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Leptin as a Novel Predictor of Somatic Depressive Symptoms in Hispanics with the Metabolic Syndrome

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LEPTIN AS A NOVEL PREDICTOR OF SOMATIC DEPRESSIVE SYMPTOMS IN HISPANICS WITH THE METABOLIC SYNDROME

By

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The association between depression and the Metabolic Syndrome (MetS) has been extensively investigated, and inflammation has been identified as an underlying link. Recent reports, however, indicate a possible role of leptin in modulating the immune response, yielding increases in inflammatory markers. The literature suggests this hormone may not only explain the metabolic abnormalities associated with depression but may also act as a biomarker of depression itself. This study aimed to determine the association between circulating leptin and total depressive symptoms and depressive symptom dimensions (cognitive and somatic) after controlling for important confounding factors such as age, gender, insulin resistance, body mass index (BMI) and inflammation. We studied 119 Hispanic participants, 60 women and 59 men, recruited for the Community Health and Risk-reduction for the Metabolic Syndrome (CHARMS) study. Depression was measured using the Beck Depression Inventory (BDI). Somatic and Cognitive subscale scores were calculated. Leptin was measured using a leptin-specific enzyme immunoassay. Inflammation was assessed using C-reactive protein (CRP) measured with a high-sensitivity assay. Participants with CRP levels greater than 10 mg/L were excluded from analysis. CRP and leptin levels were log transformed to achieve a normal distribution. Median BDI total score, BDI cognitive score and BDI

somatic score were 8, 3 and 5, respectively. Median circulating leptin levels were 30.6 ng/ml. In univariate regression, leptin levels were significantly associated with total (β =0.36, *P*=.000), cognitive (β =0.24, *P*=.011) and somatic depressive symptoms (β =0.48, *P*=.000). After controlling for age, gender, insulin resistance, BMI and inflammation, circulating leptin levels remained significantly associated with somatic depressive symptoms only (β =.41, *P*=.004). Another important predictor of somatic depressive symptoms was age (β=0.23; *P*=0.004). The model accounted for 31% of the variance in somatic depression scores. Leptin is significantly associated with somatic depressive symptoms in Hispanics with the MetS. This association was independent of important confounding factors such as gender, age, BMI, insulin resistance and inflammation. Further research is needed to elucidate the complex pathways linking depression and the MetS while incorporating the potential role of leptin.

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Chapter 1

INTRODUCTION

Depression and the Metabolic Syndrome

The Metabolic Syndrome (MetS), a cluster of anthropometric, hemodynamic and metabolic disturbances, has been linked to cardiovascular disease morbidity and mortality (Isomaa et al., 2001) as well as the risk for type 2 diabetes (Lorenzo, Okoloise, Williams, Stern, & Haffner, 2003). Although no consensus has been reached in regards to its definition, central adiposity, abnormal glucose regulation, elevated triglycerides, lowered high-density lipoprotein cholesterol (HDL-cholesterol) and elevated blood pressure are consistently recognized as components of the MetS (Alberti, Zimmet, & Shaw, 2005; Alberti & Zimmet, 1998; Grundy et al., 2005). In 2009 several major organizations including the International Diabetes Federation Task Force on Epidemiology and Prevention, the National Heart, Lung, and Blood Institute, the American Heart Association, the World Heart Federation, the International Atherosclerosis Society, and the International Association for the Study of Obesity met in an attempt to unify the criteria. A joint scientific statement was issued indicating there would not be an obligatory component and that three abnormal findings out of five would qualify a person for MetS (Alberti et al., 2009).

In 2002 the prevalence of the MetS in US adults was 23% among women and 27% among men as estimated by results from the Third National Health and Nutrition Examination Survey (NHANES III) (Ford, Giles, & Dietz, 2002). Due to the rise in obesity and sedentary behavior, as well as its prevalence across gender and age groups,

the MetS is becoming an increasingly important target of prevention strategies (Kinder, Carnethon, Palaniappan, King, & Fortmann, 2004).

Existing prevalence data from different countries indicate that the prevalence and relative frequency of the different components in the MetS vary widely across ethnicity. Population data among Hispanics is still lacking but recent reports indicate higher prevalence among U.S. Hispanic samples. Results from NHANES III showed clear differences among ethnic groups, with Mexican American showing the highest age-adjusted prevalence at 31.9% (Ford et al., 2002). It has been also been previously established that there might be an important gender-ethnicity interaction (Bouguerra et al., 2006; Florez et al., 2005; Ford et al., 2002; Hwang, Bai, & Chen, 2006; Medina-Lezama et al., 2007). Gender differences have been reported among African-American as well as Mexican-American with women having higher prevalence than men. This was not true for Caucasians. In a population-based study of Andean Hispanics, gender was also identified as a moderating factor with women showing significantly higher prevalence than men and a significantly greater age-related increase in its prevalence (Medina-Lezama et al., 2007).

Major Depressive Disorder (MDD) is the most prevalent psychiatric illness in the United States (Wittchen, Zhao, Kessler, & Eaton, 1994). Ethnic differences in prevalence have also been reported for MDD in a recent study indicating Caucasian and Hispanics individuals have the highest rates for this disorder (Woodward et al., 2011). Depression has been associated with a variety of diseases including cardiovascular disease (CVD), diabetes mellitus and all-cause mortality (Musselman, Evans, & Nemeroff, 1998; Wulsin, Vaillant, & Wells, 1999). Although the mechanisms that account for the relationship

between depression and poor health outcomes are still unclear, previous reports have speculated the MetS might play an important role (Kinder et al., 2004).

The association between psychological factors such as depression and the MetS has been extensively investigated. Cross sectional as well as longitudinal designs support an association between elevated levels of depression and increased prevalence of the MetS (Heiskanen et al., 2006; Raikkonen, Matthews, & Kuller, 2002, 2007; Skilton, Moulin, Terra, & Bonnet, 2007). Studies examining these associations in Hispanic samples are still lacking.

A recent review by Goldbacher and Mathews (2007) pointed out that gender, race and socioeconomic status (SES) are variables that affect both depression and the risk for the metabolic syndrome; thus may have a moderating role in their association. Few studies have focused on examining the possible effects of gender, race and SES. The few available studies suggest that race and education do not influence the association of depression with the MetS (Goldbacher & Matthews, 2007; Kinder et al., 2004). Some reports indicate, however, that gender may in fact be an important moderating factor (Kinder et al., 2004; Raikkonen et al., 2007). Results from NHANES III, a population based health survey, have shown that women with a history of a major depressive episode were twice as likely to have the MetS compared to those without a history of depression even after controlling for important confounders such as age, race, education, smoking, physical inactivity, carbohydrate consumption, and alcohol intake. This association was not significant for men (Kinder et al., 2004).

The relationship between individual components of the MetS and depression has also received increasing attention over the past couple of years. Research on the association between depression and hypertension as well as with dyslipidemia has yielded conflicting results, with studies reporting both positive (Jonas, Franks, & Ingram, 1997) and null findings (Toker, Shirom, & Melamed, 2008; Wiehe et al., 2006) (reference). A recent meta-analysis explored the association between impaired glucose metabolism and risk of depression (Nouwen et al., 2011). Results of this meta-analysis showed that the risk for depression is similar for those with normal and impaired glucose metabolism. Nevertheless, the association between diagnosed diabetes mellitus and elevated depressive symptoms is well documented (Hsu et al., 2011; Stuart & Baune, 2011). Similarly, the relationship between depression with central and total adiposity is well supported by the literature (Faith et al., 2011; Faith, Matz, & Jorge, 2002). In a recent review, Faith and colleagues (2011) evaluated the strength of the evidence for prospective associations among obesity and depression in an effort to elucidate the directionality of the association. They found that 80% of the studies reported significant obesity-to-depression associations, with odds ratios generally ranging from 1.0 to 2.0, while only 53% reported significant depression-to-obesity association thus concluding that being obese increases the risk of developing depression.

Possible mechanistic pathways accounting for the MetS-Depression association: The role of adiposity

Although our ability to accumulate fat tissue has long been thought to be an adaptive feature of our species, Wells (2006) noted this ability is increasingly becoming maladaptive given the fact fluctuations in energy supply have been diminished, and productivity is dependent on mechanization rather than physical effort or movement.

As opposed to brown adipose tissue (BAT), whose main purpose is to generate body heat (Enerback, 2009), white adipose tissue (WAT) is responsible for long-term storage of fat in the body and the main contributor to diseases such as type 2 diabetes and cardiovascular disease (Shelton & Miller, 2010). Adipose tissue is now recognized as an endocrine organ secreting a variety of hormones, inflammatory factors and other proteins (Vazquez-Vela, Torres, & Tovar, 2008). Commonly associated with obesity are increased production of adipokines, chemokines and cytokines which are thought to contribute to inflammatory diseases such as the MetS, type 2 diabetes and cardiovascular disease (Wellen & Hotamisligil, 2005). Adipocytokines, also known as adipokines include leptin, resistin and adiponectin (Taylor & Macqueen, 2010). Evidence suggests that inflammatory cytokines, such as interlukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) as well as adypokines, particularly leptin, play an important role in the pathogenesis of both depression and the MetS and are therefore possible mechanistic pathways involved in their association (Taylor & Macqueen, 2010).

Inflammation as an underlying link

Inflammation is an immune response that results from the activation of the innate immune system and leads to the release of inflammatory factors, in particular cytokines including interleukins, interferons, and tumor necrosis factor (Shelton & Miller, 2010). Although inflammatory markers are not currently included in the diagnosis of the MetS, chronic subclinical inflammation is believed to be an important component (Zeugmann, Quante, Heuser, Schwarzer, & Anghelescu, 2010). Recent reviews support this hypothesis (Sarti & Gallagher, 2006) and inflammation markers such tumor necrosis factor-alpha (TNF-α) and interlukin-6 (IL-6) are thought to be implicated in the development of the MetS (Sutherland, McKinley, & Eckel, 2004).

Similarly, recent evidence suggests an activation of the immune-system in major depression (Kim et al., 2007; Sperner-Unterweger, 2005). Higher levels of inflammatory cytokines have been found in patients with Major Depressive Disorder when compared to healthy controls (Goldbacher & Matthews, 2007; Howren, Lamkin, & Suls, 2009; Mossner et al., 2007). Interestingly, recent studies have shown that depressed patients with treatment resistance are more likely to exhibit increased levels of these inflammatory markers (Benedetti, Lucca, Brambilla, Colombo, & Smeraldi, 2002). In apparently healthy adults, elevated levels of C-reactive protein (CRP) were associated with depressive symptoms (Suarez, 2004). As pointed out in a recent review by Shelton and Miller (2009) the most consistently replicated findings supporting an association between depression and inflammation include elevations of serum IL-6, TNF-alpha and CRP in depressed individuals.

As evidence accumulates, the notion that inflammation may serve as a common mechanism of disease for both depression and the MetS receives increasing acceptance (Shelton & Miller, 2010). Previous research has explored the impact of having MetS on concentrations of inflammatory biomarkers among depressed individuals (Zeugmann et al., 2010). The investigators found an additive effect for depression and MetS on circulating levels of IL-6 and fibrinogen. Recent studies have also shown that CRP as well as IL-6 levels are elevated in subjects with the MetS and depression, even after adjustment for age, education and smoking status (Capuron et al., 2008). The nature of the depressive symptoms has begun to receive attention and evidence thus far suggests that somatic and not cognitive symptoms are associated with higher levels of inflammation in MetS patients after controlling for potential confounders (Capuron et al., 2008).

Sickness behavior

There are reasons to believe that inflammatory processes activated in the MetS could induce depression-like symptoms (Capuron et al., 2008). In fact, exposure to inflammatory mediators has been found to produce a constellation of sickness behaviors including anhedonia, anorexia and hyposomnia that has a strong resemblance to depressive symptoms (Miller, Freedland, Carney, Stetler, & Banks, 2003). In animal models, the most compelling evidence of this process has been found in rodents where a peripheral immune response is elicited by the administration of pro-inflammatory cytokines (Maier & Watkins, 1998). Although this kind of experiment cannot be performed in humans, clinical evidence comes from cancer radiation therapies, where patients are exposed to high doses of inflammatory cytokines. Patients have been shown

to routinely develop symptoms of depression in these circumstances (Bower, Ganz, Aziz, & Fahey, 2002). Interestingly, the nature of these symptoms are mainly somatic as opposed to cognitive and they can be prevented through administration of anti-depressant medication (Musselman et al., 2001).

Leptin as a signaling molecule

Leptin is a peptide hormone, encoded by the obese (ob) gene (X. Y. Lu, 2007) and it is produced primarily by differentiated adipocytes. It serves to communicate the state of body energy repletion to the central nervous system (CNS), suppressing food intake and permitting energy expenditure (X. Y. Lu, 2007; Munzberg, Bjornholm, Bates, & Myers, 2005). Leptin levels drop during starvation when fat deposits are depleted and rise during refeeding (Taylor & Macqueen, 2010). Therefore, it was initially identified as an antiobesity hormone that acted as a negative feedback signal to control energy homeostasis.

Leptin Resistance

It was originally hoped that exogenous leptin therapy might induce satiety and weight loss in humans (Friedman & Halaas, 1998). Indeed, both in animal models and in humans, leptin therapy seems to ameliorate the reduced energy expenditure and increased hunger associated with weight loss (Chan, Heist, DePaoli, Veldhuis, & Mantzoros, 2003). However, weight loss achieved by leptin therapy was very modest (Munzberg et al.,

2005). Conversely, it was found that most obese individuals had elevated circulating levels of leptin as a consequence of their increased fat mass and did not respond to these levels by reducing food intake. This under-responsiveness has led researchers to believe that obesity is associated with a state of leptin resistance, similar to the state of insulin resistance found in type 2 diabetes (Munzberg et al., 2005). Leptin resistance can result from abnormalities at several levels, including impaired transport of leptin across the blood-brain barrier, reduced function of the leptin receptor, and defects in leptin signal transduction (Munzberg & Myers, 2005).

Role of Leptin in Depression

Recent studies suggest that circulating levels of leptin may be associated with vulnerability to depression (X. Y. Lu, 2007) and the potential role of leptin in depression has been studied in both animal models and humans. In animal models, rats exposed to chronic stress were found to have low circulating levels of leptin and exhibited depression-like behaviors (H. Lu, Buison, Jen, & Dunbar, 2000). Interestingly, a recent report found that depression-like behaviors were reversed with leptin administration treatment (X. Y. Lu, 2007).

Current evidence on the role of leptin in human depression is limited and controversial. In line with results from animal models, some studies have found decreased levels of leptin in depressed individuals (X. Y. Lu, 2007). One study has reported that leptin levels did not differ between depressed individuals and their matched controls (Deuschle et al., 1996). Other studies, however, found elevated plasma levels of

leptin in depressed individuals which was more accentuated in female participants (Antonijevic et al., 1998). Similarly, epidemiological and clinical data suggest a link between depression and obesity, characterized by high and not low levels of leptin (Faith et al., 2002; Simon et al., 2006).

The concept of leptin resistance seems to be key in understanding these conflicting results, and therefore, total adiposity may be an important moderating factor. It appears that leptin resistance, which develops in overweight and obese individuals as evidenced by elevated circulating leptin levels, is associated with vulnerability to depression (X. Y. Lu, 2007; Taylor & Macqueen, 2010). Collectively, these findings indicate that leptin resistance may be responsible for the higher rates of depression among obese people (X. Y. Lu, 2007).

Possible mechanism driving the leptin-depression association

Along with the its role in energy metabolism, leptin appears to also play a role in the bidirectional communication between the hypothalamic pituitary adrenal (HPA) axis and adipose tissue (Taylor & Macqueen, 2010). Although the nature of these interactions is not completely understood and factors involved in this relationship are yet to be elucidated, recent reports have attempted to describe the mechanistic pathways that may drive the leptin –depression association.

Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis has been found to be a common feature among patients with depression (X. Y. Lu, 2007). This HPA axis abnormality includes increased production of corticotrophin-releasing hormone (CRH), elevated cortisol levels, heightened cortisol response to adrenocorticotropic hormone

(ACTH), impaired dexamethasone-mediated negative feedback, and enlargement of the pituitary and adrenal glands (Plotsky, Owens, & Nemeroff, 1998). Recent studies suggest that elevated glucocorticoid levels stimulate leptin synthesis and secretion (Dagogo-Jack, Selke, Melson, & Newcomer, 1997; Newcomer et al., 1998). Under regular physiological conditions, leptin enhances glucocorticoid negative feedback on HPA axis activity (Wilson, Fisher, & Brown, 2005). Nonetheless, it has been proposed that leptin regulation is moderated by stress in such a way that under chronic stress conditions the negative feedback of leptin on the HPA via glucocorticoids appears to be impaired (Munzberg et al., 2005). This means that persistently elevated levels of leptin may induce leptin resistance on the hypothalamus (Benomar et al., 2005). Additionally, recent finding suggest a possible interaction between leptin and the mesolimbic dopaminergic pathway, which has been found to be implicated in depression (Fulton et al., 2006). Furthermore, recent lines of evidence indicate leptin may have neurotrophic effects and loss of neurotrophic support has been suggested to underlie depressive disorders (Duman & Monteggia, 2006).

Recently, it was proposed that adipose tissue is not directly implicated in the elevations in inflammatory markers. Instead, some researchers have hypothesized that leptin upregulates the expression of inflammatory molecules by white cells (Miller et al., 2003). Leptin has been shown to have a role in modulating the immune response (Taylor & Macqueen, 2010). In fact, a recent study found that leptin has wide ranging effects on immunity, including the ability to increase in vitro production of IL-6 and TNF-alpha in monocytes stimulated with lipopolysaccharide (Fantuzzi & Faggioni, 2000; Loffreda et al., 1998). Obese individuals, as pointed out before, have high levels of leptin, which may

be responsible for the increases in inflammatory markers among patients with the MetS (Wozniak, Gee, Wachtel, & Frezza, 2009).

Clearly, data regarding the role of leptin is still limited and more research is needed to elucidate the pathways of leptin action and its effect on the depression-obesity association. However, taken together, there are provocative research findings that support a potential role of leptin in explaining the metabolic abnormalities that have been associated with depression and the MetS. Additionally, leptin may also act as an independent biomarker of depression itself.

The present study

The relationship between depression and the MetS has been extensively investigated. However, relatively little data on this topic have involved Hispanics. Furthermore, gender has been identified as possible moderating factor in this association. Research on the potential pathways linking depression and the MetS suggests inflammation may play an important role. Recent reports also indicate a possible role of leptin in modulating the immune response increasing the release of inflammatory markers. Additionally, leptin has been recognized to have an influence on the dysregulation of the HPA axis, which is a common feature among depressed individuals. Available data suggest that leptin may not only explain metabolic abnormalities associated with depression, but may also act as an independent marker of depression itself.

The proposed study aimed to examine the relationship between baseline measures of circulating leptin and depressive symptoms in a sample of Hispanic adults with the MetS, while controlling for the effects of inflammation. Other important confounding factors such as body mass index (BMI), insulin resistance and age were also included in the model. Additionally, the role of gender as a moderator was explored using multiple group comparison analysis within the structural equation modeling framework. Structural model analysis across groups allows assessment of the population heterogeneity in multiple structure parameters such as variances, covariances and paths.

Study aims and Hypothesis

Primary Aim 1. To describe demographic (gender, education & income), biological (age, body mass index [BMI], girth, triglycerides, LDL and HDL-cholesterol, insulin resistance, CRP & circulating leptin levels), psychological (depressive symptoms) and behavioral (diet) characteristics of participants enrolled in the CHARMS program and compare them across gender.

> **Hypothesis 1a**. Men and women will not differ in terms of education, income, age, BMI, triglycerides levels, LDL cholesterol, insulin resistance, and dietary behaviors.
>
> **Hypothesis 1b.** Compared to men, women will differ in terms of waist circumference, levels of HDL-cholesterol, CRP and circulating leptin levels and depressive symptoms.

Primary Aim 2. To determine whether higher levels of CRP are significantly associated with higher levels of depressive symptoms, assessed by the BDI total score; cognitive depressive symptoms, assessed by the BDI cognitive score; and total somatic depressive symptoms, assessed by the BDI somatic score controlling for BMI, insulin resistance and age.

> **Hypothesis 2a.** Higher levels of CRP will be significantly associated with elevated levels of depressive symptoms controlling for BMI, insulin resistance and age.
>
> **Hypothesis 2b.** Higher levels of CRP will not be significantly associated with elevated levels of cognitive depressive symptoms controlling for BMI, insulin resistance and age.
>
> **Hypothesis 2a.** Higher levels of CRP will be significantly associated with elevated levels of somatic depressive symptoms controlling for BMI, insulin resistance and age.

Primary Aim 3. To determine whether higher levels of circulating leptin are significantly associated with higher levels of depressive symptoms, assessed by the BDI total score; cognitive depressive symptoms, assessed by the BDI cognitive score; and total somatic depressive symptoms, assessed by the BDI somatic score, after controlling for the effects of CRP, BMI, insulin resistance and age.

> **Hypothesis 3a.** Higher levels of circulating leptin will be significantly associated with elevated levels of depressive symptoms, after controlling for the effects of CRP, BMI, insulin resistance and age.

Hypothesis 3b. Higher levels of circulating leptin will not be significantly associated with elevated levels of cognitive depressive symptoms, after controlling for the effects of CRP, BMI, insulin resistance and age.

Hypothesis 3a. Higher levels of circulating leptin will be significantly associated with elevated levels of somatic depressive symptoms, after controlling for the effects of CRP, BMI, insulin resistance and age.

Primary Aim 4. To determine whether the relationship between circulating leptin levels and total depressive symptoms, cognitive depressive symptoms and somatic depressive symptoms, varies as a function of gender.

Hypothesis 4. The relationship between circulating leptin levels and total depressive symptoms, cognitive depressive symptoms and somatic depressive symptoms varies as a function of gender.

Chapter 2

METHODS

Participants

Participants are 119 Hispanics, 60 women and 59 men, with the MetS. All participants are part of a larger National Heart, Lung, and Blood Institute (NHLBI) funded study (Community Health and Risk-reduction for the Metabolic Syndrome [CHARMS]). The goal of this study is to examine the effects of a structured lifestyle intervention program in patients with the MetS. Subjects include low income men and women (not pregnant or nursing) who meet the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP II) criteria for the MetS, which requires at least three of the following components: (1) central obesity: waist circumference ≥ 102 cm or 40 inches (male), ≥ 88 cm or 36 inches(female); (2) dyslipidemia: TG ≥ 1.7 mmol/L (150 mg/dl); (3) dyslipidemia: HDL-C < 40 mg/dL (male), < 50 mg/dL (female); (4) elevated blood pressure ≥ 130/85 mmHg; (5) glucose intolerance ≥ 6.1 mmol/L (110 mg/dl). The recruitment phase for the CHARMS study has already been completed.

Inclusion/Exclusion Criteria

All procedures were approved by the University of Miami Institutional Review Board (IRB). Participants included were men, or women not planning pregnancy in the forthcoming year, aged 25-70 years; who completed sixth grade and whose first language is English or Spanish. Additionally participants were excluded if they had type 1 or type 2 diabetes or established CVD; uncontrolled hypertension (systolic BP>160 and diastolic BP>100 mmHg); established liver disease; renal insufficiency (men; serum creatinine

>1.5 mg/dl: women; serum creatinine >1.4 mg/dl); psychiatric illness sufficient to impair full participation; chronic substance abuse in the past 5 years; endocrinopathy; neoplastic disease; chronic, systemic infectious or inflammatory disease; physical disability sufficient to impair full participation; chronic obstructive pulmonary disease or severe asthma; bariatric surgery or bowel resection; or current use of medication for weight loss.

Measures

All data was collected from participants during their baseline assessment visits. During these visits, demographic information as well as anthropometric measurements such as height, weight, and waist circumference were obtained. Fasting blood samples were also drawn from participants after a 12-hour fast during the early hours of the morning and following an Oral Glucose Tolerance Test (OGTT) at 30, 60 and 120 minutes.

Depression

Depression was measured using the Beck Depression Inventory (BDI). The BDI can be separated into two subscales, the cognitive and somatic subscales. Both cognitive and somatic BDI scores were additionally calculated. The BDI was created by Aaron T. Beck and is a 21-item multiple choice self-report measure widely used for the screening of depressive symptoms (Beck, 1988). The BDI was originally developed in English but has also been translated to Spanish. Studies on the validity of the Spanish version of the BDI provide evidence of comparable reliability and validity between the English and Spanish versions (Beck, 1988; Wiebe & Penley, 2005). Psychometric properties of the

Spanish version of the BDI have also been tested in medical samples (Penley, Wiebe, & Nwosu, 2003).

Adiposity

Measures of total and central adiposity were collected. Participant's height and weight were assessed during the baseline visit. Total adiposity was measured using the BMI calculation. Central adiposity was estimated by measuring waist circumference. Waist circumference was measured in centimeters at the midpoint between the upper iliac crest and lower costal margin at the midaxillary line.

Leptin

Leptin was measured from blood samples drawn from participants after a 12-hour fast during the early hours of the morning using a leptin-specific enzyme-linked immunosorbent assay (ELISA) from Mercodia. The Mercodia manufacturer's protocols were followed without modification.

Inflammation.

The extent of systemic inflammation was assessed by using levels of CRP in circulating blood. CRP was chosen for the present study because it is one of the most robust inflammatory predictors of CHD morbidity and mortality (Ridker, Cushman, Stampfer, Tracy, & Hennekens, 1997). CRP was measured using a latex particle enhanced immunoturbidimetry on a Roche 6000 auto-analyzer and reagents from the same manufacturer. Manufacturer's protocols were followed without modification.

Insulin resistance.

Insulin resistance was calculated using the homeostasis model assessment (HOMA) and the insulin sensitivity index (ISI 0,120) (Gutt et al., 2000). The HOMA model is based on fasting insulin and fasting glucose levels (Matthews et al., 1985). The ISI 0, 120 index uses fasting (0 min) and 120 min post-oral glucose (OGTT) insulin and glucose concentrations (Gutt et al., 2000). Blood samples were drawn after a 12-hour fast during participants baseline assessments.

Diet.

Trained interviewers, fluent in both English and Spanish used the Nutrition Data System for Research (NDSR) software to obtain a single 24-hour dietary recall from each participant. The total calorie intake calculation provided by the software was used as an indicator of participant's dietary habits.

Statistical Analysis

SPSS version 18.0 was for data preparation and descriptive analysis. Mplus version 6.0 was used for all regression analyses and for multiple group comparisons within the structural equation modeling framework.

Data preparation

Transformations

Each variable included in the analyses was tested for internal consistency and normality. If the univariate frequency distributions expressed non-normal distribution patterns, the data was transformed to correct for the skewness. A natural log transformation was used in order to achieve a normal distribution.

Excluded values.

Participants with CRP levels greater than 10 mg/L were excluded from the analysis, as these values are likely a sign of infection. Outlier detection and analysis was performed on all variables. Sensitivity analyses were performed on extreme outliers.

Missing values

Full information maximum likelihood (FIML) was used to estimate missing values. FIML is a likelihood function calculated at the individual rather than the group level by borrowing information from other variables for the estimation of parameters with missing values. Mplus 6.0 was used for FIML estimation.

Descriptive analysis.

Descriptive statistics were calculated (e.g. mean and standard deviation) for demographic, biological, psychological and behavioral variables which are considered possible control variables. The t-student test was used to examine any significant differences between men and women in demographic, biological, psychological and

behavioral continues variables. The chi-square test of independence was used to test differences in categorical variables.

Inferential analysis.

Separate models were tested using BDI total score, BDI cognitive score and BDI somatic score as three different outcome variables. Multiple linear regression analyses were used to test the association between CRP levels and depressive symptoms and to test the association between circulating leptin levels and depressive symptoms, separately. Important control variables suggested in the literature were included in the model (Goldbacher & Matthews, 2007; Zeugmann et al., 2010). Age, insulin resistance and total adiposity were included in the model as control variables. Additional tests were also performed to ensure that assumptions of the regression procedures were not violated. Assumptions of the regression model include linearity, independence of observations, normality, and homoscedasticity of residuals.

Moderation analysis.

Gender was further included as a control variable in all models. In models where no significant independent relationship was found between CRP and/or circulating leptin and depressive symptoms, moderation analyses were performed. The moderating effects of gender were tested using multiple group analysis within the context of structural equation modeling. Multiple group analysis in SEM allows assessment of the population heterogeneity in various structure parameters such as variances, covariances and paths. Multiple group analysis requires a multi-step procedure.

Initially, a test of baseline model fit was established. The baseline model consisted of a multiple regression model fitted by gender which included all variables. In this baseline model all intercepts and regression coefficients were constrained equal between groups.

Subsequently, a second model was tested for model fit. In this model, the regression coefficient in the CRP-depression association and/or the leptin-depression association was allowed to vary freely between men and women. A chi-square difference test was then conducted to determine whether parameters can be estimated equally between groups. A significant chi-square difference indicated moderation by gender. Different models were constructed for BDI total score, BDI cognitive score and BDI somatic score as outcome variables. Similarly, separate models were fitted to test the relationship between CRP and depressive symptoms and the association between circulating leptin and depressive symptoms.

Chapter 3

RESULTS

Sample Characteristics

The study population consisted of 119 participants (59 men and 69 women). Median age was 52 years. Median CRP levels were 3.55 mg/L and median circulating leptin levels were 30.6 ng/ml. Median BDI total score, BDI cognitive score and BDI somatic score were 8, 3 and 5, respectively. Important demographic, biological, psychological and behavioral characteristics of the study population are shown in Table 1.

There was no significant difference between men and women in terms of education and income. In this sample, men demonstrated higher waist circumference than women, but BMI was not significantly different between genders. Triglyceride levels were comparable between men and women, however, men demonstrated lower high-density lipoprotein (HDL) cholesterol, CRP and leptin levels. No differences were found in terms of insulin resistance levels measured by the HOMA index or by the ISI 120 index. Women demonstrated a higher BDI total score and a higher BDI somatic score, however, no differences were found in terms of the BDI cognitive score. Men demonstrated higher median caloric intake compared to women.

Table 2 presents the bivariate correlation matrix of the variables included in all regression models.

CRP as a correlate of depressive symptoms

In this sample, CRP levels were significantly associated with depressive symptoms measured by the BDI total score in univariate regression (standardized β=0.30 *P*=0.001). When adjusting for insulin resistance measured by the HOMA index, BMI and age, depressive symptoms remained significantly associated with CRP levels (standardized β=0.24; *P*=0.019). Further adjustment for gender resulted in a non significant relationship between CRP levels and depressive symptoms (standardized β=0.19; *P*=0.08) suggesting possible moderating or mediating effects of gender in the CRP-depressive symptoms relationship.

The moderating effects of gender in the relationship between CRP levels and depressive symptoms were tested within the SEM framework. An initial test of model fit, where all regression paths were constrained equal between genders, was performed yielding the following results χ^2=0.917, *df*=4, *P*=0.922. A second model was then tested for model fit. In this model the CRP-depressive symptoms regression path was allowed to vary by gender. The unconstrained model yielded a χ^2value of 0.888, *df=3*, *P*=0.922. No significant difference was found between the constrained and unconstrained models (χ^2 difference=0.029, *P*=0.865) suggesting no moderation effects of gender in this relationship.

Models using the ISI 0, 120 index for insulin resistance were also tested and yielded similar results (results shown in Table 3).

The relationship between cognitive depressive symptoms measured by the BDI cognitive scale, as well as somatic depressive symptoms measured by the BDI somatic

scale and CRP were also explored. Cognitive depressive symptoms were significantly associated with CRP levels in univariate regression (standardized β=0.28; *P*=0.004). In multivariate regression, CRP levels remained significantly associated with cognitive depressive symptoms after controlling for insulin resistance measured by the HOMA index, BMI and age (standardized β=0.25; *P*=0.013). Further adjustment for gender did not alter the CRP-cognitive depressive symptoms association (standardized β=0.24; *P*=0.027), suggesting the relationship between CRP and depressive cognitive symptoms is independent of gender. The final model explained 10% of the variance in cognitive symptoms. Similar results were found when using the ISI 0, 120 index for insulin resistance (results shown in Table 4).

Somatic depressive symptoms were strongly and significantly associated with CRP levels in univariate regression (standardized β=0.30; *P*=0.001). When adjusting for insulin resistance measured by the HOMA index, BMI and age, somatic depressive symptoms remained significantly associated with CRP levels (standardized β=0.23; *P*=0.011). Further adjustment for gender resulted in a non-significant relationship between CRP levels and somatic depressive symptoms (standardized β=0.17; *P*=0.075) suggesting possible moderating or mediating effects of gender in the CRP-somatic depressive symptoms relationship. Significant predictors of somatic depressive symptoms in the final model were age (standardized β=0.24; *P*=0.005), gender (standardized β=-0.21; *P*=0.024) and a trend was found for BMI (standardized β=0.18; *P*=0.051).

The moderating effect of gender in the relationship between CRP levels and somatic depressive symptoms was further tested. An initial test of model fit, in which all regression paths were constrained equal between genders, was performed yielding the

following results χ^2=3.294, *df*=4, *P*=0.510. A second model was then tested for model fit. This model included an unconstrained CRP- somatic depressive symptoms regression path. The unconstrained model yielded a χ^2value of 2.971, *df=3*, *P*=0.396. No significant difference was found between the constrained and unconstrained models (χ^2 difference=0.323, *P*=0.560) suggesting no moderation effects of gender in this relationship.

Models using the ISI 0. 120 index for insulin resistance were also tested and yielded similar results (results shown in Table 5).

Leptin as a predictor of depressive symptoms

Leptin levels were strongly and significantly associated with depressive symptoms measured by the BDI total score in univariate regression (standardized β=0.36 *P*=0.000). In this sample, leptin levels alone explained 13% of the variance in depressive symptoms. In multivariate regression leptin levels were significantly associated with depressive symptoms after adjusting for CRP levels, insulin resistance measured by the HOMA index, BMI and age (standardized β=0.23; *P*=0.05). Further adjustment for gender resulted in a non significant relationship between leptin levels and depressive symptoms (standardized β=0.15; *P*=0.15) suggesting possible moderating or mediating effects of gender in the leptin-depressive symptoms relationship.

Further analyses were completed to test gender moderation in the relationship between circulating levels and depressive symptoms. The initial test of model fit, where all regression paths were constrained equal between genders, was performed yielding the

following results χ^2=1.589, *df*=5, *P*=0.903. A second model was then tested for model fit. This model included an unconstrained regression path from circulating leptin levels to depressive symptoms. The unconstrained model yielded a χ^2value of 1.428, *df*=4, *P*=0.839. No significant difference was found between the constrained and unconstrained models (χ^2 difference=0.161, *P*=0.688) suggesting no moderation effects of gender in this relationship.

Models using the ISI 0, 120 index for insulin resistance were also tested and yielded similar results (results shown in Table 6).

The relationship between cognitive depressive symptoms measured by the BDI cognitive scale, as well as somatic depressive symptoms measured by the BDI somatic scale and circulating leptin levels were also explored. Cognitive depressive symptoms were significantly associated with leptin levels in univariate regression (standardized β=0.24; *P*=0.011). In multivariate regression, leptin levels did not remain significantly associated with cognitive depressive symptoms after controlling for insulin resistance measured by the HOMA index, BMI and age (standardized β=0.12; *P*=0.327).

The moderating effects of gender in the relationship between circulating leptin levels and cognitive depressive symptoms were then tested. An initial test of model fit, were all regression paths were constrained equal between genders, was performed yielding the following results χ^2=1.584, *df*=5, *P*=0.9032. The second model was subsequently tested for model fit. This model included an unconstrained circulating leptin – cognitive depressive symptoms regression path. The unconstrained model yielded a χ^2value of 1.573, *df*=4, *P*=0.814. No significant difference was found between the

constrained and unconstrained models (χ^2 difference=0.011, *P*=0.916) suggesting no moderation effects of gender in this relationship.

Similar results were found when using the ISI 0, 120 index for insulin resistance (results shown in Table 7).

Somatic depressive symptoms were strongly and significantly associated with circulating leptin levels in univariate regression (standardized β=0.48; *P*=0.000). Circulating leptin levels explained 23% of the variance in somatic depressive symptoms. When adjusting for CRP levels, insulin resistance measured by the HOMA index, BMI and age, somatic depressive symptoms remained significantly associated with leptin levels (standardized β=0.37; *P*=0.001). Further adjustment for gender did not alter the strength of the relationship (standardized β=0.41; *P*=0.004). Age was also found to be significantly associated with somatic depressive symptoms (standardized β=0.23; *P*=0.004), while CRP levels were not associated with somatic depressive symptoms in this model (standardized β=0.10; *P*=0.287). The final model which included circulating leptin levels, CRP levels, insulin resistance measured by the HOMA index, BMI, age, and gender explained 31% of the variance in somatic depressive symptoms. Similar results were found when using the ISI 0, 120 index for insulin resistance (results shown in Table 8).

Chapter 4

DISCUSSION

In this thesis, we report on the association between circulating leptin levels and depressive symptoms in a sample of low-income U.S. Hispanics with the MetS. We provide novel data assessing the potential role of leptin as a predictor of depressive symptoms while controlling for the effects of inflammation, measured by CRP. Furthermore, we describe the depressive symptoms dimension, cognitive or somatic, associated with circulating leptin levels. We found an important independent relationship between elevated circulating levels of leptin and somatic depressive symptoms, adjusting for CRP, BMI, insulin resistance measured both by the HOMA and the ISI 0 120 indexes, age and gender. Leptin levels were the most important predictor of somatic depressive symptoms followed only by age. No significant associations were found between leptin levels and total depressive symptoms or cognitive depressive symptoms. CRP was not a significant predictor of total depressive symptoms, somatic depressive symptoms or cognitive depressive symptoms in models that included circulating leptin, BMI, insulin resistance, age and gender. No moderating effect of gender was found in either of these relationships.

Previous studies have examined the potential role of leptin in depression in both animal models and humans (Antonijevic et al., 1998; Labad et al., 2012; X. Y. Lu, 2007; Pasco et al., 2008). However, most studies have aimed to study total depressive symptoms without elucidating the symptom dimensions more commonly associated with this metabolic disturbance. The identification of depression subtypes might enhance

diagnosis and treatment of depression in this population. This study presents, for the first time, evidence of an independent and important association between somatic depressive symptoms, as opposed to cognitive symptoms, and circulating leptin levels in both men and women adjusting for the effects of an inflammatory marker such as CRP. The association between leptin levels and somatic symptoms was also independent of BMI, insulin resistance and age.

Somatic depressive symptoms include loss of energy, changes in sleeping pattern, changes in appetite, tiredness and fatigue, loss of interest in sex and irritability; whereas, cognitive depressive symptoms are characterized by sadness, pessimism, guilty feeling, self-criticalness and dislike, suicidal thoughts, loss of interest and agitation indecisiveness and worthlessness (Dozois, 1998). This study extends the findings of previous studies that looked at somatic depressive symptoms and their relationship with inflammatory markers (Kupper, Widdershoven, & Pedersen, 2012; Lorton et al., 2006) and the MetS (Capuron et al., 2008). Moreover, the results of this study conducted on patients with the MetS are of potential interest given recent evidence suggesting somatic symptoms may be a better predictor of risk for cardiac events in patients with coronary heart disease (de Jonge et al., 2006; Doyle, Conroy, McGee, & Delaney, 2010; Hoen et al., 2010; Linke et al., 2009; Martens, Hoen, Mittelhaeuser, de Jonge, & Denollet, 2010; Roest et al., 2011; Schiffer et al., 2009; Smolderen et al., 2009). In a study looking at depressive symptom dimensions following acute coronary syndrome, for example, Roest and colleagues found that somatic symptoms were associated with disease severity and all-cause mortality at a 12-month follow-up. Similarly, a study looking at health status and prospective cardiovascular prognosis found that somatic depressive symptoms were associated with

poor health status (left ventricular ejection fraction, previous myocardial infarction, among others) and prospectively predicted cardiovascular mortality and cardiac events even after adjusting for other major prognostic medical variables (de Jonge et al., 2006). Comparable results have been reported in patients with documented medically stable cardiovascular disease (Hoen et al., 2010), chronic heart failure (Schiffer et al., 2009) and subclinical atherosclerosis (Stewart, Janicki, Muldoon, Sutton-Tyrrell, & Kamarck, 2007).

In addition to examining depression as having separate somatic and cognitive symptoms domains, we also looked at the relationship between total depressive symptoms and circulating leptin levels. In contrast to findings that reported a positive association between depressive symptoms and circulating leptin level, our study found a non-significant association between leptin levels and total depressive symptoms after controlling for BMI, insulin resistance, age and gender. This is likely to be related to a confounding effect of gender in this relationship. Interestingly, when we tested the model without gender as one of the control variables the association between circulating leptin and depressive symptoms was significant. Available studies that reported a significant association between elevated leptin levels and total depressive symptoms have not controlled for gender (Miller et al., 2003), have been done in all female samples (Antonijevic et al., 1998; Cizza et al., 2012; Pasco et al., 2008) or have reported gender-dependent associations (Hafner et al., 2012; Labad et al., 2012). In order to further explore the role of gender, we tested the moderating effects of gender in the relationship between total depressive symptoms and leptin levels and found no evidence of moderation. To our knowledge, this study is the first to formally test the moderating

effects of gender in the leptin-depression association. Clearly, gender is an important confounding factor that might explain the conflicting results and future research is needed to replicate these findings.

Other potential factors explaining the differences in the results may include the questionnaires used to assess depression and the characteristics of the study populations in terms of BMI and ethnicity. Whereas our study used the BDI-II as a measure of depression, other studies have used the Hamilton Depression scale (HAM-D) (Cizza et al., 2012) or the depression subscale of the Hospital Anxiety and Depression Scale (HADS) (Labad et al., 2012). It is possible that the HAM-D, the HADS and the BDI-II have different factor structures and perform differently as a tool to detect depressive symptoms as they relate to circulating leptin. However, the relative performance of various tools as predictors of circulating leptin levels was not the focus of the present study and should be the subject of future research. Finally, differences in terms of the study population may affect the results. Our sample was comprised of U.S. Hispanics with the MetS. This population may be culturally, genetically and clinically different than those previously studied. For example, Labad et al. (2012) looked at patients with type 2 diabetes, Pasco et al. (2008) worked with a sample of women with a life-time history of MDD, Cizza and colleges studied premenopausal women (2012) whereas Hafner et al. (2012) studied a healthy subsample of Caucasian participants.

The mechanisms relating somatic depressive symptoms and circulating leptin levels are still unknown. Leptin has also been found to be involved in modulating the immune response and increasing the production of proinflammatory cytokines such as IL-6 and TNF-a (Wozniak et al., 2009). In this study, we found a significant relationship

between leptin levels and depressive symptoms even after controlling for CRP, suggesting the mechanistic pathways are likely to be multiple. Alternative hypothesis include possible interactions between leptin signaling and the mesolimbic dopamine pathway (Fulton et al., 2006), a possible neurotrophic action of leptin (Ahima, Bjorbaek, Osei, & Flier, 1999) and the HPA hypothesis (X. Y. Lu, 2007; Plotsky et al., 1998). The HPA hypothesis, derived from research in animal models suggests leptin has the capacity to modulate the hypothalamic-pituitary-adrenal (HPA) axis (X. Y. Lu, 2007; Sandoval & Davis, 2003). Accumulating evidence so far indicates that HPA axis dysregulation is a common feature among depressed individuals (X. Y. Lu, 2007). Further research is needed to elucidate the mechanistic pathways involved in this association.

Further research is also required to elucidate the directionality of the association between leptin and depressive symptoms using longitudinal research designs. Additionally, it is important to determine whether interventions, both psychotherapeutic and pharmacological, aimed at reducing somatic symptoms have an impact on circulating leptin among men and women in this population. Although these issues for future investigation are important, we believe that our finding also have an immediate application given depression (which is a modifiable factor) appears to play a role in the MetS and thus, is an important factor to consider in the design of prevention strategies.

A strength of this study is the inclusion of U.S. Hispanic participants with the MetS. Hispanics, the fastest growing minority in the United States, have been found to be at particular disadvantage when it comes to the prevalence of the MetS (Ford et al., 2002), thus representing a significant public health concern. Nevertheless, the Hispanic community is still understudied in relation to both cardiovascular and mental health.

This study is limited by its relatively small sample size. In spite of the restricted sample size, this study found an independent association between circulating leptin and somatic depressive symptoms. This relationship is likely to be strengthened with the use of a larger sample size. Similarly, epidemiological studies that include an unselected sample of participants would provide informative data regarding the generalizability of these results. The present study was also limited by its cross-sectional nature. Therefore, the direction of the relationships between CRP, leptin and depressive symptoms cannot be determined and causal inferences cannot be made. However, pending prospective data, our findings provide important insights into the relationship between MetS and depression and the possible underlying mechanistic pathways linking these conditions.

Chapter 5

CONCLUSIONS

In summary, there was an important independent relationship between elevated circulating levels of leptin and somatic depressive symptoms, adjusting for inflammation measured by CRP, BMI, insulin resistance measured both by the HOMA and the ISI 0 120 indexes, age and gender. No significant associations were found between leptin levels and total depressive symptoms or cognitive depressive symptoms after controlling for potential confounding factors. CRP was not significantly associated with total depressive symptoms, somatic depressive symptoms or cognitive depressive symptoms in these multivariate models. There was no evidence of a moderating effect of gender in any of these relationships. Further research is needed to elucidate the complex pathways linking depression and the MetS while incorporating the potential role of leptin.

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Table 1. Important demographic, biological, psychological and behavioral characteristics of the study population.

	Median (IQR)			*P* value
	Total Sample (n=119)	Men (n=59)	Women (n=60)	
Demographics				
Education, years	12 (11-15)	12 (11-15)	12 (12-16)	0.514
Income > 20 000 US.D, n	30	18	12	0.589
Biological				
Age, years	52 (46-57)	51 (44-57)	53 (48-57)	0.121
Body Mass Index, kg/m	32.28 (29.95-34.85)	32.01 (29.59-34.33)	32.51 (30.55-35.22)	0.195
Waist Circumference, cm	105 (99-110)	109.5 (104-116.38)	101.5 (97-106)	**0.000***
Triglycerides, mg/dL	202.5 (162.5-253.75)	206 (167-256)	193 (148-241)	0.291
LDL Cholesterol, mg/dL	124.8 (102.2-147.1)	122 (100.4-143.2)	126.3 (108.5-152.5)	0.266
HDL Cholesterol, mg/dL	37 (32.75-43)	34 (31-38)	41 (37-47)	**0.000***
C-Reactive Protein	3.55 (0.85-6.3)	2.6 (0.7-5.9)	4.5 (1.36-7.5)	**0.001***
Leptin, ng/mL	30.6 (17.72-45.8)	19.77 (12.91-26.2)	45.18 (37.44-77.07)	**0.000***
HOMA	2.77 (2.04-4.11)	2.59 (2.03-4.12)	2.81 (2.03-4.11)	0.899
ISI 120	1.29 (1.07-1.76)	1.28 (1.07-1.9)	1.29 (1.09-1.67)	0.381
Psychological/Behavioral				
BDI Total Score	8 (4-16.25)	6 (3-11.14)	11 (5-17.5)	**0.003***
BDI Cognitive	3 (1-8.25)	2 (1-6)	4 (1-9)	0.139
BDI Somatic	5 (2-7)	3 (1.75-6)	6 (4-8)	**0.001***

Table 2. Bivariate correlation matrix of variables included in regression models

	Age, yr	Body Mass Index	HOMA (log)	ISI 0, 120	C-Reactive Protein (log)	Leptin (log)
Age, yr	1.000					
Body Mass Index	-0.027	1.000				
HOMA (log)	0.057	**0.267***	1.000			
ISI 0, 120	**-0.193***	**-0.309****	**-0.334****	1.000		
C-Reactive Protein (log)	0.047	**0.298***	0.140	**-0.299***	1.000	
Leptin (log)	0.096	**0.479****	0.110	**-0.316****	**0.413****	1.000

* $P<0.05$

** $P<0.001$

Table 3. CRP as a predictor of total depressive symptoms

	Models using the HOMA index			Models using the ISI 0,120 index		
	Standardized β	***P* value**	**R^2**	**Standardized β**	***P* value**	**R^2**
Univariate			0.092			0.092
C-Reactive Protein (log)	0.304	**0.001***		0.304	**0.001***	
Model 1			0.153			0.134
C-Reactive Protein (log)	0.235	**0.019***		0.214	**0.040***	
Insulin Resistance	0.035	0.704		-0.032	0.746	
Body Mass Index	0.161	0.098		0.168	0.083	
Age	0.190	**0.025***		0.186	**0.032***	
Model 2			0.140			0.148
C-Reactive Protein (log)	0.189	0.080		0.169	0.132	
Insulin Resistance	0.054	0.567		-0.032	0.751	
Body Mass Index	0.156	0.110		0.169	0.084	
Age	0.169	**0.053***		0.167	0.061	
Gender	0.137	0.150		-0.133	0.164	

* $P<0.05$

Table 4. CRP as a predictor of cognitive depressive symptoms

	Models using the HOMA index			Models using the ISI 0,120 index		
	Standardized β	***P* value**	**R^2**	**Standardized β**	***P* value**	**R^2**
Univariate			0.077			0.077
C-Reactive Protein (log)	0.278	**0.004***		0.278	**0.004***	
Model 1			0.105			0.094
C-Reactive Protein (log)	0.253	**0.013***		0.237	**0.026***	
Insulin Resistance	0.057	0.554		0.004	0.97	
Body Mass Index	0.074	0.450		0.096	0.332	
Age	0.103	0.240		0.107	0.234	
Model 2			0.097			0.086
C-Reactive Protein (log)	0.238	**0.027***		0.223	**0.046***	
Insulin Resistance	0.063	0.517		0.005	0.962	
Body Mass Index	0.071	0.474		0.095	0.340	
Age	0.095	0.291		0.101	0.274	
Gender	-0.047	0.628		-0.043	0.660	

* $P<0.05$

Table 5. CRP as a predictor of somatic depressive symptoms

	Models using the HOMA index			Models using the ISI 0,120 index		
	Standardized β	***P* value**	**R^2**	**Standardized β**	***P* value**	**R^2**
Univariate			0.091			0.077
C-Reactive Protein (log)	0.302	**0.001***		0.302	0.001*	
Model 1			0.194			0.196
C-Reactive Protein (log)	0.232	**0.011***		0.217	**0.022***	
Insulin Resistance	-0.025	0.777		-0.046	0.628	
Body Mass Index	0.194	**0.034***		0.18	**0.049***	
Age	0.270	**0.001***		0.258	**0.002***	
Model 2			0.185			0.186
C-Reactive Protein (log)	0.174	0.075		0.160	0.112	
Insulin Resistance	-0.002	0.986		-0.044	0.645	
Body Mass Index	0.180	0.051		0.173	0.060	
Age	0.238	**0.005***		0.229	**0.007***	
Gender	-0.206	**0.024***		-0.204	**0.025***	

* $P<0.05$

Table 6. Leptin as a predictor of total depressive symptoms

	Models using the HOMA index			Models using the ISI 0,120 index		
	Standardized β	***P* value**	**R^2**	**Standardized β**	***P* value**	**R^2**
Univariate			0.127			0.127
Leptin (log)	0.356	**0.000**		0.356	**0.000**	
Model 1			0.178			0.175
Leptin (log)	0.229	**0.050***		0.235	**0.046***	
C-Reactive Protein (log)	0.152	0.159		0.135	0.227	
Insulin Resistance	0.046	0.613		-0.006	0.951	
Body Mass Index	0.063	0.563		0.078	0.469	
Age	0.163	*0.055*		0.165	*0.056*	
Model 2			0.187			0.192
Leptin (log)	0.246	0.154		0.265	0.123	
C-Reactive Protein (log)	0.153	0.155		0.137	0.216	
Insulin Resistance	0.044	0.632		-0.003	0.980	
Body Mass Index	0.055	0.650		0.064	0.592	
Age	0.163	*0.053*		0.166	*0.053*	
Gender	0.019	0.893		0.033	0.817	

* $P<0.05$

Table 7. Leptin as a predictor of cognitive depressive symtpoms

	Models using the HOMA index			Models using the ISI 0,120 index		
	Standardized β	***P* value**	**R^2**	**Standardized β**	***P* value**	**R^2**
Univariate			0.057			0.057
Leptin (log)	0.239	**0.011***		0.239	**0.011***	
Model 1			0.106			0.098
Leptin (log)	0.118	0.327		0.126	0.301	
C-Reactive Protein (log)	0.202	0.069		0.189	0.099	
Insulin Resistance	0.064	0.507		0.020	0.850	
Body Mass Index	0.026	0.818		0.049	0.653	
Age	0.089	0.315		0.096	0.287	
Model 2			0.134			0.136
Leptin (log)	0.175	0.304		0.200	0.242	
C-Reactive Protein (log)	0.203	0.063		0.191	0.088	
Insulin Resistance	0.057	0.548		0.026	0.798	
Body Mass Index	0.004	0.971		0.021	0.856	
Age	0.093	0.290		0.101	0.255	
Gender	0.064	0.648		0.081	0.559	

* $P<0.05$

Table 8. Leptin as a predictor of somatic depressive symtpoms

	Models using the HOMA index			Models using the ISI 0,120 index		
	Standardized β	***P* value**	**R^2**	**Standardized β**	***P* value**	**R^2**
Univariate			0.225			0.057
Leptin (log)	0.474	**0.000**		0.474	**0.000**	
Model 1			0.275			0.275
Leptin (log)	0.372	**0.001***		0.374	**0.001***	
C-Reactive Protein (log)	0.104	0.290		0.095	0.342	
Insulin Resistance	-0.009	0.918		-0.008	0.930	
Body Mass Index	0.038	0.705		0.037	0.705	
Age	0.226	**0.004***		0.224	**0.005***	
Model 2			0.305			0.304
Leptin (log)	0.410	**0.004***		0.412	**0.004***	
C-Reactive Protein (log)	0.103	0.287		0.095	0.335	
Insulin Resistance	-0.012	0.881		-0.004	0.967	
Body Mass Index	0.022	0.831		0.022	0.831	
Age	0.226	**0.004***		0.224	**0.004***	
Gender	0.048	0.695		0.046	0.705	