23 matched controls. The author's report a larger mass of visceral fat in hypercortisolemic depressed patients ($113.0 \pm 41.6\text{cm}^2$) compared to normocortisolemic depressed patients ($74.5 \pm 55.5\text{cm}^2$). However, no differences were observed in visceral fat stores once patients were compared to controls (Lumbar 1= 113.0 ± 41.6 vs. $94.3 \pm 53.2\text{cm}^2$ and Lumbar 4 = 117.5 ± 46.3 vs. $118.1 \pm 57.2\text{cm}^2$).(Weber-Hamann, Hentschel et al. 2002)

Regional obesity has also shown to be associated with insulin resistance. Studies examining visceral adiposity have given us tremendous insight into the link between insulin resistance and obesity. Specifically abdominal adiposity has been strongly associated with insulin resistance of skeletal muscle,(Despres 1993) dyslipidemia (Tchernof, Lamarche et al. 1996) and glucose intolerance.(Bjorntorp 1991; Despres 1993) Carey et al (1996) examined the relationship between abdominal fat and insulin resistance through dual-energy x-ray absorptiometry (DEXA) and insulin sensitivity via euglycemic-hyperinsulinemic clamp in healthy women.(Carey, Jenkins et al. 1996) They found a strong negative correlation ($r = -0.89$, $P = < 0.0001$) between central abdominal fat defined as intra-abdominal plus abdominal subcutaneous fat and whole-body insulin sensitivity. In a more specific analyses, Brochu et al (2000) examined independent associations of regional adiposity and total fat mass with glucose disposal in obese older women.(Brochu, Starling et al. 2000) Upon stabilizing metabolic assessments and dietary intake for three days in all subjects, visceral adipose tissue showed a similar ($r = -0.40$, $P = < 0.01$) association to total glucose disposal expressed as per kg normal

weight body mass as the previous study even upon adjustment of total fat mass ($r = - 0.45$, $P = < 0.005$).

2.5.4 Central Obesity in Bipolar Disorder

Increased rates of abdominal adiposity have been reported in bipolar disorder.(Elmslie, Silverstone et al. 2000; Fagiolini, Frank et al. 2002; McElroy, Kotwal et al. 2004) Confounding variables such as psychological disorder, duration of illness and treatment modalities have made the primary mechanism difficult to interpret in this population. Cross sectional investigations reporting observed abdominal obesity have used waist circumference as the primary means of assessment. Although waist circumference is a surrogate of total abdominal adipose tissue, waist circumference does not distinguish visceral from subcutaneous abdominal adipose tissue. Weber-Hamann et al. (2002) compared 22 postmenopausal depressed women to 23 matched controls (Weber-Hamann, Hentschel et al. 2002) with computed tomography. A single slice was performed at the level of lumbar vertebra 1 and lumbar vertebra 4. As stated previously, no differences were observed in visceral fat stores once patients were compared to controls in either lumbar region ($L1 = 113.0 \pm 41.6$ vs. $94.3 \pm 53.2\text{cm}^2$ and $L4 = 117.5 \pm 46.3$ vs. $118.1 \pm 57.2\text{cm}^2$).

2.6 SKELETAL MUSCLE FATTY ACID METABOLISM

High proportions of upper-body or abdominal fat has been recognized to be an important component of insulin resistance in obesity and type 2 diabetes; although, there is also evidence

suggesting that thigh adipose tissue is also an important link in insulin resistance. The amount of triglyceride in skeletal muscle has been associated with insulin resistance (Pan, Lillioja et al. 1997; Kelley, Goodpaster et al. 1999; Goodpaster and Kelley 2002) and has been shown to be increased in obesity.(Kelley, Goodpaster et al. 1999; Goodpaster and Wolf 2004) Several studies have previously shown that increased skeletal muscle lipid content is associated with the severity of insulin resistance,(Goodpaster, Thaete et al. 1997; Pan, Lillioja et al. 1997) although others disagree.(Carey, Jenkins et al. 1996)

Carey et al (1996) showed that thigh fat content measured by DEXA was not associated with insulin resistance.(Carey, Jenkins et al. 1996) Philips et al (1996) examined thigh intramuscular triglycerides and its association with insulin action measured by whole-body insulin sensitivity and by the ability of insulin to activate glycogen synthase in normal glucose tolerant women.(Phillips, Caddy et al. 1996) They reported that muscle triglyceride content measured biochemically correlated with glycogen synthase activation but not with glucose tolerance, insulin resistance or central obesity. Authors believe this may have occurred because the triglyceride content of the biopsy reflects the amount of interstitial and intracellular fat which supports that not all adipose tissue accumulated in skeletal muscle is subcutaneous.

Adipose tissue can also accumulate beneath the fascia lata and within muscle itself (Nordal, Dietrichson et al. 1988; Liu, Chino et al. 1993) suggesting the distribution within the thigh may be a component of regional fat deposition that is indeed associated with insulin resistance. For example, Goodpaster et al (2000) examined compartmentalization of thigh adipose tissue, assessed by computed tomography, and its association with insulin resistance in lean glucose tolerant, obese glucose tolerant and obese type 2 diabetic subjects.(Goodpaster, Thaete et al. 2000) They observed that obese diabetic and obese glucose tolerant subjects had

lower insulin sensitivity than lean glucose tolerant subjects. Furthermore, they report that 8% of adipose tissue in the thigh was located beneath the fascia and correlated ($r = -0.36$, $P < 0.01$) with insulin sensitivity. Additionally, intramuscular adipose tissue comprised only 3% of thigh adipose tissue but showed an even stronger correlate ($r = -0.45$, $P < 0.01$) of insulin resistance. Goodpaster and associates also support previous findings (Carey, Jenkins et al. 1996) that subcutaneous adipose tissue is not a predictor of insulin resistance.

2.6.1 Mechanisms

Several mechanisms may be involved for the impairment in skeletal muscle by either uptake or oxidation of plasma fatty acids. Blaak et al (2000) showed a lower rate of appearance of free fatty acids (FFA) in type 2 diabetic subjects both under basal and exercise conditions suggestive of an impairment of disposal and oxidation of fatty acids.(Blaak, van Aggel-Leijssen et al. 2000) There have also been indications that muscle lipolysis may be increased in type 2 diabetic subjects. An increase in muscle lipolysis may overflow the muscle thereby decreasing the blood-tissue concentration gradient, one of the primary determinants of plasma fatty acid uptake and oxidation.(Van der Vusse 1996) Lastly, skeletal muscle is dependent on oxidative phosphorylation for energy production. Both obesity and type 2 diabetes involves dysregulation of both the oxidation of fat and carbohydrates as fuel.(Kelley, Goodpaster et al. 1999) Therefore, perturbations in mitochondrial function has also been implicated (Kelley, He et al. 2002) specifically related to carnitine palmitoyl transferase (Simoneau, Veerkamp et al. 1999) and lowered pattern of various fatty acid-binding proteins.(Luiken, Schaap et al. 1999)

2.7 MEDICATIONS IN BIPOLAR DISORDER

Physicians have been treating symptoms of psychiatric illness for decades with conventional antipsychotics, tricyclic antidepressants, benzodiazepines, selective serotonin reuptake inhibitors, cholinesterase inhibitors and most recently, atypical antipsychotics. As stated previously, this study is not examining medication effects on obesity or insulin resistance. This section is intended to illustrate what research has shown about specific types of medications used to treat bipolar disorder. This section is also revealing why the current study has chosen to exclude patients on certain medications such as olanzapine and clozapine.

2.7.1 Antidepressants

Weight gain may be caused by the pharmacological effect of antidepressants or an effect of recovery from depression. Antidepressant medications fall into varying classes such as tricyclic antidepressants, irreversible monoamine oxidase inhibitors and selective serotonin reuptake inhibitors (SSRI's).

2.7.2 Monoamine oxidase inhibitors (MAOI)

MAOIs are effective in treating depression and anxiety and can bind to receptors either irreversibly or reversibly. Reversible MAOIs are less likely to cause weight gain but are currently not available in the United States. Irreversible MAOIs on the other hand have been shown to cause weight gain with the most common being phenelzine.(Fava 2000)

2.7.3 Tricyclic Antidepressants

Tricyclic Antidepressants are well known for their adverse effects on weight gain (Fava 2000) and possibly as a result of excessive appetite. Fernstrom and Kupfer (1988) reported that treatment with three tricyclic compounds promoted weight gain with amitriptyline adding greater weight gain than nortriptyline and desipramine.(Fernstrom and Kupfer 1988) Frank et al (1990) reported roughly 13% to 15% of patients treated with imipramine gained 10 or more pounds by week 16 or 33.(Frank, Kupfer et al. 1990) Many mechanisms have been hypothesized including blockade of histamine H1 and serotonin 2C receptors, carbohydrate craving, changes in body fat stores and recovering from clinical depression.(Deshmukh and Franco 2003)

2.7.4 Selective Serotonin Reuptake Inhibitors (SSRI)

SSRIs elicit little to no weight gain when used for 6 months or less although literature is mixed when treatment surpasses 1 year or longer. Some short term studies have revealed a weight loss of 0.3 to 0.8kg with fluoxetine and sertraline (Croft, Settle et al. 1999; Michelson, Amsterdam et al. 1999). In contrast, Michelson et al (1999) examined changes in weight during a 1-year trial of fluoxetine and found no significant weight gain with fluoxetine.(Michelson, Amsterdam et al. 1999) Although, a 12-month placebo-controlled study revealed 4.7% of 541 patients treated with citalopram experienced weight gain of greater than 5kg.(Wade A 1999)

2.7.5 Atypical Antipsychotics

To date, there are 6 atypical antipsychotics marketed in the United States: clozapine, risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole. Atypical antipsychotics have been shown to produce substantially less extrapyramidal symptoms and prolactin increase compared to conventional antipsychotics, although impaired glucose homeostasis has recently been attributed to some atypical antipsychotic use, specifically clozapine and olanzapine.(Wirshing, Wirshing et al. 1999)

Antipsychotic induced obesity is difficult to assess and previous research to our knowledge has focused on neurotransmission and hormones as possible causes. In patients with bipolar disorder, standard risk factors may not provide a link between type II diabetes and some atypical antipsychotics. Complicating this relationship is the observation that patients with bipolar disorder have higher rates of diabetes than the general population.(Lilliker 1980; Cassidy, Ahearn et al. 1999; Regenold, Thapar et al. 2002) Little is known about the relationship between atypical antipsychotic medication and bipolar disorder since it has not been examined. With the recent use of antipsychotic medications used to treat bipolar disorder, this area needs to be further investigated.

In summary, patients with bipolar disorder have higher prevalence of type 2 diabetes. A primary factor in diabetes is insulin resistance which has been an understudied topic in this disorder. There may as well be an association between insulin resistance and bipolar disorder although it is unknown if their insulin resistance is irrespective of their generalized obesity or if they encompass sub-clinical features of insulin resistance, (i.e. reduced capacity to utilize fat.) Distinguishing insulin resistance and its sub-clinical correlates in these patients may help to

identify the appropriate targets for outcomes that could be examined further in intervention trials designed to prevent or treat their insulin resistance and type 2 diabetes. Lastly, methodological techniques (e.g. Resting Metabolic Rate, fat oxidation and CT scanning) employed in this current protocol have not been examined in bipolar patients and will provide novel information regarding insulin resistance in patients treated for bipolar disorder.

3.0 CHAPTER 3

3.1 METHODS

3.1.1 Subjects

The Pittsburgh Institutional Review Committee approved the study, and all subjects provided written, informed consent (APPENDIX A) at the time of their initial visit to the General Clinical Research Center (GCRC). Participants were excluded if taking chronic medications known to adversely affect glucose homeostasis (thiazide diuretics, oral glucocorticoids, nicotinic acid, and oral steroids) or had a history of myocardial infarction, peripheral vascular disease, neuromuscular disease, proteinuria, liver disease, current alcohol or drug abuse, or current malignancy (Table 2). Women who were pregnant or lactating or who lost or gained >5kg in the past month were also excluded. Eighteen bipolar 1 patients and 17 controls participated in this study.

Table 2 Inclusion/Exclusion Criteria

INCLUSION CRITERIA	EXCLUSION CRITERIA
18-60 years of age	Diabetic I or II
Bipolar 1 currently euthymic and race, age and BMI matched controls	Weight gain or loss of >5kg in past 1 month
Women	Inability or unwillingness to comply with the protocol
Non-diabetic	Current alcohol or substance abuse
Non-Pregnant	ALT >80, AST>80, Alk Phos >240
Stable weight for 1 month defined as no weight gain or loss of \geq 5kg in past 1 month	Proteinuria (defined as >1 + on routine dipstick), hypothyroidism (sTSH>8)
Bipolar patients currently taking \leq 3 medications	Claustrophobia
No lifetime history of olanzapine or clozapine treatment.	Treatment with thiazide diuretics, oral glucocorticoids, nicotinic acid or Females currently taking oral contraceptives or hormone replacement therapy (HRT) < 3months.

3.1.2 Bipolar Patients

The study populations was selected from participants in the Bipolar Disorders Center for Pennsylvanians (BDCP) and met DSM-IV criteria for bipolar 1 disorder, were euthymic and were treated with \leq 3 medications. Medications classified to treat the disorder are located in Table 3. Any lifetime history of Olanzapine and/or Clozapine treatment were excluded due to their effect on glucose homeostasis.(Wirshing, Wirshing et al. 1999) Patient’s history of medication was tracked through BDCP medical records and self report.

Table 3 Medications Included and Excluded

Medications Included	Medications Excluded
Depakote (valproate)	Zyprexa (Olanzapine)
Topamax (topiramate)	Clozaril (Clozapine)
Geodon (Ziprasidone)	Nicotinic acid
Lamictal (Lamotrigine)	Thiazide Diuretic
Neurontin (Gabapentin)	Oral Glucocorticoids
Seroquel (Quetiapine)	Oral contraceptives < 3 Months
Risperdone (Risperidone)	Hormone Replacement Therapy < 3
Abilify (Aripiprazole)	
Lithium	
Carbamazepine (Tegretol)	
Haloperidol (Haldol)	
Sertraline (Zoloft)	
Lorazepam (Ativan)	

3.1.3 Controls:

Matched controls were defined as participants who had no lifetime history of mood, anxiety, psychotic, eating, sleeping, and somatoform disorders and have never been treated with any neuroleptic medication. Control subjects were matched to bipolar 1 patients by race, age, and BMI.

3.2 EXPERIMENTAL DESIGN AND METHODS

3.2.1 Screening Procedures

All subjects were admitted to the GCRC after an overnight fast and completed informed consent, structured clinical interview (SCID) demographic questionnaire (APPENDIX B), food frequency questionnaire (FFQ) and a blood draw to measure CBC, electrolytes, liver function, thyroid function, blood glucose, insulin levels and blood fat levels (cholesterol, HDL, LDL, triglycerides) Table 4. As addressed in Aim 1 of this pilot study, insulin resistance were compared in women with bipolar 1 disorder to controls. Insulin resistance was defined by the homeostatic model assessment of insulin resistance (HOMA IR $[\text{glucose} \times \text{insulin}]/22.5$). (Mathews 1985) The demographic questionnaire collected information such as age, height, weight, socioeconomic status, education level, working status and psychiatric history. The food frequency questionnaire (FFQ) estimated the usual consumption frequency of 79 main food items over the preceding 12 months (Block, Hartman et al. 1986). Moreover, the FFQ comprised of questions regarding nutritional habits, preparation methods, and additions. Photographs of dishes were used to estimate habitual portion sizes. Food consumption data was converted into macronutrients and micronutrients by use of an updated version of the computerized Dutch food composition table 1996. Overall, the questionnaire enabled an estimation of the average daily consumption of 178 food items.

Upon completion of visit 1, all participants completed the following procedures to determine differences in energy expenditure, body composition and resting metabolism as stated in Aim 2 and the Secondary Aim (Visit 2).

Table 4 Protocol Visits

<i>Visit 1 (Screening)</i>	<i>5-day Energy Expenditure</i>	<i>Visit 2 (Experimental)</i>
Questionnaires-		Resting Metabolic Rate
<ul style="list-style-type: none"> ▪ Structured Clinical Interview Diagnostic (SCID) ▪ Demographic ▪ Food Frequency Questionnaire (FFQ) 	<ul style="list-style-type: none"> ▪ BodyMedia Armband 	<ul style="list-style-type: none"> ▪ Fat oxidation/ ▪ Carbohydrate oxidation
Blood Draw		Dual X-ray Absorptiometry
<ul style="list-style-type: none"> ▪ Blood Lipid Profile ▪ Glucose/Insulin 		<ul style="list-style-type: none"> ▪ Fat Free Mass ▪ Fat Mass
		Computed Tomography
		<ul style="list-style-type: none"> ▪ Scans of abdomen ▪ Scan of thigh
Total Time:		Total Time:
1.5 Hours		2.5 Hours

3.2.2 Physical Activity Measurement (Following Visit 1):

Upon the screening visit, subjects were given a Body Media Armband for approximately five days to measure total energy expenditure (kcal/24h), active energy expenditure (kcal derived from metabolic equivalent) and sleep duration. A unit of metabolic equivalent, or MET, is defined as the number of calories consumed per minute in an activity relative to the basal metabolic rate. One MET is the caloric consumption while at complete rest whereas BodyMedia

defines total energy expenditure as < 2.5 METs. The armband is a multi-sensor device consisting of a body-contoured monitor with adjustable straps to keep the sensor in contact with the arm during a variety of activities and conditions. The armband provides an assessment of overall physical activity and has recently shown to be a valid determinant of free-living energy expenditure.(Jakicic, Marcus et al. 2004) Subjects were asked to perform their visit 1 on Wednesday and were given the armband at that time. Subjects wore the armband on the upper right arm and returned back to the GCRC to complete visit 2 on Monday. At visit 2, expenditure measurements were collected on both weekdays and weekends. Data retrieved from the Armband was analyzed via customized algorithms to determine derived energy expenditure, level of activity and sleep state.

Individuals returned following the 5 day energy expenditure measurement to complete metabolic measurements (description to follow) after 12 hour overnight fast. Fasting measurements were essential due to confounding influences of preceding food intake on substrate metabolism.

3.2.3 Visit 2

The Second Aim of the study set out to compare visceral and subcutaneous abdominal, as well as lower extremity (mid-thigh), adipose tissue in women with bipolar 1 disorder to controls. Dual Energy X-Ray Absorptiometry (DEXA; model DPX-L; Lunar Corp., Madison, WI) scans performed at the Obesity Nutrition Research Center (ONRC) were used to assess body composition (i.e., total body fat and fat free mass as covariates). Computerized Tomography (CT) scans were performed at Presbyterian University Hospital Radiology Department in collaboration with Dr. F. Leland Thaete. CT was used to measure abdominal visceral and intermuscular adipose tissue as primary endpoint (independent) variables as previously described (Goodpaster, Thaete et al. 1997).

Briefly, a cross-sectional area of abdominal fat was assessed with a single CT scan centered upon the L4-L5 vertebral disk space. A single slice between the anterior superior iliac crest and the inferior margin of the patella divided by $\frac{1}{2}$ was used for the intermuscular adipose assessment. CT scans provided data on visceral abdominal adipose tissue area, subcutaneous abdominal adipose tissue area, total abdominal adipose tissue area, thigh muscle area, thigh subcutaneous adipose tissue area and thigh intermuscular adipose tissue area.

The Secondary Aim quantified resting metabolic rate and substrate (fat and carbohydrate) oxidation using systemic indirect calorimetry with an open canopy system (DeltaTrac, Anaheim, CA). The evening prior to testing, subjects received a telephone call from the study coordinator to remind the patient not to eat or drink anything after 12A.M. and to minimize movement as much as they could the morning of testing. Directions to minimize movement involved taking the elevator instead of the stairs and having another person drive them to the visit. The subject arrived at the GCRC after an over night fast where a clear plastic canopy was placed over their face and neck to collect the amount of oxygen their body used. This test was performed for 35 minutes in order to estimate carbohydrate and fat oxidation from expired O_2 and CO_2 measurements. The average rates of resting fat and carbohydrate oxidation were measured during the last 30 minutes of the measurement period. During measurements, subjects were told to refrain from talking, fidgeting and sudden movements. The equations $C = [4.55 (V_{co2} - 3.21) - (V_{o2} - 2.87)]$ (where C is grams of carbohydrates) and $F = [1.67 \times (V_{o2} - 1.67) - (V_{co2} - 1.92)]$ (where F are grams of fat per minute) developed by Frayn KN, (1983) were used to determine rates of resting fat and carbohydrate oxidation in $g \cdot \text{min}^{-1}$ (Frayn 1983).

3.3 DATA ANALYSES

Statistical analyses were performed using SPSS 13.0 (Chicago, IL) with statistical significance defined as $p \leq 0.05$. All data are expressed as mean SEM. Initially, data was analyzed to provide information on subject characteristics, insulin resistance, body composition, fat oxidation, energy expenditure and nutritional habits. Normal distribution was analyzed prior to conducting additional analyses. Differences in Primary Aims and Secondary Aims were conducted using One-Way Analyses of Variance (ANOVA). Pearson correlation coefficient was used to determine the relationship between insulin resistance and percent body fat and visceral fat.

Our sample size estimates were based on a previous study (Goodpaster, Thaete et al. 1997) in which fasting insulin levels (Primary Aim) were significantly different ($P < 0.01$) in obese (15.8 ± 10.1 mU/ml) and normal weight (6.5 ± 3.3 mU/ml) subjects. We needed 15 subjects in each of the four groups in order to have 80% power to determine a similar effect size in patients compared to controls (both obese and normal weight).

4.0 CHAPTER 4

4.1 RESULTS

4.1.1 Subjects

Insulin resistance and sub clinical features of insulin resistance were compared in 18 patients with bipolar 1 disorder and 17 controls matched for race, age and BMI. Twelve patients and 12 controls were obese by BMI criteria (BMI 35.2 ± 1.1 vs. $34.0 \pm 1.4\text{kg/m}^2$) and 6 patients and 5 controls were normal weight (BMI 22.8 ± 0.7 vs. $23.2 \pm 0.9\text{kg/m}^2$). All subjects were women.

Patients were treated with ≤ 3 medications during the study duration. Ten subjects were treated with antipsychotic medications (Abilify, Geodon, Haldol or Seroquel), 6 with antidepressants (Ativan, Wellbutrin, Effexor, Prozac, Lexapro and Zoloft) 7 with mood stabilizers (Lithium, Depakote, and Tegretol), 2 with anti-anxiety (trilafon), 6 with anti-convulsants (Neurontin, Topomax and Lamictol), 1 on an SSRI (Celexa), 1 on hypertensive medication (Licinopril) and 1 on hypothyroid medication (Synthroid). Patients were not treated with any medication known to affect glucose homeostasis. Matched controls were not treated with any psychotropic medication nor had any previous history of mental ailment. There were 2 control subjects (1 obese and 1 lean) treated with hypertensive agent and 1 on anti-Parkinson agent. By design, age, weight, race and BMI were not different between groups,

Table 5 Subject Characteristics

	Obese			Normal Weight		
	Patients	Controls	P Value	Patients	Controls	P Value
Age	42 ± 2.0	43 ± 2.5	0.65	40.8 ± 4.1	38.2 ± 4.4	0.67
Weight (kg)	97.9 ± 4.2	90.1 ± 5.0	0.24	66.3 ± 2.1	62.3 ± 3.8	0.35
BMI(kg/m ²)	35.2 ± 1.1	34.0 ± 1.4	0.53	22.8 ± 0.7	23.2 ± 0.9	0.75
Race	1.00 ± 0.0	1.08 ± 0.1	0.33	1.33 ± 0.21	1.00 ± 0.00	0.19

Values represent mean ± SEM, as expected, there were no differences observed in age, weight, BMI or Race.

4.1.2 Insulin Resistance

In both obese and normal weight women, fasting glucose and insulin levels were similar in patients with bipolar disorder compared to controls (Table 6). Insulin resistance, defined by the homeostatic model assessment of insulin resistance (HOMA IR), was not different between obese patients and controls (56.8 ± 17.2 vs. 51.0 ± 10.3 ; $P=0.84$; Figure 1), normal weight patients and controls (30.5 ± 6.3 vs. 27.0 ± 5.7 $P=0.78$; Figure 1) or when combining obese and normal weight patients to obese and normal weight controls (45.2 ± 11.1 vs. 47.5 ± 9.5 $P=0.80$; Figure 2). These results are in contrast to our primary hypothesis that patients would be more insulin resistant than non-patient controls. There was a trend for both groups of obese women, both patients and controls, to be more insulin resistant than normal weight women (54.3 ± 10.0 vs. 28.9 ± 7.2 , $P=0.10$).

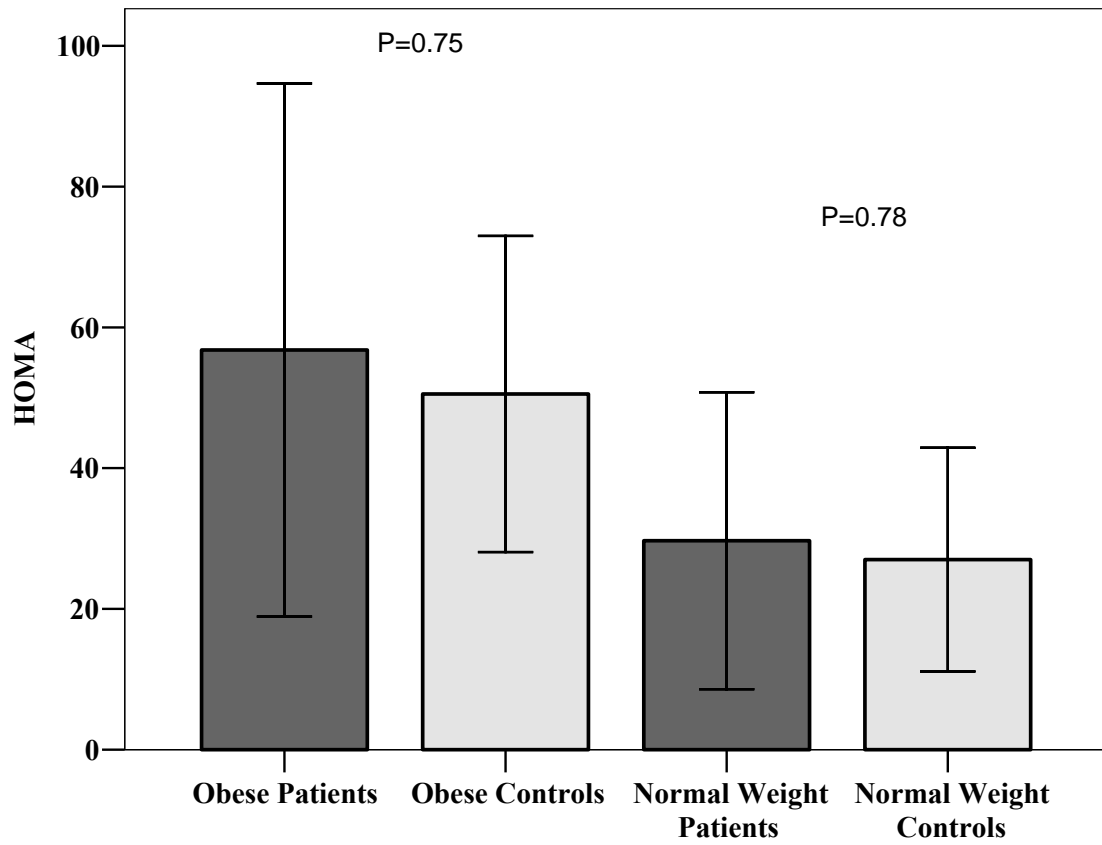


Figure 1 HOMA in Obese and Normal Weight Women

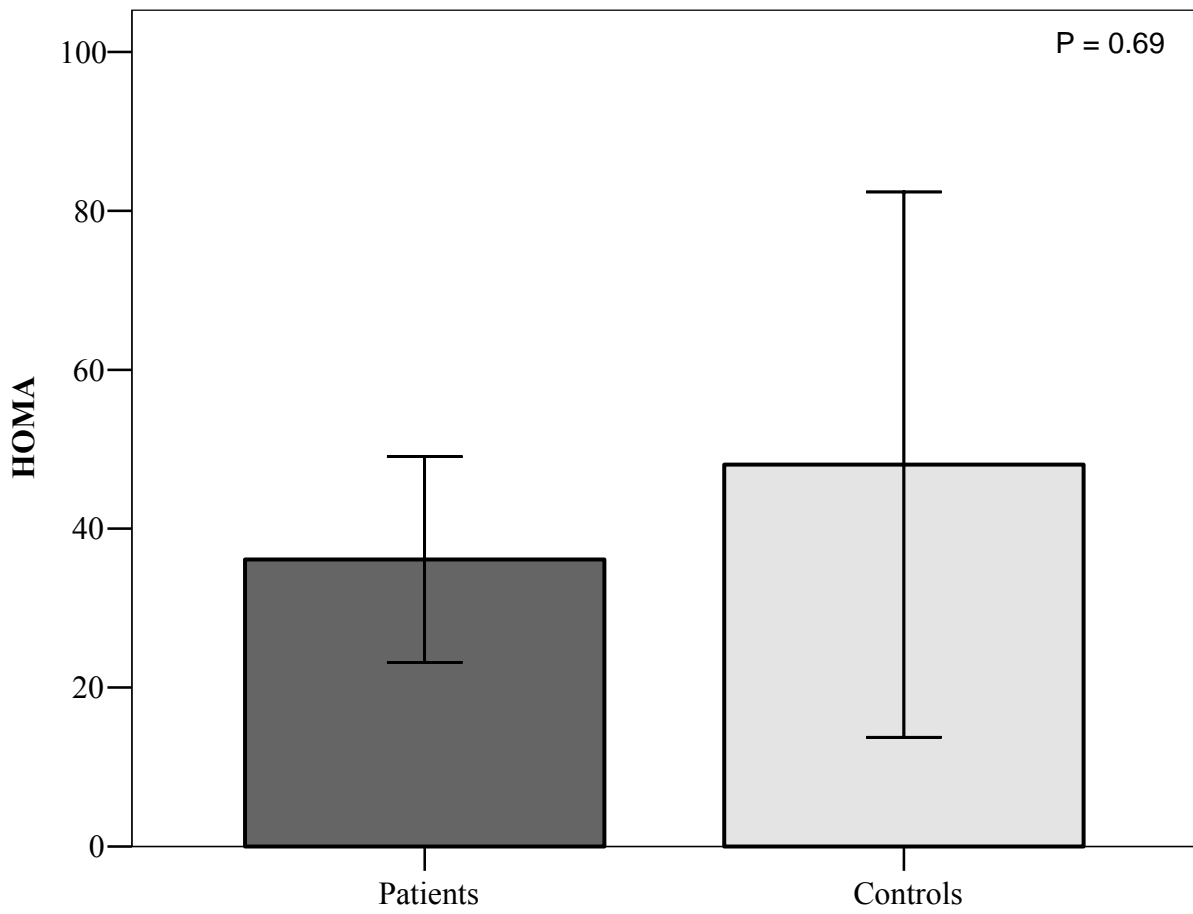


Figure 2 HOMA in Patients and Controls

4.1.3 Metabolic Characteristics

Total serum cholesterol, LDL, HDL or triglyceride levels were not different between obese patients and controls or normal weight patients and controls, Table 6. Upon combining the groups, LDL was significantly higher in controls compared to patients (124.9 ± 6.8 vs. 102.7 ± 7.7 mg/dL, $P=0.04$; Table 7) compared to patients and there was a trend for controls to have higher cholesterol (207.7 ± 11.7 vs. 182.7 ± 8.0 mg/dL, $P= 0.08$) although no other differences were observed, Table 7. One patient had a missing LDL and VLDL value due to elevated plasma triglycerides, preventing LDL and VLDL calculation. Blood pressure, a parameter of the metabolic syndrome, was significantly higher in obese patients compared to controls ($P=0.01$) although normal weight controls had higher diastolic blood pressure ($P=0.03$), but no difference in systolic, compared to normal weight patients. Controls together (obese and normal weight) had higher diastolic blood pressure compared to patients ($P = 0.04$).

Table 6 Metabolic Characteristics of Obese and Normal Weight Women

	Obese			Normal Weight		
	Patients (n = 12)	Controls (n = 12)	PValue	Patients (n = 6)	Controls (n = 5)	PValue
Cholesterol, mg/dL	187 ± 10.3	207.58 ± 15.0	0.28	180.5±17.4	198.6± 16.7	0.48
LDL, mg/dL	106.4 ± 7.0	129.6 ± 9.2	0.06	104.7± 11.6	103.2± 19.4	0.95
HDL, mg/dL	51.1 ± 2.4	55.7 ± 4.1	0.34	64.2 ± 7.1	81.6 ± 11.6	0.22
Triglycerides mg/dL	163.2 ± 35.5	116.7 ± 12.3	0.23	73.8 ± 8.9	84.8 ± 4.6	0.34
Glucose, μmol/mL	87.4 ± 2.9	89.9 ± 2.7	0.59	85.3 ± 5.2	84.8 ± 5.5	0.95
HbA1c	5.48 ± 0.1	5.6 ± 0.1	0.22	5.4 ± 0.1	7.2 ± 2.0	0.35
Insulin, μU/mL	13.5 ± 3.3	12.7 ± 2.5††	0.84	7.8 ± 1.3	7.0 ± 1.3	0.67
Syst. BP, mm/Hg	142.2 ± 2.0	126.2 ± 3.8†	0.01	117.0 ± 4.9	123.8 ± 6.4	0.41
Diast BP, mm/Hg	75.8 ± 1.7	69.0 ± 2.2	0.05	58.2 ± 1.7	72.0 ± 5.7*	0.03

Values represent mean ± SEM; LDL, low density lipoprotein; HDL, high density lipoprotein, HbA1c, hemoglobin A1c; Syst, systolic; Diast, diastolic. † P < 0.01; * P = < 0.05. Obese patients had higher systolic and diastolic blood pressure compared to controls whereas normal weight controls had higher diastolic blood pressure compared to normal weight patients. †† ANOVA reveals obese individuals (patients and controls) were significantly more insulin resistant compared to their lean counterparts.

Table 7 Metabolic Characteristics of Patients and Controls

	Patients (N=24)	Controls (N=23)	P value
Cholesterol, mg/dL	182.7 ± 8.1	207.7 ± 11.6	0.08
LDL, mg/dL	102.7 ± 7.7	124.9 ± 6.8*	0.04
HDL, mg/dL	55.9 ± 3.6	62.8 ± 4.8	0.26
Triglycerides, mg/dL	132.1 ± 24.4	108.7 ± 12.7	0.41
Glucose, µmol/mL	86.5 ± 2.6	88.5 ± 2.4	0.57
HbA1c	5.4 ± 0.11	6.1 ± 0.59	0.20
Insulin, µU/mL	10.9 ± 2.1	11.7 ± 2.1	0.80
Syst. BP, mm/Hg	130.2 ± 3.4	129.3 ± 3.6	0.86
Diast BP, mm/Hg	66.7 ± 1.9	73.3 ± 2.4*	0.04

Values represent mean ± SEM; LDL, low density lipoprotein; HDL, high density lipoprotein, HbA1c, hemoglobin A1c; Syst, systolic; Diast, diastolic. * P = < 0.05. Controls had higher LDL and diastolic blood pressure compared to patients although no other differences were observed.

4.2 OBESITY

4.2.1 Whole Body Fat and Lean Mass

Neither fat mass, fat free mass, nor percent body fat were different between obese patients and controls or normal weight patients and controls (Table 8). Obese patients had only 2% more total body fat compared to matched controls whereas normal weight patients were 1.5% less fat compared to matched controls. Patients together (obese and normal weight)

revealed a trend to have higher FFM compared to controls (Table 9) although no other differences were observed in FM or percent body fat.

Although the number of subjects in this study was small, data were examined to determine whether generalized obesity was related to insulin resistance. The proportion of total body fat was not associated ($P=0.19$) with insulin resistance determined by HOMA ($R^2=0.05$) when patients and controls were combined (Figure 3). Additionally, abdominal fat mass indicated no differences between patients and controls.

Table 8 Generalized Body Composition in Obese and Normal Weight Women

	Obese			Normal Weight		
	Patients	Controls	P Value	Patients	Controls	PValue
% BF	48.7 ± 1.0	46.9 ± 1.2	0.26	31.9 ± 3.0	33.4 ± 2.2	0.69
Fat Mass (kg)	48.4 ± 2.8	42.1 ± 3.1	0.16	21.2 ± 2.2	20.6 ± 2.3	0.75
Fat Free Mass (kg)	47.6 ± 1.5	44.2 ± 2.0	0.06	42.0 ± 1.9	38.1 ± 1.7	0.16
AbdominalFatMass (kg)	25.1 ± 1.4	21.9 ± 0.9	0.16	10.0 ± 1.2	9.4 ± 1.1	0.16

Values are means ± SE. BF, body fat. There were no differences observed between groups $P \geq 0.05$ although there was a trend for obese patients to have more fat free mass than obese controls $P = 0.06$

Table 9 Generalized Body Composition between Patients and Controls

	Patients	Controls	P Value
% BF	43.1 ± 2.2	42.9 ± 1.8	0.96
Fat Mass (kg)	39.3 ± 3.7	35.8 ± 3.3	0.48
Fat Free Mass (kg)	45.7 ± 1.3	42.4 ± 1.6	0.12
AbdominalFatMass (kg)	20.0 ± 2.0	18.3 ± 1.9	0.52

Values are means ± SE. BF, body fat. There were no differences observed between groups $P \geq 0.05$ although there was a trend for patients to have more fat free mass than controls $P = 0.12$

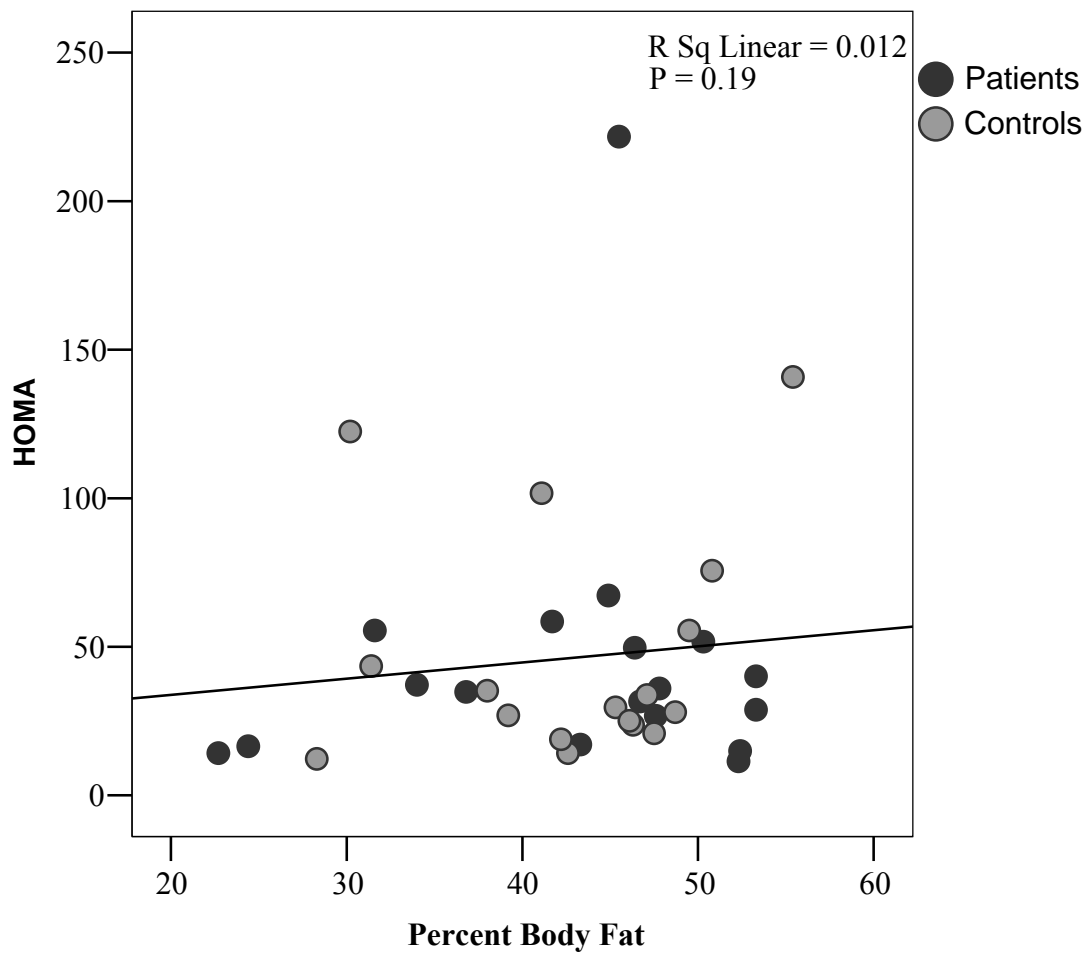


Figure 3 Correlation between HOMA and Percent Body Fat

4.2.2 Regional Fat Distribution

Obese patients had more ($P < 0.04$) total abdominal fat and a trend ($P = 0.09$) toward both greater visceral and subcutaneous abdominal fat determined by CT scans (Table 10). There were no differences observed in total abdominal fat or subcutaneous abdominal fat between normal weight patients and controls, although there was a trend for normal weight controls to have more visceral fat compared to normal weight patients. Furthermore, there were no differences observed in the ratio between visceral vs. subcutaneous abdominal fat between groups. There was an association ($P = 0.04$) between visceral adipose tissue and insulin resistance determined by HOMA IR (Figure 4, $R^2 = 0.13$), in addition to total abdominal fat and insulin resistance ($P = 0.04$, $R^2 = 0.08$) and total subcutaneous fat and insulin resistance ($P = 0.02$, $R^2 = 0.12$). Additionally, abdominal fat mass measured by DXA indicated no differences between patients and controls (obese = 25.1 ± 1.4 vs. 21.9 ± 1.7 kg and normal weight = 10.0 ± 1.2 vs. 9.4 ± 1.2 kg). Although upon removing an outlier, results revealed a trend between visceral adipose tissue and insulin resistance ($P = 0.06$) no difference between total abdominal fat and insulin resistance, a significant correlation between subcutaneous abdominal fat and insulin resistance ($P = 0.03$, $R^2 = 0.14$).

Neither total thigh adipose tissue nor intermuscular fat was significantly different between obese patients and matched controls or normal weight patients and matched controls (Table 10) although there was a trend ($P = 0.11$) for obese patients to have more subcutaneous thigh fat compared to matched controls. There were no differences observed in patients (both obese and normal weight) compared to controls, Table 11.

Table 10 Computed Tomography in Obese and Normal Weight Women

	Obese			Normal Weight		
	Patients	Controls	PValue	Patients	Controls	PValue
Total Abd Fat(cm ²)	718.1 ± 33.6	607.4 ± 38.6*	0.04	261.3 ± 37.3	332.7 ± 46.7	0.26
Abd.Visceral Fat(cm ²)	180.0 ± 11.3	151.0± 16.7	0.09	53.3 ± 8.1	78.5 ± 11.8	0.10
Abd. Subcutaneous Fat(cm ²)	483.2 ± 49.1	445.4 ± 37.7	0.09	207.9 ± 37.0	233.0 ± 23.5	0.60
Total Thigh Fat(cm ²)	219.6 ± 23.7	174.7 ± 18.3	0.15	107.3 ± 16.8	124.5 ± 10.7	0.43
Subcutaneous Thigh Fat(cm ²)	202.6 ± 24.1	153.8 ± 17.3	0.11	95.1 ± 16.2	111.2 ± 9.4	0.44
Intermuscular Thigh Fat(cm ²)	7.0 ± 0.9	6.5 ± 0.6	0.66	1.2 ± 0.3	1.7 ± 0.4	0.38
Thigh Muscle(cm ²)	128.3 ± 3.8	124.6 ± 7.7	0.65	111.5 ± 6.9	101.8 ± 2.9	0.26

Values are means ± SE. Abd, abdominal. Total abdominal fat was significantly higher in obese patients compared to controls. There was a trend for abdominal visceral and subcutaneous fat to be higher in obese patients compared to controls although normal weight patients did not display any difference in abdominal body composition. * = P < 0.05

Table 11 Computed Tomography in Patients and Controls

	Patients	Controls	PValue
Total Abd Fat(cm ²)	556.8 ± 60.0	526.6 ± 43.2	0.69
Abd.Visceral Fat(cm ²)	135.3 ± 17.0	124.4± 14.2	0.63
Abd. Subcutaneous Fat(cm ²)	386.0 ± 47.0	382.9 ± 36.3	0.96
Total Thigh Fat(cm ²)	180.0 ± 20.9	159.9 ± 14.3	0.44
Subcutaneous Thigh Fat(cm ²)	164.7 ± 20.7	141.3 ± 13.3	0.35
Intermuscular Thigh Fat(cm ²)	8.1 ± 0.6	8.2 ± 0.5	0.90
Thigh Muscle(cm ²)	122.4 ± 3.9	117.7 ± 6.0	0.52

Values are means ± SE. Abd, abdominal. There were no differences observed in abdominal adipose tissue or thigh adipose tissue between patients and controls.

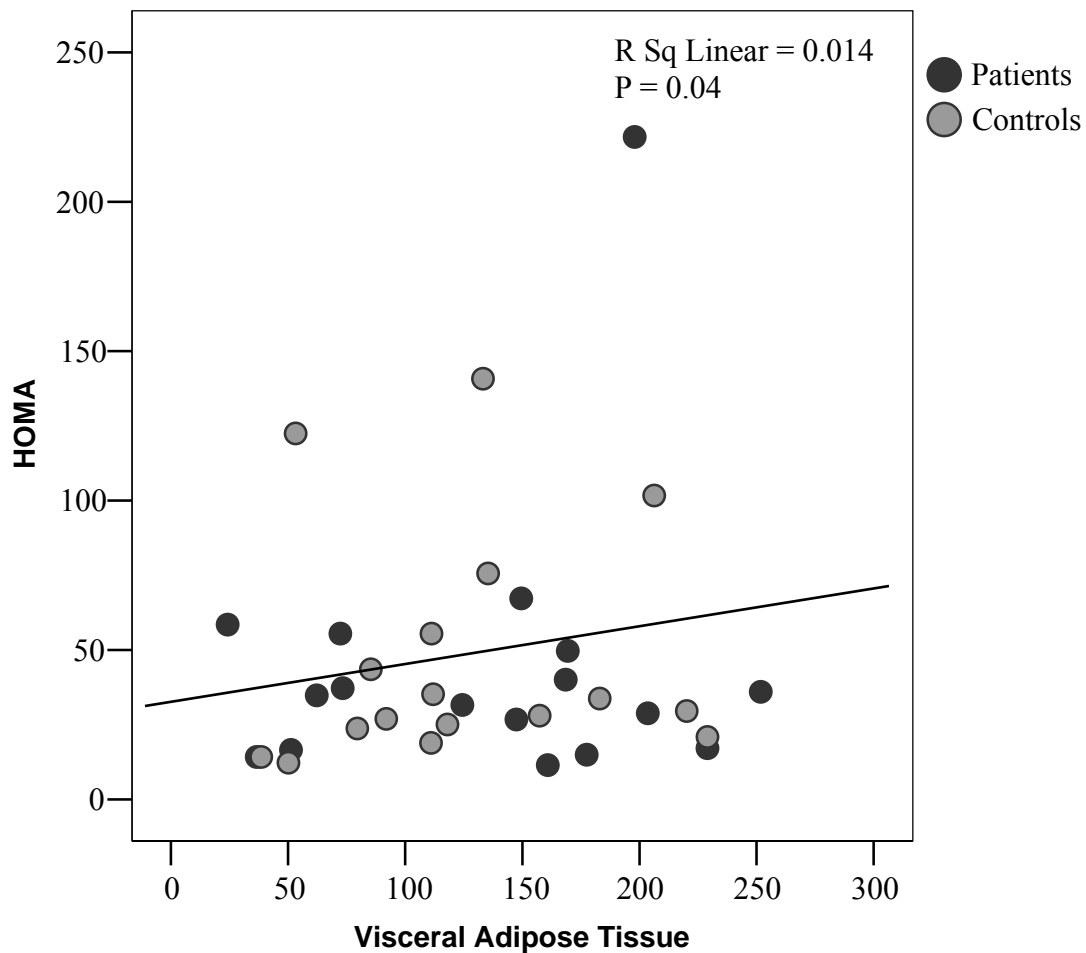


Figure 4 Correlation between HOMA and Visceral Adipose Tissue

4.3 ENERGY EXPENDITURE:

The secondary aim examined free-living energy expenditure, physical activity and nutritional habits in patients with bipolar 1 disorder and matched controls. Total daily energy expenditure did not reveal any differences in obese patients and controls or normal weight

patients and controls (Table 12). Furthermore, active energy expenditure defined as ≥ 2.5 METS, revealed no differences between obese patients and controls or normal weight patients and controls. Sleep state, based on algorithms provided by BodyMedia, indicated obese patients slept more than obese controls (5.7 ± 0.4 vs. 4.2 ± 0.5 hr/24hr; $P = 0.02$, Figure 5) whereas there was a trend in normal weight patients sleeping more than controls (7.1 ± 0.8 vs. 5.1 ± 0.4 hr/24hr; $P = 0.07$; Figure 6). Interestingly, there were no differences observed in total time the armband was worn (2134.02 ± 117.08 hrs vs. 1920.13 ± 122.01 hrs, $P = 0.22$) suggesting that obese patients and controls in addition to normal weight patients and controls (2270.33 ± 273.15 vs. 1831.9 ± 86.61 hrs, $P = 0.19$) wore the armband for equivalent periods of time.

We additionally examined total energy expenditure, active energy expenditure and sleep state during the weekdays and weekends (Table 12). Neither weekday nor weekend energy expenditure or active energy expenditure revealed a significant difference between obese patients and controls or normal weight patients and controls. Whereas obese patients slept significantly more on weekdays compared to obese controls (5.1 ± 0.4 vs. 3.4 ± 0.5 hr; $P = 0.02$; Figure 5), there was only a trend during the weekends (8.6 ± 1.4 vs. 5.4 ± 0.8 hr/24hr; $P = 0.06$; Figure 5). Neither weekday energy expenditure, activity energy expenditure or sleep state were different between normal weight patients and controls although there was a trend that normal weight patients slept more on weekends than weekdays (8.2 ± 0.7 vs. 6.3 ± 0.5 hr/24hr; $P = 0.06$; Figure 5).

Neither the combined patients (obese and normal weight) or combined controls (obese and normal weight), revealed any difference in energy expenditure or active energy expenditure over the 5 day measurement or during the weekends, Table 13. There was a trend ($P=0.12$) observed in patients to expend more energy expenditure, though not active energy expenditure,

during the weekdays. There was a significant difference revealing patients slept more overall, on weekdays and on weekends compared to controls, Figure 7. Interestingly, overall the data shows patients wore the armband more often than controls indicating a possible explanation for the difference in sleep state although during the weekend there were no differences observed in time worn but a difference in sleep state was still observed.

Table 12 Energy Expenditure Measured via BodyMedia in Patients and Controls

	Obese			Normal Weight		
	Patients	Controls	Pvalue	Patients	Controls	PValue
Total						
Time Worn (hrs)	2134.0 ± 117.1	1920.1 ± 122.0	0.21	2270.3 ± 273.2	1831.9 ± 86.6	0.19
EE (kcal/24hr)	2208.0 ± 115.8	2106.7 ± 76.0	0.47	2311.3 ± 277.7	1891.3 ± 74.0	0.10
Active EE (kcal/24hr)	545.3 ± 67.5	519.3 ± 74.6	0.80	741.1 ± 184.5	631.4 ± 124.3	0.65
Weekdays						
Time Worn (hrs)	2041.4 ± 96.9	1775.1 ± 116.5	0.09	1880.3 ± 158.8	1645.5 ± 89.0	0.26
EE (kcal/24hr)	2108.0 ± 96.4	1933.4 ± 96.9	0.21	1922.8 ± 177.1	1684.1 ± 79.1	0.28
Active EE (kcal/24hr)	476.1 ± 83.4	475.2 ± 86.2	0.99	648.4 ± 184.7	556.8 ± 118.6	0.70
Weekends						
Time Worn (hrs)	2487.7 ± 146.7	2266.5 ± 220.0	0.41	2334.5 ± 193.9	2225.6 ± 153.7	0.68
EE (kcal/24hr)	2623.2 ± 186.9	2495.6 ± 157.0	0.61	2367.3 ± 198.9	2326.9 ± 106.0	0.87
Active EE (kcal/24hr)	656.0 ± 85.5	708.9 ± 173.0	0.79	579.3 ± 227.1	795.1 ± 176.7	0.47

Values are means ± SE. EE energy expenditure. There were no significant differences in EE or active EE between obese patients and controls or lean patients and controls.

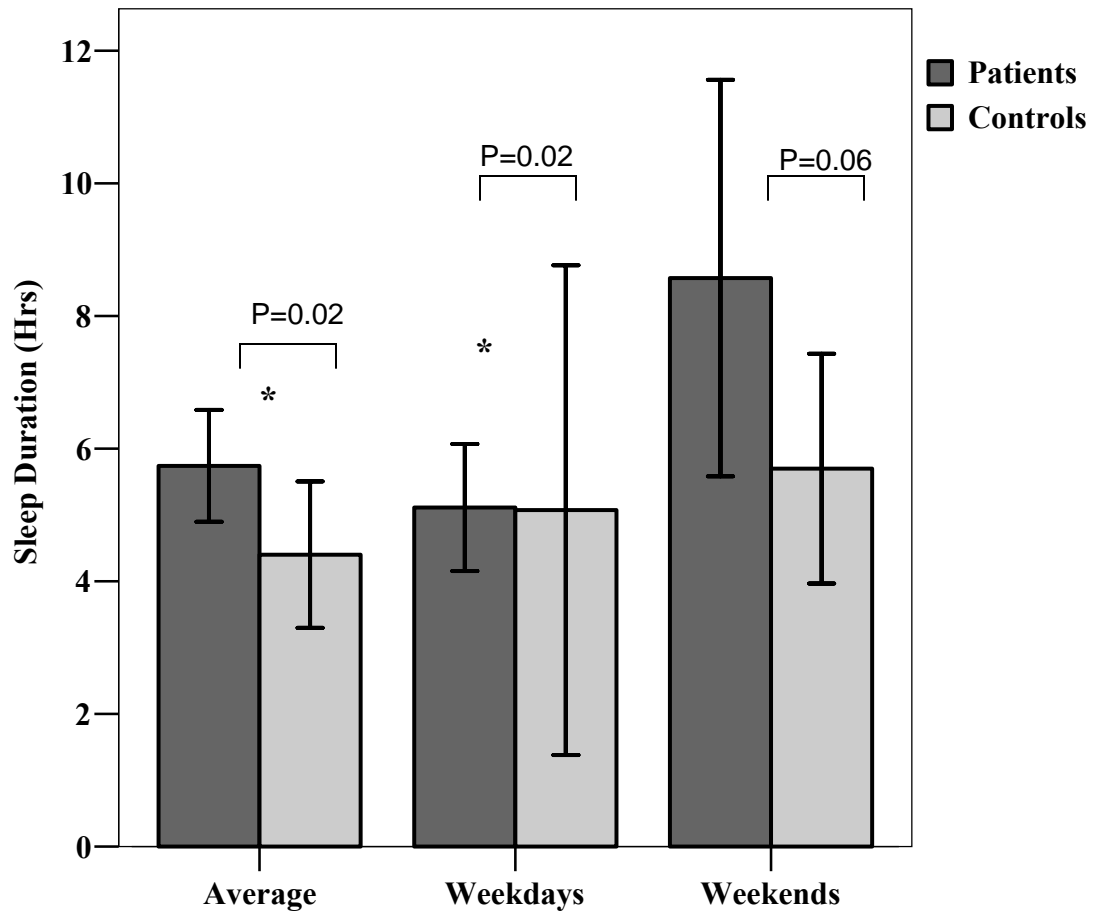


Figure 5 Sleep Duration in Obese Patients and Controls

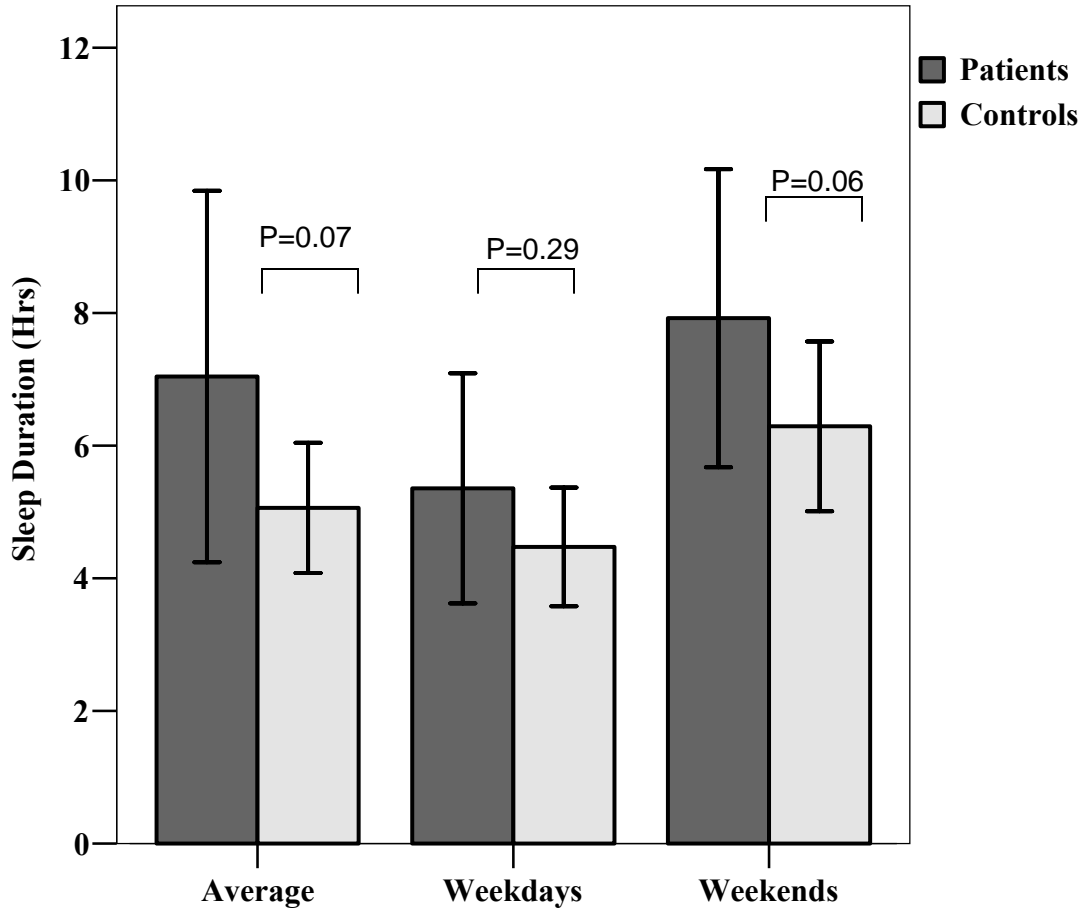


Figure 6 Sleep Duration in Normal Weight Patients and Controls

Table 13 Energy Expenditure Measured via BodyMedia in Patients and Controls

	Patients	Controls	Pvalue
Total			
Time Worn (hrs)	2179.5 ± 116.1	1894.2 ± 88.8	0.06
EE (kcal/24hr)	2242.4 ± 116.1	2043 ± 61.7	0.15
Active EE (kcal/24hr)	610.6 ± 76.2	552.2 ± 63.2	0.56
Weekdays			
Time Worn (hrs)	1987.7 ± 82.8	1737.0 ± 85.9*	0.04
EE (kcal/24hr)	2046.3 ± 86.8	1860.1 ± 76.2	0.12
Active EE (kcal/24hr)	533.5 ± 82.1	499.2 ± 58.1	0.74
Weekends			
Time Worn (hrs)	2436.6 ± 115.2	2254.4 ± 158.9	0.36
EE (kcal/24hr)	2537.9 ± 140.7	2446.0 ± 114.7	0.62
Active EE (kcal/24hr)	630.4 ± 91.0	734.2 ± 130.1	0.51

Values are means ± SE. EE energy expenditure. There were no significant differences in EE or active EE between patients and controls during the 5 day measurement or weekends although there was a trend for patients to expend more energy during the weekdays compared to controls. * P<0.05

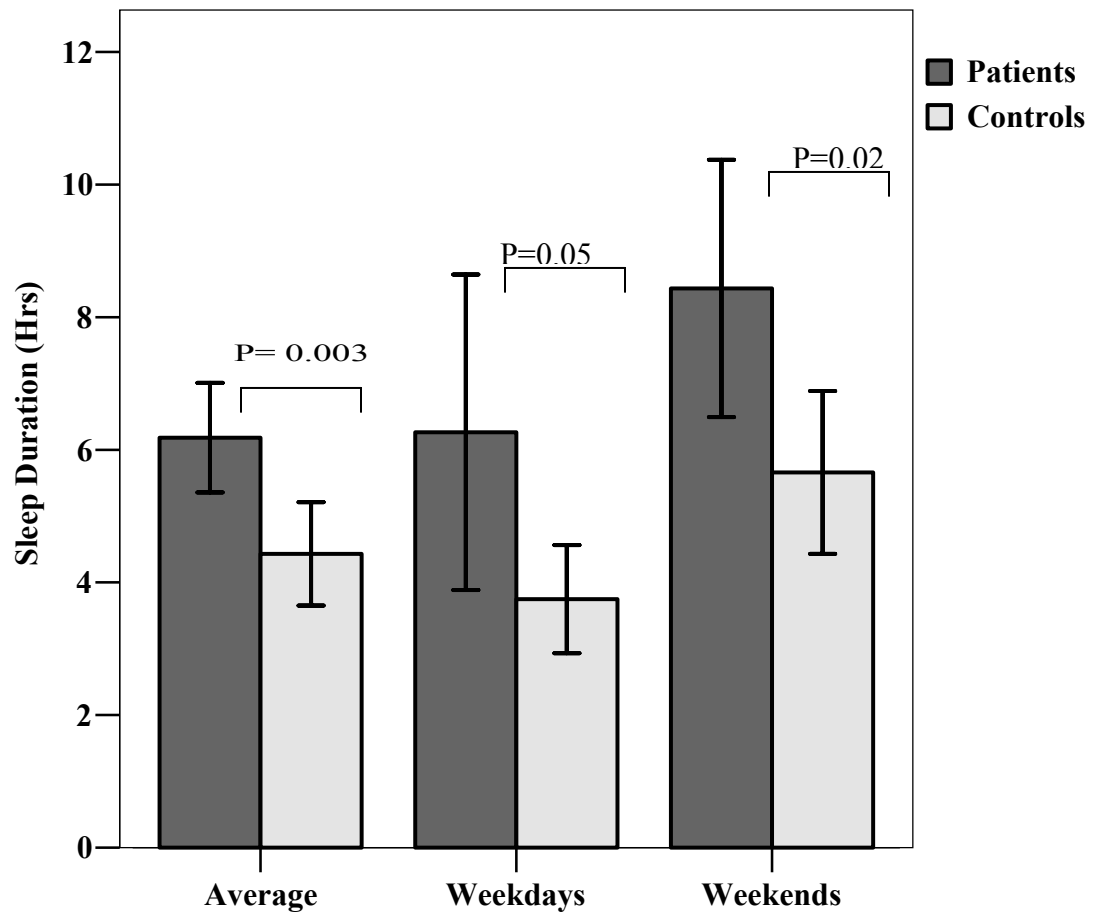


Figure 7 Sleep Duration in Patients and Controls

4.4 FATTY ACID METABOLISM

Neither relative nor absolute rates of fat oxidation were different between obese patients and matched controls (Table 14). Similarly, the proportion of fat utilized at rest was not different between obese patients and controls ($P = 0.66$). However, absolute (1.2 ± 0.1 vs. 1.8 ± 0.3 mg/FFM/min; $P = 0.06$) and relative (43.9 ± 4.8 vs. $56.7 \pm 6.0\%$; $P = 0.12$) rates of fat oxidation tended to be lower in normal weight patients than controls. Normal weight patients were oxidizing 13% less fat than matched controls during resting conditions.

Neither patients (both obese and normal weight) nor controls revealed any differences in relative or absolute energy expenditure (Table 15). There was a trend ($P = 0.07$) for patients to oxidize less fat at rest although relative fat oxidation was not different $P = 0.54$. Pearson correlation coefficients did not reveal a correlation between fat metabolism and insulin resistance, defined by HOMA, for obese ($P = 0.481$, $R^2 = 0.02$), normal weight ($P = 0.439$, $R^2 = 2.7$) or the combined groups ($P = 0.285$, $R^2 = 0.004$) even when controlling for body composition.

Table 14 Resting Rates of Fat Oxidation in Obese and Normal Weight Women

	Obese			Normal Weight		
	Patients	Controls	PValue	Patients	Controls	PValue
Respiratory Quotient	0.83 ± 0.01	0.82 ± 0.01	0.57	0.86 ± 0.01	0.82 ± 0.02	0.13
EE (Kcal/24h)	1671.1 ± 66.1	1586.3 ± 68.4	0.38	1396.8 ± 50.1	1332.0 ± 45.6	0.37
EE (Kg•FFM ⁻¹ min ⁻¹)	35.3 ± 1.4	36.1 ± 1.0	0.66	33.5 ± 1.7	35.1 ± 1.3	0.49
Fatox (mg•FFM ⁻¹ min ⁻¹)	1.5 ± 0.1	1.6 ± 0.1	0.49	1.2 ± 0.1	1.8 ± 0.3	0.06
Percent Fatox	53.4 ± 5.0	56.2 ± 3.9	0.66	43.4 ± 5.8	56.7 ± 6.0	0.12
CHOox(mg•FFM ⁻¹ /min ¹)	2.9 ± 0.3	2.7 ± 0.3	0.65	3.4 ± 0.4	3.2 ± 0.6	0.75
Percent CHOox	46.6 ± 5.0	43.8 ± 3.1	0.66	56.6 ± 5.8	43.2 ± 5.9	0.15

Values are mean ± SE. EE, energy expenditure; Fatox, fat oxidation, CHOox, carbohydrate oxidation. There were no differences observed in EE, relative fat ox or absolute or relative CHO ox although there was a trend for normal weight patients to have a lower fat oxidation compared to controls.

Table 15 Resting Rates of Fat Oxidation in Patients and Controls

	Patients	Controls	PValue
Respiratory Quotient	0.84 ± 0.01	0.82 ± 0.01	0.19
EE (Kcal/24h)	1579.7 ± 55.8	1511.5 ± 57.1	0.40
EE (Kg•FFM ⁻¹ min ⁻¹)	34.7 ± 1.1	35.8 ± 0.78	0.43
Fatox (mg•FFM ⁻¹ min ⁻¹)	1.4 ± 0.1	1.7 ± 0.1	0.07
Percent Fatox	50.2 ± 3.8	57.0 ± 3.3	0.20
CHOox(mg•FFM ⁻¹ /min ¹)	3.1 ± 0.3	2.9 ± 0.2	0.54
Percent CHOox	49.8 ± 3.8	43.0 ± 3.3	0.20

Values are mean ± SE. EE, energy expenditure; Fatox, fat oxidation, CHOox, carbohydrate oxidation. There were no differences observed in respiratory quotient or EE although there was a trend for patients to have a lower fat oxidation compared to controls.

4.5 NUTRITION BEHAVIOR

There were no significant differences in energy intake, protein, fat, carbohydrate or fiber intake between patients or controls, Table 16. Upon examining fat intake specifically, there were no differences observed in saturated, monounsaturated or polyunsaturated fat among groups. Obese controls consumed a higher proportion of alcohol compared to obese patients ($P = 0.03$) although there was no difference in the proportion of fat, carbohydrates, proteins or sweets. Normal weight controls consumed a higher proportion of sweets compared to patients ($P = 0.03$) although proportion of fat, carbohydrates, protein and alcohol were not different. Overall obese and normal weight patients consumed more servings of vegetables compared to controls ($P = 0.04$) although servings of fat, fruit, grain, meat and dairy revealed no differences.

Patients together (both obese and normal weight) consumed more calories, carbohydrates, protein, fiber, saturated fat and polyunsaturated fat (Table 17) although surprisingly, they also consumed more calcium, dairy and grains compared to controls which have been associated with lower levels of weight (Metz, Karanja et al. 1988).

Table 16 Nutritional Behavior in Obese and Normal Weight Women

	Obese			Normal Weight		
	Patients	Controls	P Value	Patients	Controls	P Value
Kilocalories (kcal)	2080.1±346.2	1544±282.9	0.24	2030.0±366.0	1833.0±419.5	0.73
Carbohydrate (g)	237.5 ± 36.5	180.2 ± 37.6	0.29	244.7 ± 49.4	218.0 ± 46.5	0.71
Fat (g)	94.3 ± 19.3	67.1 ± 12.2	0.25	89.4 ± 16.4	84.1 ± 24.8	0.86
Protein (g)	78.0 ± 12.0	54.4 ± 9.2	0.13	69.3 ± 13.0	51.4 ± 8.0	0.29
Fiber (g)	17.0 ± 2.7	11.0 ± 1.9	0.09	17.9 ± 3.5	10.4 ± 1.4	0.10
Saturated Fat (g)	29.6 ± 5.7	20.9 ± 3.7	0.22	28.2 ± 6.1	26.3 ± 7.7	0.85
Monounsaturated Fat (g)	37.7 ± 7.7	25.8 ± 4.5	0.20	31.2 ± 5.9	30.8 ± 8.0	0.97
Polyunsaturated Fat (g)	19.6 ± 4.9	15.4 ± 3.3	0.48	23.2 ± 3.5	21.6 ± 7.7	0.85
Percent Fat (%)	39.6 ± 2.5	39.3 ± 2.1	0.91	39.9 ± 3.6	38.9 ± 3.0	0.84
Percent Carbohydrate (%)	46.7 ± 3.0	45.5 ± 2.7	0.77	47.9 ± 3.5	48.3 ± 1.4	0.91
Percent Protein (%)	15.3 ± 0.9	14.6 ± 0.5	0.53	13.7 ± 0.8	12.1 ± 1.3	0.29
Percent Sweets (%)	16.3 ± 3.7	15.4 ± 3.1	0.85	13.9 ± 2.7	26.2 ± 3.9*	0.03
Percent Alcohol (%)	0.24 ± 0.2	3.04 ± 1.2*	0.03	0.97 ± 0.6	3.36 ± 1.5	0.14
Fat Serving	3.5 ± 0.5	3.1 ± 0.5	0.53	3.9 ± 0.5	4.8 ± 1.3	0.51
Fruit Serving	1.4 ± 1.1	0.9 ± 0.2	0.21	1.5 ± 0.4	0.8 ± 0.1	0.15
Vegetable Serving	3.1 ± 0.6	1.8 ± 0.2*	0.04	3.7 ± 0.4*	1.6 ± 0.4	0.04
Grain Serving	5.1 ± 1.1	3.7 ± 1.0	0.32	5.9 ± 2.2	3.1 ± 0.4	0.29
Meat Serving	2.0 ± 0.5	1.6 ± 0.3	0.52	1.8 ± 0.4	1.2 ± 0.2	0.26
Dairy Serving	2.2 ± 0.4	1.1 ± 0.4	0.06	1.6 ± 0.4	1.2 ± 0.3	0.38

Values are mean ± SE. Obese patients consumed more alcohol and servings of vegetables than controls whereas normal weight patients consumed more sweets and servings of vegetables than controls. * P < 0.05

Table 17 Nutritional Behavior in Patients and Controls

	Patients	Controls	P Value
Kilocalories (kcal)	2185.0±282.8	1500.2±163.7*	0.05
Carbohydrate (g)	258.9 ± 33.6	171.2 ± 18.4*	0.03
Fat (g)	98.3 ± 14.3	66.2 ± 9.1	0.07
Protein (g)	75.9 ± 9.1	52.6 ± 6.3*	0.05
Fiber (g)	17.5 ± 2.3	10.6 ± 0.9†	0.01
Saturated Fat (g)	30.8 ± 4.3	20.7 ± 2.9	0.07
Monounsaturated Fat (g)	37.4 ± 5.4	25.3 ± 3.4	0.07
Polyunsaturated Fat (g)	22.6 ± 3.8	15.3 ± 2.4	0.12
Percent Fat (%)	40.1 ± 1.9	38.8 ± 1.7	0.62
Percent Carbohydrate (%)	47.4 ± 43.1	46.0 ± 2.1	0.64
Percent Protein (%)	14.3 ± 0.7	14.3 ± 0.6	0.95
Percent Sweets (%)	17.5 ± 2.7	16.5 ± 2.6	0.77
Percent Alcohol (%)	0.3± 0.1	3.3 ± 0.9††	0.001
Fat Serving	4.1 ± 0.5	3.1 ± 0.4	0.15
Fruit Serving	1.4 ± 0.2	1.0 ± 0.2	0.18
Vegetable Serving	2.9 ± 0.4	2.1 ± 0.3	0.13
Grain Serving	5.6 ± 1.0	3.2 ± 0.5*	0.05
Meat Serving	2.0 ± 0.3	1.5 ± 0.2	0.36
Dairy Serving	2.1 ± 0.3	1.5 ± 0.2*	0.04

Values are mean ± SE. Patients consumed more calories, carbohydrates, protein and fiber than controls. There was a trend for patients to consume more fat than controls. The type of fat intake was not different between groups although there was a trend indicating patients consumed more saturated, monounsaturated and polyunsaturated fat compared to controls. Patients also consumed more servings of grain and dairy compared to controls although controls consumed more alcohol compared to patients. * P < 0.05 † P < 0.01 †† P < 0.001

5.0 CHAPTER 5

5.1 DISCUSSION

5.1.2 Insulin Resistance

Bipolar disorder has been associated with an increased prevalence of type 2 diabetes. One of the primary characteristics of type 2 diabetes is insulin resistance, which has been linked to hypertension, dyslipidemia and cardiovascular disease. Obesity, especially abdominal obesity, is a common thread among metabolic disorders (Reilly and Rader 2003) as well as cardiovascular disease (Haffner 1997; Lempiainen, Mykkanen et al. 1999) and is also strongly associated with insulin resistance (Goodpaster, Thaete et al. 1997). Individuals suffering from mental health diseases have higher prevalence of obesity (Fagiolini, Frank et al. 2002; Fagiolini, Kupfer et al. 2003; McElroy, Kotwal et al. 2004), diabetes (Russell and Johnson 1981; Cassidy, Ahearn et al. 1999; Regenold, Thapar et al. 2002), dyslipidemia (Yates and Wallace 1987; Atmaca, Kuloglu et al. 2002), hypertension (Elmslie, Silverstone et al. 2000), and cardiovascular disease (Elmslie, Silverstone et al. 2000; 2001; Lakka, Laaksonen et al. 2002) than the general population. It was reasonable therefore to examine whether patients with bipolar disorder are more insulin resistant than can be expected on the basis of their level of obesity alone.

A key finding in this study was that patients with bipolar disorder were no more insulin resistant than race, age and BMI-matched controls. Although the prevalence of obesity and type 2 diabetes is generally higher in these patients, insulin resistance has not yet been examined directly in bipolar disorder. Thus, this is the first study to our knowledge that has examined insulin resistance in these patients.

There are several possibilities as to why differences in insulin resistance were not observed between patients and controls. One likely explanation is that obesity may be the primary driving force in the association with insulin resistance, and that bipolar disorder itself is not associated with insulin resistance independent of obesity. In other words, once these patients become obese, they are no more insulin resistant than women without bipolar disorder. Indeed, both obese patients and controls were substantially more insulin resistant than normal weight women. However, that does not discount the possibility that bipolar disorder contributes to obesity. Obtaining a 'snapshot' in one point in time of patients with bipolar disorder and controls in a cross-sectional comparison does not permit conclusions to be drawn concerning whether or not bipolar disorder contributed to their obesity. The possibility that characteristics of normal weight patients may predispose them to weight gain will be discussed later.

It is possible that the estimate of insulin resistance in this study was inadequate. The Homeostatic model assessment of insulin resistance (HOMA IR) is only a surrogate for insulin resistance. Although HOMA IR is correlated with more direct measures of insulin resistance, for example, with the hyperinsulinemic euglycemic clamp method, this estimate of insulin resistance may not have been adequately sensitive to detect more severe insulin resistance in a small number of bipolar patients examined in this study. In support of this, abdominal fat content, a strong correlate of insulin resistance, (Jensen, Kanaley et al. 1995) was higher in patients

compared to controls. This suggests the possibility that these patients were indeed more insulin resistant. Future studies using more sophisticated techniques to quantify insulin resistance in these patients are warranted.

Another factor that may have confounded the ability to detect differences in insulin sensitivity between patients and controls was medication use by patients. Certain medications such as olanzapine and clozapine have been shown to not only increase weight but also increase risk of diabetes (Wirshing, Wirshing et al. 1999). However, this could not have contributed to insulin resistance in this study since potential volunteers using these medications were excluded from this study. Not even a lifetime history of treatment with these specific medications was allowed. In addition, not all medications used to treat bipolar disorder exacerbate insulin resistance. McIntyre et al (2006) have suggested that some antidepressants may in fact improve insulin sensitivity (McIntyre, Soczynska et al. 2006). Upon a MedLine search from 1966 to 2005, these authors reported some selective serotonin reuptake inhibitors (SSRI) reduced hyperglycemia and normalized glucose homeostasis whereas nonselective hydrazine monoamine oxidase inhibitors (MAOI) were associated with hypoglycemia and increased glucose disposal rate. These medications may have confounded the ability to detect differences in insulin resistance between patients and controls since these patients were treated with such medications prior to and during this study. These data highlight the need to further examine insulin resistance in bipolar disorder in a larger number of subjects using direct measures of insulin sensitivity while accounting for the potential influence of medication usage.

Other parameters of the insulin resistance syndrome, or metabolic syndrome were also examined in this study. Obese patients with bipolar disorder were more hypertensive than controls. This is in agreement with a growing body of literature indicating that bipolar patients

are more prevalent to have hypertension than the general population(Kilbourne, Cornelius et al. 2004; Beyer, Kuchibhatla et al. 2005). Although majority of research examines this characteristic in relation to the metabolic syndrome, the current data indicate based on ATP III criteria, that only two patients and one control met criteria for metabolic syndrome. Only two other studies to our knowledge have examined the metabolic syndrome in this population. Basu et al (2004) investigated metabolic syndrome in Schizoaffective Disorder Bipolar Subtype (Basu, Brar et al. 2004). They recruited patients currently partaking in a double-blind study of topiramate or placebo as adjunctive treatment. Basu et al. describe a 42% prevalence rate which is similar to the 30% prevalence that was reported by Fagiolini et al (2005) (Fagiolini, Frank et al. 2002). The small sample size in the current study precludes any comparison of prevalence of metabolic syndrome to these other studies.

5.2 OBESITY

5.2.1 Generalized Obesity

Neither the total body fat, proportion of body fat, nor fat free mass was different between groups. This lack of differences was largely driven by the study design; we intentionally recruited and matched patients and controls on the basis of body mass index (BMI). Since BMI is highly correlated with generalized obesity, it is highly unlikely that differences in general body composition would be observed.

5.2.2 Regional Fat Distribution

CT scans revealed higher amounts of total abdominal fat and trends towards higher visceral and subcutaneous abdominal fat in obese patients compared to controls. These differences were not observed in normal weight subjects. This is in agreement with previous reports indicating that bipolar patients were more likely to have abdominal obesity than the general population (Elmslie, Silverstone et al. 2000; Fagiolini, Frank et al. 2002; McElroy, Kotwal et al. 2004). However, these studies did not account for total body fat, which can confound differences in abdominal fat. The current results are in disagreement with Weber-Hamann et al. (2002) who used computed tomography to assess visceral adiposity in depressed postmenopausal women. Differences in visceral adiposity compared to controls were not observed. Methodology between the two studies is slightly different though this could unlikely account for the discrepancy. Weber-Hamann and associates analyzed a single slice at each L1 and L4 whereas we used a single slice in-between L4 and L5. Furthermore, the patient population is different. Though it has been shown that majority of bipolar patients stay longer in depressed state compared to manic state (Judd, Schettler et al. 2002; Judd and Akiskal 2003), our current population was recruited in euthymic state whereas in the aforementioned study, authors recruited women with at least a score of 18 on the Hamilton Depression Scale which indicates a moderate to severe state of depression. No other study to our knowledge has examined abdominal adiposity in bipolar patients using CT or other imaging modalities such as MRI.

Abdominal obesity has more typically been examined in disorders of mental health using a more common estimate of abdominal obesity such as waist circumference. For instance, Fagiolini et al. (2005) obtained waist circumference values on 171 patients with bipolar disorder from the Bipolar Disorder Center for Pennsylvanians (Fagiolini, Frank et al. 2002). They

reported that 49% of patients met criteria for abdominal obesity using waist circumference as the primary measure. Waist circumference has been shown to be correlated to visceral adiposity more so than waist to hip ratio (Pouliot, Despres et al. 1994) although it appears to have a higher correlation to total body fat rather than visceral fat (Harris, Visser et al. 2000). This is in accord with the current results indicating obese patients had higher total abdominal fat compared to controls whereas only a trend was revealed for differences in visceral adiposity.

5.3 ENERGY EXPENDITURE

Resting metabolic rate was not different between patients and controls. Obesity is a paramount public health concern because it is a primary risk factor for cardiovascular disease and type 2 diabetes. Many factors have contributed to this dramatic increase in obesity, but from a physiological perspective, this problem can be reduced to the very simple concept of energy balance. A positive energy balance leads to excess body fat and obesity is due to either an increase in energy intake, (i.e. overeating), or a decrease in energy expenditure, or likely a combination of both.

This is the first study to our knowledge that has examined energy expenditure in patients with bipolar disorder. We did not detect any differences in resting energy expenditure, resting metabolic rate or active energy expenditure between obese patients and controls or normal weight patients and controls indicating reduced energy expenditure may not be the underlying cause of their increased risk for obesity. Previous studies have examined physical activity levels in bipolar disorder using self report measurements. For instance, Elmslie et al (2001) identified lifestyle related factors through the LINZ activity questionnaire among patients with bipolar

disorder and reference subjects matched for age and race for 4 weeks preceding study measurements.(Elmslie, Mann et al. 2001) These authors reported that patients participated in fewer low to moderate intensity and high intensity activities compared to reference subjects. In contrast, another study conducted by Davidson et al. (2001) examined patients with mental illness defined as schizophrenic, schizoaffective or bipolar.(Davidson, Judd et al. 2001) Authors examined, through self report from the Risk Factor Prevalence Study,(Health 1991) that patients were more likely to walk for exercise compared to non-patient participants. Comparisons of studies are problematic for two reasons: subject matching and methodology. For instance, Elmslie et al compared bipolar patients to reference subjects based on age and race, not BMI. BMI in addition to body composition is an important factor to consider when controlling for activity level since it has been shown to correlate with BMI.¹¹⁹ Secondly Elmslie and associates and Davidson and associates used self report measurements whereas the current project assessed overall caloric expenditure. Though the participants in the previous two studies may report lower or higher exercise habits they do not measure 24 hour energy expenditure which is an important factor to consider in respect to obesity.

The only study using more objective measurements was a study conducted by Harvey et al (2005) examining sleeping patterns in bipolar patients using an accelerometer (Actigraph) for 8 consecutive days. (Harvey, Schmidt et al. 2005) Harvey et al. (2005) reported that bipolar patients had a reduced activity level during the day time although concludes this may have been due to their medications in addition to their insomnia. For instance, lower activity levels during the day may serve to protect against the lack of sleep the night prior. The discrepancy between Harvey et al. and the current project is matched controls and methodology. Harvey's group divided patients among sleeping characteristics and control subjects were not matched based on

body composition nor BMI. The current project used the BodyMedia SenseWear Armband which has provided valid and reliable estimates of energy expenditure at rest and also generates similar estimates of energy expenditure as indirect calorimetry.(Fruin and Rankin 2004) Another important consideration in assessing energy expenditure is that many instruments, including self reported activity as well as accelerometry may not capture lower levels of activity, which may be important in overall health¹²⁵. Thus an important aspect of this project was that a novel method was used to capture lower levels of activity in addition to supporting the idea that patients increased risk for obesity may not be associated with their lack of overall caloric expenditure, at least in respect to euthymic bipolar patients.

The BodyMedia armband did reveal obese patients sleeping more hours of the day over the entire 5 day period and on weekdays though only a trend was observed on weekends. Though the data only revealed a trend, normal weight patients also slept more overall and on the weekends. BodyMedia SenseWear armband utilized in this study used Innerview V4.1 algorithms and was designed to measure 24 hour use. The accuracy, determined using "by subject" cross validation from a group of subjects at The University of Pittsburgh hospital sleep lab and another group of subjects who supply self reported activity annotations. Validation data has not been published as of today using these specific 24 hour algorithms although one study conducted by Germain et al (2006) examined the validity of the BodyMedia armband in assessing wakefulness, REM sleep and NREM sleep¹²⁶. Authors revealed the algorithm correctly identified 93% of all sleep epochs, and 83% of all wakefulness epochs, for an overall epoch-by-epoch accuracy of 89%.

Interestingly, bipolar patients slept more often which is in contrast to some previously reported data. Harvey et al (2005) reported 75% of bipolar patients had a significant lack of

sleep problem whereas 55% met diagnostic criteria for insomnia.(Harvey, Schmidt et al. 2005) The discrepancy in sleep duration between this study and Harvey et al. can be in the methodology. Actigraph has been shown to be reliable in individuals without sleep complaints although has a lower reliability in individuals who lie immobile for long periods.

These noninvasive measurements of energy expenditure may be important in future studies to determine the importance of the various components of energy expenditure, including physical activity and sleep patterns, which may contribute to metabolic dysregulation in bipolar patients. Perhaps future studies using more objective measures of energy expenditure, such as doubly labeled water method, would be useful to determine whether patients with bipolar disorder have reduced physical activity or daily energy expenditure.

5.4 FATTY ACID METABOLISM

Fat oxidation after an overnight fast, a correlate of insulin resistance in previous studies (Kelley, Goodpaster et al. 1999), was similar in obese patients and controls. Interestingly, however, normal weight patients tended to have a lower fat metabolism compared to controls. This is the first study to show that pre-obese bipolar patients may utilize a lower proportion of fat during basal conditions compared to controls. This finding may provide important insight into the factors that may contribute to weight gain and obesity in patients with bipolar disorder. An impaired capacity to utilize fat is related to increased weight gain and insulin resistance (Kelley, Goodpaster et al. 1999). Patients with bipolar disorder are often more obese than the general population and a reduced capacity to utilize fat at rest is linked to increased weight gain. This reduced fat oxidation may be an underlying factor contributing to their increased risk for obesity.

Future prospective studies are needed to examine factors, including an impaired capacity for fat oxidation, which may predispose these patients to weight gain. It is possible that lifestyle factors, including physical activity and diet, as well as medication usage, may be underlying factors for altered fuel metabolism in bipolar disorder.

5.5 NUTRITION BEHAVIOR

The prevalence of obesity in the United States increased from 14.5% to 30.9% during 1971—2000 (Flegal, Carroll et al. 2002). Unhealthy diets and sedentary behaviors have been identified as the primary causes of deaths attributable to obesity (Services. 2001). Evaluating trends in dietary intake is an important step in understanding the factors that contribute to the increase in obesity. Although there were no differences observed in energy intake, carbohydrate or fat consumption, obese patients consumed over 500 more calories than controls and normal weight patients consumed over 200 more calories than controls. These results are in agreement with Elmslie et al (2001). Elmslie and associates examined 24-hour diet recall and also a 4 day estimate of nutrient intake. Authors report women with bipolar disorder had a higher energy intake, though not significant, compared to reference subjects. At first glance this would appear clinically significant although energy expenditure as measured in the current study, was also slightly higher in bipolar patients compared to controls. This would be expected since obese patients were slightly larger than obese controls. Elmslie et al. did not examine 24-hour energy expenditure therefore it cannot be concluded that the importance of their results in respect to their level of obesity. Furthermore, the methodology of the study conducted by Elmslie et al. also did not take into account body composition differences. It is difficult to compare energy

intake to reference subjects if you do not control for differences in body mass. Individuals with higher body mass would be expected to consume more calories compared to smaller body masses. It would have been nice to quantify the effects of dietary intake specific to medications however the number of subjects in each medication category were too small to allow me to draw any definitive conclusion about examine the contributions of medications.

5.6 SUMMARY AND CONCLUSIONS

A key finding from this study was that, in patients with bipolar disorder, obesity is a stronger influence on insulin resistance than is bipolar disorder itself. In other words, insulin resistance in these patients does not appear to be more severe after accounting for their obesity. This conclusion, however, should be tempered by the observation that these obese women with bipolar disorder had significantly more abdominal fat and were slightly more hypertensive than BMI-matched controls, allowing for the possibility that bipolar disorder may indeed be associated with altered metabolic profile.

Using tools to assess both energy expenditure and energy intake, this project indicates that, once these euthymic patients with bipolar disorder become obese, their energy imbalance is likely similar to non-patient controls. However, similar levels of insulin resistance in patients compared to BMI-matched controls in this cross-sectional study do not discount the possibility that bipolar disorder does not somehow predispose these patients towards weight gain and obesity. Comparing normal weight subjects perhaps provides some important clues in this regard.

Another finding in this study was that normal weight patients with bipolar disorder tended to have reduced rates of fat oxidation after an overnight fast. Thus, it is possible that reduced rates of fat oxidation in pre-obese patients might contribute to greater weight gain in these patients. However, the physiological factors that may contribute to weight gain to cause them to become more obese than the general population remain unknown. Future prospective longitudinal studies are needed to address this hypothesis.

An important practical implication of the current study was that we were able to recruit individuals diagnosed with the most severe form of bipolar disorder who were then able to tolerate and complete all procedures. This is the first study to show the feasibility of performing body composition and metabolic assessments in patients with bipolar disorder. Thus the demands of these specific studies are achievable in this patient population. Therefore, these tools may be useful to address important questions concerning the effects of lifestyle modifications, including diet and exercise programs, on obesity prevention and treatment in bipolar disorder.

5.7 LIMITATIONS AND FUTURE DIRECTION

The primary limitation of this study is the cross-sectional comparisons of patients and controls. The potential for lower rates of fat oxidation in pre-obese patients raises the possibility that there are underlying factors which contribute to weight gain and obesity in bipolar disorder, which could be addressed in a future prospective longitudinal study. Another limitation is that a small number of patients were studied; making it impossible to ease out any potential effect that specific medication usage might have on metabolic risk profile. With greater numbers of patients

on different medication regimes we could then begin to tease out medication effects from the disorder itself.

Another limitation in this study was the indirect assessment of insulin resistance. Given the higher abdominal fat content in obese patients, it is possible that our surrogate for insulin resistance was not adequately sensitive to detect differences in insulin resistance in patients compared to controls. More sophisticated measurements of insulin resistance, such as glucose tolerance testing or glucose clamp methodologies, could be employed to examine this possibility.

Future studies should be performed to examine specific medication affects on insulin resistance, understanding the effects of medications, such as antipsychotics and antidepressants, will help determine if the potential contributor of insulin resistance lies in the disorder itself or if insulin resistance has been induced through treatment. The effects of reduced fat metabolism can increase the risk and rate at which an individual gains weight. It is important to determine if this is an underlying cause to their risk for obesity and then determining whether lifestyle modification, including diet and exercise, can be effectively implemented in obese patients with bipolar disorder. Our future goals include a line of investigation that will examine the effects of physical activity and weight loss intervention on insulin resistance, regional fat distribution and fuel metabolism. Critical information would be gained to determine whether these patients can achieve similar benefits as obese men and women in the general population, or alternatively, whether there are underlying psychosocial or physiological factors causing them to be resistant to change

APPENDIX A

INFORMED CONSENT

TITLE: Obesity, Body Composition & Insulin Resistance in Women With and Without
Bipolar Disorder

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Why is this research being done?

This research study is asking the question if individuals diagnosed with Bipolar I Disorder are different from individuals not diagnosed with any form of Bipolar Disorder in regards to body fat, the hormone insulin, resting metabolism and physical activity levels. You will be asked to visit Montefiore Hospital two different times. The first visit will assess how your body uses insulin, that is, how your body responds to the hormone insulin. The second visit will assess where your body stores visceral (fat around your organs) and subcutaneous fat (fat under your skin). You will also be asked to wear an armband to determine your physical activity levels for 5 days in between visit 1 and visit 2. These studies should provide further direction on the cause of insulin resistance (your body's ability to use blood sugar) in subjects who have been diagnosed with bipolar disorder, who are at a higher risk for the development of obesity and type 2 diabetes (a metabolic disease that involves the hormone insulin).

Who is being asked to take part in this research study?

You are being invited to participate in this research study because you have already been diagnosed with bipolar disorder. Subjects are being recruited from the clinics at Western Psychiatric Institute and Clinic (WPIC). Subjects invited have to be between 18-60 years of age and, cannot be pregnant, are either of normal weight or moderately overweight based on your height and weight or Body Mass Index {your height in kilograms divided by your weight in meters ($\leq 25\text{kg/m}^2$ or $\geq 30\text{kg/m}^2$)}, and have not gained or lost >5kg (12.7lbs) within the past month. If you qualify you will be one of up to 60 subjects in this study. Participation in the study will last 7 days and will include two visits to the hospital and 5 days of wearing an armband to assess your activity level.

What procedures will be performed for research purposes?

If you agree to participate in this study, you will undergo the following procedures that are not part of your standard medical care:

Screening Procedures:

Procedures to determine if you are eligible to take part in this research study are called "screening procedures." For this study, the screening procedures include:

Screening Visit #1: (approximately 2 hours in length)

1. You will be asked to provide some background information about your general medical history (a thorough review of your health history) and your psychiatric illness.
2. You will be asked to complete a questionnaire that is going to inform us about your nutritional habits. Specifically, this questionnaire will measure how you prepare your food and the amount of food you typically eat. Overall, this questionnaire will allow us to estimate the average daily calories you intake of 178 different food items.
3. Fasting (nothing by mouth except water for 10-12 hours prior) screening laboratory work that includes a CBC (complete blood count); electrolytes (salts or chemicals in the blood like sodium, potassium, chloride, and carbon dioxide); liver function tests (Alanine aminotransferase (ALT), Aspartate aminotransferase (AST) and , Alk phos which are substances in blood that is measured to check for liver disease) thyroid function (TSH, measures your thyroid gland in the neck which is

important in controlling metabolism); and blood glucose (sugar) levels (fasting glucose and HbA1c – a number that tells us approximately what your blood sugar has been for the past three months); insulin levels; blood fat levels (Fat and cholesterol levels in the blood such as cholesterol, HDL, LDL, VLDL, triglycerides); and kidney function (blood urea nitrogen {BUN}, creatinine, and urinalysis {series of tests done on urine} will determine the kidney ability to filter blood). About 2 tablespoons (one ounce) of blood will be drawn to complete the screening labwork.

A copy of this consent (agreement) document and all laboratory results will be given to you. You are free to share these records with anyone of your choosing. To be eligible for this study, you must be free of proteinuria {protein in your urine (defined as >1 + on routine dipstick)}, hypothyroidism (your thyroid hormone does not work well), medications such as thiazide (promote water loss from the body), diuretics (help the body get rid of water and salt), oral glucocorticoids (steroid hormones), nicotinic acid {also known as niacin (vitamin B2)}, or hormone replacement therapy (the use of estrogen and progesterone from an outside source). You also will be excluded if you have taken previously or are currently taking olanzapine or clozapine (antipsychotic medication used to treat some psychiatric illnesses).

In the event that a clinically significant, unanticipated disease or condition is identified during the screening exam, you will be made aware, will be given a copy of the screening lab work and will be instructed to contact your primary care physician for follow-up.

Physical Activity Measurement following Visit 1: (approximately 5 days in length):

Immediately following your blood draw during visit one, you will be given an arm band called a SenseWear Pro to wear on your right arm for five days. This will be used to measure energy expenditure (how many calories you burn) for five days while you perform regular daily activities such as sitting and sleeping. You will be instructed not to remove the armband at anytime (excluding showering) unless irritation occurs. If irritation occurs, immediately take the armband off and see your doctor.

Metabolic Measurements Visit #2: (approximately 2 hours in length)

1. You will be instructed to return after an overnight fast (nothing by mouth except water for 10-12 hours prior), and to minimize as much movement as you can the day of the test. For an example, you will be instructed to take the elevator instead of the stairs. When you arrive, you will be instructed to lay down on a bed for 30 minutes to allow your body to return to rest. A clear plastic hood will be placed over your face and neck to collect your exhaled air (the air you breathe out) while you lie face up in the bed. This measurement is called indirect calorimetry and is done to measure your metabolic rate (amount of oxygen your body uses and how much fat and glucose it is burning).
2. Following, you will have computed tomography scans (CT scans) of your abdomen (belly), and mid-thigh to measure the amount of fat in each location. Computerized tomography (CT scan) is a method to take pictures of internal organs using X-rays. The CT scanner is located at Presbyterian University Hospital. The CT scanner

looks like a donut shaped x-ray machine. CT scanning is an x-ray that will provide a 3 dimensional (3-D) picture of your belly and thigh. You will be asked to lie on the CT exam table for about 20 minutes while the CT scanning is being done.

3. Upon a light lunch, you will have a measurement of your body’s fat and muscle content. In order to measure this, you will have a non-invasive scan performed which is called a "DEXA" or “dual-energy x-ray absorptiometry” scan which is a measure of the structure of the bones. This scan is performed similar to an x-ray study. You will lie still (not moving) on a firm table for 15 minutes while the DEXA scanner moves over your body measuring your fat and fat free mass. The test is painless except for any discomfort you may experience on your back because of lying on the firm examination table. The DEXA scanner is located on the 8th floor of Montefiore Hospital. All women of child-bearing potential (i.e., women who are not at least 1 year post-menopause or who have not undergone a surgical sterilization procedure) will be tested for pregnancy (via urine sample) within 48 hours prior to the DEXA procedures and within 48 hours prior to the CT scans. **Women who test positive for pregnancy or are breast feeding will not be permitted to undergo these procedures.** Below is a chart made to outline the specific visits you will be asked to complete.

Table 2

<i>Visit 1 (Wednesday)</i>	<i>Energy Expenditure (5 days)</i>	<i>Visit 2 (Monday)</i>
<p>Questionnaires-</p> <ul style="list-style-type: none"> • Demographic Questionnaire • Food Freq. Questionnaire 	<p>Energy Expenditure SenseWear Pro</p>	<p>Resting Metabolic Rate</p> <ul style="list-style-type: none"> • Fat oxidation • Carbohydrate oxidation
<p>Blood Draw</p> <ul style="list-style-type: none"> • Blood Lipid (fat) Profile • Glucose/Insulin • Electrolytes, general chemistry profile, blood count, sTSH 		<p>Computed Tomography</p> <ul style="list-style-type: none"> • Visceral Adiposity
		<p>Dual X-ray Absorptiometry</p> <ul style="list-style-type: none"> • Fat Free Mass • Fat Mass
<p>Total Time: 2 Hours</p>	<p>Total Time: 5 Days</p>	<p>Total Time: 2.5Hours</p>

What are the possible risks, side effects, and discomforts of this research study?

Participation may entail some risks. Information on the frequency of possible risk has been categorized using the following categories: Likely – occurs in more than 25% of

people (more than 25 out of 100 people); Common – occurs in 1% to 25% of people (1 to 25 out of 100 people); Rare – occurs in less than 1% of people (less than 1 out of 100 people). *As with any investigational study, there may be adverse events or side effects that are currently unknown and it is possible that certain of these unknown risks could be permanent, serious or life threatening.* The known risks are:

1) **Blood sampling:** The risks of blood sampling are common (occurs in 1% to 25% of people) and may include bleeding, bruising, soreness, dizziness and fainting. Infection from the blood sampling is rare (less than 1% of people). In our experience using similar protocols, subjects have not experienced adverse effects from these procedures other than a small amount of residual localized soreness at the blood sampling area.

2) **DEXA Scan:** Participation in this study involves a minimal amount of radiation exposure from the DEXA. The DEXA scan “whole body” exposure is 2mREM per total body scan which is consistent with previously published data concerning this method. For comparison, this radiation exposure is a small fraction of the annual whole body radiation exposure (300mREM) that each member of the public received from background radiation. There is no minimum level of radiation exposure which is recognized as being totally free of the risk of causing genetic mutations (abnormal cells) or cancer. However, this risk associated with the radiation exposure received from participation in this research study is considered to be low when compared to everyday risks.

3) **CT Imaging:** The CT scan will expose you to a small amount of radiation. The doses are expressed as the effective dose equivalent which weights the radiation dose according to volume and type of tissue irradiated and as such, provides a better estimate of risk than the surface dose. The units are microSievert (fSv) which is the standard SI unit for the effective dose equivalent (fSv= 0.1 mrem; 1mrem= 10 fSv). The estimated effective dose equivalent for the hip is 4-5 uSv and the whole body measurement is 10-15 fSv (1.0-1.5 mrem). The CT is associated with exposure to the thigh and abdomen to approximately 2030 mrem of absorbed dose. For comparison, a round trip transcontinental flight has an effective dose of 60 fSv (6mrem). This is substantially less than the annual radiation exposure limit of 50,000 mrem to the whole body for radiation workers allowed by federal regulation. This amount of radiation is small and the risks from exposure are so small that they are difficult to measure.

4) **Indirect Calorimetry:** During indirect calorimetry a test to measure metabolism (collecting expired oxygen and carbon dioxide) testing, individuals may become claustrophobic (rare; occurs in less than 1% of people). If claustrophobia occurs, the hood will be removed.

5) **SenseWear Pro₂ Armband:** This device worn on the back of the arm may cause some skin irritation and redness (rare; occurs in less than 1% of people).

“What are possible benefits from taking part in this study?”

At the end of your research participation, clinical information obtained from the research project relevant to your care will be shared with you. There is no guarantee that your participation will directly benefit you. However, your participation may provide useful information that will help future patients suffering from bipolar disorder.

“If I agree to take part in this research study, will I be told of any new information that may be found during the course of the study?”

You will be promptly notified if any new information develops during the conduct of this research study which may cause you to change your mind about continuing to participate.

“Will I or my insurance provider be charged for the costs of any procedures performed as part of this research study?”

There are no costs to you or to your insurance provider for the screening evaluation, the screening lab work, the Obesity Nutrition Research Center visits, laboratory tests, the CT scans, or the DEXA scan. The study will cover the costs of all research services. You and/or your insurance provider will be responsible for any routine care costs, including any applicable co pays, coinsurances and deductibles.

“Will I be paid if I take part in this research study?”

You will be given reimbursement for participation. To help defray the costs of your participation, you will be compensated a total of \$180 if you complete the entire study. An honorarium in the amount of \$50 for the completion of screening procedures and another \$130 if experimental procedures are completed will be given to you for time spent away from work, travel, childcare or related costs. You will also be reimbursed up to \$10 for transportation/parking and you will receive a copy of all results.

Visits	Visit 1	Visit 2
<i>Payment, \$</i>	<i>50</i>	<i>130</i>

“Who will pay if I am injured as a result of taking part in this study?”

University of Pittsburgh researchers and their associates who provide services at the UPMC recognize the importance of your voluntary participation in their research studies. These individuals and their staffs will make reasonable efforts to minimize, control, and treat any injuries that may arise as a result of this research. If you believe that you are injured as a result of the research procedures being performed, please contact immediately the Principal Investigator or one of the co-investigators listed on the first page of this form.

Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of the UPMC. It is possible that the UPMC may bill your insurance provider for the costs of this emergency treatment, but none of these costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care unless otherwise specifically stated below. There is no plan for monetary compensation. You do not, however, waive any legal rights by signing this form.

“Who will know about my participation in this research study?”

Any information about you obtained from or for this research study will be kept as confidential (private) as possible. You will not be identified by name in any publication of research results unless you sign a separate form giving your permission (release).

All records related to your involvement in this research study will be stored in a locked file cabinet. Your identity on these records will be indicated by a case number rather than by your name, and the information linking these numbers with your identity will be kept separate from the research records. Access to your research records will be limited to the researchers listed on the first page of this form and the study sponsor (Western Psychiatric Institute & Clinic Seed Proposal), who may need to review the records for accuracy and completeness. Representatives of the study sponsor may also be present during your participation in the research study. The fact that you are participating in a research study and that you are undergoing certain research procedures (but not the results of the procedures) may also be made known to individuals involved in insurance billing and/or other administrative activities associated with the conduct of the study. University of Pittsburgh policy states that your research records must be maintained for at least five years after study completion. The researchers conducting this study have chosen to maintain your research records indefinitely.

“Will this research study involve the use or disclosure of my identifiable medical record information?”

This research study will involve the recording of current identifiable medical information from your hospital records. The information that will be recorded will be limited to information concerning your screening laboratory work and study participation. This information will be used for the purpose of determining whether you qualify, based on study specific inclusion/exclusion criteria, for study participation. This research study will result in identifiable information that will be placed into your medical records held at the University of Pittsburgh Medical Center. The nature of the identifiable information resulting from your participation in this research study that will be recorded in your medical record possibly may include your screening laboratory work.

“Who will have access to identifiable information related to my participation in this research study?”

In addition to the investigators listed on the first page of this authorization (consent) form and their research staff, the following individuals will or may have access to identifiable information (which may include your identifiable medical record information) related to your participation in this research study:

1) Authorized representatives of the University of Pittsburgh Research Conduct and Compliance Office may review your identifiable research information (which may include your identifiable medical record information) for the purpose of monitoring the appropriate conduct of this research study.

2) In unusual cases, the investigators may be required to release identifiable information (which may include your identifiable medical record information) related to your participation in this research study in response to an order from a court of law. If the investigators learn that you or someone with whom you are involved is in serious danger or potential harm, they will need to inform, as required by Pennsylvania law, the appropriate agencies.

3) Authorized representatives of the UPMC hospitals or other affiliated health care providers (such as the General Clinical Research Center) may have access to identifiable information (which may include your identifiable medical record information) related to your participation in this research study for the purpose of (a) fulfilling orders, made by the investigators, for hospital and health care services (e.g., laboratory tests, diagnostic procedures) associated with research study participation; (b) addressing correct payment for tests and procedures ordered by the investigators; and/or (c) for internal hospital operations (i.e. quality assurance).

“For how long will the investigators be permitted to use and disclose identifiable information related to my participation in this research study?”

The investigators may continue to use and disclose, for the purposes described above, identifiable information (which may include your identifiable medical record information) related to your participation in this research study indefinitely following study completion.

“May I have access to my medical record information that results from my participation in this research study?”

In accordance with the UPMC Notices of Privacy Practices document that you have been provided, you are permitted access to information (including information resulting from your participation in this research study) contained within your medical records filed with your health care provider unless otherwise specifically stated below.

“Is my participation in this research study voluntary?”

Your participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above, is completely voluntary. (Note, however, that if you do not provide your consent for the use and disclosure of your identifiable information for the purposes described above, you will not be allowed, in general, to participate in the research study.) Whether or not you provide your consent for participation in this research study will have no effect on your current or future relationship with the University of Pittsburgh. Whether or not you provide your consent for participation in this research study will have no effect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

“May I withdraw, at a future date, my consent for participation in this research study?”

You may withdraw, at any time, your consent for participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above. (Note, however, that if you withdraw your consent for the use and disclosure of your identifiable information for the purposes described above, you will also be withdrawn, in general, from further participation in this research study.) Any identifiable research or medical record information recorded for, or resulting from, your participation in this research study prior to the date that you formally withdrew your

consent may continue to be used and disclosed by the investigators for the purposes described above.

To formally withdraw your consent for participation in this research study you should provide a written and dated notice of this decision to the principal investigator of this research study at the address listed on the first page of this form.

Your decision to withdraw your consent for participation in this research study will have no effect on your current or future relationship with the University of Pittsburgh. Your decision to withdraw your consent for participation in this research study will have no effect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

Your doctor is involved as an investigator in this research study. As both your doctor and a research investigator, he s/he is interested both in your medical care and the conduct of this research study. Before agreeing to participate in this research study, or at any time during our study participation, you may discuss your care with another doctor who is not associated with this research study. You are not under any obligation to participate in any research study offered by your doctor.

“If I agree to participate in this research study, can I be removed from the study without my consent?” You may be removed from this research study by the investigators in the event that the investigators feel that the study may adversely influence your health, if you don't comply with study requirements.

If you do not qualify for this particular study, would you like to be contacted for future research studies? They would explain what any additional project studies involve before you would agree to volunteer.

(Please check one)

- I do not agree to be contacted for future studies.
- I do agree to be contacted for future studies.

If you agree to be contacted, please provide a day time phone number where you can be reached: _____

VOLUNTARY CONSENT

All of the above has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by the researchers listed on the first page of this form.

Any questions I have about my rights as a research participant will be answered by the Human Subject Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668)

By signing this form, I agree to participate in this research study. A copy of this consent form will be given to me.

Participant's Signature

Date

CERTIFICATION OF INFORMED CONSENT

I certify that I have explained the nature and purpose of this research study to the above-named individual, and I have discussed the potential benefits and possible risks of study participation. Any questions the individual has about this study have been answered, and we will always be available to address future questions as they arise.

Printed Name of Person Obtaining Consent

Role in Research Study

Signature of Person Obtaining Consent

Date

APPENDIX B

BASELINE DEMOGRAPHIC AND MEDICAL HISTORY FORM

Date: ___/___/___

Date of Consent: ___/___/___

Rater: _____

Subject ID: _____

Protocol: _____

Height: ___ (inches) ___ (cm)

Weight: ___ (lbs.) ___ (kg)

Systolic BP: _____

Diastolic BP: _____

Sex: 1=Male 2=Female

RELIGION:

1=Catholic

2=Protestant*

Subject Type:

01=Inpatient 02=Outpatient

03=Control

10=SUBJECT 10=OTHER

1 = English is first language

2 = English is not first language

(Native language: _____)

1. MARITAL STATUS

INSTRUCTIONS: Complete each item by circling or filling in information which best characterizes the subject at time of study entry.

2 = Married (or sustained conjugal situation for 6 or more months)

3 = Separated (if legally married, or apart from common law spouse with chance of return)

4 = Divorced (or left common law spouse "for good")

5 = Widowed

2. CHILDREN

2a. Number of biological children (living and nonliving): ___

2b. Number of non-biological children (living and nonliving): ___

3. EDUCATION

3a. Total number years of full-time equivalent formal academic education:

(from first grade on; not including trade school) ___

4. CURRENT/MOST RECENT EMPLOYMENT

4a. Is subject working in paid employment?

0 = No 1 = Yes, Part-time 2=Yes, Full-time

4b. Number of months in current employment:: ___ months (0 = not employed)

4c. If 0 months: give final date of last employment (at least half-time): ___/___/___

(0 = never employed) MO DAY
YR

4d. Occupation of current or most recent position: _____

HIGHEST LEVEL OF EDUCATION (Check one for subject, parents and most recent spouse, even if separated, divorced or widowed)				
	3b. Subject	3c. Mother	3d. Father	3e. Spouse
Completed post-graduate training				
Completed college, received four year academic degree				
Attended college, but did not receive four year academic degree				
Completed HS, trade school or other non-academic training requiring HS completion for admission				
Partial high school (10 th or 11 th grade)				
Junior high school (7 th , 8 th , or 9 th grade)				
Less than 7 th grade				
Does not apply (no spouse)				
Information not available (specify why)				

5. FAMILY EMPLOYMENT

What is the highest level of occupational attainment achieved by subject, subject's mother, father, and spouse? (Write in actual occupation below and describe.)

5a. Subject: _____

5b. Mother: _____

5c. Father: _____

5d. Spouse: _____ (if applicable)

5e-h. Highest level of occupational attainment achieved (use Hollingshead Scale to determine occupation level, for occupations that are at least half-time and includes jobs held by students) [NOTE: "mother" and "father" refer to biological parents, if present during subject's childhood. If parental surrogate reared subject, code occupation for parental surrogate(s).] See below:

HIGHEST LEVEL OF OCCUPATIONS: (Check one for subject, parents and most recent spouse, even if separated, divorced or widowed)				
	5e. Subject	5f. Mother	5g. Father	5h. Spouse
Higher executives, Proprietors of large business (>\$250,000) Major professional				

Administrators, Lesser professionals, Proprietors of medium sized business (\$100-250,000)				
Small business owners (\$75-100,000), Farm owners, Mangers, Minor professionals				
Technicians, Semi-professionals, Smaller business owners (\$50-75,000)				
Clerical and Sales workers, Very small farm and business owner (\$25-50,000)				
Smallest business owners (<25,000), Skilled manual worker, Craftsmen and Tenant farmers				
Machine operators and Semi Skilled Workers				
Medial service workers, Dependent upon welfare, No regular occupation, Never employed				
Does not apply (no spouse)				

6. SUBJECT'S LIVING ARRANGEMENT (During one month prior to hospitalization/initial assessments)

- 1 = Alone
2 = Parent household
3 = Own or spousal household
4 = Children's household
5 = Household of other relative
6 = Household shared with others (non-relatives)
7 = Structured environment (transition housing, halfway house)
8 = Other Specify:

Pregnancy/Obstetric Complications

7. Any pregnancy complications (e.g., heavy bleeding, high blood pressure, diabetes, anemia, seizures, physical injuries, infection requiring medical care, weight gain > 25 pounds)? 1 = Yes 0 = No

7a. If yes, explain: _____

8. Any birth problems [e.g., cord around neck, breech, emergency C-section, jaundice, blue coloration at birth, absence or irregular breathing, absent crying, small for dates, premature birth (> 2 weeks)]? 1 = Yes 0 = No

8a. If yes, Explain: _____

Infancy and Childhood (through 12 years of age)

9. Significant illnesses/infections affecting CNS function? 1 = Yes 0 = No

9a. If yes, explain: _____

10. Any delay in growth or development? 1 = Yes 0 = No

10a. If yes, explain: _____

11. Any history of enuresis or encopresis? 1 = Yes 0 = No

11a. If yes, explain: _____

12. Any learning difficulties in school? 1 = Yes 0 = No

12a. If yes, explain: _____

13. Any special education? 1 = Yes 0 = No

13a. If yes, explain: _____

13b-d. If yes, for what?

Learning Disabilities	1 = Yes	0 = No
Mental Retardation	1 = Yes	0 = No
Emotional Problems	1 = Yes	0 = No

14. Were you ever held back in school? 1 = Yes 0 = No

14a. If yes, explain: _____

History of head injury

15. Ever had a head injury? 1 = Yes 0 = NO (If NO, go to item 11j)

15a. If yes, explain: _____

15b. If yes: How many times? _____ occasions

15c. Give age of most severe episode: _____

15d. What type of injury? 1 = Closed 2 = Open

16. Any open brain surgery? 1 = Yes 0 = No

17. Ever knocked unconscious? 1 = Yes 0 = No (If NO, go to item 11k)

17a. If yes, explain: _____

17b. If yes, how many times? _____

17c. If yes, for how long (longest duration episode)? _____ minutes

Major medical problems during adolescence or adulthood (13 years and older)

18. If subject endorses one or more chronic illnesses, specify below (Circle 1 = "Yes" or 0 = "No")

	<u>YES</u>	<u>NO</u>	<u>Specify</u>
= Epilepsy	1	0	_____
= Asthma	1	0	_____
= Diabetes	1	0	_____
= Cardiac problems	1	0	_____
	1		
= Hypertension		0	_____
		0	
= Renal disease	1		_____
= G.I. problems	1	0	_____
= Thyroid problems			

	1	0	_____
= Rheumatological problems	1	0	_____
= Pulmonary problems	1	0	_____
= Other	1	0	_____
= N/A (NONE)	1	0	_____

19. ESTIMATE TYPICAL DAILY CONSUMPTION OF TOBACCO

1 = Non smoker 2 = Light (0-10) 3 = Moderate (11-20) 4 = Heavy (21-40 +)

20. DEVELOPMENTAL HISTORY

Mother

20a. What is mother's age? _____ (-8 = deceased)

20b. Calculate age of mother when subject was born: _____

Father

20c. What is the father's age? _____ (-8 = deceased)

20d. Calculate age of father when subject was born: _____

Siblings

20e. How many full siblings does subject have (living and nonliving)? _____

20f. How many half siblings does subject have (living and nonliving)? _____

20g. When was subject born in relation to siblings?

- 1 = First 3 = Third 5 = Fifth
- 2 = Second 4 = Fourth 6 = Sixth +

20h. Did any of subject's siblings die? 1 = Yes 0 = No

20h-1. If yes, how old was subject when a sibling died (youngest age applicable)? _____ (-8 = not applicable)

Other

21. Was subject adopted? 1 = Yes 0 = No

21a. If yes, how old was subject when he/she was adopted? _____ (-8 = not applicable)

22. Has social services ever been involved with subject? 1 = Yes 0 = No

22a. If yes, how old was subject? _____ (0 = at birth; -8 = not applicable)

23. Any history of physical and/or sexual abuse over lifetime?

0 = No 1 = Yes, Physical 2 = Yes, Sexual 3 = Yes, Both

23a. If yes, how old was subject? _____ (0 = at birth; -8 = not applicable)

23b. If yes, describe: _____

24. Has subject ever lived outside parental household for greater than 6 months?

1 = Yes 0 = No

24a. If yes, age at first residency outside parental household greater than 6 months: _____ (-8 = n

24b. Details outsider residency: _____

25. HANDEDNESS

Which hand does the subject use to write? to cut with a knife? to comb his/her hair? to play sports? Does the subject do anything with the (opposite) hand

1 = Right 2 = Left 3 = Mixed

26. HORMONAL/FERTILITY ISSUES (if male, check here ____: skip to Strauss and Carpenter Outcome Scale on following page)

26a. Date of onset of last monthly period __ __/__ __/__ __ (including if currently menopausal)

26b. Is subject currently on birth control pills? 1 = Yes 0 = No

26c. Is subject currently undergoing estrogen replacement therapy? 1 = Yes 0 = No

26d. Is subject currently pregnant? 1 = Yes 0 = No

26e. Date of pregnancy test: __ __/__ __/__ __

26f. Type of test: 1 = urine 0 = blood

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