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## Sex-specific roles of cellular inflammation and cardiometabolism in obesity-associated depressive symptomatology

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### Abstract

**Background:** Obesity and depression are complex conditions with stronger comorbid relationships among women than men. Inflammation and cardiometabolic dysfunction are likely mechanistic candidates for increased depression risk, and their prevalence differs by sex. Whether these relationships extend to depressive symptoms is poorly understood. Therefore, we analyzed sex in associations between inflammation and metabolic syndrome (MetS) criteria on depressive symptomatology. Specifically, we examined whether sex positively moderates the relationship between depressive symptoms and inflammation among women, and whether MetS has parallel effects among men.

**Methods:** Depressive symptoms, MetS, and inflammation were assessed in 129 otherwise healthy adults. Depressive symptoms were assessed using Beck Depression Inventory (BDI-Ia). Monocyte inflammation regulation (BARIC) was quantified using flow cytometry measurement of TNF- $\alpha$  suppression by  $\beta$ -agonist. Moderation effects of sex on associations between BARIC, MetS criteria, and BDI were estimated using two-way ANOVA and linear regression, adjusting for BMI, and by sex subgroup analyses.

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Conflict of Interest

The authors declare that they have no conflict of interest.

**Results:** Obese individuals reported more depressive symptoms. Sex did not formally moderate this relationship, though BDI scores tended to differ by BMI among women, but not men, in subgroup analysis. Poorer inflammation control and higher MetS criteria were correlated with somatic depressive symptoms. Sex moderated associations between MetS criteria and somatic symptoms; among men, MetS criteria predicted somatic symptoms, not among women. Subgroup analysis further indicated that poorer inflammation control tended to be associated with higher somatic symptoms in women.

**Conclusions:** These results indicate that obesity-related inflammation and MetS factors have sex-specific effects on depressive symptoms in a non-clinical population. Although pathophysiological mechanisms underlying sex differences remain to be elucidated, our findings suggest that distinct vulnerabilities to depressive symptoms exist between women and men, and highlight the need to consider sex as a key biological variable in obesity-depression relationships. Future clinical studies on comorbid obesity and depression should account for sex, which may optimize therapeutic strategies.

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## 1. Introduction

Depression is twice as prevalent among obese individuals, with over 40% of obese US adults reporting clinically-relevant depressive symptoms<sup>1</sup>, notably higher than the 7% prevalence rate of major depression among adults in general. Although obesity and depression are complex conditions, there are significant bidirectional associations between them<sup>2</sup>. Higher body mass index (BMI) is associated with poorer responses to classical antidepressant treatment<sup>3</sup>, and comorbid depression predicts unfavorable outcomes in weight-loss trials<sup>4</sup>. Intriguingly, meta-analyses suggest that these associations may be more pronounced in women than men<sup>5</sup>. Systematic reviews have identified a number of biopsychosocial mediators of sex differences in the links between obesity and depression, including sex hormones, stress, and social stigma<sup>6</sup>. While ‘sex’ generally refers to strictly biological attributes based on chromosomal, genetic, and hormonal factors, ‘gender’ relies on socially influenced identities and behavioral expressions, defined by a combination of variables, including biological sex. Because biology and environment reciprocally interact throughout the lifespan, sex differences in biological outcomes are not entirely sex-driven. Our primary use of the term ‘sex’ throughout this paper is for literal consistency and with acknowledgment of this complex interplay. For instance, sexual dimorphisms exist across brain structures that regulate the stress response<sup>7</sup> and energy homeostasis<sup>8</sup>, particularly within the hypothalamic-pituitary-adrenal and sympathoadrenalmedullary systems, but these differences may be reinforced (or attenuated) by gender<sup>9</sup>. Sex differences are also observed in neurological pathways implicated in mental illnesses<sup>10</sup> that are more prevalent in women, such as compulsive eating and major depression, which are in turn affected by gender role<sup>11</sup>. Despite the higher prevalence of comorbid depression among women than men in the US<sup>1</sup>, and recent National Institutes of Health’s effort in identifying sex as a biological variable (SABV), sex and gender differences in pathophysiological processes linking obesity and depression remain poorly understood.

Chronic, low-grade inflammation and cardiometabolic dysfunction have been identified as common links between obesity and depression<sup>12</sup>, and each tends to affect women and men

differentially. In obese persons, regardless of sex, inflammation manifests as increased plasma levels of pro-inflammatory cytokines (e.g., tumor necrosis factor- $\alpha$  [TNF- $\alpha$ ]), adipokines (e.g., leptin), and C-reactive protein, an independent risk factor for cardiovascular disease and mortality<sup>13</sup>. As the major source of obesity-related inflammation<sup>14</sup>, adipose tissue macrophages accumulate with increased body weight. Similar to obesity, depressed patients exhibit elevated cytokine levels in serum and cerebrospinal fluid<sup>15</sup>, which can access the brain and reduce the bioavailability of monoamine neurotransmitters, such as serotonin and norepinephrine, involved in mood regulation<sup>16</sup>, or decrease levels of brain-derived neurotrophic factor (BDNF)<sup>17</sup>, which normally promotes neurogenesis and may exert antidepressant-like effects. Cytokine administration induces clinically-relevant depression and fatigue symptoms<sup>18</sup>, and treatment with TNF- $\alpha$  antagonist improves depressive symptomatology in patients with high inflammation<sup>19</sup>. Thus, inflammation is a likely candidate for the increased comorbidity with depression.

Notably, women generally exhibit higher levels of inflammation and greater autoimmune disease burden than men, and recent work suggests that women may be more vulnerable to inflammation-induced mood changes<sup>20</sup>. For instance, experimental endotoxin exposure evoked similar increases in interleukin-6 and TNF- $\alpha$  between women and men<sup>21</sup>, but their effects on depressed mood were stronger in women. Sex-specific relationships between inflammation and mood disturbances, particularly somatic complaints such as fatigue<sup>22</sup>, have also been reported. Hyper-inflammation and depressive symptoms are often linked to neuroendocrine dysregulation<sup>23</sup>, which modulates immune function during stress. Notably, women are reported to experience greater physiological stress reactivity than men<sup>24</sup>, secrete more pro-inflammatory cytokines in response to stressors<sup>25</sup>, and more readily develop glucocorticoid resistance<sup>26</sup>. Some of these effects may be attributable to endocrine modulation of stress-regulatory structures that contain high steroid receptor densities (e.g., estrogen receptor), particularly the hippocampus<sup>27</sup>. However, emerging evidence indicates that obesity itself produces distinct immunological changes in women, which may feed back upon the brain and further depress mood<sup>28</sup>. For instance, a meta-analytic review concluded that obesity was more strongly associated with C-reactive protein levels in women than men<sup>29</sup>. Adiposity may elicit higher inflammation in women due to differing adipose tissue metabolism<sup>30</sup> and patterns of fat accumulation<sup>31</sup>. Despite evidence of heightened mood disturbances subsequent to immune activation in women, the role of obesity-associated inflammation in mood disturbances among women versus men remains unclear, which may represent a missed opportunity for targeted therapies to treat comorbid depression.

Meanwhile, men generally exhibit the metabolic syndrome (MetS) at higher rates<sup>32</sup>. MetS is a cluster of markers of cardiometabolic dysfunction, including dyslipidemia, hypertension, and hyperglycemia, that are primarily driven by obesity and bi-directionally associated with depression<sup>33</sup>. Among US adults, lean (BMI <25 kg/m<sup>2</sup>) men are 34% more likely to have MetS<sup>34</sup> than lean women, and fewer obese men are “metabolically healthy” than obese women (29.2% versus 35.4%). This suggests that obesity-related MetS may be more prominent in men than women, leading to a question of sex-specific MetS-related mood disturbance. Multiple mechanisms by which MetS is associated with depressed mood have been described, including insulin and leptin resistance<sup>35</sup>. Studies in metabolically healthy

obese persons suggest that obesity-depression associations depend upon metabolic profile<sup>36</sup>. To date, the data on sex differences in this association have been equivocal. For example, somatic depressive symptoms, such as fatigue, appetite and sleep disturbances, are associated with abdominal obesity among both men and women, but only among men were symptoms also driven by cardiometabolic dysfunction in an older-aged Dutch cohort<sup>37</sup>. Conversely, a similar survey in Korea reported an effect of MetS on depression among women, but not men<sup>38</sup>. Furthermore, depressed women tend to report higher levels of somatic symptoms than depressed men<sup>39</sup>, suggesting sexual dimorphism in symptom manifestation, especially somatic symptoms. Differences in experimental methods, populations, or depression instruments may account for the mixed findings, and very few studies to our knowledge have sought to determine the independent effects of obesity and MetS on depressive symptoms in a sex-specific manner.

To that end, the current study examined the role of sex and obesity in associations between cellular inflammation, cardiometabolic dysfunction, and depressive symptoms in adults. As outlined above, there is growing evidence to suggest that sex-specific sensitivities to inflammation and cardiometabolism, particularly within the context of overweight/obesity, may underlie the higher incidence of comorbid depression among women or obscure MetS-depression associations among men. The following hypotheses were tested: (1) associations between obesity and depressive symptomatology would be stronger in women, (2) women would be more susceptible to the effects of obesity-associated inflammation on depressive symptoms, and (3) men would be more vulnerable to the effects of MetS criteria on depressive symptoms.

## 2. Materials and methods

### 2.1. Participants

All participants gave informed consent to the protocol, approved by the University of California, San Diego Institutional Review Board. One hundred twenty-nine otherwise healthy, non-smoking men and women between 18-65 years were recruited from the local community for a larger study of the role of obesity on vascular inflammation and immune cell activation in stage 1 hypertension (SBP <145 mmHg; to exclude stage 2 hypertension with consideration for exaggerated BP in laboratory settings). Initial screening via telephone interviews, followed by face-to-face confirmation, established the absence of the following exclusion criteria: diabetes, current or recent history (<6 months) of smoking or substance abuse, history of cardiovascular disease (e.g., symptomatic coronary or cerebrovascular disease, arrhythmia, myocardial infarction, cardiomyopathy, heart failure), history of bronchospastic pulmonary disease, inflammatory disorders or health-related factors affecting immune function (e.g., vaccinations within 10 d of study visit, active infections/illness, immunomodulatory medication, uncontrolled thyroid disease), psychosis, major depressive disorder, and stage 2 clinical hypertension indicated by use of anti-hypertensive medication or laboratory-assessed BP ≥ 145/90 mmHg. A power analysis determined that a sample size of approximately 130 would be needed to detect small-to-medium ( $r=0.24$ ) main effects (e.g., of BMI, MetS, and BARIC) at 80% power with two-tailed  $\alpha=0.05$  on depressive symptoms in linear regression models, given previous studies<sup>5,40,41</sup>. Furthermore, we

expected similar power to detect moderation effects by sex in these models, despite known challenges regarding sample size inflation required to detect moderation<sup>42</sup>, as prior meta-analyses of sex-stratified studies have reported near zero effects of the obesity and obesity-related risk factors in one of the two sexes<sup>5,33</sup>.

## 2.2. Sample collection and laboratory procedures

Average basal systolic (SBP) and diastolic blood pressures (DBP) were calculated from two sets of three consecutive measurements at 5-min intervals, using a Dinamap Compact BP monitor (Critikon, Tampa, FL). Sets were separated by 40-60 min. Standard anthropometrics (i.e., height, weight, hip and waist circumference) were collected via conventional tape and scale. BMI was calculated by weight in kg/(height in m)<sup>2</sup> and individuals categorized by BMI (lean: <25 kg/m<sup>2</sup>; overweight: 25 BMI<30 kg/m<sup>2</sup>; obese: 30 kg/m<sup>2</sup>). Dual x-ray absorptiometry was performed in a subset of men (N=25) and women (N=29) to calculate total body fat. Women provided first date of last menstrual period (if applicable), from which cycle phase was estimated (i.e., menstrual versus ovulatory), and whether they were currently taking hormonal contraceptives (i.e., yes versus no). Blood samples were obtained between 0800-1000 hr for all participants after 12h of fasting and collected in EDTA or heparin anti-coagulant vacutainers (BD, Franklin Lakes, NJ). Lipid profiles and glucose levels were assessed at UCSD Medical Center Clinical Laboratory. EDTA-treated blood remained on ice until plasma was separated by centrifugation and stored at -80C for measurement of insulin, leptin, and estradiol.

Cellular inflammation regulation assays were performed on whole blood aliquots from heparin vacutainers within 1h of collection. Briefly, lipopolysaccharide (LPS; 200 pg/mL) (E.coli 0111:B4, catalog #L4391, Sigma-Aldrich, St. Louis, MO) was added to 300 µL of heparinized blood and incubated for 30 min at 37°C with 5% CO<sub>2</sub> in sterile 96-well polypropylene cell culture plates, along with a non-LPS-treated sample. This LPS dose was previously determined to elicit significant activation of monocytes, with 30-90% producing TNF-α<sup>40</sup>. To inhibit cytokine excretion, thus allowing for intracellular detection of TNF-α (cat. #502906, BioLegend, San Diego, CA), Brefeldin A (10 µg/mL, Sigma-Aldrich) was added to each sample for the final 3 h of incubation. Intracellular TNF-α production by monocytes was evaluated using multi-color flow cytometry, as previously described<sup>40</sup>. The proportion of CD14<sup>+/dim</sup>HLA-DR<sup>+</sup> (CD14: cat. #301808; HLA-DR: cat. #307606, BioLegend, San Diego, CA) cells that were TNF-α<sup>+</sup> was determined using FlowJo software (v10, TreeStar, Ashland, OR), and gates adjusted for each TNF-α-stained sample using fluorescence-minus-one controls.

## 2.3. Beta-adrenergic receptor-mediated inflammation control (BARIC)

BARIC was determined based on the inhibitory effect of isoproterenol, a non-specific β<sub>1/2</sub>-AR agonist, on monocytic intracellular TNF-α production in LPS-stimulated blood as described above. In addition to LPS, blood was co-incubated with isoproterenol in 10<sup>-8</sup> M final concentration and evaluated for intracellular monocyte TNF-α production. Monocyte β-AR-mediated responsiveness to TNF-α inhibition by isoproterenol (i.e., BARIC) was calculated as the arithmetic difference in %TNF-α<sup>+</sup> monocytes between LPS-treated and LPS+isoproterenol-treated samples. Greater BARIC values indicate greater β-AR

responsivity, and thus, better  $\beta$ -AR-mediated inflammation regulation. Smaller BARIC values may indicate impairment in cellular pathways that regulate inflammatory responses mediated by  $\beta$ -ARs (e.g., diminished receptor sensitivity to agonists), though BARIC itself does not directly reflect receptor sensitivity *per se*. Simply put, BARIC measures monocytes' responsivity to a  $\beta$ -AR agonist during an inflammatory response to LPS. We have previously demonstrated that reduced BARIC is associated with hypertension, cardiovascular disease risk factors, and higher serum cytokine levels<sup>40</sup>. Given sex differences reported in neuroendocrine pathways<sup>7</sup> and stress responses, examination of  $\beta$ -AR-mediated inflammatory activity of monocytes is particularly relevant and functionally meaningful to this investigation.

#### 2.4. Cardiometabolic assessment and sex-hormone assays

Cardiometabolic dysfunction was assessed by the number of MetS criteria satisfied (represented by integers 0-5) according to the International Diabetes Foundation consensus statement, which include (1) central obesity (94 cm in men, 80 cm in women), (2) hypertension (SBP 130 or DBP 85 mmHg), (3) hypertriglyceridemia (150 mg/dL), (4) hypoalphalipoproteinemia (HDL < 50 mg/dL in men, HDL < 40 in women), and (5) hyperglycemia (fasted glucose 100 mg/dL). Insulin and leptin concentrations were measured using electro-chemiluminescent assay (cat. #K15164C, Meso Scale Diagnostics, Rockville, MD), and estradiol using competitive enzyme immunoassay (catalog #KGE014, R&D Systems, Minneapolis, MN). Sample luminescent intensities were determined using a Sector Imager 2400 (Meso Scale Diagnostics) and a VersaMax ELISA microplate reader (Molecular Devices, Sunnyvale, CA). Quantification was based on a four-parameter logistic curve generated per manufacturer's protocol. The intra- and inter-assay CVs were 3.5% and 8.1% for insulin, 3.1% and 9.5% for leptin, respectively, and the intra-assay CV was 16.1% for estradiol.

#### 2.5. Measurement of depressive symptoms

Depressive symptoms were measured via the Beck Depression Inventory (BDI-Ia), a comprehensive and clinically robust self-report 21-item questionnaire. Each question was scored from 0-3, summed to a BDI total score (BDI-T), and then subcategorized into cognitive-affective (BDI-C) and somatic (BDI-S) depression scores based on previous findings that the two symptomatically distinct constructs (e.g., BDI-C: guilt, pessimism; BDI-S: fatigue, sleep disruption) are reliably captured by BDI-Ia<sup>43</sup>.

#### 2.6. Statistical analysis

Statistical analyses were conducted using *R* v3.3.3 in *RStudio* (v1.0.136, Boston MA). Results of statistical tests were considered statistically significant if  $p < 0.05$ , and all tests were two-tailed. Data were visually inspected for normality and tested using the Kolmogorov-Smirnov test. Variables that were not normally distributed were log-transformed (e.g., BDI scores). To explore sex and obesity differences in depressive symptoms, cardiometabolism, and BARIC, two-way analysis of variance (ANOVA) was used to determine differences by sex, BMI category, and their interactions based on *F*-statistics. Multiple linear regression models were implemented to examine effects on depressive symptoms and quantify effect sizes (betas) and *t*-test regression coefficients. Age

and ethnicity (entered categorically as Caucasian, African-American, Asian, or Other) were included as covariates in all models. Simple associations among variables were assessed using univariate correlations of Pearson's  $r$  across all participants. Goodness-of-fit was compared between models that included MetS or BARIC terms and BMI-only models using likelihood ratio tests to compute chi-squared statistics. MetS and BARIC were included in separate models to minimize case removal due to missing data ( $N_{BARIC}=113$ ; 88% of total cases). Serum estradiol levels were related to menstrual cycle phase ( $\beta=59.0$ ,  $t_{40}=2.79$ ,  $p=0.007$ ) based on self-reported date of last menstrual period. Thus, residual serum estradiol levels were calculated by regressing out menstrual cycle phase and hormonal contraceptive use, and then entered into women-only models to control for sex hormone effects on depressive symptoms. Family-wise error rate was corrected using Hommel's method in subgroup analyses to mitigate Type I error. Model residuals were visually inspected and tested for homoscedasticity using the Breusch-Pagan test, and normality was assessed using Wilks-Shapiro test. Studentized residuals and variance inflation factors were  $<3.0$  for all predictors in each model, and influence (dfbetas) and leverage (hat-value) statistics were assessed.

### 3. Results

#### 3.1. Participant characteristics and sex-based differences

**Demographic and anthropometrics.**—Participants ( $N=129$ ) were young to middle-aged adults ( $39\pm 12$  years), of whom 30% ( $N=39$ ) were obese, 40% ( $N=51$ ) were overweight, and 30% ( $N=39$ ) were lean, which closely reflects US overweight and obesity rates (CDC, 2016). A higher proportion of women than men were obese (38% vs. 22%), but no significant sex differences by BMI category ( $\chi^2=6.0$ ,  $p=0.20$ ) or BMI values (men:  $28.4\pm 5.6$ ; women:  $28.9\pm 7.7$ ;  $t_{119}=0.47$ ,  $p=0.64$ ) were observed. Waist circumference (WC) and waist-hip ratio (WHR) were strongly correlated ( $r=0.67$ ,  $t_{121}=9.80$ ,  $p<0.001$ ) and both were significantly larger among men (Table 1,  $p<0.001$ ). Obesity had a stronger effect on both WC and WHR in men than women (Table 1,  $p<0.05$ ), reflecting an android pattern of central adiposity.

**Cardiometabolism.**—Men had significantly higher SBP relative to women, as well as higher triglyceride and lower HDL levels (Table 1). Accordingly, men tended to have higher MetS burden than women (19/64 versus 10/65;  $\chi^2=3.79$ ,  $p=0.052$ ), though MetS criteria incidence did not significantly differ by sex (Table 1). Serum insulin and leptin levels were elevated among obese individuals (Table 1). Leptin levels were significantly higher among women, even after controlling for BMI (Table 1), and positively associated with MetS criteria incidence ( $\beta=0.38$ ,  $t=4.20$ ,  $p<0.001$ ). Despite similar sex differences in the relationship of WC and WHR to obesity in our sample (Table 1), sex-adjusted WC was more strongly predictive of cardiometabolic MetS criteria incidence than WHR ( $\beta_{WC}=0.49$ ,  $t=5.16$ ,  $p<0.001$  vs.  $\beta_{WHR}=0.32$ ,  $t=3.12$ ,  $p=0.002$ ). Men had less proportional total body fat than women ( $24.5\pm 1.6\%$  versus  $36.0\pm 1.3\%$ ;  $t_{36}=5.45$ ,  $p<0.001$ ). Nevertheless, obesity had a stronger effect on leptin in men versus women, such that leptin levels increased at a greater rate in relation to increasing BMI in men ( $F_{2,122}=3.14$ ,  $p=0.047$ ) (Fig. S1).



**Inflammation and depressive mood.**—In response to LPS, monocytes from men and women expressed similar proportions of TNF- $\alpha$  ( $55.0\pm 1.8\%$  versus  $54.5\pm 1.9\%$ ;  $t_{110}=-0.18$ ,  $p=0.86$ ) and were similarly sensitive to  $\beta$ AR-mediated suppression of TNF- $\alpha$  (Table 1). For nearly all participants (95%), depressive symptoms ranged from minimal (BDI-T score  $\leq 13$ ) to mild ( $13 < \text{BDI-T} \leq 19$ ). Six subjects scored in the moderate range ( $19 < \text{BDI-T} \leq 28$ ), though none had a concurrent depression diagnosis. Average BDI-T score was  $5.7\pm 6.3$ , and BDI-C and BDI-S subscale scores were  $2.9\pm 3.8$  and  $2.8\pm 3.1$ , respectively. As anticipated, BDI-C and BDI-S scores were intercorrelated ( $r=0.62$ ,  $t_{127}=8.79$ ,  $p<0.001$ ). On average, women scored significantly higher on the BDI-S than men, though sex differences were not observed on the BDI-C subscale (Table 1).

### 3.2. Associations between obesity, depressive symptomatology, and sex

In all participants, BMI was positively correlated with both BDI-C ( $r=0.23$ ,  $t_{127}=2.60$ ,  $p=0.01$ ) and BDI-S scores ( $r=0.34$ ,  $t_{127}=4.14$ ,  $p<0.001$ ). In agreement with our previous findings<sup>40,44</sup>, obese individuals reported more depressive symptoms than lean or overweight individuals (obese vs. lean:  $\beta_{\text{BDI-S}} = 0.65$ ,  $p<0.001$ ;  $\beta_{\text{BDI-C}}=0.54$ ,  $p=0.013$ ; obese vs. overweight:  $\beta_{\text{BDI-S}}=0.42$ ,  $p=0.02$ ;  $\beta_{\text{BDI-C}}=0.35$ ,  $p=0.08$ ). No significant differences were observed between lean and overweight groups ( $p \geq 0.05$ ).

Women reported significantly more somatic, but not cognitive, depressive symptoms than men ( $\beta_{\text{sex}}=0.32$ ,  $p=0.02$ ) (Table 1). Although the effects of obesity on depressive symptoms were not formally moderated by sex (i.e., BMI  $\times$  sex interaction) (Table 1), separate analyses by sex subgroups indicated that depressive symptoms tended to differ by BMI in women for both somatic ( $F_{2,58}=3.63$ ,  $p_{\text{adj}}=0.06$ ) and cognitive-affective symptoms ( $F_{2,58}=3.51$ ,  $p_{\text{adj}}=0.073$ ), but not men ( $p_{\text{adj}} \geq 0.10$ ) (Fig. 1). More specifically, obese women reported more depressive symptoms than lean women (BDI-S:  $\beta=0.59$ ,  $t=2.48$ ,  $p_{\text{adj}}=0.048$ ; BDI-C:  $\beta=0.68$ ,  $t=2.65$ ,  $p_{\text{adj}}=0.032$ ). Symptoms did not differ between obese and overweight or overweight and lean women ( $p_{\text{adj}} \geq 0.10$ ).

### 3.3. Sex-specific effects of cardiometabolic dysfunction on somatic depressive symptoms

Obese and overweight individuals had significantly higher incidence of MetS factors than lean individuals (obese versus lean:  $\beta=1.79$ ,  $t=7.00$ ,  $p<0.001$ ; overweight vs. lean:  $\beta=0.96$ ,  $t=4.03$ ,  $p<0.001$ ). Across all participants, MetS factors were positively correlated with somatic depressive symptomatology ( $r=0.23$ ,  $t_{127}=2.72$ ,  $p=0.007$ ), but not cognitive-affective symptoms ( $r=0.10$ ,  $t_{127}=1.08$ ,  $p=0.28$ ). Adjusting for BMI and sex, MetS factors were associated with BDI-S scores across the study sample ( $\beta_{\text{MetS}}=0.15$ ,  $p=0.041$ , Table 2) and explained an additional 4.7% of the variance in BDI-S ( $\chi^2=9.10$ ,  $p=0.011$ ). Stepwise addition of serum leptin and insulin levels into the model did not explain additional variance or improve model fit ( $\chi^2=0.31$ ,  $p \geq 0.10$ ). MetS factor incidence was also negatively correlated with BARIC values ( $r=-0.20$ ,  $t_{111}=-2.18$ ,  $p=0.032$ ) and age ( $r=0.25$ ,  $t_{129}=2.91$ ,  $p=0.004$ ), and was significantly higher in overweight/obese individuals (Table 1).

Regression models also showed that sex significantly moderated the association between MetS factor incidence and somatic symptoms ( $F_{1,119}=5.49$ ,  $p=0.021$ , Table 2). Analysis

within each sex subgroup indicated that higher MetS factor incidence was linearly associated with increased somatic symptoms in men ( $\beta_{\text{MetS}}=0.20$ ,  $p_{\text{adj}}=0.027$ ), but not in women ( $p_{\text{adj}} 0.10$ ) (Fig. 2A). Estradiol levels were not related to BDI-S in women ( $p_{\text{adj}} 0.10$ ).

### 3.4. Sex-specific effects of $\beta$ -adrenergic receptor mediated inflammation control on somatic depressive symptoms

BARIC values were negatively correlated with somatic symptoms ( $r=-0.22$ ,  $t_{110}=-2.36$ ,  $p=0.02$ ), but not cognitive-affective symptoms ( $r=-0.11$ ,  $t_{110}=-1.18$ ,  $p=0.24$ ), across all participants. BARIC was significantly lower among older individuals ( $\beta_{\text{age}}=-0.15$ ,  $t_{111}=-2.23$ ,  $p=0.028$ ) and tended to differ by BMI category ( $F_{2,110}=2.84$ ,  $p=0.06$ ). Post hoc comparisons indicated that BARIC was significantly lower among obese individuals ( $\beta=-4.88$ ,  $t_{110}=-2.32$ ,  $p_{\text{adj}}=0.045$ ) and somewhat lower among overweight compared to lean individuals ( $\beta=-3.49$ ,  $t_{110}=-1.72$ ,  $p_{\text{adj}}=0.088$ ), indicating poorer inflammation control in obesity.

BARIC values did not significantly differ between men and women (Table 1), adjusting for age, ethnicity, and BMI. However, beyond the effects of obesity, lower BARIC values tended to be associated with higher somatic depressive symptoms in all participants ( $\beta_{\text{BARIC}}=-0.14$ ,  $p=0.057$ ) and explained an additional 2.1% of the variance in somatic symptoms ( $\chi^2=3.96$ ,  $p=0.046$ ). Sex did not significantly moderate the association between BARIC and somatic symptoms ( $F_{1,102}=0.76$ ,  $p=0.39$ ), though analysis within each sex indicated that BARIC values tended to be associated with increased BDI-S scores in women ( $\beta_{\text{BARIC}}=-0.20$ ,  $t=-2.18$ ,  $p_{\text{adj}}=0.069$ ), but not in men ( $p_{\text{adj}} 0.10$ ) (Fig. 2B, Table 2). Estradiol levels were not related to depressive symptoms in the women-only model ( $p_{\text{adj}} 0.10$ ).

## 4. Discussion

Mounting evidence indicates that obesity and depression are linked by inflammation and cardiometabolic dysfunction. Men and women may be differentially susceptible to these conditions, and thus it is critical to examine sex differences in their effects on depressive symptomatology. In this investigation, we found that obesity was more strongly associated with depressive symptomatology in women than men, which is consistent with the literature<sup>5,6</sup>. As hypothesized, we also found that sex moderated the depressive symptom-cardiometabolic dysfunction relationship such that higher MetS risk factor incidence was linearly associated with somatic symptom scores among men, but not among women. In addition, poorer inflammation control tended to be associated with increased somatic symptoms among women, but not among men. These sexual dimorphisms in obesity-related biological factors that contribute to depressive mood may offer insight into potentially differing pathophysiological processes underlying obesity-depression comorbidity between men and women.

Subgroup analysis indicated that BMI-depressive symptom associations tended to occur in women, but not in men, which generally aligns with the literature<sup>45</sup>. It is well-recognized that harsher social attitudes toward obesity and stronger weight biases exist toward women<sup>6</sup>, which may intensify feelings of guilt and worthlessness (i.e. cognitive-affective symptoms), and that depressed women may report somatic symptoms (e.g., fatigue and sleep

disturbance) with greater frequency and intensity than depressed men<sup>46</sup>. Somatic, or “atypical,” symptoms of depression predict future MetS<sup>47</sup> across sexes, which aligns with our cross-sectional findings, though prior studies investigating sex effects have been inconclusive. Of note, the MetS-somatic symptom relationship observed here controlled for obesity, highlighting the role of cardiometabolic pathophysiology beyond adiposity in depressive symptomatology.

The biological mechanisms linking MetS and depression are complex. Neuroendocrine regulators of energy metabolism, specifically leptin and insulin, have been associated with atypical depression<sup>48</sup>. Here, neither was associated with somatic symptoms, though obesity-leptin associations were stronger among men than women, despite higher leptin levels among women at any given BMI. Our findings somewhat differ from a prior study that reported both stronger obesity-leptin relationships and greater leptin levels among women<sup>49</sup>. Leptin had previously been shown to predict depression onset among men<sup>50</sup> and may exert these effects via leptin receptors within corticolimbic neuronal pathways or by modulating the hypothalamic-pituitary-adrenal axis. Multiple studies have reported longitudinal associations between insulin resistance or type 2 diabetes and depression<sup>51</sup>, and vice versa in both sexes, but have focused on clinical populations rather than depressive symptoms in non-clinical populations. Nevertheless, the moderating effect of sex on the MetS-depressive symptom association suggests distinct pathophysiological differences between women and men, warranting further mechanistic investigations and consideration of sex in future studies of the MetS-depression link.

We observed that impaired monocyte inflammation control by  $\beta$ -agonist was correlated with somatic depressive symptomatology and obesity. An emerging literature indicates that inflammation plays a key role in the development of neuropsychiatric comorbidities in obesity<sup>12</sup>. Specifically, monocytes have been implicated in relation to pro-inflammatory signals originating from the periphery and disrupting neuronal homeostasis. For instance, in diet-induced obesity, monocytes are recruited into adipose tissue and adopt an M1 macrophage phenotype characterized by heightened TNF- $\alpha$  secretion<sup>52</sup>. TNF- $\alpha$  then communicates with the brain in part by stimulating the hypothalamic-pituitary-adrenal axis, decreasing central serotonin levels, and activating microglial cells, all of which have been implicated in depression. In addition, transmigration of peripheral, pro-inflammatory monocytes into the brain has been associated with depressive behavior in rodent models<sup>53</sup>. Monocyte migration is driven by adrenergic signals from the sympathetic nervous system, which tends to be hyperactive in depression<sup>54</sup>. Sympathetic activity was not assessed in this study, though the observed trend between reduced monocyte sensitivity to  $\beta$ -agonist and higher depressive symptoms likely reflect a compensatory downregulation of  $\beta$ -AR signaling secondary to autonomic imbalance. Interestingly, gene transcriptional data suggest that chronic stress alters  $\beta$ -AR-mediated signaling pathways in monocytes and increases pro-inflammatory monocyte subsets<sup>55</sup>. Further studies are needed to examine whether such alterations lead to functional differences in inflammation regulation and immunity, and whether they are associated with depressive symptoms.

Although sex did not moderate inflammation-depressive symptom associations, subgroup analyses revealed that reduced BARIC among women, but not men, tended to be associated

with increased somatic symptomatology. An emerging literature suggests female-specific sensitivity to immune activation on mood and cognitive disturbances<sup>21</sup>. Our findings support this hypothesis and provide initial evidence that women may be more vulnerable to somatic symptoms in the context of obesity-associated inflammation. While animal studies suggest that estrogens may be protective against inflammation<sup>56</sup>, we did not find that somatic symptoms were related to estradiol levels in blood plasma. However, clinical investigations into the protective effects of sex hormones in inflammation-mood relationships are warranted. It has been hypothesized that female-specific vulnerabilities to the cognitive-behavioral effects of inflammation reflect an evolutionary trade-off: women of reproductive age may have benefitted from enhanced healing and pathogen exposure avoidance afforded by depressed mood during infection, at the expense of increased depressive disorders in contemporary, pro-inflammatory contexts<sup>57</sup>. Together with the trend toward stronger effects of obesity on depressive symptoms among women, this hypothesis highlights a potentially multifaceted inflammation-depression relationship in women.

Treating depression in obese individuals poses unique challenges, such as poorer antidepressant responses and more severe symptomatology<sup>3</sup>. Thus, pharmacological interventions have begun to target inflammatory and cardiometabolic pathways as therapeutic adjuvants to psychotherapy or conventional pharmacotherapy. Unlike cognitive-behavioral therapy or selective serotonin reuptake inhibitor treatment, such interventions would require detection of cardiometabolic dysfunction or inflammation to prescribe the appropriate adjuvant, with consideration of patient sex, as our findings support. A review of randomized controlled trials, investigating depression interventions for adults with diabetes<sup>58</sup>, found that pharmacological antidepressant treatment improved both depressive symptoms and glycemic control, whereas psychological treatment alone did not affect glycemic outcomes. Recent work suggests that MetS may be a stronger predictor of depression prognosis than obesity or diet<sup>59</sup>. Our results indicate that this may be particularly pertinent to obese men. Therefore, targeting cardiometabolic pathways in obese persons with depression may optimize treatment outcomes. To that end, insulin sensitization using a peroxisome proliferator-activated receptor gamma (PPAR- $\gamma$ ) agonist significantly improved depressive symptoms in patients with comorbid insulin resistance<sup>60</sup>. Integrative behavioral approaches to treat comorbid depression are also being explored, which involve coordinated strategies that address cognitive, behavioral, and weight management goals. Meta-analyses indicate that adherence to a Mediterranean diet is associated with decreased risk for MetS and incident depression<sup>61</sup>, and thus may be a particularly effective intervention for depressed individuals who satisfy MetS criteria. Lastly, recent studies suggest that gut microbial composition is altered in both obesity and depression, and that treatment with probiotic or prebiotic compounds produces anti-obesogenic and anti-inflammatory effects, leading to improvements in depressive-like behavior in rodent models<sup>62</sup>.

There are a handful of limitations in the current study. Firstly, the cross-sectional nature of the design limits causal interpretation of the associations among obesity, depression, cardiometabolic dysfunction, and inflammation. Second, we did not recruit individuals with clinical depression or cardiometabolic disease, but rather a medically healthy population of adults with a wide range of depressive symptoms and obesity/adiposity. Therefore, our findings cannot be directly extrapolated into populations with comorbid clinical depression.

However, our findings do translate to subclinical mood disturbances that are likely a significant barrier to adopting healthy behavior in combating obesity, which bears meaningful public health implications. Subclinical symptomatology often results in significant functional difficulties, exerts a negative impact on quality of life, and poses an increased risk for later development of major depression and other psychiatric conditions<sup>63</sup>. Another limitation is that sex-specific manifestations of depressed mood may not be captured by the BDI, though a recent review of sex differences in obesity-depression associations reported that stronger associations among women were not likely due to depression measurement methods<sup>45</sup>. We also acknowledge the possibility that, while sufficient to detect main effects, the study's sample size may have limited statistical power to detect moderation (i.e., interaction) effects of sex. Our sex-stratified findings, while adjusted for multiple comparisons, should therefore be interpreted as differences in significance within men versus women, rather than significant differences between the sexes. Finally, somatic complaints in otherwise healthy populations may reflect impairments concurrent with undetected or otherwise undiagnosed medical illnesses, rather than depression per se. Importantly, however, participants in the present study were thoroughly screened and excluded if they had a history of cardiovascular disease, were stage 2 hypertensive, or had abnormal blood cell profiles.

In conclusion, results from the present study indicate that obesity-related inflammation and cardiometabolic dysregulation may have sex-specific effects on somatic depressive symptoms in a non-clinical population. Although the pathophysiological mechanisms underlying sex differences in these associations remain to be elucidated, our findings highlight the continued need to consider sex as a key biological variable in these relationships. Future clinical studies on comorbid obesity and depression should therefore take sex into account, which will potentially optimize therapeutic strategies to treat these conditions.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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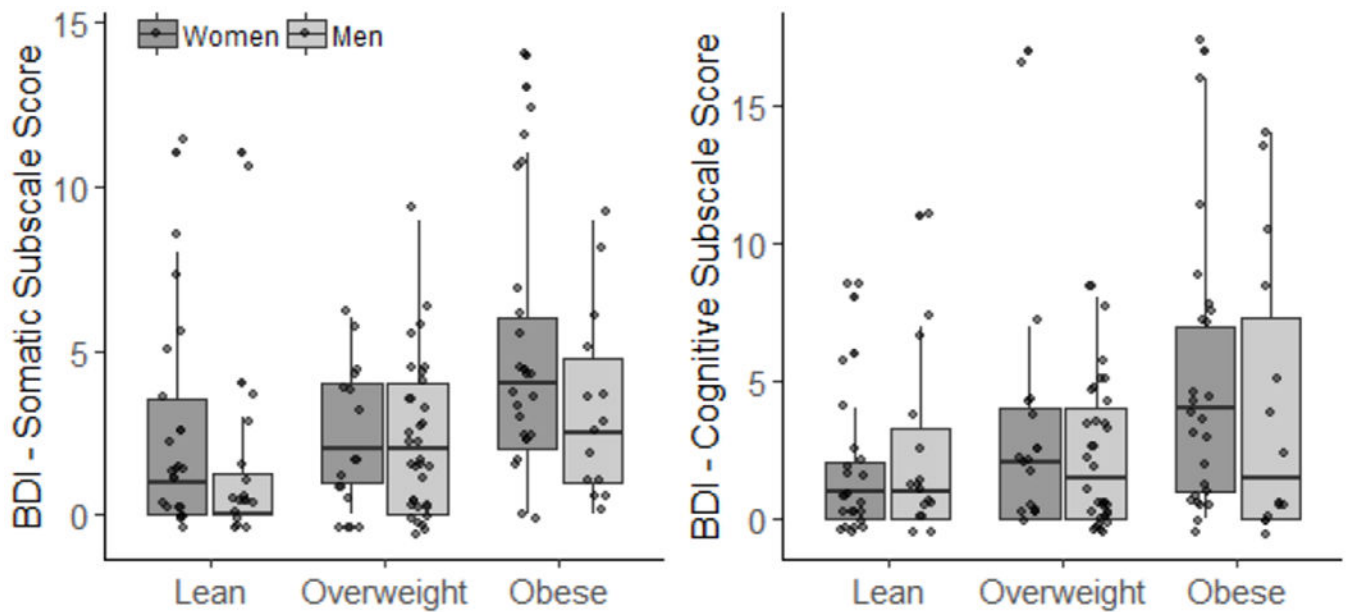
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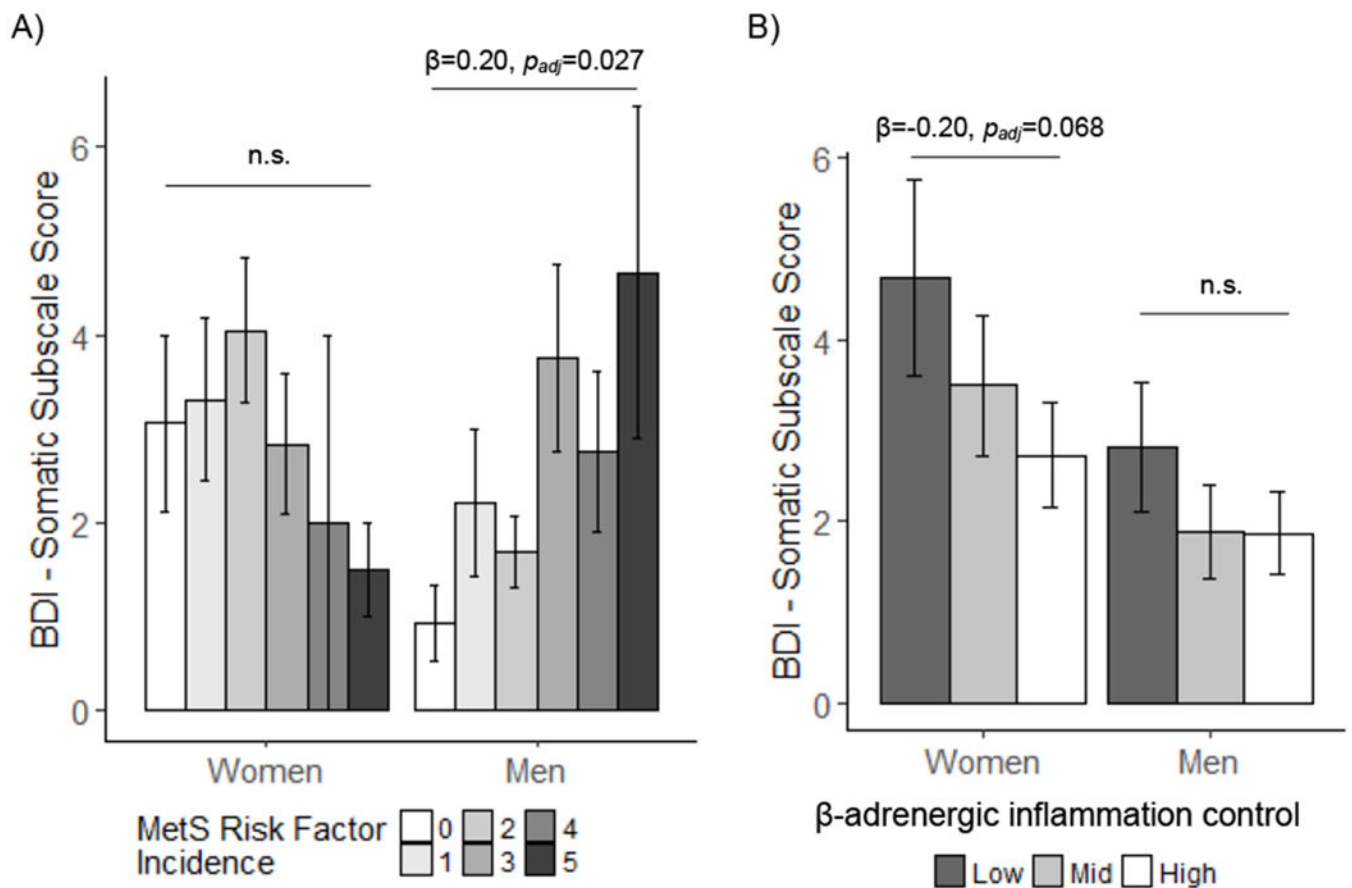
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**Figure 1. Somatic and cognitive depressive symptoms according to BMI category and sex.** Subject-wise data are shown overlaid onto box-and-whisker plots grouped by BMI category and sex. Subgroup analysis by sex (ANOVA) indicated that depressive symptoms tended to be elevated with increasing BMI in women (left panel, somatic:  $F_{2,58}=3.63$ ,  $p_{adj}=0.06$ ; right panel, cognitive-affective:  $F_{2,58}=3.51$ ,  $p_{adj}=0.073$ ), but not in men ( $p_{adj} 0.10$ ). In particular, linear regression revealed that obese women reported more depressive symptoms than lean women (BDI-S:  $\beta=0.59$ ,  $t=2.48$ ,  $p_{adj}=0.048$ ; BDI-C:  $\beta=0.68$ ,  $t=2.65$ ,  $p_{adj}=0.032$ ). BDI scores were log-transformed for normality. Points were jittered to minimize overplotting. P-values adjusted for multiple comparisons using Hommel's family-wise error rate correction. Abbreviations: BMI=body mass index; BDI-S=Beck Depression Inventory somatic subscale score; BDI-C=Beck Depression Inventory cognitive/affective subscale score.



**Figure 2. Somatic depressive symptoms according to sex, MetS risk factor incidence, and inflammation control.**

(A) BDI somatic subscale scores grouped by sex, presenting with MetS risk factors. (B) BDI somatic subscale scores grouped by sex, according to BARIC, split by tertile for visualization purposes. Beta values shown derive from multivariate linear regression performed on log-transformed BDI-S scores, covarying for age, ethnicity, and BMI category. Data are presented as mean  $\pm$  s.e.m. *P*-values adjusted ( $p_{adj}$ ) using Hommel's family-wise error rate correction. Abbreviations: BMI=body mass index; BDI=Beck Depression Inventory; MetS=Metabolic syndrome; BDI-S=Beck Depression Inventory somatic subscale score; BARIC=Beta-adrenergic receptor-mediated inflammation control; n.s.=not significant at  $p_{adj}<0.05$ .

**Table 1.**

Sex- and obesity category-based differences in anthropometric, cardiometabolic, depressive, and immune characteristics of 129 study participants.

	Men			Women			$F_{\text{sex}}$	$F_{\text{BMI}}$	$F_{\text{sex} \times \text{BMI}}$
	Lean N = 16	Overweight N = 34	Obese N = 14	Lean N = 23	Overweight N = 17	Obese N = 25			
Age (yrs)	35.9 ± 3.6	43.3 ± 2.0	40.4 ± 2.2	32.1 ± 2.1	41.1 ± 3.2	38.6 ± 2.4	1.01	<b>5.67</b>	0.17
Waist (cm)	81.2 ± 1.7	97.4 ± 1.5	121.3 ± 3.5	78.9 ± 2.1	90.4 ± 2.5	107.9 ± 2.2	<b>14.1<sup>a</sup></b>	<b>97.6<sup>c,d</sup></b>	<b>3.41</b>
Waist-hip ratio	0.85 ± 0.01	0.94 ± 0.01	1.01 ± 0.01	0.86 ± 0.02	0.87 ± 0.02	0.88 ± 0.01	<b>13.7<sup>a</sup></b>	<b>7.29<sup>c,d</sup></b>	<b>5.01</b>
Insulin (pg/mL)	167 ± 23	297 ± 32	785 ± 146	171 ± 19	219 ± 32	516 ± 88	1.35	<b>31.8<sup>c,d</sup></b>	1.47
Leptin (ng/L)	1.5 ± 0.3	6.6 ± 1.4	26.0 ± 7.1	10.2 ± 1.9	22.1 ± 3.4	50.2 ± 5.8	<b>87.0<sup>b</sup></b>	<b>43.2<sup>c,d</sup></b>	<b>3.14</b>
Glucose (mg/dL)	83.3 ± 1.7	85.9 ± 2.7	87.8 ± 4.5	74.1 ± 2.0	87.2 ± 6.4	81.1 ± 2.0	2.84	2.28	1.32
HOMA-IR	0.9 ± 0.1	1.6 ± 0.2	4.1 ± 0.9	0.8 ± 0.1	1.1 ± 0.2	2.6 ± 0.5	1.19	<b>25.8<sup>c,d</sup></b>	0.90
TG (mg/dL)	98.6 ± 10.8	165 ± 35.3	117 ± 12.8	75.4 ± 10.2	88.4 ± 14.1	120 ± 13.0	<b>8.46<sup>a</sup></b>	<b>9.63<sup>d</sup></b>	1.98
LDL (mg/dL)	104 ± 7.8	108 ± 4.9	127 ± 10.7	87.6 ± 6.4	115 ± 7.9	115 ± 4.8	0.38	<b>5.15</b>	1.61
HDL (mg/dL)	58.9 ± 4.1	52.4 ± 3.3	43.3 ± 2.1	69.9 ± 4.1	57.9 ± 2.7	54.0 ± 3.1	<b>6.99<sup>b</sup></b>	<b>8.42<sup>c</sup></b>	0.53
Systolic BP (mmHg)	120 ± 3.3	121 ± 2.4	130 ± 2.4	103 ± 2.2	117 ± 3.6	120 ± 3.5	<b>12.2<sup>a</sup></b>	<b>6.68</b>	1.73
Diastolic BP (mmHg)	72.1 ± 2.4	71.0 ± 1.4	76.4 ± 2.1	63.4 ± 1.6	70.6 ± 2.2	72.4 ± 2.3	3.79	<b>3.74</b>	2.04
Estradiol	-	-	-	161 ± 17	118 ± 18	138 ± 10	-	1.10	-
BDI-T	3.8 ± 1.4	4.6 ± 0.7	7.3 ± 2.0	4.1 ± 1.0	5.2 ± 1.4	9.5 ± 1.6	3.01	<b>5.13</b>	0.16
BDI-S	1.4 ± 0.7	2.2 ± 0.4	3.2 ± 0.8	2.4 ± 0.6	2.3 ± 0.5	4.9 ± 0.8	<b>5.59<sup>b</sup></b>	<b>6.13<sup>c</sup></b>	0.56
BDI-C	2.4 ± 0.8	2.4 ± 0.5	4.1 ± 1.4	1.7 ± 0.5	2.9 ± 1.0	4.6 ± 0.9	0.64	<b>3.30</b>	0.56
MetS criteria met	0.75 ± 0.3	1.8 ± 0.2	2.8 ± 0.3	0.63 ± 0.1	1.3 ± 0.2	2.3 ± 0.3	0.92	<b>24.1<sup>c,d</sup></b>	0.54
BARIC	32.0 ± 2.1	28.9 ± 1.6	26.6 ± 2.3	34.4 ± 2.1	31.6 ± 2.2	29.8 ± 2.0	2.12	1.16	0.12

Values presented as mean ± s.e.m. Bold values signify ANOVA  $F$ -ratio at  $p < 0.05$ . Superscripts denote post-hoc  $t$ -test of predictor coefficient significance at  $p < 0.05$ :

<sup>a</sup>Men > women.

<sup>b</sup>Women > men.

<sup>c</sup>Obese significantly different than lean.

<sup>d</sup>Overweight significantly different than lean. Age and ethnicity included as covariates in all models.

Abbreviations: BMI=body mass index; TG=triglycerides; LDL=low density lipoprotein; HDL=high density lipoprotein; BP=blood pressure; BDI-T=Beck Depression Inventory total score; BDI-S=Beck Depression Inventory somatic subscale score; BDI-C=Beck Depression Inventory cognitive/affective subscale score; MetS=Metabolic syndrome; BARIC=Beta-adrenergic receptor-mediated inflammation control.

**Table 2.**

Contribution of sex, MetS factor incidence, and  $\beta$ -adrenergic inflammation control (BARIC) to somatic depressive symptoms (BDI somatic subscale score).

Dependent Variable	Sex	Predictors	$\beta$	SE	<i>t</i>
BDI Somatic Subscale Score	All participants	BMI (overweight)	0.20	0.18	1.15
		BMI (obese)	0.63	0.22	2.87**
		Sex	0.65	0.21	3.11**
		MetS	0.15	0.07	2.07*
		Sex $\times$ MetS	-0.24	0.10	-2.34*
	Women	BMI (overweight)	0.16	0.26	0.63
		BMI (obese)	0.80	0.30	2.69**
		MetS	-0.11	0.10	-1.16
	Men	BMI (overweight)	0.14	0.24	0.58
		BMI (obese)	0.24	0.33	0.71
MetS		0.20	0.08	2.55*	
BDI Somatic Subscale Score	All participants	BMI (overweight)	0.14	0.18	0.81
		BMI (obese)	0.61	0.19	3.24**
		Sex	0.36	0.14	2.56*
		BARIC	-0.07	0.11	-0.63
		Sex $\times$ BARIC	-0.12	0.14	-0.87
	Women	BMI (overweight)	0.04	0.25	0.17
		BMI (obese)	0.55	0.24	2.32*
		BARIC	-0.20	0.09	-2.18 <sup>#</sup>
	Men	BMI (overweight)	0.26	0.26	1.02
		BMI (obese)	0.67	0.31	2.16 <sup>#</sup>
BARIC		-0.05	0.11	-0.44	

Significance of predictors within each linear regression model at

\*\*  $p < 0.01$ ,

\*  $p < 0.05$ ,

<sup>#</sup>  $p < 0.10$  is shown in the table.

*P*-values in sex subgroup models were adjusted for family-wise error rate correction using Hommel's method. Age and ethnicity were included as covariates in all models. Analyses performed using log-transformed BDI scores. Abbreviations: BMI=body mass index; BDI=Beck Depression Inventory; MetS=Metabolic syndrome; BARIC=Beta-adrenergic receptor-mediated inflammation control.