Distribution Agreement

In presenting this thesis as a partial fulfillment of the requirements for a degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis in whole or in part in all forms of media, now or hereafter know, including display on the World Wide Web. I understand that I may select some access restrictions as part of the online submission of this thesis. I retain all ownership rights to the copyright of the thesis. I also retain the right to use in future works (such as articles or books) all or part of this thesis.

Shaylan Hill March 28, 2021

The Effects of Posttraumatic Stress Disorder, Major Depressive Disorder, and Emotion Dysregulation Symptom severity on Insulin response in African American Women with Type 2 Diabetes Mellitus

by

Shaylan Hill

Vasiliki Michopoulos, PhD.
Adviser

Neuroscience and Behavioral Biology

Vasiliki Michopoulos, PhD.
Adviser

Charles Gillespie, MD, PhD.
Committee Member

Paul Lennard, PhD.
Committee Member

2021

The Effects of Posttraumatic Stress Disorder, Major Depressive Disorder, and Emotion Dysregulation Symptom severity on Insulin response in African American Women with Type 2 Diabetes Mellitus

By

Shaylan Hill

Vasiliki Michopoulos, PhD.
Adviser

An abstract of
a thesis submitted to the Faculty of Emory College of Arts and Sciences
of Emory University in partial fulfillment
of the requirements of the degree of
Bachelor of Science with Honors

Neuroscience and Behavioral Biology

2021

Abstract

The Effects of Posttraumatic Stress Disorder, Major Depressive Disorder, and Emotion Dysregulation Symptom Severity on Insulin Response in African American Women with Type 2 Diabetes Mellitus

By Shaylan Hill

Background: Type 2 Diabetes Mellitus disproportionately affects African American women, as they are twice as likely to have T2DM compared to Caucasian women. T2DM is highly comorbid with psychiatric disorders like post-traumatic stress disorder (PTSD), major depressive disorder (MDD), and emotion dysregulation (ED). Additionally, urban dwelling women of color experience higher rates of trauma exposure, MDD, and PTSD compared to the general population.

Objective: To determine whether symptoms of PTSD, MDD, and ED are predictive of altered glucose homeostasis and elevated insulin resistance in urban dwelling, African American women with T2DM.

Methods: The present study utilized a cross-sectional design in which participants were recruited from the diabetic clinic Grady Memorial Hospital. Participants came in a fasted state to the laboratory for baseline blood draws, a clinical assessment, and the 2-hour Oral Glucose Tolerance Test (OGTT). PTSD, MDD, and ED symptoms were assessed through the Modified PTSD Symptom Scale (MPSS), Beck Depression Inventory-II (BDI), and Difficulties in Emotion Regulation Scale (DERS) questionnaires, respectively. Area under the curve measures were obtained from the OGTT and used in the assessment of insulin and glucose homeostasis.

Results: More severe symptoms of PTSD, MDD, and ED were all associated with lower insulin sensitivity and higher blood glucose levels. Compared to other symptoms, depressive symptoms were most predictive of dampened insulin sensitivity, while ED symptoms were most predictive of heightened plasma glucose.

Conclusion: Symptoms of PTSD, MDD, and ED were all predictive of reduced insulin sensitivity and increased blood glucose in women with T2DM, which is indicative of heightened insulin resistance. These findings suggest that glucose regulation is highly related to the symptom severity of PTSD, MDD, and ED in women with T2DM and may inform future therapeutic avenues.

The Effects of Posttraumatic Stress Disorder, Major Depressive Disorder, and Emotion Dysregulation Symptom Severity on Insulin Response in African American Women with Type 2 Diabetes Mellitus

By

Shaylan Hill

Dr. Vasiliki Michopoulos

Adviser

A thesis submitted to the Faculty of Emory College of Arts and Sciences
of Emory University in partial fulfillment
of the requirements of the degree of
Bachelor of Science with Honors

Neuroscience and Behavioral Biology

2021

Acknowledgements

I would like to thank Dr. Vasiliki Michopoulos for her unwavering support and guidance throughout both this project as well as my experience with the Grady Trauma Project. I would also like to thank Dr. Charles Gillespie for providing his data and expertise for this project.

Table of Contents

1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic condition characterized by reduced insulin sensitivity and elevated levels of blood glucose. Worldwide, the prevalence of T2DM and its accompanying healthcare spending has risen over recent decades and continues to rise (Roden & Shulman, 2019). In 2017 alone, global healthcare expenditure related to T2DM was $850 billion, and is expected to reach $958 billion by 2045 (Cho, 2018). In the United States, T2DM is a leading cause of morbidity and mortality and accounts for 90 to 95% of all diabetes cases (CDC, 2020). African American women are disproportionately affected by T2DM, as they are almost twice as likely to have T2DM compared to Caucasian women (CDC, 2017). There is not yet a clear explanation for this health disparity, but modern lifestyle factors, socioeconomic status, genetics, and environmental interactions may play a role (Galicia-Garcia, 2020).

Two key factors contribute to the pathogenesis of T2DM: insufficient insulin secretion by pancreatic β-cells, and inability for insulin-sensitive tissues to respond to insulin (Galicia-Garcia, 2020; Roden & Shulman, 2019). The synthesis and release of insulin are essential for maintaining glucose homeostasis, and alterations in related mechanisms can lead to metabolic imbalances that increase risk for the development of T2DM. As T2DM progresses, insulin secretion becomes insufficient to maintain glucose homeostasis, leading to elevated blood glucose, or hyperglycemia (Galicia-Garcia, 2020). Clinically, T2DM is primarily characterized by obesity and excess body fat, especially in the abdominal region. This excess adiposity may lead to insulin resistance (IR), a known precursor of T2DM that is characterized by a reduction in the metabolic response of insulin-responsive cells, or a reduced response in blood glucose levels to circulating insulin (Nasca et al., 2019; Czech, 2017).

T2DM is highly comorbid with psychiatric disorders such as post-traumatic stress disorder (PTSD) and major depressive disorder (MDD). African Americans living in urban environments often experience extreme amounts of trauma with a high exposure occurring during youth (Alim, Charney, and Melman, 2006). Because emotional development begins early in life, upbringing in a harmful or unsupportive environment confers higher risk of developing emotional regulation deficits (i.e., emotional dysregulation) in adolescence and adulthood (Kim, 2010; Powers, 2016). This relationship produces a higher risk for psychological disorders like PTSD and MDD, as well as risk for adverse physiological conditions such as chronic inflammation (Powers, 2016).

PTSD is a severe, debilitating psychiatric disorder that occurs following exposure to a traumatic event (American Psychological Association, 2013). PTSD is heterogenous with a diverse symptom profile that includes reexperiencing, avoidance/numbing, hyperarousal, and negative changes in cognition and mood (Kessler, 1995). Epidemiological data indicate that approximately 70% of the general population will experience a traumatic event in their lifetime, and of those, around 7% will subsequently develop PTSD (Keane, 2009). However, higher rates of PTSD are seen in combat veterans (30.9% lifetime prevalence) (Dohrenwend, 2006) and in civilians residing in areas with high levels of violence (17.1% lifetime prevalence) (Breslau, 1991; Gillespie, 2009; Goldmann, 2011). Physiologically, individuals with PTSD have exhibited a hyperinsulinemic response to an oral glucose tolerance challenge, suggesting heightened insulin resistance (Rao, 2014). Moreover, data from a recently conducted longitudinal study indicates an association between the presence of PTSD and increased risk of developing T2DM in traumatized women (Roberts et al., 2015).

PTSD is often comorbid with MDD (Kessler, 1995), a mental disorder characterized by at least one depressive episode lasting at least two weeks comprised of explicit changes in mood, interests, cognition, and/or vegetative functions (Otte et al., 2016). Globally, MDD affects approximately 6% of the adult population (Seedat et al., 2009), and occurs twice as often in women than in men (Otte et al., 2016; Bromet et al., 2011). Clinically, symptoms of MDD include anhedonia (i.e., depressed mood) combined with at least three to four additional symptoms of altered appetite, disturbed sleep, inappropriate feelings of guilt, impaired concentration, psychomotor changes, or suicidal thoughts (APA, 2014). MDD is often comorbid with IR and is associated with increased risk for the development of T2DM (Nasca et al., 2019).

Another important factor that may confer risk for altered glucose homeostasis is emotion dysregulation, a transdiagnostic feature of PTSD, MDD, and other psychiatric disorders (Bradley et al., 2011a). Emotion regulation is the process in which individuals control the emotions they have, as well as the timing, subjective experience, and expression of such emotions (Gross, 1998b). This multidimensional process plays a crucial role in sustaining healthy physiological functioning (Gross & Muñoz, 1995). Conversely, emotion dysregulation (ED) is characterized by deficits in awareness and acceptance of emotions, maintenance of goal-directed behavior in intense negative emotional states, and the utilization of efficacious emotion regulation strategies (Gratz & Roemer, 2004).

Consequently, the present study aims to better understand the physiological mechanisms through which PTSD, MDD, and ED contribute to T2DM by assessing the relationship between symptom profile and insulin response to a glucose metabolic stressor over the course of a 2-hour oral glucose tolerance test (OGTT). The OGTT is widely used in clinical settings and has been the primary method of diagnosing prediabetes and T2DM for several decades (Jagannathan,

2020; Fra, 2010). Plasma glucose and insulin responses during the 2-hour OGTT reflect the ability of pancreatic beta-cells to secrete insulin as well as the sensitivity of tissues to insulin (DeFronzo, 1998; Matsuda & DeFronzo, 1999). Plasma glucose levels during the OGTT are dependent on both insulin sensitivity and secretion (Fra, 2010), and each are measured by Area Under the Curve (AUC) in the present study.

Importantly, the relationship between psychopathology symptoms and metabolic dysfunction will be examined in a sample of urban dwelling, African American women with T2DM. The current study sample represents a particularly relevant study population as urban minority women experience particularly high levels of interpersonal trauma exposure, as well as elevated rates of PTSD and MDD compared to the general population. Studying this population will contribute to a more robust understanding of the psychological factors that contribute to stress-and trauma-related pathologies, as well as metabolic dysfunction through the structured participant interviews. I hypothesized that elevated symptoms of PTSD, MDD, and ED will be associated with altered glucose metabolism and a dampened insulin response to a glucose challenge in African American women with T2DM.

2. Methods

2.1 Participants and Study Components

Study participants were recruited from the diabetic clinic at Grady Memorial Hospital, a publicly funded hospital in Atlanta, GA from 2012-2017. For recruitment, participants were approached by trained study staff in the waiting room of the clinic where written and verbal informed consent was obtained for all subjects. Exclusion criteria included developmental delay, bipolar or psychotic disorder, treatment for an autoimmune disorder, cancer, or HIV, treatment with prescription oral non-steroidal anti-inflammatory, corticosteroid, anticonvulsant (other than gabapentin), antipsychotic drugs, or benzodiazepine class pharmaceuticals. Participants had to be between the ages of 18 and 65 and able to provide informed consent. Participants were asked to come into the laboratory in a fasted state for baseline blood draws, a clinical assessment, and the OGTT. The OGTT and time-point blood draws were performed during the structured clinical interview. T2DM status for each participant was determined from electronic medical records, and BMI was assessed by a clinician as opposed to self-report. The Emory Institutional Review Board and the Research Oversight Committee of Grady Memorial Hospital, Atlanta, GA approved all study procedures.

2.2 Measures Collected During Structured Clinical Interview

2.2.1 Demographics

The demographics questionnaire assesses participant age, relationship status, education level, household monthly income, employment, and diabetes treatment status (Gillespie, 2009).

2.2.2 Difficulties in Emotion Regulation Scale (DERS)

The DERS is a psychometrically validated 36-item self-report measure of emotion regulation difficulties that has six subscales: Non-acceptance, Goals, Impulse, Awareness, Strategies, and Clarity (Gratz and Roemer, 2004). It measures various aspects of emotion regulation such as awareness and understanding of one's emotions, acceptance of negative emotions, ability to successfully engage in goal-directed behavior and control impulse behavior when experiencing negative emotions, and the ability to use situationally appropriate emotion regulation strategies (Powers, 2016).

2.2.3 Beck Depression Inventory-II (BDI-II)

The BDI is a 21-item assessment of current symptoms of depression. This assessment is able to generate a continuous measure of depression symptoms as well as a categorical diagnosis of current depression (Beck, 1961).

2.2.4 The Modified PTSD Symptom Scale (MPSS)

The MPSS is a psychometrically validated 17-item self-report measure that evaluates PTSD symptoms over the previous 2 weeks (Falsetti, 1993). From this, a continuous measure of symptom severity can be obtained, ranging from 0 to 51 using the summed MPSS frequency items. A categorical diagnosis of PTSD is also determined by the MPSS. Symptom subclusters include hyperarousal, avoidance/numbing, and intrusive behaviors.

2.3 OGTT Protocol, blood sample collection, processing, and biomarker assays

2.3.1 Oral Glucose Tolerance Test (OGTT)

During the OGTT, blood samples were obtained at 0, 15, 30, 60, 90, and 120 minutes after oral administration of a 75-gram glucose solution, which had to be consumed in less than 5 minutes. Blood samples were used to measure plasma glucose and insulin. Area under the curve ground (AUCg) and area under the curve with respect to increase (AUC_I) will be calculated to quantify the total secretion of plasma glucose and insulin over the two-hour OGTT, and to assess glucose homeostasis and insulin sensitivity (Pruessner, 2003).

2.3.2 Area Under the Curve (AUC)

Area Under the Curve (AUC) is a commonly used in endocrinological and neuroscience to identify changes in time-dependent variables and potential associations between repeated measures over time with other variables (Pruessner et al., 2003). In the case of this study, AUC is used to record changes in insulin and glucose over the 2-hour OGTT. There are two formulas, derived from the trapezoid formula, used to derive different information from the same repeated measurements: Area Under the Curve with respect to ground (AUC_G), and Area Under the Curve with respect to increase (AUC_I) (Pruessner et al., 2003).

2.3.3 Area Under the Curve with respect to ground (AUC_G)

AUC_G is calculated in reference to zero (i.e., 'ground'), accounting for the total area under the curve of all measurements. For endocrinological or metabolic data like insulin and glucose measures, AUC_G is a measure that is related to the total hormonal output of the system (Fekedulegn et al., 2007).

2.3.4 Area Under the Curve with respect to increase (AUC_I)

AUC_I is calculated in reference to the baseline measurement and ignores the distance from zero for all measurements, thus emphasizing changes over time. AUC_I is a parameter that is related to the sensitivity of the system (Pruessner et al., 2003).

2.3.5 Glucose

Measurements of plasma glucose (mg/dL) samples were obtained from fasting blood samples at baseline and during the OGTT. Samples were stored at -80° C until the time of assay. Glucose is measured on the Beckman AU480 using reagents from Beckman Coulter in Fullerton, CA.

2.3.6 Insulin

Serum insulin measurements (μIU/mL) were obtained from fasting blood samples and throughout the OGTT. Insulin concentrations were measured by immunoturbidometric methods on the Beckman AU480 using reagents from Sekisui Diagnostics in Exton, PA.

2.3.7 Hemoglobin A1c (HbA1c)

Whole blood samples stored at -80° C until assay. HbA1C was measured using high performance liquid chromatography by ARUP laboratories (Salt Lake City, Utah).

2.3.8 Highly Sensitive CRP (hsCRP)

Serum samples were stored at -80° C until the time of the hsCRP (mg/L) assay. Serum concentrations of hsCRP were obtained using immunoturbidometric methods on the Beckman AU480 using reagents from Sekisui Diagnostics (Lexington, MA). This analyzer has an

interassay coefficient of variation (CV) of 5.2% and intra-assay CV of 3.1% (Powers et al., 2016).

2.4 Statistical Analysis

Descriptive statistics and frequencies were used to summarize demographic, metabolic, and psychiatric characteristics of study participants. The primary study objective was to assess the potential relationship between PTSD, MDD, and ED symptoms and altered glucose homeostasis. AUC measures were used as a proxy for metabolic output and insulin sensitivity in response to the OGTT. Relationships between psychiatric symptom and subcluster scores and AUC measures were assessed using Pearson's r correlations and linear regression. A stepwise linear regression was performed to determine which symptoms were the most robust predictors of altered glucose homeostasis. The stepwise regression was performed controlling for diabetes treatment and BMI. BMI is linked to both altered glucose homeostasis and insulin sensitivity (Kahn and Flier, 2000), as well as with major depression in women (Li et al., 2017; Stunkard, 2003). Additionally, the presence of PTSD symptoms has been associated with increased risk of weight gain and obesity in women (Kubzansky, 2014). Diabetes treatment is linked with improved glucose homeostasis in individuals with T2DM. All data are presented as mean ± standard error of the mean (SEM). All analyses were conducted with RStudio version 3.5.2 and SPSS 26 software package, and a $P \leq 0.05$ was considered statistically significant.

3. Results

3.1 Demographic and metabolic descriptive statistics

Table 1 provides a summary of the demographics of the study sample. The mean age of study participants was 51 ± 0.05 years. Regarding education status, 26.2% (n = 27) of participants listed 12th grade as the highest level of education obtained, with 23.3% (n = 24) of participants having graduated from technical school or college. The majority of study participants (n = 74, 71.8%) were unemployed at the time of enrollment. The majority of our sample was also of low socioeconomic status, with 80.2% (n = 81) of participants having a mean monthly income below $2000.

Table 2 outlines the metabolic profile of the study sample. With regards to diabetes treatment, 95% (n = 95) of participants were being treated for T2DM at the time of the assessment, with the remaining 5% receiving no diabetes treatment. The mean BMI of study participants was 36.3 ± 0.04. The mean hsCRP of the sample was 6.8 ± 0.04 mg/L and the mean A1c was 8.0 ± 0.01. The mean insulin AUC_I and AUC_G values were 2684± 18.0 and 6651 ± 21.8, respectively, and the mean glucose AUC_I and AUC_G values were 12763 ± 31.0 and 31960 ± 69.9, respectively.

3.2 Relationship between total PTSD, MDD, and ED symptom severity and OGTT AUC measures

Table 3 summarizes descriptive statistics for each symptom severity measure and their respective subclusters, and Pearson's r correlations for PTSD, MDD, and ED symptom scores by insulin and glucose AUC with respect to both increase and ground. Lower insulin AUC_I (r= -0.27, p = 0.01) and AUC_G (r = -0.24, p = 0.03) were associated with greater PTSD symptom

severity (Figure 1). Additionally, PTSD symptom severity was positively associated with glucose AUC_G (r =0.27, p = 0.01) but not AUC_I (r = 0.09, p = 0.40). Lower insulin AUC_I was associated with higher levels of emotion dysregulation (r= -0.25, p = 0.02; Figure 2). Greater glucose AUC_G was also associated with higher levels of emotion dysregulation (r = 0.26, p = 0.02; Figure 2). Furthermore, greater depressive symptoms were associated with a lower insulin AUC_I (r = -0.35, p = 0.0001; Figure 3) and greater glucose AUC_G (r = 0.26, p = 0.02; Figure 3).

3.2.1 Relationship between ED subcluster severity and OGTT AUC measures

Linear regressions were performed on AUC measures by each DERS symptom subcluster score: nonacceptance, goals, impulse, awareness, and strategies (Table 3). Lower insulin AUC_I was associated with greater impulse symptom severity (r = -0.26, p = 0.02). Greater glucose AUC_G was associated with more severe nonacceptance symptoms (r = 0.27, p = 0.02). Additionally, an increase in strategies symptom severity was associated with lower insulin AUC_I (r = -0.27, p = 0.02) and AUC_G (r = 0.27, p =0.04), and greater glucose AUC_G (r = 0.27, p = 0.02).

3.2.2 Relationship between PTSD symptom subcluster severity and OGTT AUC measures

Linear regressions were performed on AUC measures by each MPSS symptom subcluster score: intrusive, avoidance, and hyperarousal (Table 3). Lower insulin AUC_I was associated with increased intrusive (r = -0.22, p = 0.04), avoidance (r = -0.27, p = 0.01), and hyperarousal (r = -0.22, p = 0.04), symptom severity. Increased intrusive symptom severity was also associated with lower insulin AUC_G (r = -0.25, p = 0.02), and greater glucose AUC_G (r = 0.36, p = 0.0006).

3.3 Predictors of altered glucose and insulin response

Stepwise linear regression analyses revealed that depressive symptom severity ($\beta = -0.29$, $p = 0.01$) was the most robust predictor of dampened insulin response, indicated by a lower insulin AUC_I, while DERS and MPSS total scores did not play a significant role in altered insulin response ($p's > 0.3$). A second stepwise regression revealed that ED symptom severity ($\beta = 0.24$, $p = 0.04$) was the strongest predictor of elevated glucose levels, indicated by glucose AUC_G, while MDD and PTSD symptoms did not contribute to heightened glucose over the course of the OGTT ($p's > 0.65$).

4. Discussion

The present study examined the relationship between PTSD, MDD, and ED symptomatology and insulin and glucose homeostasis in African American women with T2DM. In support of our hypothesis, we found that elevated symptoms of PTSD, ED, and MDD are negatively associated with insulin sensitivity, as measured by insulin AUC_I, and thus positively associated with insulin resistance. Heightened PTSD, ED, and MDD symptoms were positively associated with total blood glucose levels, as measured by glucose AUC_G, also supportive of increased insulin resistance. These findings contribute to a growing body of literature on physical and psychiatric racial health disparities, particularly among Black women. Additionally, these findings may implicate symptom reduction in future treatment of comorbid T2DM. The high comorbidity of PTSD and MDD with cardiometabolic disorders like T2DM suggests common underlying biological mechanisms (Dixon et al.,2020) including dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and increased inflammation (Michopoulos, 2016).

4.1 Relationship between T2DM and MDD, PTSD, and ED symptom profiles and implications for treatment

PTSD is known to be associated with T2DM, and this relationship may be mediated by glucose dysregulation (Scherrer et al., 2019; Boyko et al., 2010; Boscarino, 2004). In the current study, we found that each PTSD symptom subtype (intrusive, avoidance, and hyperarousal) was predictive of decreased insulin sensitivity. Increased intrusive PTSD symptoms were also predictive of lower blood insulin and greater blood glucose levels, implicating intrusive symptoms as the most significant driver of the link between PTSD and glucose dysregulation. However, PTSD symptom severity (measured by MPSS total) was excluded from our stepwise

linear model as it was least predictive of dampened insulin sensitivity in the presence of emotion dysregulation and depressive symptoms.

In our first stepwise regression model, depressive symptoms were the dominant predictor of dampened insulin response, as measured by AUC_I. Though PTSD symptoms were excluded from this stepwise model, our subcluster-specific findings may have future treatment implications for comorbid PTSD and T2DM. As mentioned previously, participants with more severe intrusive PTSD symptoms have greater disruptions in glucose regulation. Intrusive symptoms of PTSD consist of recurrent, distressing memories of the traumatic event, flashbacks, upsetting dreams or nightmares of the traumatic event, or severe emotional or physical reactions to reminders of the traumatic event. Knowledge of this association between PTSD symptoms and glucose dysregulation potentially inform future PTSD treatment interventions. For example, one study by Scherrer et al. found that clinically meaningful reductions in PTSD symptoms, through either treatment or spontaneous improvement, are associated with a decreased risk for T2DM. Their additional exploratory analyses also suggested that symptoms of depression decreased in subjects who had a clinically meaningful improvements in PTSD symptom severity (Scherrer et al., 2019).

Previous research has demonstrated that MDD increases the risk for development of T2DM. Numerous prospective studies have shown that previous depression confers increased risk for T2DM incidence (Campayo et al., 2010; Kumari et al., 2004; Arroyo et al., 2003). For example, a longitudinal study of individuals ≥ 55 years revealed a 65% increased risk of T2DM in subjects with clinical MDD (Campayo et al., 2010). Additionally, a 10-year prospective study of civil servants aged 35-55 years by Kumari et al. demonstrated the association between depression and T2DM incidence as well as impairment on glucose tolerance tests. While these findings highlight

how MDD elevates risk for T2DM, further research supports the bidirectionality of the MDD-T2DM relationship. In a meta-analysis of 11 studies, researchers concluded that subjects with T2DM experienced a 24% increased risk of developing MDD compared to healthy controls (Nouwen et al., 2010). Similarly, our findings indicate that increased severity of depressive symptoms is associated with decreased insulin sensitivity, and increased blood glucose levels, suggestive of heightened insulin resistance.

As previously mentioned, ED is a transdiagnostic feature of PTSD and MDD and may confer lifetime risk for many psychiatric disorders (Bradley et al., 2011; Powers et al., 2016). We found that increased impulse and strategies symptom severity was associated with reduced insulin sensitivity, while strategies symptoms were also associated with a hyperinsulinemic response. Additionally, both nonacceptance and strategies symptoms were associated with increased blood glucose levels. In our second stepwise regression model, increased ED symptom severity alone was the most robust predictor of elevated levels of blood glucose (measured by AUC_G). Altogether, these findings are suggestive of elevated insulin resistance, and may have meaningful implications for comorbid T2DM.

Our results suggest that presence or development of emotion regulation strategies may reduce insulin resistance. Though causality cannot be addressed, previous research has suggested that improving one's ability to manage negative emotions (i.e., one's emotion regulation strategies) may be a useful focal point in the treatment of patients with comorbid psychopathology and T2DM (Powers et al., 2016). The development of emotion regulation strategies will help individuals to better manage both acute and chronic psychosocial stressors, possibly attenuating biological mechanisms underlying psychiatric-T2DM comorbidities such as allostatic load, HPA activity, and glucose dysregulation.

4.2 Biological mechanisms underlying psychiatric and metabolic comorbidities

The HPA axis is responsible for the body's stress response and generates glucocorticoids (e.g., cortisol) in response to perceived stress. The cumulative severity of stress (both mental and physical) an individual experiences is referred to as allostatic load, which is a key component of stress pathophysiology and observed in individuals with MDD (Rasgon and McEwen, 2016). Typically a result of chronic stress, a high allostatic load describes elevated HPA axis activity, resulting in increased cortisol levels, sympathetic nervous system tone, systemic inflammation, and insulin resistance (Watson et al., 2018). Glucocorticoids not only modulate stress response, but also modulate glucose levels and work synergistically with insulin (Biessels and Reagan, 2015). Therefore, insulin resistance and allostatic load may cooperate through a positive feedback loop, increasing the risk for metabolic and depressive comorbidities (Watson et al., 2018).

Dysregulated HPA axis activity and increased sympathetic nervous system tone are also characteristic features of PTSD (Michopoulos, 2015). Similar to MDD, the enhanced systemic inflammation induced by PTSD confers increased risk for T2DM incidence (Michopoulos, 2016; Spitzer et al., 2010). This is seen in individuals that have experienced traumatic life events, which are predictive of increased insulin concentrations and increased insulin resistance (Stojek et al., 2019; Mooy et al., 2000). The positive association between past experience of trauma and insulin resistance provides strong support for the association of adulthood insulin resistance and exposure to childhood trauma.

Because emotional development begins early in life and emotion regulation strategies are learned from caregivers, there is a strong association between early childhood maltreatment and subsequent deficits in emotion regulation in adolescence and adulthood (Powers et al., 2016;

Alink et al., 2009). Additionally, ED has been shown to be associated with and predictive of elevated levels of peripheral CRP concentrations, a marker for systemic inflammation. Each symptom subcluster of ED is associated with CRP in women with T2DM, but a lack of strategies to mitigate strong negative emotions had the strongest associations with CRP (Powers et al., 2016). CRP has also been positively associated with MDD (Kuo, 2005; Howren, 2009; Ford, 2004), and PTSD (Michopoulos, 2015; Sptizer, 2010; Miller. 2001). Chronic inflammation may be the underlying mechanism that modulates the comorbidity of psychiatric and physical disorders in the context of psychological stress or trauma (Powers, 2016). Because recent research has demonstrated that emotional functioning during childhood predicts elevated CRP in adulthood, the presence of childhood trauma could be an important mediator of comorbid psychiatric disorders.

4.3 Behavioral mechanisms that increase risk for T2DM

Exposure to traumatic events during childhood is predictive of PTSD, ED, and MDD (Otte et al., 2016). Previous research has suggested that women with more severe childhood trauma may have increased cortisol levels, which promotes increased food-seeking behaviors (Epel, Lapidus, McEwen, and Brownell, 2001; Warne et al., 2007). The dysregulated HPA activity observed in those with PTSD may decrease the availability of D2 receptors in the brain's reward system, resulting in increased consumption of calorically dense foods. From a behavioral perspective, pathological consumption of calorically dense foods, a risk factor for T2DM, has been shown to be a learned emotion regulation strategy (Stojek et al., 2019; Brockmeyer et al., 2014; Heatherton and Wagner, 2011.)

Another major risk factor for T2DM is low levels of physical activity, and increased sedentary behavior (Biswas et al., 2015). Depression and physical activity have a bidirectional relationship in which individuals with MDD are typically less active (De Moor et al., 2006), and lower levels of physical activity is a risk factor for MDD (Mammen and Faulkner, 2013). A recent meta-analysis concluded that physical activity was significantly more effective in decreasing PTSD and depressive symptoms than other interventions in individuals with PTSD (Rosenbaum et al., 2015). Moreover, physical activity can improve depressive symptoms among individuals with MDD (Schuch et al., 2016a,b, Schuch et al., 2015).

4.4 Limitations and Strengths

The current study has some limitations that may affect the interpretation and application of our findings. First, we utilized a cross-sectional approach to retrospectively analyze the relationship between current psychopathology symptoms and insulin and glucose metabolism during the OGTT. The cross-sectional design of this study does not allow us to address causality. Thus, we cannot elucidate whether MDD, ED, and PTSD symptoms increase an individual's risk for T2DM, or whether T2DM impacts psychiatric symptom profile. Additionally, this study represents a homogenous sample and results can only be generalized to African American women of low SES with a diagnosis of T2DM. However, the homogeneity of the sample is also a strength of the present study because African American women are at especially high risk for adverse mental and physical health outcomes (Gillespie, 2009). Additionally, the prevalence of T2DM among African American women is among the highest of all racial groups (Centers for Disease Control, 2017). Hence, African American women with T2DM are certainly an at-risk sample that would greatly benefit from improved T2DM and

psychiatric interventions. Furthermore, women are at higher risk than men for developing PTSD (Breslau, 2009; Breslau, 1997), MDD (Albert, 2015; Leach, 2008), and comorbid T2DM and MDD (Deischinger et al., 2020).

4.5 Conclusions

In summary, we found that symptoms of PTSD, MDD, and ED were all predictive of reduced insulin sensitivity and increased blood glucose, indicative of heightened insulin resistance. The results of the present study stress the need for future research into biological mechanisms that underlie psychiatric and metabolic comorbidities, as well as prospective intervention studies to determine possible avenues for their treatment.

Tables and Figures

Table 1: Demographic characteristics of 103 African American women recruited from the waiting room of the diabetic clinic at Grady Memorial Hospital in Atlanta, GA.

Continuous (N=103)	**Mean ± SEM**
Age	51 ± 0.05
Categorical	**N(% of total)**
Education (N=103)	
Did not complete 12th grade	22(21.4%)
High School Graduate	27(26.2%)
Graduate equivalency diploma	5(4.9%)
Some college/technical school	25(24.3%)
Technical school graduate	6(5.8%)
College graduate	15(14.6%)
Graduate School	3(2.9%)
Marital Status (N=103)	
Single or never married	47(45.6%)
Married	11(10.7%)
Divorced	28(27.2%)
Separated	3(2.9%)
Widowed	8(7.8%)
Domestic Partner	5(5.8%)
Household Monthly Income (N=101)	
$0-249	16(15.8%)
$250-499	8(7.9%)
$500-999	25(24.8%)
$1000-1999	32(31.7%)
$2000+	20(19.8%)
Employment (N=103)	
Currently unemployed	74(71.8%)
Currently employed	29(28.2%)

Table 2: Descriptive statistics for metabolic measures involved in altered glucose homeostasis and insulin sensitivity. Note that the N is listed for each sample. Because some participants declined to answer or skipped some questions, the total N is lower in some categories. The N for each measure was determined by the number of participants with completed data for the specified metabolic measure.

Metabolic Measure		**Mean ± SEM**
Body Mass Index (BMI; kg/m^2) (N=103)		36.3 ± 0.04
A1c (%) (N=96)		8.0 ± 0.01
C-reactive protein (CRP; mg/L) (N=96)		6.8 ± 0.04
Insulin Area Under the Curve (N=90)	AUC_I	2684± 18.0
	AUC_G	6651 ± 21.8
Glucose Area Under the Curve (N=90)	AUC_I	12763 ± 31.0
	AUC_G	31960 ± 69.9
Diabetes Treatment (N=100)		**N(% of total)**
No treatment		5(5%)
T2DM treatment		95(95%)

Table 3: Descriptive statistics for each psychiatric symptom measure and accompanying subclusters, and correlation coefficients generated from Pearson's r correlations. The N value for each measure was determined by the number of participants who had data for both the psychopathology score and metabolic insulin and glucose measures.

* $p < 0.05$

Psychopathology Measures		Mean ± Standard Error	Correlation Coefficients			
			Insulin		Glucose	
			AUC_I	AUC_G	AUC_I	AUC_G
PSS (n=85)	Total	15.0 ± 0.07	-0.27(0.01*)	-0.24(0.03*)	0.09(0.4)	0.27(0.01*)
	Intrusive	3.7 ± 0.02	-0.22(0.04*)	-0.25(0.02*)	0.14(0.2)	0.36(0.0006*)
	Avoidance	5.3 ± 0.03	-0.27(0.01*)	-0.18(0.09)	0.04(0.7)	0.18(0.1)
	Hyperarousal	5.9 ± 0.03	-0.22(0.04*)	-0.21(0.06)	0.05(0.7)	0.20(0.06)
DERS (n=80)	Total	71.0 ± 0.1	-0.25(0.02*)	-0.17(0.1)	0.05(0.6)	0.26(0.02*)
	Nonacceptance	11.8 ± 0.03	-0.18(0.1)	-0.19(0.09)	0.06(0.6)	0.27(0.02*)
	Goals	11.8 ± 0.03	-0.17(0.1)	-.10(0.4)	0.05(0.6)	0.21(0.06)
	Clarity	9.6 ± 0.02	-0.19(0.08)	-0.17(0.1)	0.1(0.4)	0.19(0.1)
	Impulse	10.9 ± 0.03	-0.26(0.02*)	-0.15(0.2)	-0.04(0.7)	0.08(0.5)
	Awareness	12.8 ± 0.03	-0.1(0.4)	0.07(0.5)	0.05(0.7)	0.17(0.1)
	Strategies	14.2 ± 0.03	-0.27(0.02*)	-0.23(0.04*)	0.04(0.7)	0.27(0.02*)
BDI (n= 86)	Total	15.8 ± 0.07	-0.35(0.001*)	-0.19(0.08)	0.03(0.8)	0.26(0.02*)

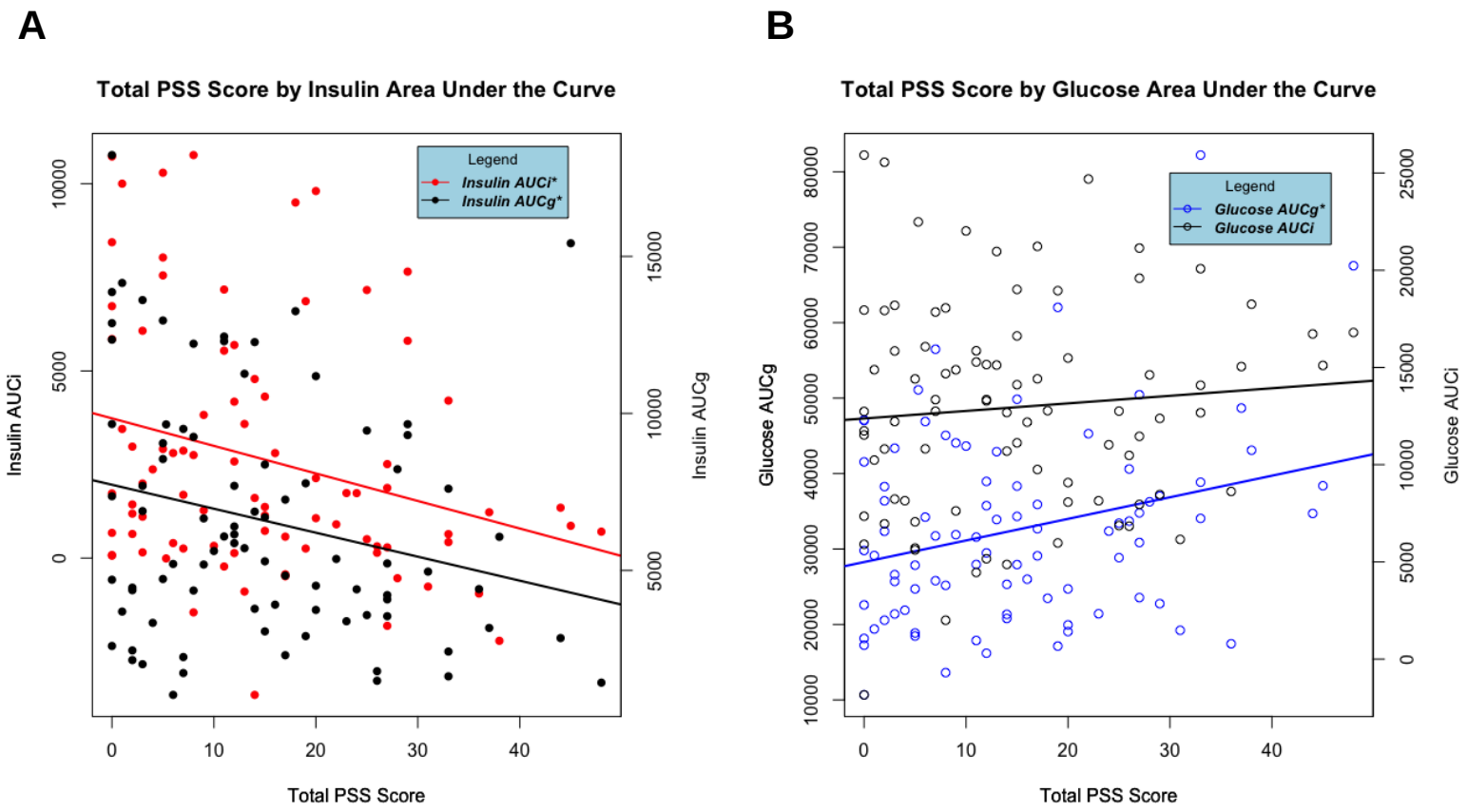

Figure 1. Associations between AUC measures of insulin and glucose and PTSD symptom severity (MPSS). **A)** Insulin AUC_I and AUC_G (red and black, respectively) based on participants' total MPSS score is shown. **B)** Glucose AUC_I and AUC_G (black and blue, respectively) based on participants' total MPSS score is shown. As MPSS score increases, participants' insulin AUC_I (r = -0.27*) and AUCg (r = -0.24*) levels decreased while their glucose AUC_I (r = 0.09) and AUC_G (r= 0.27*) levels increased. Asterisks (*) denote $p \leq 0.05$.

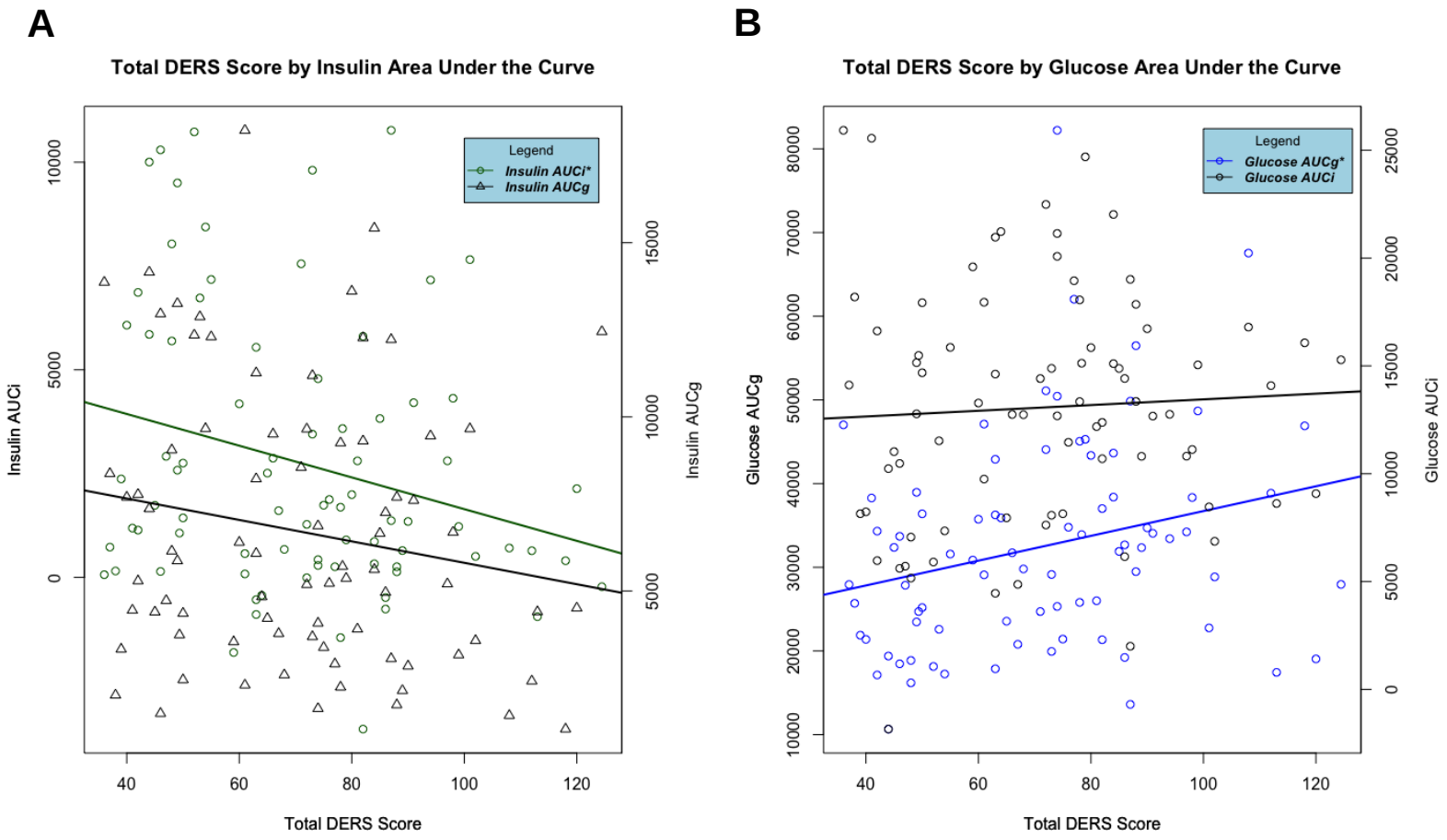

Figure 2. Associations between AUC measures of insulin and glucose and ED symptom severity. **A)** Insulin AUC_I and AUC_G (green and black, respectively) based on participants' total DERS score is shown. **B)** Glucose AUC_I and AUC_G (black and blue, respectively) based on participants' total DERS score is shown. As DERS score increases, participants' insulin AUC_I ($r = -0.25^*$) and AUC_G ($r = -0.17$) levels decreased while their glucose AUC_I ($r = 0.05$) and AUC_G ($r = 0.26$) levels increased. Asterisks (*) denote $p \leq 0.05$.

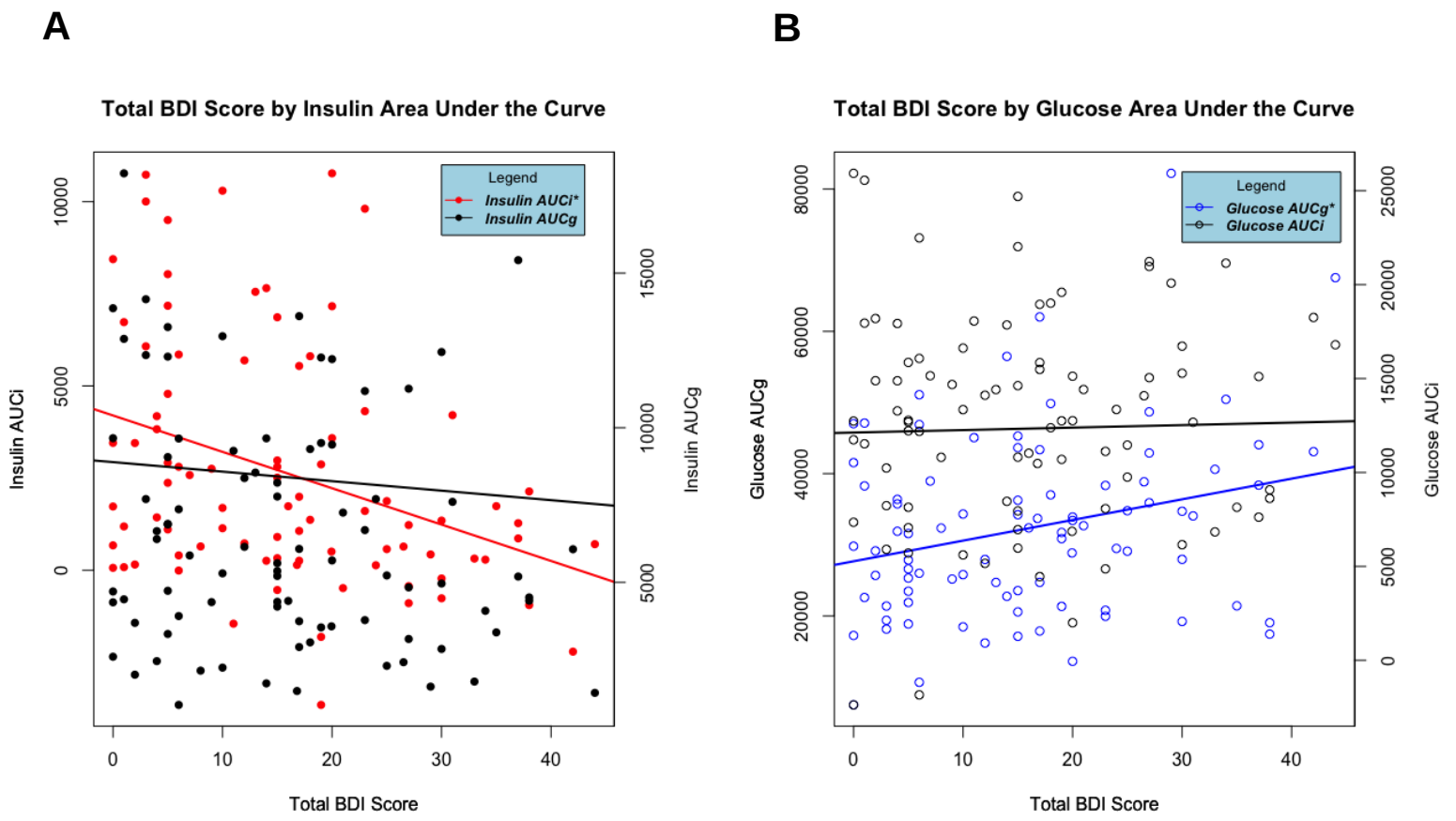

Figure 3. Associations between AUC measures of insulin and glucose and depressive symptom severity. **A)** Insulin AUC_I and AUC_G (red and black, respectively) based on participants' total BDI score is shown. **B)** Glucose AUC_I and AUC_G (black and blue, respectively) based on participants' total PSS score is shown. As BDI score increases, participants' insulin AUC_I (r = -0.35*) and AUC_G (r = -0.19) levels decreased while their glucose AUC_I (r = 0.03) and AUC_G (r = 0.26*) levels increased. Asterisks (*) denote $p \leq 0.05$.

References

Albert, P. (2015). Why is depression more prevalent in women? *Journal of Psychiatry & Neuroscience, 40*(4), 219–221. https://doi.org/10.1503/jpn.150205

Alim, T. N., Charney, D. S., & Mellman, T. A. (2006). An overview of posttraumatic stress disorder in African Americans. *Journal of Clinical Psychology, 62*(7), 801-813. doi:10.1002/jclp.20280

Alink, L. R., Cicchetti, D., Kim, J., & Rogosch, F. A. (2009). Mediating and Moderating Processes in the Relation between Maltreatment and Psychopathology: Mother-Child Relationship Quality and Emotion Regulation. *Journal of Abnormal Child Psychology*, *37*(6), 831–843. https://doi.org/10.1007/s10802-009-9314-4

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th ed, DSM-5. Washington, DC, American Psychiatric Association, 2013

APA. Diagnostic and Statistical Manual of Mental Disorders. (2014). Washington, DC: American Psychiatric Association.

Arroyo, C., Hu, F. B., Ryan, L. M., Kawachi, I., Colditz, G. A., Speizer, F. E., & Manson, J. (2003). Depressive Symptoms and Risk of Type 2 Diabetes in Women. *Diabetes Care*, *27*(1), 129–133. https://doi.org/10.2337/diacare.27.1.129

Beck, A. T. (1961). An Inventory for Measuring Depression. *Archives of General Psychiatry, 4*(6), 561. doi:10.1001/archpsyc.1961.01710120031004

Biessels, G. J., & Reagan, L. P. (2015). Hippocampal insulin resistance and cognitive dysfunction. *Nature Reviews Neuroscience*, *16*(11), 660–671. https://doi.org/10.1038/nrn4019

Biswas, A., Oh, P. I., Faulkner, G. E., Bajaj, R. R., Silver, M. A., Mitchell, M. S., & Alter, D. A. (2015). Sedentary Time and Its Association With Risk for Disease Incidence, Mortality, and Hospitalization in Adults. *Annals of Internal Medicine*, *162*(2), 123. https://doi.org/10.7326/m14-1651

Boscarino, J. A. (2004). Posttraumatic Stress Disorder and Physical Illness: Results from Clinical and Epidemiologic Studies. *Annals of the New York Academy of Sciences, 1032*(1), 141-153. doi:10.1196/annals.1314.011

Boyko, E. J., Jacobson, I. G., Smith, B., Ryan, M. A., Hooper, T. I., Amoroso, P. J., … Smith, T. C. (2010). Risk of Diabetes in U.S. Military Service Members in Relation to Combat Deployment and Mental Health. *Diabetes Care*, *33*(8), 1771–1777. https://doi.org/10.2337/dc10-0296

Bradley, B., DeFife, J. A., Guarnaccia, C., Phifer, J., Fani, N., Ressler, K. J., & Westen, D. (2011). Emotion Dysregulation and Negative Affect. *The Journal of Clinical Psychiatry, 72*(05), 685–691. https://doi.org/10.4088/jcp.10m06409blu

Bradley, B., Westen, D., Mercer, K. B., Binder, E. B., Jovanovic, T., Crain, D., . . . Heim, C. (2011). Association between childhood maltreatment and adult emotional dysregulation in a low-income, urban, African American sample: Moderation by oxytocin receptor gene. *Development and Psychopathology, 23*(2), 439-452. doi:10.1017/s0954579411000162

Breslau, N. (1991). Traumatic Events and Posttraumatic Stress Disorder in an Urban Population of Young Adults. *Archives of General Psychiatry, 48*(3), 216. doi:10.1001/archpsyc.1991.01810270028003

Breslau, N. (1997). Sex Differences in Posttraumatic Stress Disorder. *Archives of General Psychiatry*, *54*(11), 1044. https://doi.org/10.1001/archpsyc.1997.01830230082012

Breslau, N. (2009). The Epidemiology of Trauma, PTSD, and Other Posttrauma Disorders. *Trauma, Violence, & Abuse*, *10*(3), 198–210. https://doi.org/10.1177/1524838009334448

Brockmeyer, T., Skunde, M., Wu, M., Bresslein, E., Rudofsky, G., Herzog, W., & Friederich, H.-C. (2014). Difficulties in emotion regulation across the spectrum of eating disorders. *Comprehensive Psychiatry*, *55*(3), 565–571. https://doi.org/10.1016/j.comppsych.2013.12.001

Bromet, E., Andrade, L. H., Hwang, I., Sampson, N. A., Alonso, J., de Girolamo, G., … Kessler, R. C. (2011). Cross-national epidemiology of DSM-IV major depressive episode. *BMC Medicine*, *9*(1). https://doi.org/10.1186/1741-7015-9-90

Campayo, A., de Jonge, P., Roy, J. F., Saz, P., de la Cámara, C., Quintanilla, M. A., … Lobo, A. (2010). Depressive Disorder and Incident Diabetes Mellitus: The Effect of Characteristics of Depression. *American Journal of Psychiatry*, *167*(5), 580–588. https://doi.org/10.1176/appi.ajp.2009.09010038

Centers for Disease Control (2017). National diabetes statistics report. Atlanta, GA https://www.cdc.gov/diabetes/data/statistics/statistics-report.html.

Cho, N. H., Shaw, J. E., Karuranga, S., Huang, Y., da Rocha Fernandes, J. D., Ohlrogge, A. W., & Malanda, B. (2018). IDF diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections FOR 2045. *Diabetes Research and Clinical Practice*, *138*, 271–281. https://doi.org/10.1016/j.diabres.2018.02.023

Ciaraldi, T. P. (2009). Cellular Mechanisms of Insulin Action. *Principles of Diabetes Mellitus,* 75-87. doi:10.1007/978-0-387-09841-8_5

Czech, M. P. (2017). Insulin action and resistance in obesity and type 2 diabetes. *Nature Medicine*, *23*(7), 804–814. https://doi.org/10.1038/nm.4350

Deischinger, C., Dervic, E., Leutner, M., Kosi-Trebotic, L., Klimek, P., Kautzky, A., & Kautzky-Willer, A. (2020). Diabetes mellitus is associated with a higher risk for major depressive disorder in women than in men. *BMJ Open Diabetes Research & Care*, *8*(1). https://doi.org/10.1136/bmjdrc-2020-001430

De Moor, M. H. M., Beem, A. L., Stubbe, J. H., Boomsma, D. I., & De Geus, E. J. C. (2006). Regular exercise, anxiety, depression and personality: A population-based study. *Preventive Medicine*, *42*(4), 273–279. https://doi.org/10.1016/j.ypmed.2005.12.002

Dohrenwend, B. P. (2006). The Psychological Risks of Vietnam for U.S. Veterans: A Revisit with New Data and Methods. *Science*, *313*(5789), 979–982. https://doi.org/10.1126/science.1128944

Falsetti, S. A., Resnick, H. S., Resick, P. A., & Kilpatrick, D. G. (1993). The Modified PTSD Symptom Scale: A brief self-report measure of posttraumatic stress disorder. *the Behavior Therapist*, *16*, 161–162.

Fekedulegn, D. B., Andrew, M. E., Burchfiel, C. M., Violanti, J. M., Hartley, T. A., Charles, L. E., & Miller, D. B. (2007). Area under the curve and other summary indicators of repeated waking cortisol measurements. *Psychosomatic Medicine*, *69*(7), 651–659. https://doi.org/10.1097/PSY.0b013e31814c405c

Ford, D. E., & Erlinger, T. P. (2004). Depression and C-Reactive Protein in US Adults: Data from the Third National Health and Nutrition Examination Survey. *Archives of Internal Medicine*, *164*(9), 1010. doi:10.1001/archinte.164.9.1010

Galicia-Garcia, U., Benito-Vicente, A., Jebari, S., Larrea-Sebal, A., Siddiqi, H., Uribe, K. B., … Martín, C. (2020). Pathophysiology of Type 2 Diabetes Mellitus. *International Journal of Molecular Sciences*, *21*(17), 6275. https://doi.org/10.3390/ijms21176275

Gillespie, C. F., Bradley, B., Mercer, K., Smith, A. K., Conneely, K., Gapen, M., . . . Ressler, K. J. (2009). Trauma exposure and stress-related disorders in inner city primary care patients. *General Hospital Psychiatry*, *31*(6), 505-514. doi:10.1016/j.genhosppsych.2009.05.003

Goldmann, E., Aiello, A., Uddin, M., Delva, J., Koenen, K., Gant, L. M., & Galea, S. (2011). Pervasive exposure to violence and posttraumatic stress disorder in a predominantly African American Urban Community: the Detroit Neighborhood Health Study. *Journal of traumatic stress*, *24*(6), 747–751. https://doi.org/10.1002/jts.20705

Gratz, K. L., & Roemer, L. (2004). Multidimensional Assessment of Emotion Regulation and Dysregulation: Development, Factor Structure, and Initial Validation of the Difficulties in Emotion Regulation Scale. *Journal of Psychopathology and Behavioral Assessment*, *26*(1), 41–54. https://doi.org/10.1023/b:joba.0000007455.08539.94

Gross, J. (1998b). The emerging field of emotion regulation: An integrative review. Review of General Psychology, 2(3), 271–299. https://doi.org/ 10.1037/ 1089-2680.2.3.271

Gross, J., & Muñoz, R. (1995). Emotion regulation and mental health. Clinical Psychology: Science and Practice, 2(2), 151–164.

Heatherton, T. F., & Wagner, D. D. (2011). Cognitive neuroscience of self-regulation failure. *Trends in Cognitive Sciences*, *15*(3), 132–139. https://doi.org/10.1016/j.tics.2010.12.005

Howren, M. B., Lamkin, D. M., & Suls, J. (2009). Associations of Depression With C-Reactive Protein, IL-1, and IL-6: A Meta-Analysis. *Psychosomatic Medicine*, *71*(2), 171–186. https://doi.org/10.1097/psy.0b013e3181907c1b

Jagannathan, R., Neves, J. S., Dorcely, B., Chung, S. T., Tamura, K., Rhee, M., & Bergman, M. (2020). The Oral Glucose Tolerance Test: 100 Years Later. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, *Volume 13*, 3787–3805. https://doi.org/10.2147/dmso.s246062

Kim, J., & Cicchetti, D. (2009). Longitudinal pathways linking child maltreatment, emotion regulation, peer relations, and psychopathology. *Journal of Child Psychology and Psychiatry*, *51*(6), 706–716. https://doi.org/10.1111/j.1469-7610.2009.02202.x

Keane, T. M., LeDoux, J. E., & Shiromani, P. J. (2009). Post-traumatic stress disorder: definition, prevalence, and risk factors. In *Post-traumatic stress disorder: basic science and clinical practice* (pp. 1–19). essay, Humana Press.

Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB (1995): Posttraumatic stress disorder in the National Comorbidity Survey. Arch Gen Psychiatry 52:1048–1060.

Kumari, M., Head, J., & Marmot, M. (2004). Prospective Study of Social and Other Risk Factors for Incidence of Type 2 Diabetes in the Whitehall II Study. *Archives of Internal Medicine*, *164*(17), 1873. https://doi.org/10.1001/archinte.164.17.1873

Kuo, H.-K., Yen, C.-J., Chang, C.-H., Kuo, C.-K., Chen, J.-H., & Sorond, F. (2005). Relation of C-reactive protein to stroke, cognitive disorders, and depression in the general population: systematic review and meta-analysis. *The Lancet Neurology*, *4*(6), 371–380. https://doi.org/10.1016/s1474-4422(05)70099-5

Leach, L. S., Christensen, H., Mackinnon, A. J., Windsor, T. D., & Butterworth, P. (2008). Gender differences in depression and anxiety across the adult lifespan: the role of psychosocial mediators. *Social Psychiatry and Psychiatric Epidemiology*, *43*(12), 983–998. https://doi.org/10.1007/s00127-008-0388-z

Mammen, G., & Faulkner, G. (2013). Physical Activity and the Prevention of Depression. *American Journal of Preventive Medicine*, *45*(5), 649–657. https://doi.org/10.1016/j.amepre.2013.08.001

Mooy, J. M., de Vries, H., Grootenhuis, P. A., Bouter, L. M., & Heine, R. J. (2000). Major stressful life events in relation to prevalence of undetected type 2 diabetes: the Hoorn Study. *Diabetes Care*, *23*(2), 197–201. https://doi.org/10.2337/diacare.23.2.197

Nasca, C., Watson-Lin, K., Bigio, B., Robakis, T. K., Myoraku, A., Wroolie, T. E., … Rasgon, N. (2019). Childhood trauma and insulin resistance in patients suffering from depressive disorders. *Experimental Neurology*, *315*, 15–20. https://doi.org/10.1016/j.expneurol.2019.01.005

Nouwen, A., Winkley, K., Twisk, J., Lloyd, C. E., Peyrot, M., Ismail, K., & Pouwer, F. (2010). Type 2 diabetes mellitus as a risk factor for the onset of depression: a systematic review and meta-analysis. *Diabetologia*, *53*(12), 2480–2486. https://doi.org/10.1007/s00125-010-1874-x

Michopoulos, V., Rothbaum, A. O., Jovanovic, T., Almli, L. M., Bradley, B., Rothbaum, B. O., … Ressler, K. J. (2015). Association of CRP Genetic Variation and CRP Level With Elevated PTSD Symptoms and Physiological Responses in a Civilian Population With High Levels of Trauma. *American Journal of Psychiatry*, *172*(4), 353–362. https://doi.org/10.1176/appi.ajp.2014.14020263

Michopoulos, V., Vester, A., & Neigh, G. (2016). Posttraumatic stress disorder: A metabolic disorder in disguise? *Experimental Neurology*, *284*, 220–229.

Otte, C., Gold, S. M., Penninx, B. W., Pariante, C. M., Etkin, A., Fava, M., … Schatzberg, A. F. (2016). Major depressive disorder. *Nature Reviews Disease Primers*, *2*(1). https://doi.org/10.1038/nrdp.2016.65

Rasgon, N. L., & McEwen, B. S. (2016). Insulin resistance—a missing link no more. *Molecular Psychiatry*, *21*(12), 1648–1652. https://doi.org/10.1038/mp.2016.162

R.J.Miller,A.G.Sutherland, J. D. Hutchison, andD.A. Alexander, "C-reactive protein and interleukin 6 receptor in post-traumatic stress disorder: a pilot study," Cytokine,vol.13, no. 4, pp. 253–255, 2001.

Roden, M., & Shulman, G. I. (2019). The integrative biology of type 2 diabetes. *Nature*, *576*(7785), 51–60. https://doi.org/10.1038/s41586-019-1797-8

Rosenbaum, S., Vancampfort, D., Steel, Z., Newby, J., Ward, P. B., & Stubbs, B. (2015). Physical activity in the treatment of Post-traumatic stress disorder: A systematic review and meta-analysis. *Psychiatry Research*, *230*(2), 130–136. https://doi.org/10.1016/j.psychres.2015.10.017

Scherrer, J. F., Salas, J., Norman, S. B., Schnurr, P. P., Chard, K. M., Tuerk, P., … Lustman, P. J. (2019). Association Between Clinically Meaningful Posttraumatic Stress Disorder Improvement and Risk of Type 2 Diabetes. *JAMA Psychiatry*, *76*(11), 1159. https://doi.org/10.1001/jamapsychiatry.2019.2096

Schuch, F. B., Vasconcelos-Moreno, M. P., Borowsky, C., Zimmermann, A. B., Rocha, N. S., & Fleck, M. P. (2015). Exercise and severe major depression: Effect on symptom severity and quality of life at discharge in an inpatient cohort. *Journal of Psychiatric Research*, *61*, 25–32. https://doi.org/10.1016/j.jpsychires.2014.11.005

Schuch, F. B., Vancampfort, D., Richards, J., Rosenbaum, S., Ward, P. B., & Stubbs, B. (2016a). Exercise as a treatment for depression: A meta-analysis adjusting for publication bias. *Journal of Psychiatric Research*, *77*, 42–51. https://doi.org/10.1016/j.jpsychires.2016.02.023

Schuch, F. B., Vancampfort, D., Rosenbaum, S., Richards, J., Ward, P. B., & Stubbs, B. (2016b). Exercise improves physical and psychological quality of life in people with depression: A meta-analysis including the evaluation of control group response. *Psychiatry Research*, *241*, 47–54. https://doi.org/10.1016/j.psychres.2016.04.054

Seedat, S., Scott, K. M., Angermeyer, M. C., Berglund, P., Bromet, E. J., Brugha, T. S., … Kessler, R. C. (2009). Cross-National Associations Between Gender and Mental Disorders in the World Health Organization World Mental Health Surveys. *Archives of General Psychiatry*, *66*(7), 785. https://doi.org/10.1001/archgenpsychiatry.2009.36

Spitzer, C., Barnow, S., Völzke, H., Wallaschofski, H., John, U., Freyberger, H. J., … Grabe, H. J. (2010). Association of posttraumatic stress disorder with low-grade elevation of C-reactive protein: Evidence from the general population. *Journal of Psychiatric Research*, *44*(1), 15–21. https://doi.org/10.1016/j.jpsychires.2009.06.002

Stojek, M. M., Maples-Keller, J. L., Dixon, H. D., Umpierrez, G. E., Gillespie, C. F., & Michopoulos, V. (2019). Associations of childhood trauma with food addiction and insulin resistance in African-American women with diabetes mellitus. *Appetite*, *141*, 104317. https://doi.org/10.1016/j.appet.2019.104317

Watson, K., Nasca, C., Aasly, L., McEwen, B., & Rasgon, N. (2018). Insulin resistance, an unmasked culprit in depressive disorders: Promises for interventions. *Neuropharmacology*, *136*, 327–334. https://doi.org/10.1016/j.neuropharm.2017.11.038

Weiss, T., Skelton, K., Phifer, J., Jovanovic, T., Gillespie, C. F., Smith, A., … Ressler, K. J. (2011). Posttraumatic stress disorder is a risk factor for metabolic syndrome in an impoverished urban population. *General Hospital Psychiatry*, *33*(2), 135–142. https://doi.org/10.1016/j.genhosppsych.2011.01.002

Appendix

This study was performed using data from the Stress and Diabetes (SAD) study led by Dr. Charles Gillespie. This work was primarily supported by the National Institute of Mental Health (MH099211). Participants were recruited from the diabetic clinic at Grady Memorial Hospital from 2012-2017 by researchers at the Grady Trauma Project. Researchers also obtained written and verbal informed consent from participants during recruitment. Participants were instructed to fast after 9 pm on the evening prior to the OGTT and clinical interview assessments. Phlebotomy and structured clinical interviews were performed by research staff. Additionally, research staff performed AUC calculations of insulin and glucose levels.

In terms of my responsibilities, I developed and formalized the present research question and performed all of the relevant literature search. Though I did not perform participant recruitment for the current study, I helped to recruit participants and acquire their mental health data for other ongoing studies at the Grady Trauma Project while concurrently working on the current completed dataset. I performed all analyses of the current dataset in R Studio version 3.5.2. I was also responsible for all data interpretation, creation of figures, and the writing of the current thesis.